Original Article

Revisiting the Debate of 'Routine' vs 'Selective' Microscopic Evaluation of Cholecystectomies: Observations from an Indian Archipelago on the Incidence of Dysplasia and Incidental Gallbladder Cancer

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Abstract

Background: Gallstone disease or cholelithiasis is a common indication for cholecystectomy globally, with various histopathological alterations in gallbladder mucosa. Understanding these changes is crucial for determining their relationship with gall bladder cancer and justifying histopathological examination policies. In this context, this study was undertaken to investigate the range of histomorphological abnormalities found in gall bladder specimens removed for cholelithiasis. Additionally, the study seeks to establish the prevalence of dysplasia and incidental gall bladder cancer in these specimens.

Materials and Methods: A retrospective study spanning five years was conducted at a tertiary care hospital. Demographic data, macroscopic features, and histopathological findings of all cholecystectomy specimens were recorded and analyzed.

Results: Among 1,380 patients, chronic cholecystitis (75.3%) was most common, followed by cholesterolosis (17.9%) and xanthogranulomatous cholecystitis (1.7%). Only two cases (0.14%) of gallbladder cancer were found. Low-grade dysplasia was present in 0.9% of cases. No cases of incidental gallbladder cancer were encountered.

Conclusion: Chronic cholecystitis predominates in cholecystectomy specimens for cholelithiasis in our setting, with low rates of neoplastic pathology. The absence of incidental gallbladder cancer in the study favors selective over routine histopathological examination. However, further validation studies and cost-benefit analyses are needed to form evidence-based guidelines regarding the policy of selective histopathological examination of resected gallbladder specimens in the Indian setup.

Keywords:

Cancer, Cholelithiasis, Cholesterolosis, Dysplasia, Gallbladder

Introduction

Gallstone disease (cholelithiasis) is a prevalent global health issue and forms the most common indication for cholecystectomy, whether open or laparoscopic. Apart from inflammatory changes, cholelithiasis induces various other histopathological alterations in the gallbladder mucosa, including cholesterolosis, metaplasia, adenomatous hyperplasia, and even carcinoma [1]. Other than advancing age, ethnicity, and female gender, cholelithiasis and other chronic inflammatory conditions affecting the gallbladder have been implicated as additional risk factors for gallbladder carcinogenesis [2][3]. Zhu Z et al. have shown that gallstones larger

than 1.95 cm and cholelithiasis persisting for more than 10 years are independent risk factors for GBC [4]. The occurrence of symptomatic gallstones in North India is significantly greater, being 20 times more frequent than in Southern India [1][3]. The same holds true for gallbladder cancer (GBC) as well, with North, East, Northeast, and Central India revealing higher incidence rates [3]. Interestingly, several Indian studies have reported that 70–90% of patients diagnosed with GBC also have co-existing gallstones [3].

Understanding the histopathological changes related to gallbladder disorders is crucial for determining their incidence, distribution, and relationship with GBC. Cholecystectomy specimens have traditionally been subjected to histopathological examination to confirm the underlying pathology and rule out incidental GBC. However, this practice of subjecting all cholecystectomy specimens to pathological examination has been a matter of debate, with recent advocacy for a more selective approach to histopathological evaluation.

With this background, this study was carried out to analyze the histomorphological spectrum of gallbladder pathologies encountered in cholecystectomies performed for cholelithiasis. The study also aims to determine the rates of dysplasia and incidental GBC in these specimens to justify or nullify the policy of selective histopathological examination.

Materials and Methods

A retrospective descriptive study spanning five years (January 2015 to December 2019) was conducted at a tertiary care hospital. The study involved reviewing histopathology reports of all cholecystectomies (both open and laparoscopic) performed between January 2015 and December 2019. Demographic data, such as age, gender, preoperative diagnosis, and macroscopic features, were extracted from archived pathology reports. Relevant radiological details and intraoperative findings were collected from medical records. Cases lacking adequate clinical or pathological information for any reason, and cases where microscopic slides were not available for review, were excluded from the study sample. Cases of acalculous cholecystitis were also excluded.

