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RESEARCH PAPER

# Expression of Estrogen Receptors, Progesterone Receptors and Human Epidermal Growth Factor Receptor-2 in Endometrial Carcinoma and their Correlation with Histopathological Type, Grade and FIGO Surgical Stage

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## Abstract

**Background:** Endometrial carcinoma is influenced by estrogen, progesterone and human epidermal growth factor. So, expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor2 (HER-2) play pivotal roles in tumor pathogenesis and therapeutic response. Hormonal receptor expression is linked to tumor differentiation and response to hormone therapy.

**Objective:** This study aimed to evaluate the expression of ER, PR and HER-2 in endometrial carcinoma and their correlations with histological type, histological grade, and FIGO surgical stage.

**Methods:** This cross-sectional study was conducted at the Department of Gynecological Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, from November 2019 to October 2020. A total of 31 histologically confirmed cases of endometrial carcinoma scheduled for surgery were included by non probability sampling. Clinicopathological data were collected, and immunohistochemistry was performed to assess ER, PR, and HER2 expression. Chi square test was done to evaluate associations of receptor expression with tumor characteristics and disease staging. A p-value of <0.05 was considered statistically significant.

**Results:** The mean age of patients was 57.87 ± 8.91 years, with 45.2% aged ≥60 years. Endometrioid adenocarcinoma (58.06%) was the most common subtype, and deep myometrial invasion was observed in 54.8% cases. ER and PR positivity rates were 51.6% and 48.4%, respectively, with their significant co-expression ($p < 0.001$). Both ER and PR were strongly associated with histological type I and histological grade 2 endometrial carcinoma but showed no significant correlation with its FIGO surgical stage. HER-2 expression was rare (3.2%) in endometrial carcinoma.

**Conclusion:** Endometrial carcinoma, shows significant co-expression of ER and PR. The expression of ER and PR were significantly associated with histological types I and histological grade II; suggesting their (ER, PR) potential as biomarkers for clinical decision regarding hormone therapy in endometrial carcinoma.

**Key words:** Endometrial carcinoma, Estrogen receptor, Progesterone receptor, Human Epidermal Growth factor Receptor2, Hormone therapy.

## Introduction

Endometrial carcinoma ranks as the sixth most common cancer in women and the 15th most common malignancy overall, with over 380,000 new cases reported globally in 2018.[1] In 2019, the American Cancer Society estimated 61,880 new cases and 12,160 deaths in the United States.[2] Its incidence is higher in high-income countries (5.9%) than in low-resource countries (4.0%), though mortality rates are higher in the latter.[3] Recently, developing countries have seen an increase in incidence.[4] In Bangladesh, the prevalence of endometrial carcinoma is approximately 2.86%.[5] This cancer primarily affects postmenopausal women, commonly in the sixth and seventh decades, with 2–5% of cases occurring in women under 40.[6]

Endometrial cancers are classified into two types: type I (estrogen-dependent) and type II (estrogen-independent). Type I accounts for 80–85% of cases,

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often linked to hyperestrogenism, obesity, infertility, late menopause, and endometrial hyperplasia, occurring in younger, perimenopausal women.[7] Type II, more common in older, postmenopausal women, lacks these associations.[7] Molecular alterations differ between types: type I commonly shows PTEN, β-catenin, PIK3CA, K-ras mutations, and Microsatellite instability, while type II is associated with p53 mutations and HER2 overexpression.[8-10]

Most patients are diagnosed at an early stage, resulting in favorable outcomes.[11] Surgery is the primary treatment, with adjuvant therapy guided by clinical and pathological risk factors.[12] Advanced-stage disease (stages III and IV) has poor five-year survival rates of 47–69% and 15– 17%, respectively.[13] Prognostic factors include tumor grade, stage, histology, myometrial invasion, lymphovascular space invasion (LVSI), and hormone receptor status.[13,14] Estrogen (ER) and progesterone (PR) receptors expressed in 32–77% and 54–72% of cases, respectively, are linked to early-stage disease and better prognosis.[15-19] HER2, expressed in 9–30% of cases, correlates with poor outcomes but responds to targeted therapies like trastuzumab.[20-24]

## Rationale

Surgery is the primary treatment for endometrial carcinoma followed by adjuvant chemotherapy and radiotherapy where indicated. Recent studies have highlighted the role of hormone receptors, such as ER, PR and HER2 in predicting clinical outcomes and these immunohistochemical markers are associated with surgical stage, histological type and grade. Therefore, these markers (ER, PR, HER2) could help in predicting biological behavior and prognosis of endometrial carcinoma and also may help in treatment planning, specially adjuvant hormone therapy for selected endometrial carcinoma patients.

