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EXPRESSION PATTERNS AND CLINICAL SIGNIFICANCE OF ESTROGEN RECEPTOR, PROGESTERONE RECEPTOR, AND HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2/neu IN GALLBLADDER CANCER

Background. Gallbladder carcinoma (GBC) is a rare cancer. However, it is the most common malignancy of the biliary tract system and ranks as the sixth most common malignancy of the digestive tract. It occurs primarily in females, and previous reports indicate that the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2/neu (HER2/neu) play significant roles in GBC. However, reported findings remain inconsistent. This study **aimed** to determine the expression status of ERα, ERβ, PR, and HER2/neu in GBC and to investigate their associations with clinicopathological features of patients. **Materials and Methods**. 55 GBC patients were included in the study. The expression levels of ERα, ERβ, PR, and HER2/neu proteins were evaluated using immunohistochemistry method. **Results**. ERα expression was absent in all cases, while PR and HER2/neu positivity were observed in 5.5% and 18.2% cases, respectively. Of total, 34 (61.8%) cases showed positive expression of ERβ. Compared with adjacent normal tissues, ERβ mean positivity was higher in GBC tissues. Significant associations were found between ERβ expression and tumor differentiation and gallstones ($p < 0.05$). Predominant expression of ERβ was observed in GBC of stages II and III. **Conclusion**. ERβ was frequently expressed in GBC and significantly associated with tumor differentiation, suggesting its potential role in progression of GBC.

Keywords: gallbladder cancer, estrogen receptor, progesterone receptor, HER2/neu, estrogen receptor beta.

Gallbladder cancer (GBC) is a common malignancy of the biliary tract and represents a significant public health challenge due to high lethality. Worldwide, 122,500 new cases and 89,000 mortalities occurred in 2022 [1]. The incidence of GBC varied according to the geographical distribution, ethnicity, and gender. The highest incidence of GBC was recorded in South Central Asia, Eastern Asia, and South America [2]. According to the Cancer Registry Program data from India, a higher prevalence of GBC has been reported in Northern India (4.5 per 100,000 males and 10.1 per 100,000 females), in contrast to

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Southern India (1.2 per 100,000 males and 0.9 per 100,000 females). Particularly, the states along the Gangetic belt, such as Bihar, Uttar Pradesh, and Uttarakhand, present the highest rates of GBC [3].

GBC is a multifactorial disease, with cholelithiasis being the most common risk factor. Others include exposure to carcinogens, inflammatory bowel disease, oxidative stress, sedentary lifestyle, and a high-fat diet. The notable geographic and ethnic variations suggest significant genetic and environmental factors of GBC [4]. GBC affects females 2—6 times more often than males. Previous studies indicate that a higher prevalence of GBC in females might be due to the use of oral contraceptive pills, experiencing early menarche, late menopause, or shorter reproductive lifespan [5, 6]. Furthermore, earlier reports suggest that female hormones may participate in the development of GBC. Few studies have evaluated the role of estrogen receptor (ER) or ERα, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu) in GBC among the Indian population, but the findings are inconsistent [7—9]. Additionally, a study also reported the significant role of an isoform of estrogen receptor (ERβ) in GBC [10]. The roles of ER, PR, and HER2/neu are well established in the routine diagnosis of breast cancer, where antihormonal and targeted therapies are used to improve patient survival based on the expression profile of these biomarkers. Nevertheless, published data on the expression status of ERs (ERα and ERβ), PR, and HER2/neu in GBC have presented contradictory results in terms of the type and extent of receptor expression. This knowledge gap provides rationale for the present study, which aims to analyze ERα, ERβ, PR, and HER2/neu expressions in GBC and correlate these biomarker profiles with the patients' clinicopathological characteristics.

Materials and Methods

Study setting, design, and recruitment of patients. The present study was conducted at Kalyan Singh Super Speciality Cancer Institute (KSSSCI), Lucknow, Uttar Pradesh, India, a tertiary care cancer center in Northern India, providing comprehensive cancer diagnosis and treatment services. The institute caters predominantly to patients from Northern India, particularly Uttar Pradesh, as well as neighboring states, including Uttarakhand and Himachal Pradesh, Bihar, Chhattisgarh, Haryana, and Delhi. All the patients included in the present study were residents of Uttar Pradesh, India.

