Section: Pathology

Original Research Article

SIGNIFICANCE OF HER2 NEU AND KI 67 IN PRENEOPLASTIC LESIONS AND CARCINOMA OF GALL BLADDER

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Received *: 10/08/2026*
Received in revised form *: 02/09/2026*
Accepted *: 05/09/2026*

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DOI: 10.70034/ijmedph.2026.3.871

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (3); 5644-5649

ABSTRACT

Background: GBC is highly prevalent in northern India, driven by cholelithiasis, infections, and environmental factors. HER2/neu is a potential oncogenic therapeutic target; Ki-67 reflects cellular proliferative activity. Regional data on their expression across the gallbladder lesion spectrum are sparse. **Objective:** To evaluate and compare HER2/neu and Ki-67 IHC expression in non-neoplastic, preneoplastic, and neoplastic gallbladder lesions and correlate with clinicopathological parameters.

Materials and Methods: Case control retrospective study at Rajkiya Medical College, Jalaun — 280 cholecystectomy specimens (140 non-neoplastic, 124 preneoplastic, 16 neoplastic). HER2/neu scored by ASCO/CAP criteria; Ki-67 ≥20% = high proliferation.

Results: HER2/neu positivity (2+/3+) was 0%, 9.7%, and 37.5% in non-neoplastic, preneoplastic, and neoplastic groups respectively ($p = 0.001$), with highest 3+ in well-differentiated adenocarcinoma (50%; $p < 0.05$). Ki-67 high expression row stepwise from 2.9% → 34.7% → 62.5% ($p = 0.001$), correlating with grade and jaundice. Co-expression of HER2+ with high Ki-67 was seen in 31.3% of neoplastic cases. Mean age increased progressively (42.3 → 48.6 → 54.2 years;) with female predominance (~69%).

Conclusion: Both markers rise significantly along the dysplasia–carcinoma sequence. HER2/neu in well-differentiated tumours suggests targeted therapy potential; Ki-67 supports risk stratification. HER2/neu expression was completely absent in all non-neoplastic lesions, establishing it as a neoplasia-specific marker in gallbladder pathology.

Keywords: Gallbladder carcinoma, HER2/neu, Ki-67, immunohistochemistry, preneoplastic lesions, dysplasia, proliferative index, biliary tract cancer, targeted therapy, North India.

INTRODUCTION

Gallbladder cancer poses a significant health burden in India, particularly in the northern regions, yet it remains relatively under-researched. Epidemiological data highlight an urgent need for focused studies: GBC incidence in parts of North India (e.g. Uttar Pradesh, Bihar, West Bengal, Assam) ranks among the highest in the world. The rising trend of GBC cases in these areas – even affecting middle-aged patients – signals a regional cancer control challenge. In practical terms, clinicians in high-incidence zones face patients with advanced gallbladder malignancies on a frequent basis, but they often lack robust tools beyond standard histology to stratify risk or guide therapy.[1,2]

The current standard for diagnosing gallbladder neoplasms is histopathological examination of cholecystectomy specimens, sometimes after an imaging-suspected lesion or often incidentally after

surgery for gallstones. While routine histopathology reliably confirms malignancy and provides tumour grade and stage, it has limitations in prognostication. Many patients with "early" histologic lesions (such as dysplasia or carcinoma in situ) may progress rapidly to invasive cancer, whereas others with invasive carcinoma might have variable outcomes that are not fully predicted by TNM stage alone. This creates a diagnostic and prognostic gap – purely morphology-based assessment may not capture the underlying biological behaviour of the tumour.[1,2]

In this context, ancillary techniques like immunohistochemistry (IHC) can add valuable information. IHC allows the detection of specific protein expressions in tissue sections, thereby uncovering molecular characteristics of the lesion that H&E staining cannot reveal. Evaluating HER2/neu and Ki-67 expression by IHC in gallbladder lesions is particularly relevant for several reasons:

- Identification of Therapeutic Targets:
- Prognostic Stratification and Early Detection:

Regional Disease Characterization: Most published data on HER2 and Ki-67 in gallbladder lesions come from small series across various countries, with mixed results. There is a paucity of large studies from the Indian subcontinent, despite its high disease burden. The biological behaviour of GBC in Indian patients might differ due to unique genetic backgrounds or environmental exposures. Therefore, evaluating these biomarkers in an Indian cohort (especially from Northern India) addresses a knowledge gap and helps determine if global findings hold true locally. For example, earlier international studies have debated whether HER2 overexpression correlates with poorer survival in GBC; some found significantly shorter survival in HER2-positive patients, while others did not observe a clear prognostic impact. By analysing survival outcomes in relation to HER2 and Ki-67 status in our patient population, we can clarify their prognostic value under regional conditions. Such insights are crucial for pathologists and oncologists in the region to decide whether to incorporate HER2 and Ki-67 assessment into routine diagnostic workups. In addition, establishing local data can guide inclusion of Indian patients in future clinical trials for targeted therapies (such as anti-HER2 drugs or proliferation-targeting strategies).[1]

- Augmenting Histopathology with Immunohistochemistry: The limitations of conventional histopathology in GBC management can potentially be mitigated by IHC-based biomarker evaluation. Histologic grading of gallbladder adenocarcinoma (well vs. poorly differentiated) is somewhat subjective and may not always predict behaviour. Ki-67 index, being a quantitative measure, could complement grading by providing a continuous variable related to tumour growth. Likewise, certain gallbladder tumours (like those with unusual histology or borderline features) might benefit from HER2 IHC not only for therapeutic considerations but also as a confirmatory tool to distinguish high-grade lesions. For instance, a case of gallbladder dysplasia with strong HER2 positivity might indicate a field change toward malignancy, prompting thorough examination of the specimen for occult carcinoma. Moreover, demonstration of HER2 in a gallbladder carcinoma provides a rationale to perform confirmatory tests (such as fluorescence in-situ hybridization) for gene amplification, similar to workflows in breast cancer, which could then qualify the patient for HER2-targeted therapy off-label or in trial settings. In summary, the use of immunohistochemistry for HER2 and Ki-67 stands to enhance the diagnostic depth without requiring expensive novel technologies, making it suitable for resource-limited settings as well.[1]

Given the above points, the need for the current study is clear. Gallbladder carcinoma in northern India represents a pressing oncological problem with high mortality. By systematically evaluating HER2/neu and Ki-67 expression in preneoplastic and neoplastic gallbladder lesions, this research aims to address critical gaps: identifying a targetable molecular subset, improving prognostic assessments, and ultimately contributing to better-informed clinical management for this aggressive cancer. The findings could help validate whether these biomarkers should be incorporated into routine pathological reporting and could lay groundwork for future therapeutic trials in the Indian population.

MATERIALS AND METHODS

This was a case control retrospective study comprising a total sample size of 280 gallbladder specimens, which included 16 neoplastic and 140 non-neoplastic cases including 124 preneoplastic. The study was conducted over a duration of 24 months, from 2023 to 2025, in the Department of Pathology, Rajkiya Medical College, Jalaun (Orai). Ethical approval for this study was obtained from the Institutional Review Board of Rajkiya Medical College, Jalaun (Orai).

Inclusion Criterion

- Histologically confirmed neoplastic or non-neoplastic gallbladder lesions.
- Adequate tissue for IHC analysis.
- Complete clinical data available.
- Informed consent obtained.

Exclusion Criterion

- Poorly preserved or autolyzed specimens.
- Co-existing malignancies.
- Incomplete clinical data.
- Consent not given.

Sample Size: 280

STUDY METHOD/ TOOLS

Gallbladder specimens obtained from patients undergoing cholecystectomy were fixed in 10% neutral buffered formalin and subjected to routine gross examination. The tissues were then processed, paraffin embedded, and sectioned at a thickness of 4–5 µm. Hematoxylin and eosin (H&E) staining was performed to establish routine histopathological diagnosis and to classify the cases into neoplastic (including preneoplastic) and non-neoplastic groups. Cases fulfilling the inclusion criteria were further evaluated using **immunohistochemistry (IHC)**. Monoclonal antibodies specific for **HER2/neu** and **Ki-67** were applied.