Since the risk of gallbladder dysplasia and incidental cancer is more closely associated with cholelithiasis, chronic inflammation, and other risk factors linked to calculous cholecystitis, including acalculous cases, which lack these risk factors, would have diluted the study's results [2,3,4]. Moreover, acalculous cholecystitis is relatively uncommon, especially in elective cholecystectomy settings, compared to its calculous counterpart.

A total of 1,380 cholecystectomy specimens received by the Pathology department during the study period underwent careful macroscopic examination following standard guidelines. Grossly, normal-looking gallbladder specimens underwent processing with a minimum of three sections taken, one from each of the fundus, body, and neck. Additional representative tissue was submitted in cases where the gallbladder wall was thickened or any mural lesions were observed. All surgical specimens were fixed in 10% phosphate-buffered formaldehyde, embedded in paraffin, and sections were prepared for routine light microscopy after staining with haematoxylin and eosin.

Microscopic slides were independently reviewed by two pathologists. Demographic details, macroscopic findings, and histopathological findings were recorded in an Excel sheet and analyzed using SPSS software version 20. Categorical variables were presented as frequencies (%) and mean values.

Results

Among the 1380 patients, there were 250 males (18.11%) and 1130 females (81.89%), with a statistically highly significant female

predominance (male-to-female ratio of 1:4.5; p value <0.0001). The average age at presentation was 40.47 years, ranging from 4 to 85 years.

Microscopic analysis of the surgical specimens (n = 1380) predominantly revealed non-neoplastic pathology in 1365 cases (98.9%). Chronic cholecystitis (n = 1039; 75.3%) was the commonest finding, followed by chronic cholecystitis with cholesterolosis (n = 248; 17.9%) and xanthogranulomatous cholecystitis (n = 23; 1.7%) [Table 1, Figure 1, Figure 2].

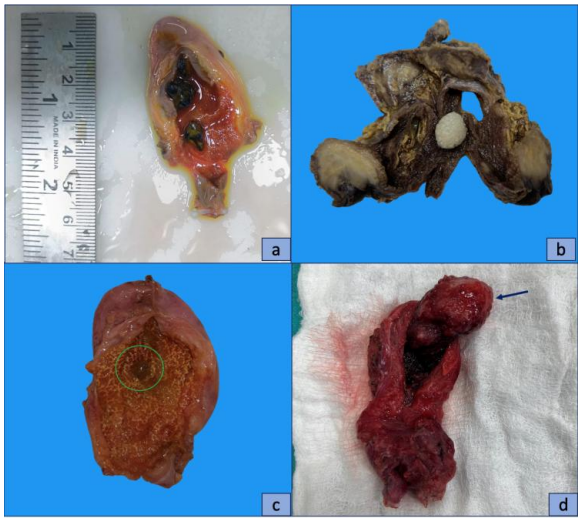

Figure 1: a) Gall bladder with multiple calculi; b) Gall bladder with a single large calculus; c) A case of adenomyoma presenting as a small nodule (circled) along with diffuse numerous mucosal yellow specks (cholesterolosis); d) Case of gallbladder cancer presenting as a fundal polypoidal mass (arrow).