This observational study was carried out in the Department of Pathology and Cancer Genetics, KSSSCI, Lucknow, Uttar Pradesh, India. A total of 55 patients with histopathologically confirmed GBC were included in this study from August 2023 to October 2025. All the tissue samples were obtained from patients who underwent biopsy of inoperable and locally advanced tumors or surgically removed GBC in the Department of Surgical Oncology, KSSSCI. The Institutional Ethics Committee, KSSSCI, approved this study (Letter No. KSSSCI/IEC/11/59/2023), and informed consent was obtained from all patients enrolled in the study.

The previous clinical history and demographic data were collected from hospital records. Clinical staging of GBC patients was performed using the AJCC (8th edition) TNM staging system.

Sample collection and immunohistochemistry. The specimens of gallbladder tumor tissue were fixed in 10% buffered formalin and processed following the standard protocol for histopathological investigations. Further, samples were stained in hematoxylin & eosin (H&E) and examined by the pathologist.

ERα, ERβ, PR, and HER2/neu were detected by immunohistochemistry (IHC). 4-μm tissue sections were mounted to Poly-L-Lysine-coated slides and followed by a standard IHC protocol. After deparaffinization of tissue sections, endogenous peroxidase activity was blocked using 3% hydrogen peroxide, followed by antigen retrieval in EDTA buffer (pH 9.0). Further, the sections were incubated with ready-to-use primary antibodies at room temperature for 2 h: ERα (clone SP1, cat # RM9101-R7), PR (clone SP2, cat # RM9102-R7), and HER2/neu (clone SP3, cat # RM9103-R7) from Epredia, Netherlands. For ERβ, tissue sections were incubated at 4 °C overnight with polyclonal primary antibody (clone ERb455, cat # ab187291, Abcam USA, dilution 1:100). For detection, an HRP-labelled secondary antibody kit (cat # TL-125-QHD, Epredia, Netherlands) was used, followed by visualization with DAB chromogen and counterstaining with hematoxylin. Nuclear staining for ERα, ERβ, and PR, as well as membranous staining for HER2/neu, were considered positive. The known positive cases of ER, PR, and HER2/neu of breast cancer were taken as a positive control. IHC scoring of ERα, ERβ, and PR was done using the Allred method. HER2/neu scoring

was done according to breast cancer scoring criteria. The intensity of staining was defined as weak (1), moderate (2), or strong (3) for all biomarkers.

Statistical analysis. The categorical data were summarized as numbers and percentages, whereas the continuous data were presented as mean ± SD. Statistical analysis was performed using a two-tailed chi-square test/Fisher's exact test and unpaired *t*-test for assessing associations between variables. A p-value < 0.05 was considered statistically significant. All analyses were performed through the SPSS software (version 16.0, IBM Corp., IL, USA).

