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RESEARCH PAPER

Correlation of Estrogen and Progesterone Receptor Expression with Clinicopathological Features in Epithelial Ovarian Cancer in Bangladesh

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Abstract

Background: Ovarian cancer is often diagnosed at an advanced stage, resulting in poor prognosis despite modern management strategies. Estrogen receptor (ER) and progesterone receptor (PR) expression in epithelial ovarian cancer (EOC) may serve as prognostic biomarkers and guide potential hormonal therapy.

Objective: To determine the prevalence of ER and PR expression in epithelial ovarian cancer (EOC) and to assess their association with clinical and histopathological characteristics.

Methods: A cross-sectional observational study was conducted at the National Institute of Cancer Research & Hospital (NICRH), Dhaka, from July 2020 to June 2021. Forty women with histologically confirmed primary EOC were enrolled. Demographic, reproductive, and clinical data were collected. Histological grading and subtyping were performed, and ER/PR expression was assessed using immunohistochemistry. Associations of hormone receptor status with clinical and histopathological features were analyzed using Chi-squared and t-tests, with $p < 0.05$ considered significant.

Results: Among the study population, 30% of tumors were ER positive and 22.5% PR positive. Histologically, 65% were serous, 30% mucinous, and 5% clear cell carcinomas, with 80% being Grade-III. ER overexpression was significantly associated with high-grade tumors (Grade-III, $p = 0.038$) and marginally associated with advanced stage (Stage III, $p = 0.051$). PR positivity was significantly associated with serous histology ($p = 0.044$) and higher clinical stage (Stage III, 55.6%). No significant associations were observed between ER status and reproductive characteristics, whereas PR-positive patients were significantly older than PR-negative counterparts ($p = 0.039$).

Conclusion: ER overexpression in EOC is significantly associated with higher histological grade, while PR overexpression is associated with serous subtype and advanced FIGO stage. These findings suggest potential prognostic and therapeutic implications of hormone receptor status in EOC. Further studies with larger cohorts are recommended to confirm their role in guiding endocrine therapy.

Keywords: Epithelial ovarian cancer, estrogen receptor, progesterone receptor, immunohistochemistry, prognostic biomarker

Introduction

Cancer remains one of the leading causes of mortality worldwide and continues to be a major barrier to improvements in life expectancy. According to the World Health Organization (WHO), cancer was the first or second leading cause of death before the age of 70 years in most countries in 2019.[1] Ovarian cancer contributes substantially to this burden among women, with an estimated 313,959 new cases and 207,252 deaths reported globally in 2020.[2] In Bangladesh, ovarian cancer accounted for approximately 2% of all cancer cases, with a considerable mortality rate, highlighting its public health importance.[2]

Ovarian cancer is the deadliest of all gynecological malignancies, primarily due to late diagnosis and aggressive disease progression. The ovaries are located deep within the pelvis, and early-stage disease

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is often asymptomatic or associated with vague symptoms, resulting in delayed detection. Consequently, nearly 75% of patients are diagnosed at an advanced stage, when the disease has already spread beyond the ovaries.[3,4] Despite advances in cytoreductive surgery and platinum–taxane–based chemotherapy, recurrence rates remain high, with approximately 70% of patients relapsing within two years of initial treatment.[5] Survival following recurrence is poor, and five-year survival rates for advanced-stage disease remain below 25%, underscoring the urgent need for improved prognostic markers and alternative therapeutic strategies.

Epithelial ovarian cancer (EOC) accounts for approximately 90% of all ovarian malignancies and represents a heterogeneous group of tumors with distinct histological and molecular characteristics.[6] The World Health Organization classifies ovarian tumors based on histological features and presumed cell of origin. Emerging evidence suggests that ovarian carcinomas arise through at least two major pathogenetic pathways. High-grade serous carcinomas are now thought to originate from precursor lesions in the fimbrial epithelium of the fallopian tube, whereas low-grade serous, endometrioid, and clear cell carcinomas are believed to arise from endometriosis or other extra-ovarian tissues.[7–9] These distinct origins contribute to differences in tumor behavior, treatment response, and prognosis.

Steroid hormones, particularly estrogen and progesterone, have long been implicated in ovarian carcinogenesis. Epidemiological associations such as nulliparity, early menarche, late menopause, and prolonged lifetime ovulation support the role of hormonal exposure in the development of epithelial ovarian tumors.[10,11] Estrogens exert their biological effects primarily through estrogen receptors (ERá and ERβ), which regulate genes involved in cell proliferation and survival.[12] Immunohistochemical studies have demonstrated ER expression in 43–81% of epithelial ovarian carcinomas.[13,14] In contrast, progesterone is believed to exert a protective effect against ovarian cancer development through anti-proliferative and pro-apoptotic mechanisms mediated by the progesterone receptor (PR).[15]

The expression of ER and PR varies across histological subtypes of EOC. ER expression is more common in serous and endometrioid carcinomas, whereas PR expression is highest in endometrioid and low-grade serous tumors and lowest in mucinous and clear cell carcinomas.[13] Numerous studies have evaluated the prognostic significance of ER and PR expression in EOC, but results remain inconsistent. While some reports associate ER or PR positivity with improved survival, others demonstrate no significant association or even adverse outcomes.[16–18] These discrepancies suggest that the prognostic value of hormone receptor expression may depend on tumor subtype, disease stage, detection methods, and population-specific factors.

