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ORIGINAL ARTICLE

Is there need of routine histopathological analysis of cholecystectomy specimens.

Wahb Noor Zia[1], Muhammad Ghayasuddin[2], Ramsha Waseem[3], Mahnoor Zia[4], Muhammad Ali[5], Muhammad Dawood Hussain[6]

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ABSTRACT… Objective: To determine the prevalence of incidental gallbladder carcinoma (GBC) and premalignant lesions in routine histopathological examination (HPE) of all cholecystectomy specimens at a tertiary-care hospital in Karachi. **Study Design:** Prospective Cohort study. **Setting:** Kulsoom Bai Valika Hospital. **Period:** April 2024 to April 2025. **Methods:** All adult patients (≥18 years) undergoing elective or emergency cholecystectomy were enrolled. Exclusions comprised preoperatively known or suspected GBC and lost specimens. Demographic, clinical, ultrasonographic, operative, and histopathological data were collected on 600 patients. Specimens underwent standard paraffin embedding, sectioning, and hematoxylin-eosin staining. Histological diagnoses were classified into chronic cholecystitis (with/without stones), acute cholecystitis, cholesterolosis, adenomyomatosis, adenoma, metaplasia (intestinal/pyloric), xanthogranulomatous cholecystitis, high-grade dysplasia/carcinoma in situ, and invasive carcinoma (staged T1a/T1b). Continuous variables are presented as mean ± SD; categorical variables as n (%). Group comparisons used Student's t-test or chi-square/Fisher's exact tests; $p < 0.05$ was significant. **Results:** Among 600 patients (344 elective, 256 emergency; mean age 48.0 ± 12.0 years; 72.7% female), chronic cholecystitis was predominant (411/600, 68.5%). Acute cholecystitis occurred in 107 (17.8%). Benign neoplasms and non-neoplastic lesions were infrequent: adenoma 0.8%, adenomyomatosis 3.8%, cholesterolosis 1.7%, cholesterol polyps 1.0%, and metaplasia 2.8%. High-grade dysplasia/carcinoma in situ was identified in 12 (2.0%). Incidental invasive GBC was found in 6 elective patients (1.0%; all T1 lesions). No carcinomas were detected in emergency cases. Emergency surgery was associated with higher white blood cell counts (14.65 ± 2.94 vs. 8.02 ± 2.93 × 10^9/L; $p < 0.001$) and fever (61.3% vs. 0%; $p < 0.001$). **Conclusion:** Routine HPE of all cholecystectomy specimens in this high-incidence setting identified early-stage GBC and premalignant lesions in a meaningful proportion (3.0%), justifying universal submission. Selective protocols risk missing occult neoplasia and should be applied cautiously in similar populations.

Key words: Cholecystectomy, Dysplasia, Gallbladder Carcinoma, Histopathology, Incidental Findings.

INTRODUCTION

The gallbladder is a small organ that stores and concentrates bile before it drains via the cystic duct into the biliary tree. Gallstone disease and cholecystitis are among the most common surgical conditions worldwide, with especially high prevalence in South Asian populations.[1] Chronic inflammation from gallstones is the main risk factor for gallbladder carcinoma (GBC).[2] GBC often presents late and carries a poor prognosis, but early-stage GBC (confined to the lamina propria or muscularis) may be cured by simple cholecystectomy. Importantly, early or in situ GBC is usually asymptomatic and not visible on preoperative imaging.[2,3] Thus, an incidental GBC discovered only on routine histopathology can significantly alter patient management (e.g., extended re-resection or surveillance).[4]

Routine histopathological examination (HPE) of all cholecystectomy specimens aims to identify unexpected pathology (GBC, dysplasia, premalignant polyps, or rare entities like xanthogranulomatous cholecystitis). Literature showed that selective submission based on gross appearance risks missing occult malignancy.[3,5] In one large Indian series (n=4115), incidental GBC was found in 0.44% of cases and most were early-stage.[6] In our region (Pakistan/India), multiple reports have noted incidental GBC rates of ~1–3%, as well as premalignant changes in a few percent of cases.[1,2]

1. MBBS, Resident General Surgery, Kulsoom Bai Valika Hospital Site Area, Karachi.
2. MBBS, FCPS, Consultant Supervisor, Head General Surgery, KBVHSS.
3. MBBS, MRCS, Post-graduate Trainee General Surgery, KBVHSS.
4. MBBS, PG Trainee Surgical and Allied, KBVHSS.
5. FCPS, PGR Surgery, KBVHSS.
6. MBBS, Resident General Surgery, KBVHSS.