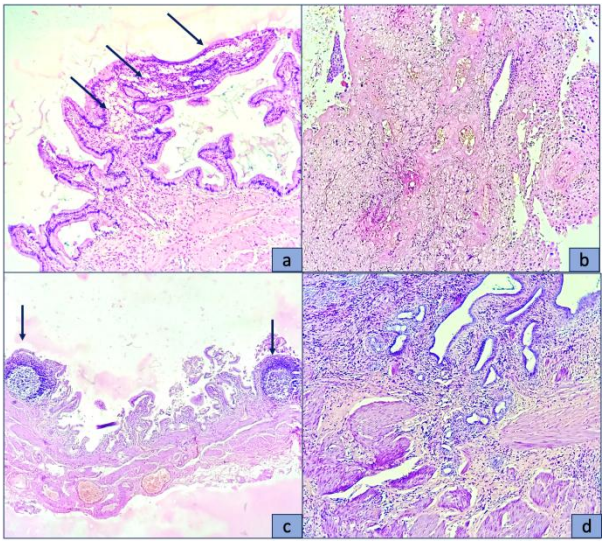

Figure 2: a) Focal cholesterolosis with foamy lipid laden macrophages (arrow) expanding the lamina propria (H&E stain, 40×); b) Xanthogranulomatous cholecystitis displaying sheets of foamy histiocytes admixed with mild lymphocytic infiltrate (H&E stain, 40×); c) Follicular cholecystitis showing marked lymphocytic infiltrate in the lamina propria with germinal centre formation (arrow) (H&E stain, 40×); d)Well differentiated adenocarcinoma with irregular neoplastic glands infiltrating the muscularis propria (H&E stain, 40×).

Pyloric and intestinal metaplasia were observed in 8 cases (0.58%) and 27 cases (1.96%) respectively, associated with chronic cholecystitis. Only two cases (0.14%) exhibited GBC, both in female patients aged 53 and 75 years. Both patients presented with symptoms of right hypochondriac pain, weight loss, and fever, with one experiencing severe jaundice. Preoperative imaging facilitated diagnosis in both cases.

Gross examination revealed diffuse asymmetric gallbladder wall thickening, with one case showing a friable mass in the lumen with papillary projections. Histologically, both cases exhibited features consistent with adenocarcinoma of the gallbladder with invasion of peri-muscular connective tissue on the peritoneal side, without serosal involvement (pT2b). The case with friable papillary growth displayed characteristics of papillary adenocarcinoma.

Although 13 cases (0.9%) showed focal low-grade mucosal dysplasia, no incidental GBC cases were encountered in our study. Specimens with metaplasia or dysplasia did not display any macroscopic abnormalities.

Discussion

Histopathological Spectrum in Resected Gall Bladders:

The commonest pathology encountered in our study cohort was chronic cholecystitis. The histopathological spectrum noted in our study cohort fairly corroborates with the findings of similar Indian studies, as compared under Table 1 [5–10]. Kumar H et al. compared the diversity of gallbladder diseases in North and South Indian populations and observed that in North India, the gender distribution was skewed with a ratio of 1 male to 4.88 females, while in South India, it was more balanced at 1 male to 1.33 females [11]. The incidence of GBC was higher in North India (2%) than in the South (1.25%). Dysplasia related to cholecystitis was also more prevalent in North India (2.50%) than in the Southern population (1.75%). Cholesterolosis was significantly associated with the North Indian group, with 17.75% affected, whereas no cases were observed in the Southern cohort [11]. We encountered a higher female predominance and higher incidence of cholesterolosis, akin to studies on the North Indian population. This may be due to the unique heterogeneous population comprising migrants from other Indian states and indigenous tribal groups inhabiting the territory of Andaman and Nicobar Islands, India.

The second most common lesion encountered in our study was cholesterolosis. Cholesterolosis, a condition stemming from lipid metabolism dysfunction, results in elevated cholesterol build-up within the gallbladder mucosa, thereby manifesting histologically as the presence of abundant foamy macrophages in the lamina propria. Few preliminary reports have associated cholesterolosis with metabolic syndrome and chronic pancreatitis [12,13]. Dairi S et al. reviewed 6,868 patients who underwent cholecystectomy and concluded that cholesterolosis was not significantly associated with hypercholesterolemia, pancreatitis, and biliary dyskinesia [14]. In our series, none of the patients had associated pancreatitis. Furthermore, Yaylak F et al., in their analytical study of 429 cholecystectomy specimens, found that cholesterolosis was significantly associated with decreased gallbladder wall thickness and metaplastic changes [15]. We did not encounter such associations.