In addition to prognostic implications, hormone receptor expression may have therapeutic relevance. Hormonal therapy offers a less toxic alternative to conventional chemotherapy and has shown clinical benefit in selected patients with hormone receptor–positive ovarian cancer.[19] However, routine assessment of ER and PR status in ovarian cancer has not been universally adopted, particularly in low- and middle-income countries, due to inconsistent evidence and limited local data.

Despite extensive international research, information on estrogen and progesterone receptor expression in epithelial ovarian cancer in Bangladesh is scarce. Given potential ethnic, genetic, and environmental influences on tumor biology, locally generated evidence is essential. Therefore, the present study aims to evaluate ER and PR expression in epithelial ovarian cancer and to assess their association with clinical presentation and histopathological characteristics in a Bangladeshi population, with the goal of improving prognostic stratification and informing future therapeutic strategies.

Materials and Methods

This was a hospital-based cross-sectional observational study. The study was carried out in the Department of Gynecological Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, over a period of one year from July 2020 to June 2021.

The study population included women with histopathologically confirmed primary epithelial ovarian cancer (EOC) who underwent primary debulking surgery at NICRH during the study period.

Patients were excluded if they had metastatic tumors involving the ovary, non-epithelial ovarian malignancies, received neoadjuvant chemotherapy followed by interval debulking surgery, had unavailable or unsuitable histopathological slides or tissue blocks, or had any previous or concurrent malignancy other than ovarian cancer.

The sample size was calculated to detect a difference in estrogen receptor (ER) expression between high-grade (Grade III) and low-/intermediate-grade (Grade I–II) epithelial ovarian cancers. Assuming a 95% confidence level ($Z\alpha = 1.96$), 90% power ($Z\beta = 1.28$), and anticipated ER positivity of 64% in Grade III tumors and 29% in Grade I–II tumors, the calculated sample size was approximately 40. Accordingly, 40 consecutive eligible patients were enrolled using a purposive sampling technique.

Independent variables included sociodemographic factors (age, body mass index, educational status), reproductive characteristics (menstrual status, age at menarche, age at menopause, duration of reproductive years, parity), contraceptive history (oral contraceptive pill use), clinical stage, and histopathological characteristics (tumor subtype and grade). The dependent variables were estrogen receptor (ER) and progesterone receptor (PR) expression status.

All surgical specimens were fixed in 10% neutral buffered formalin and processed using standard paraffin-embedding techniques. Hematoxylin and eosin–stained sections were examined for histological diagnosis. Tumors were classified according to the 2014 World Health Organization (WHO) classification into serous, mucinous, endometrioid, and clear cell carcinomas.[27] Tumor grading was performed using the Shimizu and Silverberg grading system based on architectural pattern, nuclear pleomorphism, and mitotic activity, and categorized into Grade 1 (well differentiated), Grade 2 (moderately differentiated), and Grade 3 (poorly differentiated).[28] Tumor staging was determined according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 staging system.[29]

Immunohistochemical staining for ER and PR was performed on formalin-fixed, paraffin-embedded tissue sections using the streptavidin–biotin technique. Sections of 3 ìm thickness were mounted on poly-L-lysine–coated slides. After deparaffinization and rehydration, antigen retrieval was carried out using citrate buffer in a microwave oven. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide. Sections were incubated with ready-to-use monoclonal mouse anti-human ER and PR primary antibodies (DAKO, USA), followed by Dako REAL EnVision secondary antibody. Diaminobenzidine was used as the chromogen, and Harris hematoxylin was used for counterstaining. Appropriate positive and negative controls were included with each staining run.

Nuclear staining in tumor cells was considered positive for ER and PR. Ten representative high-power fields were examined per case. The proportion of positively stained tumor cells was expressed as a percentage, and staining intensity was assessed qualitatively.

Relevant sociodemographic, reproductive, clinical, and pathological data were collected using a structured questionnaire and review of medical records.

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 25. Descriptive statistics were used to summarize study variables. Associations between ER/PR expression and clinical or histopathological variables were assessed using the Chi-square (χ^2) test for categorical variables and Student's t-test for continuous variables. A p-value < 0.05 was considered statistically significant.