Correspondence Address:
Dr. Wahb Noor Zia
Department of General Surgery
Kulsoom Bai Valika Hospital Site Area, Karachi.
wahb.zia72@gmail.com

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By contrast, studies from low-incidence countries (e.g. Australia) often find negligible GBC on histology and argue for selective HPE.[7,8] A recent systematic review and meta-analysis reported a pooled incidental GBC rate of ~0.6% globally, but with wide regional variation (up to ~0.8% in high-incidence areas).[8,9]

Given the ongoing debate and the lack of prospective data from Karachi, we performed a 1-year prospective study of consecutive elective and emergency cholecystectomies at Kulsoom Bai Valika Hospital. Our objectives were to (1) determine the prevalence of incidental GBC and other significant histopathological findings, (2) compare pathology between elective and emergency cases, and (3) assess whether routine HPE yields clinically important diagnoses that would justify the resources required.

METHODS

This prospective cohort study enrolled all adult patients (≥18 years) undergoing cholecystectomy at Kulsoom Bai Valika Hospital, Karachi from April 2023 to April 2025. Both elective (scheduled) and emergency (acute cholecystitis) operations were included. We excluded patients with known or suspected GBC preoperatively (e.g., imaging-detected mass) and those whose specimens were lost to analysis. Ethical approval was obtained from the hospital's Institutional Review Board (3507-30/5/25), and written informed consent was obtained from all participants.

Before data collection, we performed a power analysis to ensure adequate sample size. Based on prior regional data, we anticipated an incidental GBC prevalence of ~2%[2]. We used a two-proportion chi-square framework to detect a difference between elective and emergency groups (assuming, for example, 3% vs 0.5% GBC) with $\alpha=0.05$ and power 0.8. This yielded a required sample of several hundred patients per group. Alternatively, estimating a single proportion of ~2% with 95% CI width ±1% also indicated ~400–500 total patients. Following guidelines for sample size determination[10], we set a target enrollment of ~600 patients over one year. Actual recruitment (N=600) met this target.

Demographic (age, sex), clinical (presentation, symptoms, comorbidities), and laboratory data were recorded in a standardized form. Operative details were noted: indication, surgical approach (laparoscopic, open, or converted), intraoperative findings (gallbladder wall thickness, presence of gallstones or polyps macroscopically, adhesions), and complications. All resected gallbladders were sent intact to pathology. Surgeons inspected specimens visually and reported any obvious lesions, but no specimens were discarded or withheld.

Each specimen underwent routine pathological processing: sectioning and hematoxylin-eosin staining. Histological diagnoses were categorized as chronic cholecystitis (with or without stones), acute cholecystitis (including acute-on-chronic, mucocele, empyema), cholesterolosis, adenomyomatosis/hyperplasia, xanthogranulomatous cholecystitis, gallbladder polyp (non-neoplastic) or adenoma, intestinal or pyloric metaplasia, and dysplasia/carcinoma in situ. Carcinoma findings were classified by type (adenocarcinoma, papillary, etc.) and staged. Pathologists were blinded to patient clinical data.

All data were analysed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Continuous variables (age, BMI, white blood cell count) were first assessed for normality with the Shapiro–Wilk test and are presented as mean ± standard deviation. Differences between the elective and emergency groups for normally distributed continuous variables were evaluated with independent-samples Student's t-tests. Categorical variables (sex, comorbidities, clinical features, ultrasound findings, operative conversions, gross pathology and histopathological categories) are expressed as counts and percentages. Between-group comparisons were made using Pearson's chi-square test. When any expected cell count was less than five, Fisher's exact test was used instead; likelihood-ratio χ^2 statistics are also reported for tables with sparse data. All tests were two-sided, and a p-value < 0.05 was considered statistically significant. The study was reported following STROBE guidelines for cohort studies.