## Materials and Methods

This descriptive cross-sectional study was carried out at the Department of Gynecological Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, from November2019 to October2020.

The study population included the patients with histologically confirmed endometrial carcinoma admitted for surgery to the Department of Gynecological Oncology at NICRH during the study period. A purposive sampling method was used for selecting patients based on their availability and their eligibility to meet the inclusion and exclusion criteria.

Inclusion criteria were histologically confirmed endometrial carcinoma and eligibility for surgery; while patients with previous chemotherapy or radiotherapy, those with secondary cancers, incompletely treated patients, recurrent disease, critical illnesses, or those who declined participation were excluded. The main variables were the immunohistochemical expression of ER, PR, and HER2; histological type; histological grade, and FIGO surgical stage (I, II, II, IV) of endometrial carcinoma. Demographic variables included age, body mass index (BMI), hypertension, and diabetes mellitus.

Data collection began with a thorough clinical evaluation, including demographic and clinical history, physical examination, diagnostic imaging, and histopathological examination. Patients underwent hysterectomy, and the collected specimens were processed for immunohistochemical analysis. Formalin-fixed, paraffin-embedded tissue samples were sectioned and stained with primary antibodies for ER, PR, and HER2. Immunostaining was assessed based on the percentage of positivity by Allred score for ER & PR and for HER2 it was done according to Herceptest criteria.

Data were entered into the SPSS software for analysis. Descriptive statistics, including frequency and percentage for categorical variables; mean and standard deviation for continuous variables, were used. Chi-square tests were performed to assess the statistical association between receptor status and histological type, grade, and stage. A p-value of <0.05 was considered statistically significant.

## Results

A total of 31 patients with histologically confirmed endometrial carcinoma were included in this study. The mean age of the patients was 57.87 ± 8.91 years, with an age range of 40 to 70 years. Nearly half of the participants (45.2%) were aged 60 years or older (Figure 1).

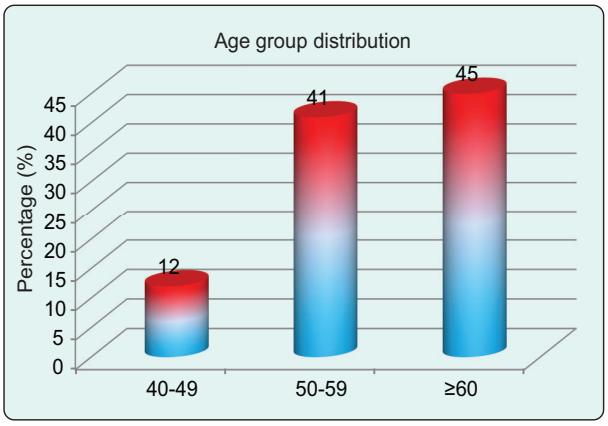


**Figure 1 :** Age group distribution of patients ( n = 31)

Endometrioid adenocarcinoma was the most common histological subtype, observed in 18 patients (58.06%), followed by papillary serous adenocarcinoma in 10 patients (32.26%) and carcinosarcoma in 3 patients (9.68%). Type I endometrial carcinoma was slightly more frequent, affecting 51.6%, compared to Type II in 48.4%. Grade 2 tumors were predominant, accounting for 58.1%, with Grade 1 and Grade 3 tumors observed in 19.4% and 22.6% cases, respectively. Myometrial invasion of >50% was present in 17 cases (54.8%), and pelvic lymph node metastases were noted in 3 cases (9.7%). The majority of patients presented with FIGO stage IA disease 13(41.94%), followed by stage IB 10(32.26%) and more advanced stages in the remaining cases (table I).

Estrogen receptor expression was positive in 16 patients (51.6%) and negative in 15 patients (48.4%). Progesterone receptor expression was positive in 15 patients (48.4%) and negative in 16 patients (51.6%). HER2 expression was positive in only 1 patient (3.2%), while 30 patients (96.8%) were negative (table II).

A significant association was found between estrogen receptor positivity and histological type; with 87.5% of Type I carcinomas expressing ER compared to only 12.5% of Type II carcinomas ($p < 0.001$). Similarly, progesterone receptor positivity was significantly associated with histological type; with 93.33% of Type I carcinomas expressing PR versus 6.67% of Type II carcinomas ($p < 0.001$). Both ER and PR expression were significantly associated with tumour grade, with lower grades (Grade 2) showing higher receptor positivity ($p = 0.001$ for ER, $p = 0.002$ for PR). ER & PR did not show any significant correlation with FIGO surgical stage of endometrial carcinoma. No associations were explored between HER2 expression and any clinicopathological parameters due to its low positivity rate (table III & IV).