In our study cohort, we encountered 23 cases of xanthogranulomatous cholecystitis, and all showed increased wall thickness and stiffness. Adequate sections were processed, and none of the xanthogranulomatous cholecystitis cases showed dysplastic or neoplastic change. Xanthogranulomatous cholecystitis is an uncommon, focal or diffuse, chronic inflammatory disease characterized by thickening of the gallbladder wall and infiltration of lipid-laden macrophages. However, its clinical and imaging features often mimic gallbladder carcinoma, creating diagnostic challenges. This resemblance is due to the presence of irregular wall thickening, mass-like lesions, and possible involvement of adjacent organs, all of which can raise suspicion for malignancy

Table 1: Findings of the present study in comparison with other Indian studies

	Present study	**Beena et al**	**Degloorkar et al**	**Savanur et al**	**Kotasthane et al**	**Munjal et al**	**Shah et al**	**Mali et al**
Study Site	AN Islands	Karnataka	Maharashtra	Maharashtra	Uttar Pradesh	Uttar Pradesh	Gujarat	Rajasthan
Time frame	2015-2019	2013-2015	2017-2023	2016-2020	2018-2019	2021-2022	2016-2021	2018-2022
Sample size	1380	200	1728	471	86	170	360	2221
M:F ratio	1:4.5	0.86:1	1:2.1	1:1.4	1:2.4	1:4.15	2:3	1:4.5
HISTOPATHOLOGIC FINDINGS								
Chronic calculous cholecystitis [n (%)]	1039 (75.3)	164 (82.0)	1223 (70.8)	280 (59.4)	63 (73.3)	35 (20.6)	222 (61.7)	1820 (82.0)
Acalculous cholecystitis [n (%)]	---	---	---	156 (33.1)	12 (13.9)	83 (48.8)	57 (15.8)	---
Acute cholecystitis [n (%)]	11 (0.8)	7 (3.5)	480 (27.8)	2 (0.4	1 (1.2)	---	35 (9.7)	---
Acute suppurative cholecystitis [n (%)]	1 (0.07)	1 (0.5)	17 (1.0)	1 (0.2)	---	---	---	---
Acute gangrenous cholecystitis [n (%)]	1 (0.07)	---	---	1 (0.2)	1 (1.2)	---	2 (0.6)	3 (0.14)
Acute on chronic cholecystitis [n (%)]	4 (0.3)	20 (10.0)	---	19 (4)	---	---	7 (1.9)	207 (9.3)
Xanthogranulomatous cholecystitis [n (%)]	23 (1.7)	2 (1.0)	1 (0.1)	3 (0.6)	2 (2.3)	4 (2.4)	3 (0.8)	97 (4.4)
Chronic follicular cholecystitis [n (%)]	2 (0.14)	---	---	1 (0.2)	---	---	---	1 (0.05)
Eosinophilic cholecystitis [n (%)]	---	---	---	1 (0.2)	---	1 (0.6)	---	27 (1.2)
Choledochal cyst [n (%)]	---	---	---	3 (0.6)	---	---	---	---
Cholesterolosis [n (%)]	248 (17.9)	5 (2.5)	14 (0.8)	---	5 (5.8)	30 (17.7)	1 (0.3)	---
Porcelein gallbladder [n (%)]	---	---	1 (0.1)	---	---	---	---	---
Metaplasia [n (%)]	35 (2.5)	---	---	2 (0.4)	---	---	---	---
Tubercular Cholecystitis [n (%)]	---	---	---	---	---	---	---	2 (0.1)
Mucosal polyp, NOS [n (%)]	---	---	---	---	---	---	2 (0.6)	---
Papillary/ Adenomatous hyperplasia [n (%)]	---	---	---	---	---	1 (0.6)	---	8 (0.4)
Tubular/Papillary adenoma [n (%)]	---	---	1 (0.1)	---	---	---	1 (0.3)	1 (0.05)
Adenomyoma [n (%)]	1 (0.07)	---	---	---	---	---	4 (1.1)	---
Low-grade dysplasia [n (%)]	13 (0.9)	---	---	---	---	13 (7.6)	---	---
High-grade dysplasia [n (%)]	---	---	---	---	---	1 (0.6)	---	---
Gallbladder cancer [n (%)]	2 (0.14)	1 (0.5)	8 (0.5)	1 (0.2)	2 (2.3)	2 (1.2)	24 (6.7)	30 (1.4)