RESULTS

Of 618 cholecystectomies performed during the study period, 18 were excluded (12 known gallbladder carcinoma, 6 lost specimens), leaving 600 patients i.e. 344 (57.3%) elective and 256 (42.7%) emergency procedures. The mean age was 48.01 ± 11.95 years, with no significant difference between elective (48.24 ± 11.99) and emergency (47.69 ± 11.99) groups (p = 0.578). Overall, 438 (72.7%) patients were female, distributed similarly between elective (70.9%) and emergency (75.0%) cohorts (p = 0.269). Body mass index averaged 27.22 ± 4.21 kg/m^2 (27.12 ± 4.38 vs. 27.37 ± 3.97; p = 0.461). Comorbidities were comparable: diabetes mellitus in 199 (33.2%; 32.8% vs. 33.6%; p = 0.848), hypertension in 151 (25.2%; 26.5% vs. 23.4%; p = 0.401), and hypothyroidism in 32 (5.3%; 4.4% vs. 6.6%; p = 0.219). Indicators of acute inflammation were markedly higher in the emergency group: mean white blood cell count was 14.65 ± 2.94 × 10^9/L versus 8.02 ± 2.93 × 10^9/L (p = 0.001), and fever (>38 °C) occurred in 157 patients (26.2%), all in the emergency cohort (61.3% vs. 0%; p = 0.001). Jaundice was rare (6 cases, 1.0%; p = 0.704). Preoperative ultrasonography detected gallstones in 562 (93.7%) patients (93.6% vs. 93.8%; p = 0.942), gallbladder wall thickening (>3 mm) in 137 (22.8%; 13.1% vs. 35.9%; p = 0.001), common bile duct stones in 41 (6.8%; 4.4% vs. 10.2%; p = 0.005), and polyps >5 mm in 14 (2.3%; no intergroup difference, p = 0.988). (Table-I)

Laparoscopic cholecystectomy was attempted in 584 cases (97.3%), with similar rates for elective (96.5%) and emergency (98.4%) groups (p = 0.148). Conversion to open surgery occurred in 33 patients (5.5%), more frequently in emergencies (8.6%) than electives (3.2%; p = 0.004). Specimen perforation was observed only in emergency cases (5.1%; p = 0.001). Severe adhesions were significantly more common in emergencies (65.2% vs. 13.1%; p = 0.001), as was gross wall thickening >5 mm (33.6% vs. 11.3%; p = 0.001). Macroscopic polyps were rare (1%; p = 0.196), and gallstones were identified intraoperatively in 580 cases (96.7%), with a higher detection rate in the emergency cohort (99.2%) compared to elective (94.8%; p = 0.003). (Table-II)

Histological examination confirmed chronic cholecystitis as the predominant finding in 411 patients (68.5%), subdivided into chronic cholecystitis without gallstones in 317 (52.8%; 50.0% elective vs. 56.6% emergency) and chronic cholecystitis with gallstones in 94 (15.7%; 14.8% vs. 16.8%). Acute cholecystitis was diagnosed in 107 patients (17.8%), slightly more often in elective cases (19.8%) than in emergencies (15.2%). Benign lesions were uncommon: adenomyomatosis in 23 (3.8%; 4.1% vs. 3.5%), gallbladder adenoma in 5 elective patients (0.8%), cholesterolosis in 10 (1.7%; 2.0% vs. 1.2%), cholesterol polyps in 6 (1.0%; 1.5% vs. 0.4%), intestinal metaplasia in 9 (1.5%; 1.5% vs. 1.6%), pyloric metaplasia in 8 (1.3%; 1.2% vs. 1.6%), and xanthogranulomatous cholecystitis in 3 (0.5%; 0.3% vs. 0.8%). High-grade dysplasia or carcinoma in situ was identified in 12 patients (2.0%; 1.7% elective vs. 2.3% emergency). Notably, all six incidental invasive carcinomas (1.7% of elective cases; 1% overall) occurred in the elective cohort, comprising four T1a and two T1b tumors. No carcinomas were detected in emergency specimens. (Table-III)

DISCUSSION

In this prospective series of 600 cholecystectomies we found chronic cholecystitis by far to be the dominant pathology (52.8%). Most importantly, 6 cases (1.0%) harbored incidental gallbladder adenocarcinoma (all diagnosed in the elective group) and 12 cases (2.0%) showed high-grade dysplasia. Notably, none of the emergency specimens contained carcinoma, whereas elective cases yielded all occult cancers. These findings underscore that routine histopathological examination (HPE) of even grossly normal gallbladders can detect occult malignancies. Although our carcinoma rate (1%) is lower than some earlier regional reports (e.g. ~2.7–3.3% in Pakistani cohorts)[11,12] it remains in line with published ranges for high-risk populations. Chronic cholecystitis is a well-known precursor and was overwhelmingly common.[13,14]