Co-expression of ER and PR was observed in 15 cases. Among the 16 ER positive cases, 93.75% showed positive co-expression with PR ($p < 0.001$) (table V).

**Table I:** Pathological characteristics of endometrial carcinoma patients (N=31)

| Pathological features | n (%) |
|---|---|
| Histopathology | |
| Endometroid adenocarcinoma | 18 (58.06) |
| Papillary serous adenocarcinoma | 10 (32.26) |
| Carcinosarcoma | 3 (9.68) |
| Histological type | |
| Type I | 16 (51.6) |
| Type II | 15 (48.4) |
| Histological Grade of tumor | |
| Grade 1 | 6 (19.4) |
| Grade 2 | 18 (58.1) |
| Grade 3 | 7 (22.6) |
| Myometrial invasion | |
| <50% | 14 (45.2) |
| >50% | 17 (54.8) |
| Cervical stromal invasion | |
| Present | 2 (6.5) |
| absent | 29 (93.5) |
| Pelvic Lymph node metastasis | |
| Present | 3 (9.7) |
| Absent | 28 (90.3) |
| FIGO Surgical stage | |
| IA | 13 (41.94) |
| IB | 10 (32.26) |
| II | 1 (3.23) |
| IIIA | 3 (9.68) |
| IIIC | 3 (9.68) |
| IVB | 1 (3.23) |

**Table II:** Immunohistochemical expression of endometrial carcinoma patients (N=31)

| Immunohistochemical expression | n (%) |
|---|---|
| ER status | |
| Positive | 16 (51.6) |
| Negative | 15 (48.4) |
| PR status | |
| Positive | 15 (48.4) |
| Negative | 16 (51.6) |
| HER/neu status | |
| Positive | 1 (3.2) |
| Negative | 30 (96.8) |

**Table III:** Association of ER expression with histological type, grade and FIGO surgical stage of the endometrial carcinoma (N=31)

| Characteristics | Estrogen receptor (ER) | | p value* |
|---|---|---|---|
| | Positive(n=16) No. (%) | Negative(n=15) No. (%) | |
| Histological type | | | <0.001 |
| I | 14 (87.5) | 2 (13.33) | |
| II | 2 (12.5) | 13 (86.67) | |
| Histological Grade | | | 0.001 |
| 1 | 6 (37.5) | 0 (0) | |
| 2 | 10 (62.5) | 8 (53.33) | |
| 3 | 0 (0) | 7 (46.67) | |
| FIGO Surgical Stage | | | 0.293 |
| I | 14 (87.5) | 9 (60) | |
| II | 0 (0) | 1 (6.67) | |
| III | 2 (12.5) | 4 (26.67) | |
| IV | 0 (0) | 1 (6.67) | |

* Chi-square test done

**Table IV:** Association of PR expression with histological type, grade and FIGO surgical stage of the endometrial carcinoma (N=31)

| Characteristics | Progesterone receptor (PR) | | p value* |
|---|---|---|---|
| | Positive (n=15) No. (%) | Negative (n=16) No. (%) | |
| Histological type | | | <0.001 |
| I | 14 (93.33) | 2 (12.5) | |
| II | 1 (6.67) | 14 (87.5) | |
| Histological Grade | | | 0.002 |
| 1 | 6 (40) | 0 (0) | |
| 2 | 9 (60) | 9 (56.25) | |
| 3 | 0 (0) | 7 (43.75) | |
| FIGO Surgical Stage | | | 0.387 |
| I | 13 (86.67) | 10 (62.5) | |
| II | 0 (0) | 1 (6.25) | |
| III | 2 (13.33) | 4 (25) | |
| IV | 0 (0) | 1 (6.25) | |

* Chi-square test done

**Table V:** Co-expression of ER and PR (N=31)

| ER expression | PR expression | | Total | p value* |
|---|---|---|---|---|
| | Positive | Negative | | |
| Positive | 15 | 1 | 16 | <0.001 |
| Negative | 0 | 15 | 15 | |
| Total | 15 | 16 | | |

* Chi-square test done

## Discussion:

Endometrial carcinoma often arises from endometrial hyperplasia due to prolonged estrogen exposure without adequate progesterone. Ovarian steroid hormones, estrogen, and progesterone, play crucial roles in the development of both benign lesion and endometrial cancer via their receptors.[22] The treatment response of endometrial carcinoma to hormonal therapy is closely linked to the degree of tumor differentiation, which is associated with hormonal receptor levels, particularly progesterone receptor expression.[23] Understanding the hormonal receptor status, therefore, becomes essential for tailoring treatment strategies. This cross-sectional study was designed to evaluate the expression of ER, PR, and HER2 in endometrial carcinoma, assess their correlation with histological types, grades, and stages of the disease, and identify patients who could benefit from adjuvant hormone therapy.