during surgery. Bolukbasi H and Kara Y examined 34 patients with xanthogranulomatous cholecystitis, and none received an accurate preoperative diagnosis [16]. Hence, in such cases, frozen section analysis is employed to differentiate

xanthogranulomatous cholecystitis from gallbladder cancer. Conducting intraoperative frozen section analysis is essential to avoid unnecessary extensive surgical procedures [17]. Xanthogranulomatous cholecystitis has also been linked to an increased risk of GBC. Hence, we suggest that in situations where intraoperative and gross results are suggestive of xanthogranulomatous cholecystitis, adequate sampling followed by diligent microscopic evaluation should be carried out to rule out occult malignancy. This procedure helps guide the surgical approach, avoiding overly aggressive or unnecessary radical surgery if malignancy is excluded. Despite its utility, frozen sections may not always yield definitive results due to the overlap in histological features between xanthogranulomatous cholecystitis and malignancies, necessitating careful clinical and pathological correlation.

Incidence of Dysplasia and Incidental GBC:

We, like several other investigators, did not encounter any incidental GBC in our cohort [18,19]. By definition, incidental GBC is identified during histopathological examination of gallbladders resected under the presumption of gallstone disease or benign pathology, whether diagnosed clinically, through imaging, or during surgery, including inspection of the cholecystectomy specimen's cut surface. Two cases of GBC in our study showed increased gallbladder wall thickness and mural growth. Both these cases had abnormal gallbladder imaging and macroscopic appearance. Few investigators have reported a low incidence of incidental GBC (0.6%), whereas others have observed its incidence to be as high as 11% [20–22]. These contrasting results might be attributed to variations in geographic location, patient socio-demographics, dietary habits, co-existing risk factors, tumour characteristics, access to healthcare facilities, etc. Swank and colleagues found that the prevalence of incidental GBC was higher in Asian studies than in Western studies [23].

In the present study, only 13 (0.9%) cases demonstrated low-grade dysplasia, with none showing high-grade dysplastic changes. Few other investigators have encountered similarly low numbers of dysplastic lesions (<0.2%) in macroscopically normal gallbladders [19,24–26]. Munjal et al. reported 13 (7.6%) and 1 (0.6%) cases of low-grade and high-grade dysplastic lesions, respectively, in their study cohort of 170 resected gallbladders [9]. Paliogiannis et al. retrospectively reviewed 311 consecutive elective cholecystectomies and encountered dysplasia in 13 (4.3%) instances [27]. Chronic cholecystitis and dysplasia of the gallbladder are intricately linked, largely due to prolonged inflammatory processes that affect the gallbladder epithelium [3,4]. Gallstones, a key cause of chronic cholecystitis, contribute to prolonged bile stasis and mechanical irritation, compounding the inflammatory response [3,4]. Studies indicate that the size and duration of gallstone presence increase the risk of epithelial dysplasia and GBC [4]. Although variable incidence of dysplasia has been reported in various cohorts of cholecystectomies, simple cholecystectomy is sufficient and no revision surgery is warranted.