Results

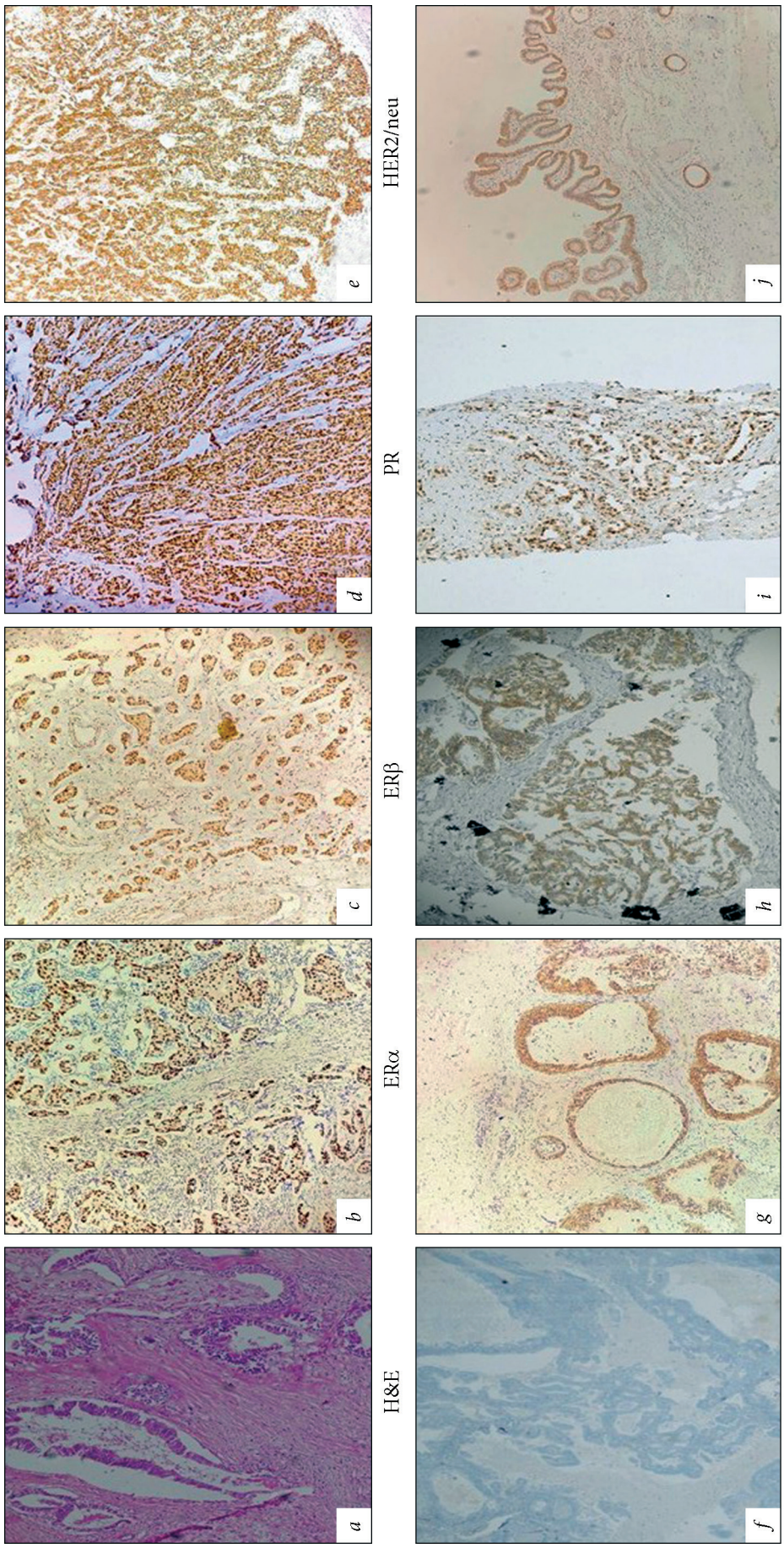
The demographic and clinicopathological characteristics of the GBC patients included in the study are summarized in the Table. The mean age of the patients at the time of GBC diagnosis was 53.2 ± ± 10.5 (35—70 years). Radiological investigations revealed that 12.7% of patients had a history of gallbladder stones (GBS) along with GBC. At the time of clinical diagnosis, most of the patients presented with stage III (45.5%), followed by stage II (29.1%), stage IV (14.5%), and stage I (10.9%). None of the patients received neoadjuvant therapy/ palliative chemotherapy before surgery/core biopsy. On histopathological evaluation, 53 patients were diagnosed with adenocarcinoma, and 2 patients were diagnosed with squamous cell carcinoma. Among all cases, 50.9% were moderately differentiated tumors, 36.4% were well differentiated, and 12.7% were poorly differentiated.

The Figure presents the IHC findings of ERα, ERβ, PR, and HER2/neu expression. ERα expres-

Association between ERβ expression and clinicopathological characteristics of GBC patients

Variables	Number of patients n = 55 (%)	ERβ expression		p value
		Positive n = 34 (%)	Negative n = 21 (%)	
Age (years)				
≤ 40	15 (27.3)	8 (23.5)	7 (33.3)	0.474
41—60	24 (43.6)	17 (50.0)	7 (33.3)	
> 60	16 (29.1)	9 (26.5)	7 (33.3)	
Gender				
Female	41 (74.5)	27 (79.4)	14 (66.7)	0.348
Male	14 (25.5)	7 (20.6)	7 (33.3)	
Menopausal status				
Premenopausal	11 (26.8)	6 (22.2)	5 (35.7)	0.382
Postmenopausal	30 (73.2)	21 (77.8)	9 (64.3)	
GBS				
Absent	48 (87.3)	29 (85.3)	19 (90.5)	**0.036***
Present	7 (12.7)	5 (14.7)	2 (9.5)	
Tumor differentiation grade				
Well differentiated	20 (36.4)	16 (47.1)	4 (19.0)	**0.048***
Moderately differentiated	28 (50.9)	13 (38.2)	15 (71.5)	
Poorly differentiated	7 (12.7)	5 (14.7)	2 (9.5)	
Clinical stage (TNM)				
I	6 (10.9)	4 (11.8)	2 (9.5)	0.273
II	16 (29.1)	12 (35.3)	4 (19.0)	
III	25 (45.5)	12 (35.3)	13 (61.9)	
IV	8 (14.5)	6 (17.6)	2 (9.5)	

Notes: GBS — gallbladder stone. * $p < 0.05$ (chi-square test (χ^2)/Fisher's exact test).



