



## Correlation of Estrogen Receptor and Progesterone Receptor Expression with WHO Grading of Malignant Epithelial Ovarian Tumors

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### ABSTRACT:

**Introduction:** Malignant epithelial ovarian tumors are a significant health concern for women worldwide. Identifying markers that could help predict the prognosis of these tumors is crucial for improving patient outcomes. Among such markers, estrogen receptor (ER) and progesterone receptor (PR) have been proposed as potential indicators of tumor behavior. Previous studies have reported conflicting results regarding the correlation between ER and PR expression and tumor grade in ovarian cancers. This study aims to investigate the association between ER and PR expression and tumor grade in malignant epithelial ovarian tumors using the World Health Organization (WHO) grading system, with the goal of identifying potential biomarkers for prognostic prediction. **Methods:** This cross-sectional observational study was conducted at the Department of Gynecology and Obstetrics, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh. The study duration was 2 years, from January 2018 to December 2019. During this period, a total of 45 adult female patients with histopathologically diagnosed malignant epithelial ovarian tumors by H&E staging were selected for the study. **Result:** The study included 45 participants (mean age 51.29 years, range 35-70 years) with most participants (73.33%) between 41-60 years old. The majority of participants (86.67%) were nulliparous. Most participants (88.89%) had CA-125 levels between 101-299, with a mean level of 149.51. Of the cases, 31 (68.89%) were serous cystadenocarcinoma, 8 (17.78%) were mucinous cystadenocarcinoma, 4 (8.89%) were endometrioid

carcinoma, and 2 (4.44%) were clear cell carcinoma. ER positivity was found in 64.52% of serous cystadenocarcinoma cases and in none of the mucinous cystadenocarcinoma cases. Endometrioid carcinoma had the highest proportion of patients with positive PR status (50%), but the difference between subtypes lacked statistical significance (P-value=0.303). The difference in ER positivity between serous and mucinous cystadenocarcinoma, as well as other subtypes, was statistically significant (P-value=0.001). The study found that Grade 3 tumors had the highest prevalence (44.44%), and the highest percentage of positive ER expression (63.64%), while Grade 1 tumors had the highest percentage of positive PR expression (77.78%). The difference in ER positivity between the three grades was statistically significant (P=0.032), as was the association between PR expression and tumor grade (P=0.001). Grade 2 tumors had the highest percentage of negative ER expression (47.83%), while Grade 3 tumors had the highest percentage of negative PR expression (52.78%). **Conclusion:** The study found that ER positivity was higher in Grade 3 tumors, which is consistent with previous research. PR expression was highest in Grade 1 tumors and significantly associated with low-grade tumors. ER expression was significantly associated with serous carcinoma and high-grade diseases. PR was expressed in all tumors except clear cell carcinoma and was significantly associated with low-grade tumors.

**Keywords:** Estrogen, Progesterone, Carcinoma, Ovarian, Tumor, Grading



## I. INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy in women, accounting for a considerable proportion of cancer diagnoses and deaths globally. Ovarian cancer was responsible for 7.1 percent of all new cancer diagnoses and 4.1 percent of all cancer deaths in women in 2020, according to the World Ovarian Cancer Coalition (2018) and Globacon projections.(1,2)Ovarian cancer accounted for 2% of cancer-related fatalities in Bangladesh in 2018.(3) The median age of ovarian cancer diagnosis is 63 years, and this older age is associated with more advanced disease and lower survival rates.(4)Geographical, ethnic, and economic development variables all contribute to the uneven distribution of ovarian cancer occurrence over the world. Age, marital status, menstrual history, obstetric history, hormonal state, and family history are the most frequent risk factors for ovarian cancer.(5)The ovarian surface epithelium (OSE), a single layer of epithelial cells that lines the ovary, is the primary source of ovarian cancers. The epithelial layer is responsible for around 90% of ovarian cancers, with the fallopian tube epithelium and peritoneal mesothelium being other probable sites of genesis.(6)Hormones and growth factors have an important role in controlling cell proliferation, differentiation, and death in epithelial ovarian cancers. These pathways are dysregulated, allowing cells with mutations in proto-oncogenes and tumor suppressor genes to survive and spread clonally. Pituitary gonadotropins like luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as androgens, estrogens, progesterones, and insulin-like growth factor I (IGF-I), have all been linked to the development of ovarian cancer.(7)The ovaries' release of steroid hormones, estrogen and progesterone, has been linked to the etiology of cancers such as breast, endometrial, and ovarian cancer.(8)The development and progression of ovarian cancer are strongly linked to estrogen.(9)Estrogen supports the physiological effects of cell survival and proliferation after attaching to their unique receptors (estrogen receptor (ER) and progesterone receptor (PR)). ER expression varies in human epithelial ovarian carcinoma, and ER-positive instances are more common in malignant and borderline tumors than in benign tumors.(10,11)Progesterone, on the other hand, is essential for follicular maturation and works in tandem with estrogen to induce ovulation and the creation of the corpus luteum. Increased PR expression is linked to a higher survival rate in epithelial ovarian cancer, and PR-positive cases are