Perspectives on 'Routine' vs 'Selective' Histopathology:

There is ongoing debate over whether to perform routine or selective histopathological examination of gallbladders resected for cholelithiasis. Investigators advocating routine histopathological examination have reported higher frequencies of incidental GBC in their study cohorts [22]. However, this practice is costly and burdensome for pathology departments, despite the low prevalence of incidental GBC. The selective approach is supported by the argument that a macroscopically normal-appearing gallbladder has minimal chances of harboring GBC [19,23]. Several investigators have reported that incidental GBC often presents with macroscopic abnormalities, such as diffuse thickening of the gallbladder wall, mucosal irregularity, or localized masses [28–30]. Conversely, macroscopically normal gallbladders are unlikely to harbor malignancy [21,26].

Our study highlights the low incidence of incidental GBC in macroscopically normal specimens, with only two cases (0.14%) of GBC identified, both of which exhibited macroscopic abnormalities. These findings align with other studies advocating selective

histopathological examination based on preoperative imaging, intraoperative findings, and macroscopic assessment of the specimen.

Additionally, when no abnormalities are detected, any cancer present is typically at an early stage, and simple cholecystectomy already serves as adequate treatment for early-stage tumors (carcinomas in situ and T-stage Ia tumors) [28,29]. A recently conducted meta-analysis by Bastiaenen et al. found that the incidence of incidental GBC was less than 0.5%, dropping further to less than 0.1% when surgeons conducted thorough macroscopic examinations [31]. Their findings suggest that selectively examining the gallbladder histopathologically after initial macroscopic assessment by the surgeon appears to be safe and could lead to cost savings. Olthof et al., after analyzing 2,763 patients undergoing cholecystectomy, concluded that selective pathological examination of gallbladder specimens could significantly reduce healthcare costs [26]. The 2016 Dutch national guidelines on handling cholecystectomy specimens for cholelithiasis advocated a selective histopathologic policy rather than routinely examining all specimens microscopically [32].

In a multicentric Dutch study involving 22,025 gallbladders, Corten et al. developed a clinical prediction model for selecting gallbladder specimens for histopathologic examination after cholecystectomy [33]. Factors such as age above 60 years, female sex, urgency, type of surgery, and surgical indications were identified as crucial parameters for decision-making. They also recommended that all cases of gallbladder polyps, primary sclerosing cholangitis, Mirizzi syndrome, and porcelain gallbladder undergo thorough histopathological examination [33]. Similarly, Alabi et al. recommended that patients aged 50 years and above, visibly abnormal gallbladders, emergency surgery, and cases of difficult laparoscopic dissection resulting in conversion to open surgery should undergo histological evaluation of cholecystectomy specimens [24]. A pictorial representation of the selective histopathological approach, drawing from previous studies, is presented in Figure 3 [18,24,29,33].