Photomicrograph showing: *a* — H&E adenocarcinoma; IHC images (*b*—*e*) — positive controls; *f* — ERα negative expression; *g* — PR moderate positive expression; *h* — HER2/neu positive expression (3+); *i* — ERβ strong positive expression in GBC cases; *j* — ERβ poor positive expression in adjacent normal tissue (ANT). (DAB, digital magnification x100)

sion was absent in all cases. PR positivity was identified in only 3 (5.5%) cases, and positive expression of HER2/neu in 10 (18.2%) cases. In contrast, ERβ expression was observed in 34 (61.8%) cases of GBC. Due to a limited number of PR-positive and HER2/neu-positive cases in our cohort, further statistical analyses assessing their associations with clinico-pathological characteristics of GBC patients could not be performed.

Furthermore, ERβ expression in GBC was compared with that in 20 adjacent normal tissues (ANT) of surgically resected specimens. Among 20 ANT samples, only 5 (25%) showed positive ERβ expression. The mean percentage positivity in GBC vs. ANT samples was found as 55.7 ± 14.5 vs 32.4 ± 10.2, respectively, but the difference was insignificant.

The associations between clinicopathological profiles of GBC patients and ERβ expression status are presented in the Table. ERβ positivity was more frequently observed in the 41—60 years age group, females, and post-menopausal patients. A significant association was found between ERβ positivity and the presence of GBS ($p = 0.036$), although the proportion of patients with GBS was small. The ERβ protein expression was significantly higher in well- and moderately differentiated tumors compared to poorly differentiated tumors ($p = 0.048$). Moreover, an increased ERβ expression was noted in tumors of stages II and III.

Discussion

According to GLOBOCAN 2022 data, the global age-standardized incidence and mortality rates for GBC were 1.2 per 100,000 and 0.83 per 100,000 population, respectively. The highest disease burden was reported in South-Central and Eastern Asia, particularly in India (1.5 per 100,000 population) and China (1.1 per 100,000 population). However, the highest age-standardized incidence rates were found in South America, notably in Bolivia (7.6 per 100,000 population) and Chile (5.7 per 100,000 population) [1]. A study conducted in the Chilean population presented that HER2/neu overexpression occurred in about 14% of the GBC cases, suggesting that this subgroup of GBC patients may benefit from HER2/neu targeted therapy [11].

The incidence of GBC in India shows significant regional variations. The Gangetic belt of Northern India reports the highest incidence, increasing from 15.2 to 18 per 100,000 population from 2018 to 2023, whereas Southern India presents the lower rates, 3.5 to 4.1 per 100,000 [12]. Earlier studies suggest that the high incidence of GBC in the Gangetic area may be associated with dietary patterns, environmental exposures, including contaminated water and high levels of heavy metals, and genetic predisposition.

GBC predominantly affects older patients and occurs more frequently in women than men. In the present study, the occurrence of GBC was more prevalent (43.6%) in the age group 41—60 years, with a mean age of 53.2 ± 10.5 years. These findings are consistent with other studies conducted in India. Vikash et al. [9] reported a mean age of GBC patients of 51.7 ± 11.32 years, and Gupta et al. [13] reported 50.51 ± 11.97 years. In our cohort, most patients were female (74.5%) and a female-to-male ratio of 2.9:1. Another study among the Indian population reported that the incidence of GBC in female patients was 82.5%, with a female-to-male ratio of 4.8:1 [14]. The observed gender disparity in GBC might result from hormonal factors, reproductive phase, and a higher prevalence of GBS among females.

Chronic inflammation of the gallbladder, frequently associated with gallstone disease, is a significant risk factor for GBC. In the present study, 12.7% of patients were primarily diagnosed with gallstone disease. In contrast, previous Indian studies reported GBS in more than 70% of patients with GBC [15]. Although gallstone disease remains the major risk factor for GBC, a proportion of patients do not exhibit detectable GBS at the time of diagnosis. Worldwide, GBS are identified in roughly 70%—90% of cases, but may be absent in advanced tumors (stages II/III) due to the replacement of the gallbladder lumen by tumor mass. Additionally, GBS-independent carcinogenic pathways, including chronic inflammation, porcelain gallbladder, environmental factors, and genetic susceptibility, have also been suggested as risk factors for GBC.

In postmenopausal women, adipose tissue is the primary source of estrogen synthesis. High estrogen levels increase biliary cholesterol secretion and reduce gallbladder contractility, which may contribute to carcinogenesis. However, in premenopausal women, hormonal fluctuation associated with the menstrual cycle, pregnancy, and use of contraceptives causes changes in gallbladder function and increases the risk of GBS development. In

the present study, we observed an association between ERβ expression and gallstone disease.