more common in borderline tumors than in malignant tumors.(11,12) However, some studies have suggested that ER and PR positivity in epithelial ovarian cancer is associated with better clinical outcomes.(10)These findings are relevant to the correlation between ER and PR expression and WHO grading in patients with malignant epithelial ovarian tumors.The WHO grading system for ovarian cancer guides treatment decisions based on histological features and tumor differentiation.(13,14) High-grade tumors have a poor prognosis and require aggressive treatment, while low-grade tumors have a better prognosis and need less intensive treatment.Several studies have investigated the correlation between ER and PR expression and WHO grading in patients with malignant epithelial ovarian tumors.(10,15) One such study found that the expression of ER and PR was significantly associated with tumor grading, with high-grade tumors having lower levels of ER and PR expression than low-grade tumors.(10,15–17) Other studies have also reported similar findings, indicating that ER and PR expression levels can serve as potential markers for tumor grading.The implications of these findings are significant, as they suggest that the expression of ER and PR could potentially be used as an additional tool for predicting tumor behavior and guiding treatment decisions for patients with ovarian cancer. For instance, patients with high-grade tumors and low ER and PR expression levels may require more aggressive treatment approaches, while those with low-grade tumors and high ER and PR expression levels may be candidates for less intensive treatments. However, there exists a scarcity of such studies in Bangladesh. The present study was conducted to observe any possible correlation of the ER and PR hormone receptors with WHO grading of ovarian tumors.

## II. METHODS

This cross-sectional observational study was conducted at the Department of Gynecology and Obstetrics, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh. The study duration was 2 years, from January 2018 to December 2019. During this period, a total of 45 adult female patients with histopathologically diagnosed malignant epithelial ovarian tumors by H&E staging were selected for the study. Any patients being treated with radiotherapy or chemotherapy, and patients declining consent were excluded from the study. Informed written consent was obtained from each participant, and ethical approval was also obtained from the ethical review committee of the study hospital prior to data



collection. Participants were ensured complete anonymity and right to withdraw from the study at any time. Estrogen Receptor (ER) and Progesterone Receptor (PR) immunostained sections were examined under light microscope. ER and PR positive cells were subjected to manual counting. ER, PR expression was evaluated by the Allred

system of scoring (semi-quantitative method) for ER and PR.(18,19) Data was collected using a premade data collection sheet, and statistical analysis was done by using Fisher's Exact test, with 95% confidence interval and p-value of <0.05 was considered significant.

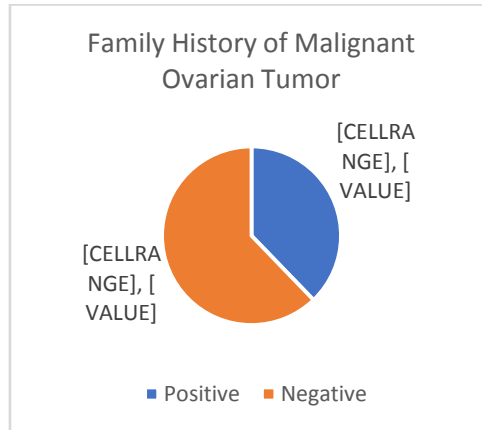
### III. RESULTS

**Table 1:** Distribution of participants by baseline characteristics (n=45).

Variables	Frequency	Percentage
<b>Age</b>		
≤40	4	8.89%
41-50	21	46.67%
51-60	15	33.33%
61-70	5	11.11%
Mean±SD	51.29±7.9	
Range(min-max)	(35-70)	
<b>Menstrual Status</b>		
Regular	1	2.22%
Irregular	33	73.33%
Post-menopausal	11	24.44%
<b>Age At Menarche</b>		
≤10	13	28.89%
>10	32	71.11%
Mean±SD	10.86±0.91	
Range(min-max)	(9 -13)	
<b>Parity</b>		
Nulliparity	39	86.67%
Multiparity	6	13.33%
<b>CA-125 level</b>		
61-100	5	11.11%
101-299	40	88.89%
Mean±SD	149.51±42.58	
Range (min-max)	(80-250)	

The participants had a mean age of 51.29 years, ranging from 35 to 70 years. Most of them (73.33%) were in the age range of 41-60 years, and 24.44% were post-menopausal. The mean age at menarche was 10.86 years, with 71.11% reporting an age of >10 years at menarche. The majority of

participants (86.67%) were nulliparous, while only 13.33% reported being multiparous. The mean CA-125 level was 149.51, with 88.89% of the participants having a level in the range of 101-299.



**Figure 1:** Family History of malignant ovarian tumor (n=45)

Among the participants of the present study, 37.78% of the participants had a family history of

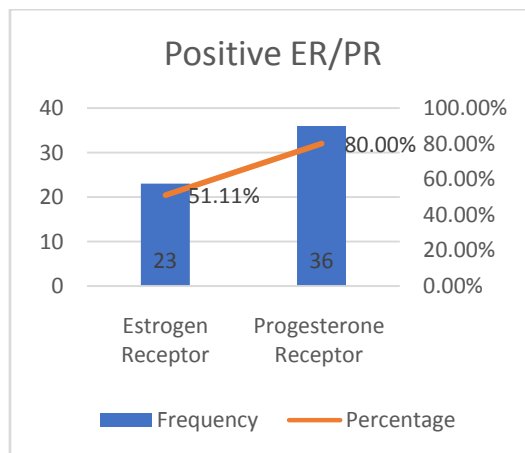
malignant ovarian tumor, while 62.22% of participants had no such family history.