Characteristic	All (N=600)	Elective (N=344)	Emergency (N=256)	P-Value
Age (years)	48.01±11.95	48.24 ± 11.99	47.69 ± 11.99	0.578
Female sex	438 (72.7)	244 (70.9)	192 (75)	0.269
BMI (kg/m^2)	27.22±4.21	27.12± 4.38	27.37±3.97	0.461
Diabetes mellitus	199 (33.2)	113 (32.8)	86 (33.6)	0.848
Hypertension	151 (25.2)	91 (26.5)	60 (23.4)	0.401
Hypothyroidism	32 (5.3)	15 (4.4)	17 (6.6)	0.219
WBC×10^9/L	10.85±4.40	8.02±2.93	14.65±2.94	0.001*
Fever (>38°C)	157 (26.2)	0 (0)	157 (61.3)	0.001*
Jaundice	6 (1)	3 (0.9)	3 (1.2)	0.704
Ultrasound gallstones	562 (93.7)	322 (93.6)	240 (93.8)	0.942
Ultrasound wall thickening (>3 mm)	137 (22.8)	45 (13.1)	92 (35.9)	0.001*
Ultrasound CBD stones	41 (6.8)	15 (4.4)	26 (10.2)	0.005*
Ultrasound polyps (>5 mm)	14 (2.3)	8 (2.3)	6 (2.3)	0.988
Data presented as mean±SD or n (%)				

Table-I. Patient demographics and clinical features (elective vs. emergency)

Finding	Elective (N=350)	Emergency (N=250)	P-Value
Laparoscopic (vs open)	332 (96.5)	252 (98.4)	0.148
Conversion to open	11 (3.2)	22 (8.6)	0.004*
Specimen perforation	0 (0)	13 (5.1)	0.001*
Severe adhesions	45 (13.1)	167 (65.2)	0.001*
Gross wall thickening >5 mm	39 (11.3)	86 (33.6)	0.001*
Macroscopic polyps seen	5 (1.5)	1 (0.4)	0.196
Gallstones found	326 (94.8)	254 (99.2)	0.003*
Data presented as n (%)			

Table-II. Operative and gross pathology findings (elective vs. emergency)

Histopathological Diagnosis	Elective (n = 344)	Emergency (n = 256)	Total (n = 600)
Acute cholecystitis	68 (19.8)	39 (15.2)	107 (17.8)
Gallbladder adenoma	5 (1.5)	0	5 (0.8)
Adenomyomatosis (hyperplastic change)	14 (4.1)	9 (3.5)	23 (3.8)
Incidental gallbladder carcinoma	6 (1.7)	0	6 (1)
Cholesterol polyps (non-neoplastic)	5 (1.5)	1 (0.4)	6 (1)
Cholesterolosis	7 (2)	3 (1.2)	10 (1.7)
Chronic cholecystitis without gallstones	172 (50)	145 (56.6)	317 (52.8)
Chronic cholecystitis with gallstones	51 (14.8)	43 (16.8)	94 (15.7)
High-grade dysplasia / carcinoma in situ	6 (1.7)	6 (2.3)	12 (2)
Intestinal metaplasia	5 (1.5)	4 (1.6)	9 (1.5)
Pyloric (gastric) metaplasia	4 (1.2)	4 (1.6)	8 (1.3)
Xanthogranulomatous cholecystitis	1 (0.3)	2 (0.8)	3 (0.5)
Data presented as n (%)			

Table-III. Histopathological findings by presentation

The discovery of high-grade dysplasia in 2% of cases further highlights that premalignant changes often accompany chronic inflammation and would be missed without histology[13,15] In summary, our study confirms that in this setting routine histopathology yields clinically significant findings, including early-stage cancers and precancerous lesions, which cannot be reliably predicted intraoperatively or by preoperative imaging.

Our results broadly agree with other studies from South Asia, where incidental gallbladder cancer (GBC) has been reported in roughly 0.6–3% of cholecystectomy specimens.[11,16] For example, a series from Pakistan found incidental carcinoma in 2.8% of elective cases (6/220), all without gross abnormalities.[11] Similarly, Sangwan et al. in North India reported 1.9% incidental GBC and advocated routine HPE.[17] In contrast, a large Karachi cohort (N=521) reported a higher carcinoma frequency (3.3%).[12] Our 1% carcinoma rate is somewhat lower, possibly reflecting differences in patient selection or the inclusion of emergency cases. Notably, our study was large and prospective, enhancing confidence in the findings.

Chronic cholecystitis was the predominant lesion in all series. We observed it in 52.8% of cases, whereas Siddiqui et al. found chronic inflammation in >90%[11] and Almas et al. reported it in 78.6%.[13] The variation likely reflects differing case mixes (for example, many acute cholecystitis cases in our cohort) and reporting definitions. Nevertheless, the strong association of chronic cholecystitis with GBC is well established.[18] High-grade dysplasia is less frequently reported, but its identification in 2% of our cases is noteworthy. Dysplasia is a recognized precursor to invasive carcinoma[19], and its detection underscores the premalignant potential of chronic gallbladder disease.