In this study, the mean age of participants was 57.87 ± 8.91 years, with 45.2% aged 60 years or older. This aligns with findings from Shekhar et al., where the mean age was 58.47 years.[24] Several other studies have also reported a predominance of older age groups among endometrial carcinoma patients, including average ages of 64 years, 62 years, 63.6 years, and 56.16 years, as observed by Morrison et al. [25], Srijaipracharoen et al. [26] Lapiñska-Szumczyk et al. [27], and Ali et al. [28], respectively.

In this study, endometrioid adenocarcinoma was the most common histological type (58.06%), followed by papillary serous adenocarcinoma (32.26%) and carcinosarcoma (9.68%). Most patients (51.6%) had type I carcinoma, consistent with prior studies.[23,27,28] Deep myometrial invasion (>50%) was observed in 54.8% of cases, comparable to findings from other studies.[27,29,30] However, Mohapatra et al. reported less than 50% myometrial invasion in 63% of cases, likely due to their inclusion of low-grade tumors.[23]

The majority of patients in this study had grade 2 tumors (58.1%), followed by grade 3 (22.6%) and grade 1 (19.4%). Pelvic lymph node metastasis was found in 9.7% of patients, while cervical stromal invasion was observed in 6.5%. No para-aortic lymph node involvement was reported. FIGO staging revealed early-stage (stage I) disease in 74.2% of cases, consistent with previous studies.[23,27,30] However, Voss et al. reported 12.8% of patients with stage IV disease, likely due to their inclusion of high-grade tumors.[29]

Immunohistochemical analysis showed positive ER and PR expression in 51.6% and 48.4% of patients, respectively. These rates are within the ranges reported by other studies.[17,26] Variations in receptor expression rates across studies may result from differences in histological types, sample sizes, scoring methods, inter-observer variability, and tumor grade proportions. Srijaipracharoen et al. observed ER and PR positivity rates of 59.3% and 65.7%, respectively.[26] Wang et al. reported positive rates of 59.8% for ER and 75.0% for PR [30]. However, Shen et al. found significantly higher expression rates (85%) for both receptors in a Chinese cohort [31], potentially reflecting receptor loss over time and disease progression, as their study did not stratify patients by diagnosis year or disease duration.

HER2 expression was rare, observed in only one patient (3.2%). This finding aligns with studies by Srijaipracharoen et al. (2.8%), Mohapatra et al. (2.8%), and other reports from Thai cohorts showing HER2 expression in 1.5% of cases.[23,26] These rates are much lower than the 9-30% reported in other studies.[20-24] Due to the limited number of HER2-positive cases in this study, no definitive conclusions could be drawn regarding its prognostic value.

This study found significant associations between ER and PR positivity with type I (87.5% and 93.33%, respectively) and grade 2 tumors (62.5% and 60%, respectively). While FIGO stage did not show significant associations with ER or PR expression, stage I had the highest positivity rates (87.5% and 86.67%, respectively). Similar trends were reported by previous study highlighting higher PR expression in type I tumors compared to type II. [31]

The findings also suggest a significant positive co-expression of ER and PR, as 93.75% of ER- positive cases exhibited PR positivity ($p < 0.001$). This concordance aligns with previous reports that estrogen regulates PR expression, potentially explaining resistance to prolonged progestin therapy.[22] Strengths of this study include its focus on immunohistochemical expression of ER, PR, and HER2 in endometrial carcinoma, providing valuable insights into their correlation with histological type, grade, and stage. The study identifies potential biomarkers for hormone therapy, with statistically significant findings on ER and PR co-expression. However, limitations include the small sample size (n=31), which restricts generalizability, and the cross-sectional design, which prevents assessment of causal relationships. Additionally, the low HER2 expression limits its prognostic evaluation, and reliance on a single-center dataset may introduce selection bias. Further research with larger, multicenter cohort is recommended.

## Conclusion

This study concludes that, significant number of endometrial carcinoma patients express ER & PR. There is significant associations between ER and PR expression with histological type (type-1) and histological grade (grade 2) in endometrial carcinoma. Positive PR expression showed strong co-expression with ER. These findings suggest that ER and PR could serve as biomarkers for identifying patients suitable for adjuvant hormone therapy.

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*Ethical Clearence: we have adhered to ethical standards throughout the study. We also confirm that appropriate patient consent was obtained, and ethical approval was taken from National Institute of Cancer Research Hospital.*

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