The study was conducted in accordance with the Declaration of Helsinki (1964, amended in 2013). Ethical approval was obtained from the Institutional Review Board of NICRH. Written informed consent was obtained from all participants prior to enrollment, and confidentiality of patient information was strictly maintained.

Results

A total of 40 women with histologically confirmed epithelial ovarian cancer (EOC) were included in the analysis. Estrogen receptor (ER) and progesterone receptor (PR) expression was evaluated, and their associations with demographic, reproductive, clinical, and histopathological characteristics were examined.

The majority of patients were aged over 50 years (52.5%), followed by those aged 41–50 years (27.5%) and ≤40 years (20.0%). The mean age at diagnosis was 48.9 ± 12.6 years (range: 18–75 years). Nearly half of the patients were underweight (45.0%), while

55.0% had a normal body mass index. Most women were illiterate (60.0%), with only 15.0% having secondary-level education or higher (Table I).

Table I: Distribution of the patients by their demographic characteristics (N=40)

Demographic & Reproductive characteristics	Frequency	Percentage
Age* at diagnosis (years)		
≤30	5	12.5
31 – 40	3	7.5
41 – 50	11	27.5
>50	21	52.5
Mean age = 48.9±12.6 (range: 18-75) yrs.		
Reproductive status (n = 40)		
Premenopausal	16	40.0
Postmenopausal	24	60.0
Parity (n = 40)		
Nullipara	6	15.0
Low parity (up to 1 child)	15	37.5
Normal parity (2 or more children)	19	47.5
Use of OCP (n = 40)		
Never used	32	80.0
Used for < 5 yrs	8	20.0

Among the study participants, 60.0% were postmenopausal and 40.0% were premenopausal. Normal parity (≥2 children) was observed in 47.5% of patients, whereas 37.5% had low parity and 15.0% were nulliparous. The majority of women (80.0%) reported never using oral contraceptive pills. Reproductive characteristics are summarized.

According to the FIGO staging system, 45.0% of patients were diagnosed at stage I disease, 20.0% at stage II, and 35.0% at stage III (Table II).

Table II: Distribution of the subjects by FIGO staging of EOC (N= 40)

Stage of EOC	Frequency	Percentage
Stage I	18	45.0
Stage II	8	20.0
Stage III	14	35.0

Serous carcinoma was the predominant histological subtype, accounting for 65.0% (n = 26) of cases, followed by mucinous carcinoma (30.0%, n = 12) and clear cell carcinoma (5.0%, n = 2). Most tumors were poorly differentiated, with 80.0% classified as Grade III and 20.0% as Grade II (Table VII).

Estrogen receptor positivity was detected in 30.0% (n = 12) of patients, while progesterone receptor positivity was observed in 22.5% (n = 9). Further analysis showed that 12.0% of patients were ER-positive only, 5.0% were PR-positive only, and 18.0% expressed both ER and PR, whereas 65.0% were negative for both receptors (Table III).

Table III: Distribution of the subjects by hormone receptor status (N=40)

Hormone receptor status	Frequency	Percentage
ER		
Positive	12	30.0
Negative	28	70.0
PR		
Positive	9	22.5
Negative	31	77.5

With respect to disease stage, ER positivity was more frequent in stage III tumors compared with ER-negative cases (58.3% vs. 25.0%), showing a marginally significant association (p = 0.051) (Table IV).

Table IV: Association of ER with FIGO Staging of EOC (N=40)

Stage of EOC*	ER		p-value
	Positive (n = 12)	Negative (n = 28)	
Stage I	2(16.7)	16(57.1)	
Stage II	3(25.0)	5(17.9)	0.051
Stage III	7(58.3)	7(25.0)	

*Data were analyzed using Chi-squared (χ^2) Test and were presented as n(%).

Histopathological analysis revealed that serous carcinoma was more common among ER-positive tumors than ER-negative tumors (83.3% vs. 57.1%), although this difference was not statistically significant (p = 0.252). Notably, all ER-positive tumors were Grade III, compared to 71.4% of ER-negative tumors, and this association was statistically significant (p = 0.038) (Table V).

Table V: Association of ER with histological characteristics

Histological characteristics	ER		p-value
	Positive (n = 12)	Negative (n = 28)	
Sub-type*			
Serous	10(83.3)	16(57.1)	
Mucinous	2(16.7)	10(35.8)	0.252
Clear cell carcinoma	0(0.0)	2(7.10)	
Grading*			
Grade II	0(0.0)	8(28.6)	0.038
Grade III	12(100.0)	20(71.4)	

*Data were analyzed using Chi-squared (χ^2) Test and were presented as n(%).

PR expression was significantly associated with advanced disease stage, with stage II and III disease occurring more frequently among PR-positive patients compared with PR-negative patients (p = 0.039) (Table VI).