However, the analysis of ERβ association was based on a limited number of GBS-positive GBC cases, thereby restricting statistical power. Consequently, these findings should be interpreted with caution, and larger multicentric studies with expanded sample sizes are required to further study and validate the relationship between hormone receptor expression and gallstone disease-associated GBC.

Various studies have reported differing findings regarding the nuclear expression of ER and PR in GBC, ranging from 0 to 60%. Saranga et al. [8] reported ER and PR expression in 23.4% (11/47) of GBC patients, while simultaneous expression of both receptors was observed in 8 patients. In contrast, we found no expression of ERα in any of the GBC cases. In support of our findings, previous reports have also confirmed that there is no significant nuclear expression of ER and PR in GBC and control groups. However, HER2/neu expression was observed in 10%—16% of GBC cases [7, 9, 10, 16—18]. Chaube et al. [19] documented 25% of HER2/neu positivity in GBC, while another report confirmed negative HER2/neu expression in the normal epithelium of the gallbladder [20]. Furthermore, Park et al. [21] assessed the expression of ERα, ERβ, and PR in GBC and reported negative ERα and PR expression. However, 73.3% (22/30) of GBC cases were positive for ERβ and significantly associated with tumor differentiation. These findings are consistent with our results, which demonstrated significant associations between ERβ positivity and tumor differentiation in GBC. This protein level was also high in patients with stages II—III of the disease. In contrast, ERβ positivity was comparatively lower in adjacent normal gallbladder tissue compared to malignant tissue. This heterogeneity in positivity in ER, PR, and HER2/neu in GBC could be linked to ethnic and regional variations, environmental factors, small sample sizes, and differences in the interpretation used to determine the status of these biomarkers.

All patients included in the present study were residents of Uttar Pradesh state, located in Northern India. The higher ERβ expression level observed in GBC from this Northern Indian cohort suggests a potential role for hormonal therapeutic strategy, although such approaches may differ from those established in breast cancer. There is a lack of research on ERβ expression in GBC within the Indian population, underscoring the necessity to explore it at the molecular level in a larger sample size.

Conflict of interests

All authors declare no conflict of interest.

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ПАТЕРНИ ЕКСПРЕСІЇ ТА КЛІНІЧНЕ ЗНАЧЕННЯ РЕЦЕПТОРА ЕСТРОГЕНУ, РЕЦЕПТОРА ПРОГЕСТЕРОНУ ТА РЕЦЕПТОРА 2/NEU ЕПІДЕРМАЛЬНОГО ФАКТОРА РОСТУ ПРИ РАКУ ЖОВЧНОГО МІХУРА

Стан питання. Рак жовчного міхура (РЖМ) — досить рідкісне захворювання, хоча це найпоширеніше злоякісне новоутворення жовчовивідних шляхів і посідає шосте місце серед злоякісних новоутворень травного тракту. РЖМ зустрічається переважно у жінок, і попередні дослідження, незважаючи на певні розбіжності, свідчать, що рецептори естрогену (РЕ), прогестерону (РП) та епідермального фактора росту (HER2/neu) відіграють значну роль у патогенезі РЖМ. **Метою** цього дослідження було визначити статус експресії РЕα, РЕβ, РП та HER2/neu при РЖМ і дослідити їх зв'язок із клініко-патологічними особливостями пацієнтів. **Матеріали та методи**. У дослідження було включено 55 пацієнтів з РЖМ. Рівні експресії білків РЕα, РЕβ, РП та HER2/neu оцінювали за допомогою імуногістохімії. **Результати**. Експресія РЕα була відсутня у всіх випадках, тоді як позитивність за РП та HER2/neu спостерігалася у 3 та 10 випадках, відповідно. У 34 (61,8%) випадках спостерігалася позитивна експресія РЕβ, яка була вищою, ніж у суміжних з пухлиною нормальних тканинах. Виявлено вірогідну асоціацію між експресією РЕβ та рівнем диференціювання пухлини, а також наявністю жовчних каменів ($p < 0,05$). Переважна експресія РЕβ спостерігалася у випадках II та III стадій захворювання. **Висновки**. Експресія РЕβ при РЖМ, яка пов'язана з рівнем диференціювання пухлини, може свідчити про потенційне прогностичне значення цього маркера.

Ключові слова: рак жовчного міхура, рецептор естрогену, рецептор прогестерону, HER2/neu, рецептор естрогену бета.