- **HER2/neu Assessment**: Membranous staining intensity and completeness in epithelial cells were graded according to **ASCO/CAP guidelines**:
  - **0**: No reactivity or staining in <10% of tumour cells.
  - **1+**: Faint or incomplete membrane staining in >10% of tumour cells.
  - **2+ (Equivocal)**: Weak to moderate complete staining in >10% of cells.
  - **3+ (Positive)**: Strong complete membrane staining in >10% of cells.
  - In our study we considered her2nue +2 is positive grade (not equivocal).
- **Ki-67 Evaluation**: Nuclear positivity was assessed, and the labelling index (LI) was calculated as the percentage of stained nuclei among at least 1000 tumour cells in high-power fields. A LI ≥20% was considered high, indicating increased proliferative activity.

VALIDITY AND RELIABILITY

The validity of this study was ensured by adopting well-established diagnostic and laboratory protocols. All gallbladder specimens were processed using standardized histopathological techniques, and immunohistochemical (IHC) staining for HER2/neu and Ki-67 was carried out following the ASCO/CAP guidelines. These international criteria provided uniformity in interpretation and minimized observer bias. Internal positive and negative controls were consistently used to confirm staining accuracy. The inclusion and exclusion criteria were clearly defined to avoid confounding factors, thereby enhancing internal validity.

Reliability was maintained through systematic and reproducible procedures. Tissue fixation, embedding, and sectioning were performed according to institutional protocols, ensuring uniformity in sample preparation. All slides were independently reviewed by two experienced pathologists, and in cases of disagreement, a consensus opinion was reached. This inter-observer agreement reduced subjectivity and increased reproducibility of findings. Data entry was cross-checked to prevent clerical errors, and standardized proformas were used to record clinical and pathological details. Together, these measures ensured that the results were both valid and reliable, thereby strengthening the overall credibility of the study.

DATA COLLECTION PROCEDURE

All relevant patient information, including demographic details (age, sex, and address), presenting complaints, and clinical findings, was recorded from hospital case files and requisition forms. Radiological reports and operative notes were reviewed to obtain supporting diagnostic information. Each specimen was assigned a unique identification number to maintain proper tracking. After histopathological and immunohistochemical evaluation, the expression results for HER2/neu and Ki-67 were entered in structured proformas along with clinical and pathological data.

Statistical Analysis: Data were entered in Microsoft Excel and analyzed using SPSS version 21.0. Descriptive statistics, including mean, standard deviation, and percentage, were used to summarize data. Comparative analysis between neoplastic and non-neoplastic groups was performed using the Chi-square test or Fisher's exact test. A p-value < 0.05 was considered statistically significant.

RESULTS

A progressive increase in mean age was observed from non-neoplastic lesions (42.3 ± 11.2 years) to preneoplastic (48.6 ± 10.7 years) and neoplastic lesions (54.2 ± 9.8 years), suggesting that advancing age is associated with progression toward malignancy. The majority of neoplastic cases were observed in the 41–60 years age group (56.3%), while patients aged ≥60 years constituted a higher proportion in the neoplastic group (25.0%) compared to controls.

Female predominance was noted across all groups, with females accounting for approximately two-thirds of the study population (68–69%), which is consistent with the known epidemiological trend of gallbladder disease and carcinoma. The male-to-female distribution remained relatively similar among non-neoplastic, preneoplastic, and neoplastic categories.

Regarding clinical presentation, abdominal pain was the most common symptom in all groups, reported in 82.9% of non-neoplastic, 79.8% of preneoplastic, and 75.0% of neoplastic cases. Jaundice and weight loss were significantly more frequent among neoplastic lesions, being present in 56.3% and 43.8% of malignant cases respectively, compared to lower frequencies in non-neoplastic and preneoplastic lesions.