Table VI: Association of PR with FIGO Staging of EOC

Stage of EOC*	PR		p-value
	Positive (n = 9)	Negative (n = 31)	
Stage I	1(11.1)	17(54.8)	
Stage II	3(33.3)	5(16.1)	0.067
Stage III	5(55.6)	9(29.0)	

*Data were analyzed using Chi-squared (χ^2) Test and were presented as n(%).

Table VII: Association of PR with histological characteristics:

Histological findings	PR		p-value
	Positive (n = 9)	Negative (n = 31)	
Sub-type*			
Serous		9(100.0)	17(54.8)
Mucinous	0(0.0)	12(38.7)	0.044
Clear cell carcinoma	0(0.0)	2(6.5)	
Grading*			
Grade II		1(11.1)	7(22.6)
0.449			
Grade III	8(88.9)	24(77.4)	

*Data were analyzed using Chi-squared (χ^2) Test and were presented as n(%).

Regarding histopathology, all PR-positive tumors were of serous subtype, compared with 54.8% of PR-negative tumors, and this association was statistically significant (p = 0.044). Tumor grade, however, did not show a significant association with PR expression (p = 0.449) (Table VII).

Discussion

Ovarian cancer remains a clinically challenging malignancy due to its late detection and rapid progression, resulting in poor prognosis. Over 70% of patients are diagnosed at advanced stages, with a 5-year survival rate of approximately 30%.[1,2] Despite advances in cytoreductive surgery and adjuvant chemotherapy, many patients fail to benefit from these interventions, and 60–70% experience disease recurrence within 18 months.[3,4] These clinical realities underscore the urgent need for reliable prognostic biomarkers to improve outcomes in epithelial ovarian cancer (EOC).

In the present study, ER overexpression was observed in 30% of patients and PR overexpression in 22.5%. These findings are comparable to reports from Tunisia, where ER and PR expressions were 35.1% and 33.3%, respectively.[5] Similar prevalence rates have been reported in Nigeria and Germany, with ER and PR positivity ranging from 31–38% and 22–31% .[6,7] Previous studies have reported wide variability in steroid receptor expression (32–77% for ER and 15–69% for PR), likely reflecting differences in assay methods, sample populations, and detection techniques, with higher rates in earlier biochemical studies compared to more recent immuno-histochemical approaches.[8-11]

Histopathological analysis in this study revealed that 80% of tumors were poorly differentiated (Grade III), with serous carcinoma comprising 65%, mucinous 30%, and clear cell 5%. ER overexpression was significantly associated with higher histological grade (Grade III), while PR overexpression was more frequently observed in serous subtypes. These findings align with previous reports demonstrating a correlation between ER positivity and higher-grade tumors, and PR positivity with serous histology.[5,6,12]

Regarding FIGO staging, ER overexpression was marginally associated with stage III disease (p = 0.051), whereas PR positivity was associated with higher-stage tumors, with 55.6% of PR-positive

patients presenting with stage III disease. This is partially consistent with Burges et al., who reported a significant association between ER and advanced-stage EOC, although other studies have reported no association between hormone receptor status and FIGO stage.[6,10,13]

No significant associations were found between ER status and reproductive characteristics, including age at menarche, menopause, parity, or oral contraceptive use. Interestingly, PR-positive patients were significantly older than PR-negative patients, consistent with earlier studies suggesting PR expression is more frequently associated with older age.[14-16]

The prognostic and therapeutic implications of ER and PR expression in EOC remain under investigation. Several studies suggest that steroid hormone receptor status may predict response to hormonal therapy, as demonstrated in breast and endometrial cancers.[17] In ovarian cancer, anti-estrogen therapies such as tamoxifen have shown variable anti-proliferative effects on primary tumors.[18,19] However, responses to endocrine therapy are not always directly correlated with absolute ER or PR expression, suggesting the involvement of alternative pathways or receptor-independent mechanisms.[20]

The present study has several limitations. It was conducted at a single center with a relatively small sample size, and patients who received neoadjuvant chemotherapy were excluded, potentially affecting the stage distribution. Despite these limitations, the study highlights significant associations between ER/PR expression and histopathological features of EOC.

In conclusion, ER overexpression was significantly associated with high-grade tumors, and PR overexpression was more frequent in serous subtypes. These findings support the potential utility of hormone receptor status as a prognostic indicator in EOC. Future studies with larger, multicenter cohorts and stratification by histological subtype are warranted to validate these findings and explore the predictive value of ER and PR for endocrine therapy response.

Conclusions

ER overexpression in epithelial ovarian cancer (EOC) is significantly associated with higher histological grade, whereas PR overexpression shows a significant association with the serous subtype and advanced FIGO stage. These findings indicate that hormone receptor expression is related to important clinicopathological characteristics of EOC and may have potential prognostic and therapeutic relevance.

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