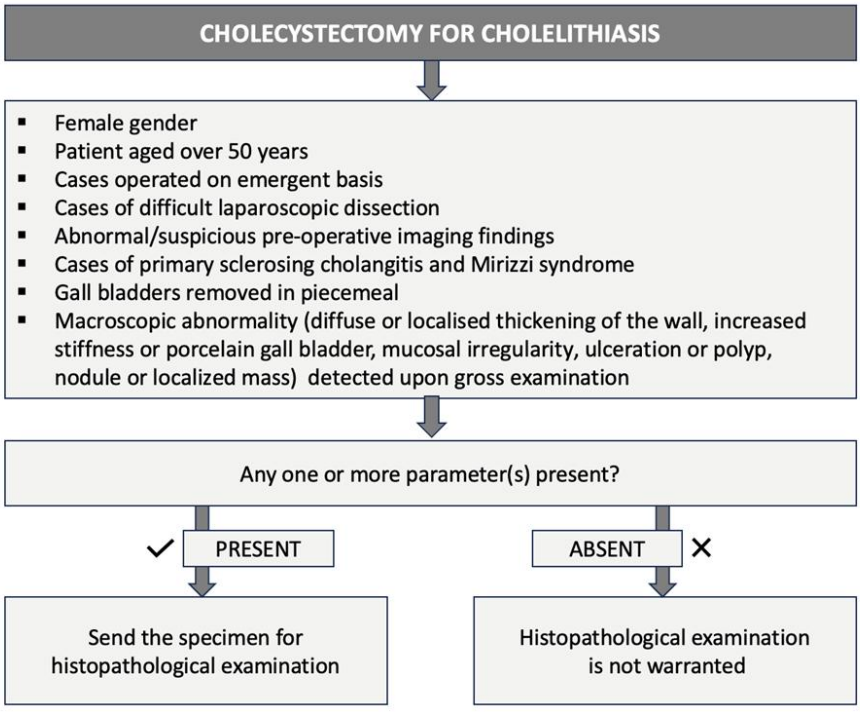

Figure 3: Proposed model of selective histopathology approach in gall bladders resected for cholelithiasis,based on the findings of published literature.[18,24,29,33]

The FANCY multicentric study, evaluating the safety and cost-benefit of selective histopathology following cholecystectomy, concluded that the method is oncologically sound and decreases pathology workload and expenses [31]. In a meta-analysis encompassing 26 studies with 80,228 patients operated for benign gallbladder disease, the incidental GBC rate was 0.7% [34]. However, not all incidental GBC cases were early lesions, with T2 and T3 lesions accounting for a significant proportion [34]. A more recent meta-analysis also revealed that most incidental GBC cases were staged at pT2 [35].

Thus, although the incidence of incidental GBC is low, rare cases of advanced incidental GBC (requiring revision surgery due to higher pT stage) might be missed under the selective histopathology policy [28,30]. Other disadvantages of selective histopathology include the potential loss of valuable material for education and research, as well as issues in medicolegal scenarios.

Limitations of the Study and Future Directions:

In India, traditionally, all resected gallbladder specimens undergo routine histopathological examination regardless of macroscopic appearance. This practice aligns with the 2005 recommendations by the Royal College of Pathologists. Besides establishing a definitive diagnosis, it helps uncover unexpected pathologies, provides material for education and research, and serves as documentation for medicolegal purposes. Although some previous Indian studies have recommended selective histopathology for cholecystectomies performed for cholelithiasis, research gaps persist in this area [20,21]. Whether the selective histopathology approach is both safe and cost-effective within the Indian healthcare framework remains debatable. Further validation studies and clinical prediction models are required to establish this practice across Indian laboratories.

Our study offers initial insights based on a relatively limited patient cohort from a single center. The retrospective nature of this study and the low number of gallbladder carcinoma cases may influence outcomes and conclusions. Cost-benefit analysis was not within the scope of this study.

It is essential for surgeons, histopathologists, and their professional organizations to collaborate on establishing guidelines and evidence-based protocols. Additionally, the literacy and socio-economic status of the Indian population should be considered before implementing selective histopathology for gallbladder specimens. Lastly, whether surgeons possess equivalent proficiency to pathologists in identifying subtle macroscopic abnormalities remains uncertain and may necessitate additional training.

Conclusion

In conclusion, our study sheds light on the histomorphological spectrum of gallbladder pathologies encountered in cholecystectomies performed for cholelithiasis in an Indian Archipelago. Chronic cholecystitis emerged as the most common condition in our study, followed by cholesterolosis. This higher incidence of cholesterolosis is akin to studies on the North Indian population. We identified a low incidence of neoplastic gallbladder pathology in this region, with only 0.9% of cases of dysplasia and 0.14% of cases of GBC, which align more closely with existing data from Southern India. We did not encounter any incidental GBC cases in our study and hence favour ‘selective’ over ‘routine’ histopathological examination strategy. Although the findings of this study cannot be generalised, it serves as the basis for future research endeavours in this direction. The adoption of the strategy of selective histopathological examination of resected gallbladder specimens necessitates comprehensive validation studies and cost-benefit analyses in order to frame evidence-based guidelines and optimize diagnostic practices in gallbladder pathology within the Indian healthcare context.

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