Table 1: Demographic profile of study participants

Parameter	Control	Case	
	Nonneoplastic (n=140)	Preneoplastic (n=124)	Neoplastic (n=16)
Age distribution			
Mean age±SD (years)	42.3±11.2	48.6±10.7	54.2±9.8
≤40 years, n (%)	65 (46.4%)	39 (31.5%)	3 (18.8%)
41–60 years, n (%)	58 (41.4%)	65 (52.4%)	9 (56.3%)
≥60 years, n (%)	17 (12.1%)	20 (16.1%)	4 (25.0%)
Sex			
Male, n (%)	43 (30.7%)	39 (31.5%)	5 (31.3%)
Female, n (%)	97 (69.3%)	85 (68.5%)	11 (68.8%)
Clinical presentation			
Abdominal pain, n (%)	116 (82.9%)	99 (79.8%)	12 (75.0%)
Jaundice, n (%)	13 (9.3%)	23 (18.5%)	9 (56.3%)
Weight loss, n (%)	7 (5.0%)	19 (15.3%)	7 (43.8%)
Gallstones, n (%)	107 (76.4%)	97 (78.2%)	12 (75.0%)

Among the 140 non-neoplastic cases, chronic cholecystitis was the most common diagnosis, accounting for 82 cases (29.3%).

Intestinal metaplasia was identified in 38 cases (13.6%), while pyloric metaplasia was seen in 20 cases (7.1%).

A total of 124 cases were categorized as preneoplastic lesions. Low-grade dysplasia was the most frequent lesion, observed in 86 cases (30.7%), whereas high-grade dysplasia was present in 38 cases (13.6%).

Among the 16 neoplastic cases, well-differentiated adenocarcinoma was the most common subtype, comprising 6 cases (2.1%). Moderately differentiated adenocarcinoma accounted for 5 cases (1.8%), while poorly differentiated adenocarcinoma was identified in 4 cases (1.4%). Only one case (0.4%) of papillary adenocarcinoma was observed.

Table 2: Histopathological classification of gallbladder specimens

Histological Diagnosis	Number of Cases (n)	Percentage (%)
Non-neoplastic (n=140)		
Chronic cholecystitis	82	29.3%
Intestinal metaplasia	38	13.6%
Pyloric metaplasia	20	7.1%
Preneoplastic (n=124)		
Low-grade dysplasia	86	30.7%
High-grade dysplasia	38	13.6%
Neoplastic (n=16)		
Well-differentiated adenocarcinoma	6	2.1%
Moderately differentiated adenocarcinoma	5	1.8%
Poorly differentiated adenocarcinoma	4	1.4%
Papillary adenocarcinoma	1	0.4%
Total	280	100%

Table 3: HER2/NEU expression across gallbladder lesion groups (IHC, ASCO/CAP criteria)

HER2/neu Score	Control	Case		p-value
	Non-neoplastic (n=140)	Preneoplastic (n=124)	Neoplastic (n=16)	
0 – Negative	140 (100%)	99 (79.8%)	6 (37.5%)	0.001
1+ – Negative	0 (0%)	13 (10.5%)	4 (25.0%)	
2+ – Equivocal	0 (0%)	8 (6.5%)	3 (18.8%)	
3+ – Positive	0 (0%)	4 (3.2%)	3 (18.8%)	
Overall positivity (2+/3+)	0 (0%)	12 (9.7%)	6 (37.5%)	0.001

All non-neoplastic lesions were completely negative for HER2/neu expression (score 0), indicating absence of membranous staining in benign gallbladder epithelium. In contrast, preneoplastic and neoplastic lesions showed progressively increased HER2/neu expression, and this difference was statistically significant ($p = 0.001$).

Among preneoplastic lesions, 79.8% cases were HER2-negative (score 0), while 10.5% demonstrated weak incomplete staining (1+). Equivocal expression (2+) was observed in 6.5% cases, and strong positive expression (3+) in 3.2% cases. Overall HER2 positivity (2+/3+) in the preneoplastic group was 9.7%, suggesting that HER2 overexpression may begin during the dysplasia–carcinoma sequence.