Geographically, our findings align with the high-incidence pattern of this region. Indeed, global data show Asian studies report higher incidental GBC rates (median ~1.2%) than Western series (~0.4%).[20] Pakistan's gallbladder cancer incidence is among the world's highest (South Karachi: ~13.8/100,000 in women).[14] In such endemic areas, even a low-percent incidental rate translates to substantial absolute numbers. Local reports consistently argue for routine HPE: e.g., Shukla et al. in India noted that routine examination is "the only capability through which malignancies can be detected at an early, potentially curable stage".[21] Soomro et al. similarly concluded that routine histology of all gallbladders is the "only reliable, cost-effective" means to early diagnosis and improved survival.[12] These observations are consonant with our data demonstrating occult neoplasia that would otherwise be missed.

Our data reinforce the clinical value of routine histopathological evaluation of gallbladder specimens. Even at a 1% incidental cancer rate, routine HPE had profound impact: all identified cancers prompted further staging or surgery. In our series, elective HPE led to timely management of carcinoma cases (including completion hepatectomy for T2–T3 lesions) that would have been overlooked without pathology.[11] Likewise, identifying high-grade dysplasia permits closer surveillance or prophylactic measures. Almas et al. emphasized that HPE is "imperative in the detection of premalignant and malignant lesions that might otherwise evade macroscopic detection".[13] In practical terms, our findings suggest that discarding gallbladder specimens risks missing early carcinomas and dysplasia in this population.

That said, we acknowledge the resource implications of universal submission. The selective–routine controversy remains unsettled. Proponents of selective submission point to data suggesting that experienced surgeons can detect most GBC by gross examination. For example, Talreja et al. found incidental GBC in 11 of 973 cholecystectomies (1.1%), with all 11 showing macroscopic abnormalities; no malignancies occurred in normal-looking gallbladders.[22] Rosenberg et al. noted that in several series every incidental carcinoma had visible wall thickening or tumor upon specimen review.[23] A recent systematic review similarly concluded that with careful intraoperative inspection and risk-factor assessment, selective histology could

avoid overuse of pathology.[20,24] In countries like Australia with very low GBC incidence, a selective policy has been argued to be safe and cost-effective.[7,20]

However, we caution that in our high-risk setting even a few missed cancers can have grave consequences. Importantly, in our study none of the incidental malignancies had preoperative suspicion, and all were unsuspected macroscopically. This echoes Swank et al.'s finding that Asian studies had a significant number of unexpected GBCs that were not predicted pre- or intraoperatively.[20] Moreover, routine HPE ensures detection of unusual histologies (e.g. carcinoma in situ, xanthogranulomatous inflammation, tuberculosis) that can alter management. On balance, in endemic regions the potential benefit of identifying curable early cancers and of diagnosing premalignant lesions appears to outweigh the incremental pathology workload. Accordingly, we support routine submission of all gallbladder specimens for histopathology in similar settings.[21,24]

This study's strengths include its prospective design and large sample size. Limitations include its single-center scope and lack of long-term follow-up on incidental case outcomes. We did not perform formal cost-effectiveness analysis or quantify the additional workload for pathology. It is also possible that occasional subtle lesions (e.g. microcarcinomas) went undetected despite thorough sectioning. Future work could involve multi-center cohorts and standardized macroscopy protocols to identify preoperative predictors of malignancy. Molecular or imaging biomarkers might aid in triaging specimens. Moreover, long-term surveillance data for patients with incidentally detected dysplasia or carcinoma would clarify the true clinical impact of early detection.

CONCLUSION

Our findings strongly reinforce that in high-incidence areas routine histopathological examination of gallbladder specimens remains clinically valuable. It enables detection of otherwise occult carcinoma and high-grade dysplasia, facilitating timely intervention. While selective policies may be debated in low-risk contexts, centers serving high-GBC-burden populations should consider retaining universal submission to optimize patient care.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Wahb Noor Zia:** Conceptualization, methodology, formal analysis, final review.
2	**Muhammad Ghayasuddin:** Conceptualization, supervision, results interpretation.
3	**Ramsha Waseem:** Data collection, literature review.
4	**Mahnoor Zia:** Manuscript writing, editing, final review.
5	**Muhammad Ali:** Literature review, manuscript writing.
6	**Muhammad Dawood Hussain:** Data collection, methodology.