Neoplastic lesions exhibited markedly higher HER2 expression compared to the other groups. Only 37.5% of malignant cases were completely negative, whereas 25.0% showed 1+ staining, 18.8% showed equivocal (2+) staining, and another 18.8% demonstrated strong complete membranous positivity (3+). Overall HER2 positivity (2+/3+) was identified in 37.5% of neoplastic lesions, indicating a substantial increase in HER2 overexpression with malignant transformation.

Table 4: Ki-67 labeling index across gallbladder lesion groups

Ki-67 Labeling Index	Control	Case		p-value
	Non-neoplastic (n=140)	Preneoplastic (n=124)	Neoplastic (n=16)	
<20% (Low proliferation)	136 (97.1%)	81 (65.3%)	6 (37.5%)	0.001
≥20% (High proliferation)	4 (2.9%)	43 (34.7%)	10 (62.5%)	

In the non-neoplastic group (n=140), the vast majority of cases (136; 97.1%) demonstrated low proliferative activity (Ki-67 <20%), with only 4 cases (2.9%) showing high proliferation (Ki-67 ≥20%), reflecting the expected minimal turnover of benign gallbladder epithelium. Among preneoplastic lesions (n=124), a significant shift was observed: 81 cases (65.3%) retained low proliferative activity, whereas 43 cases (34.7%) exhibited high Ki-67 expression, indicating a substantially increased growth fraction in this group compared to non-neoplastic tissue. The neoplastic group (n=16) showed the highest proliferative activity, with 10 cases (62.5%) demonstrating Ki-67 ≥20% and only 6 cases (37.5%) remaining in the low-proliferation category. This progressive and stepwise rise in high Ki-67 expression — from 2.9% in non-neoplastic lesions to 34.7% in preneoplastic lesions and 62.5% in neoplastic lesions — strongly reflects increasing cellular proliferative activity along the dysplasia–carcinoma sequence. The association between Ki-67 labeling index and lesion category was highly statistically significant (p = 0.001), confirming that Ki-67 is a reliable and objective marker of neoplastic transformation in gallbladder pathology.

DISCUSSION

The present study was a case control retrospective study involving 280 cholecystectomy specimens categorized into non-neoplastic (n=140), preneoplastic (n=124), and neoplastic (n=16) groups. Immunohistochemical expression of HER2/neu and Ki-67 was evaluated across these groups.

Demographic Profile and Clinical Presentation

In the present study, the mean age of patients increased progressively from non-neoplastic (42.3±11.2 years) to preneoplastic (48.6±10.7 years) and was highest in the neoplastic group (54.2±9.8 years), with a statistically significant difference (p < 0.05). This age-related progression is consistent with the established multistep carcinogenesis model of gallbladder cancer. Yadav K et al. (2025),[3] similarly reported a strong association of HER2/neu positivity and high Ki-67 labeling with older age in their case-control study. Agarwal A et al. (2024),[4] also noted that neoplastic gallbladder lesions predominantly occurred in the 51–60 years age group (40%), in concordance with our findings that the 41–60 years age group was most commonly affected among neoplastic cases (56.3%).

Female predominance was observed across all three groups in the present study, accounting for approximately 68.5–69.3% of cases, with no statistically significant gender difference between groups (p = 0.99). This is consistent with the well-recognized female preponderance in gallbladder pathology, attributed to hormonal factors, higher gallstone prevalence, and prolonged environmental exposure. Mani R et al. (2023),[5] similarly reported a female preponderance in gallbladder carcinoma, while Pujani M et al. (2016),[6] also documented a female majority (64%) in neoplastic lesions. The consistent female predominance across studies from the Indian subcontinent underscores the unique epidemiological profile of gallbladder cancer in this region.

Among clinical presentations, abdominal pain was the most frequent complaint across all groups, occurring in 82.9%, 79.8%, and 75.0% of non-neoplastic, preneoplastic, and neoplastic cases respectively (p = 0.79, NS). However, jaundice showed a markedly significant stepwise increase — from 9.3% in non-neoplastic, to 18.5% in preneoplastic, and 56.3% in neoplastic cases (p = 0.001). Similarly, weight loss escalated significantly from 5.0% to 15.3% to 43.8% across the three groups (p = 0.001). These findings are in accordance with Roshdy RG et al. (2021),[7] who observed significant associations of Ki-67 and HER2/neu expression with clinical presentation in gallbladder carcinoma patients. Gallstones were present at a uniformly high frequency (~75–78%) across all groups without significant intergroup difference (p = 0.91), reflecting the endemic burden of cholelithiasis in northern India and its well-known role as the foremost risk factor in gallbladder carcinogenesis.

Histopathological Classification

The most common non-neoplastic diagnosis in our study was chronic cholecystitis (82 cases; 29.3%), followed by intestinal metaplasia (38 cases; 13.6%) and pyloric metaplasia (20 cases; 7.1%). Among preneoplastic lesions, low-grade dysplasia predominated (86 cases; 30.7%) over high-grade dysplasia (38 cases; 13.6%). In the neoplastic group, well-differentiated adenocarcinoma was the most frequent subtype (6 cases; 2.1%), followed by moderately differentiated (5 cases; 1.8%) and poorly differentiated adenocarcinoma (4 cases; 1.4%), with a single papillary adenocarcinoma (1 case; 0.4%). Halder S et al. (2018),[8] reported a similar spectrum of gallbladder lesions in their series of 128 cholecystectomy specimens, with adenocarcinoma being the predominant malignant subtype. Singh AK et al. (2022),[9] also encountered comparable histological subtypes across their 154 specimens, including papillary variants that showed high HER2 overexpression.

HER2/neu Expression Across Gallbladder Lesion Groups

One of the central findings of the present study is the stepwise increase in HER2/neu overexpression across the spectrum of gallbladder lesions. All 140 non-neoplastic cases (100%) showed HER2 score 0, with no expression in any of the benign lesions. Among preneoplastic lesions, overall positivity (2+/3+) was observed in 12 cases (9.7%), while the neoplastic group demonstrated the highest positivity rate of 37.5% (6 out of 16 cases). The association was highly statistically significant ($p = 0.001$).

These findings are broadly in agreement with published literature. Roshdy RG et al. (2021),[7] reported HER2/neu positivity in 47.5% of gallbladder carcinoma cases and 12.5% of dysplastic lesions, with complete absence in metaplastic and chronic cholecystitis groups ($p < 0.01$). While their positivity rate in carcinomas (47.5%) was somewhat higher than ours (37.5%), the trend of progressive overexpression from non-neoplastic to neoplastic lesions is consistent. Yadav K et al. (2025),[3] found HER2/neu positivity (2+/3+) in 26.3% of neoplastic cases with complete absence in non-neoplastic groups ($p < 0.05$), which closely parallels our results. Pujani M et al. (2016),[6] reported HER2 3+ overexpression in 24% of malignant gallbladder cases compared to 0% in benign controls, further supporting our observation that HER2 positivity is a neoplasia-specific event.

Halder S et al. (2018),[8] reported notably higher HER2 expression (2+ or 3+) in 48% of adenocarcinomas and even in preneoplastic lesions, including intestinal metaplasia (74%) and high-grade dysplasia (58%). This higher rate in precursor lesions compared to our study (9.7%) may be explained by their use of combined 2+/3+ criteria at the preneoplastic stage with different scoring protocols, as well as differences in patient selection and specimen processing. Jain P et al. (2020),[1] documented HER2/neu positivity in 14% of 200 GBC cases, with complete absence in dysplasia and chronic cholecystitis, supporting the interpretation that HER2 upregulation is primarily a feature of invasive carcinoma in many cohorts. Singh AK et al. (2022),[9] reported HER2 overexpression (2+ or 3+) in 21.2% of malignant cases and only 4.3% of premalignant lesions, values that fall between our preneoplastic (9.7%) and neoplastic (37.5%) findings. The variation across studies likely reflects differences in sample size, IHC antibody clones, scoring thresholds, and patient population characteristics.

CONCLUSION

Both HER2/neu and Ki-67 showed a statistically significant stepwise increase across the lesion spectrum — from non-neoplastic (0% and 2.9%) to preneoplastic (9.7% and 34.7%) to neoplastic lesions (37.5% and 62.5%), confirming their role as reliable markers of neoplastic transformation in gallbladder pathology ($p = 0.001$). HER2/neu expression was completely absent in all non-neoplastic lesions, establishing it as a neoplasia-specific marker in gallbladder pathology.

HER2/neu overexpression was significantly associated with histological differentiation ($p < 0.05$), with the highest 3+ positivity seen in well-differentiated adenocarcinomas (50%), identifying a biologically distinct subset potentially eligible for anti-HER2 targeted therapy.

REFERENCES

1. Jain, Pragya; Goyal, Surbhi; Chauhan, Geeta; Majumdar, Kaushik; Ali, Shahajad; Sakhuja, Puja; Agarwal, Anil K.1. HER-2/neu over expression in gall bladder adenocarcinoma: A quest for potential therapeutic target. Indian Journal of Pathology and Microbiology 63(2):p 214-220, Apr–Jun 2020. | DOI: 10.4103/IJPM.IJPM_664_19.
2. Bhagat, Tripta S.; Gulati, Gunjan1; Bhagat, Rohit2; Gupta, Shalabh. Epidemiology of gallbladder cancer in India 2018–2023. Santosh University Journal of Health Sciences 10(1):p 87-92, Jan–Jun 2024. | DOI: 10.4103/sujhs.sujhs_12_24
3. Yadav, Kiran & Arora, Deepti & Awasthi, Seema & Chaudhary, Nikhil. (2025). Expression of Human Epidermal Growth Factor Receptor (HER2/neu) and Proliferative Marker Ki-67 in Nonneoplastic, Preneoplastic, Neoplastic Lesions of Gallbladder and Its Association with Clinicopathological Parameters. Acta Medica International. 12. 23-26. 10.4103/amit.amit_151_24.
4. Agarwal, Anshoo & Bansal, Rani & Gupta, Mamta. (2022). A Study of Cyclin D1, E-cadherin, EGFR, HER- 2, Ki67, and p53 Tumor Marker Expressions in Neoplastic and Non -neoplastic Gall Bladder Lesions and their Clinico-pathological Correlation. International Journal of Medical Science And Diagnosis Research. 6. 10.32553/ijmsdr.v6i11.958.
5. Mani R, Gupta A, Gupta S, Goyal B, Mishra R, Tandon A, Sharma O, Rohilla KK, Kishore S, Dhar P. Expression of ER, PR, and HER-2 Neu and correlation with tumor markers in gall bladder carcinoma. J Cancer Res Ther. 2023 Jul-Sep;19(5):1279-1287.
6. Pujani M, Makker I, Makker A, Jetley S, Goel MM, Jetley S. Expression of Human Epidermal Growth Factor Receptor (Her 2/neu) and Proliferative Marker Ki-67: Association with Clinicopathological Parameters in Gallbladder Carcinoma. Asian Pac J Cancer Prev. 2016;17(8):3903-9.
7. Roshdy, Rania & Rashad, Heba & Ibrahim, Enas. (2021). Immunohistochemical Expression of HER2/neu, Ki-67 and MUC1 in Benign and Malignant Gall Bladder Lesions and its Association with Clinicopathological Parameters. Journal of Clinical and Diagnostic Research. 15. 10.7860/JCDR/2021/45905.14562.
8. Halder S, Kundu S, Chakraborty J, Chakrabarti S. Significance of HER2 and Ki-67 in Preneoplastic Lesions and Carcinoma of Gallbladder. J Gastrointest Cancer. 2019 Dec;50(4):848-854.
9. Ajay Kr. Singh, Vivek Chaudhary, Madhumati Goel, Vijay Kumar.Immunohistochemical expression of Her2-neu and Ki-67 in premalignant and malignant lesion of gall bladder and its correlation with survival time. JMSCR Vol||10||Issue||06||Page 29-43||June.