**Table 2:** Distribution of the study patients according to histopathological diagnosis (n=45)

Histopathological Diagnosis	Frequency	Percentage
Serous Cystadenocarcinoma	31	68.89%
Mucinous Cystadenocarcinoma	8	17.78%
Endometrioid Carcinoma	4	8.89%
Clear Cell Carcinoma	2	4.44%

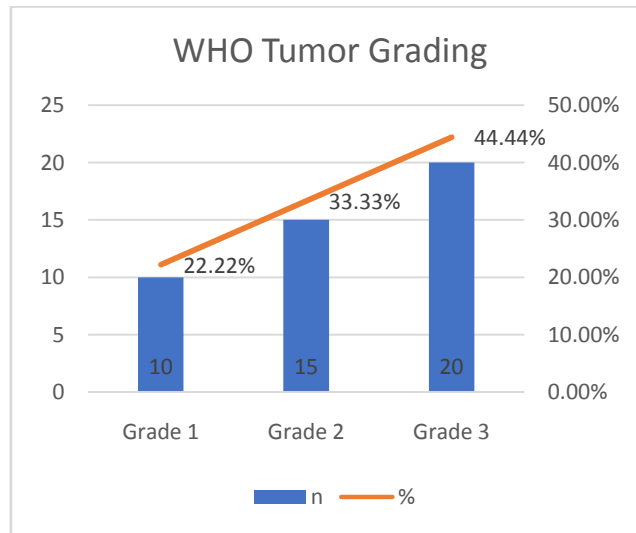
Out of the total number of cases, 31 (68.89%) were diagnosed with serous cystadenocarcinoma, 8 (17.78%) with mucinous

cystadenocarcinoma, 4 (8.89%) with endometrioid carcinoma, and 2 (4.44%) with clear cell carcinoma.



**Figure 2:** Prevalence of positive Estrogen and Progesterone receptor expression among participants (n=45)

Out of the 45 participants, 23 (51.11%) were positive for ER, while 36 (80.00%) were positive for PR.



**Figure 3:** Distribution of participants by WHO grading of tumors (n=45)

The study observed that grade 3 tumor had the highest prevalence among participants at 44.44%. Grade 1 tumor was observed in 22.22% of participants, while grade 2 tumor was observed in 33.33% of the participants.

**Table 3:** Distribution of the different histopathological diagnosis according to estrogen receptor (ER) status (n=45)

Estrogen receptor (ER)	Serous cystadenocarcinoma (n=31)		Mucinous cystadenocarcinoma (n=8)		Endometrioid carcinoma (n=4)		Clear cell carcinoma (n=2)		P value
	n	%	n	%	n	%	n	%	
Positive	20	64.52%	0	0.00%	2	50.00%	0	0.00%	0.001s
Negative	11	35.48%	8	100.00%	2	50.00%	2	100.00%	

The study found that among the 31 cases of serous cystadenocarcinoma, 20 (64.52%) had a positive ER status, while none of the 8 cases of mucinous cystadenocarcinoma were positive for ER. Out of the 4 cases of endometrioid carcinoma, 2 (50.00%) were positive for ER, and none of the 2

cases of clear cell carcinoma were positive for ER. The difference in ER positivity between serous and mucinous cystadenocarcinoma, as well as other subtypes, was found to be statistically significant with a P-value of 0.001.

**Table 4:** Distribution of the different histopathological diagnosis according to progesterone receptor (PR) status (n=45)

Progesterone receptor (PR)	Serous cystadenocarcinoma (n=31)		Mucinous cystadenocarcinoma (n=8)		Endometrioid carcinoma (n=4)		Clear cell carcinoma (n=2)		P-value
	n	%	n	%	n	%	n	%	
Positive	5	16.13%	2	25.00%	2	50.00%	0	0.00%	0.303ns
Negative	26	83.87%	6	75.00%	2	50.00%	2	100.00%	

The results indicate that endometrioid carcinoma had the highest proportion of patients with positive PR status (50%), trailed by mucinous cystadenocarcinoma (25%) and serous

cystadenocarcinoma (16.13%), with no clear cell carcinoma patients exhibiting positive PR status. Nonetheless, the non-significant P-value of 0.303



indicates that this disparity lacks statistical significance.

**Table 5:** Association of WHO Grading with Histopathological diagnosis of patients (n=45)

WHO Grading	Serous cystadenocarcinoma (n=31)		Mucinous cystadenocarcinoma (n=8)		Endometrioid carcinoma (n=4)		Clear cell carcinoma (n=2)		P value
	n	%	N	%	n	%	n	%	
Grade 1	5	16.13%	4	50.00%	1	25.00%	0	0.00%	0.115
Grade 2	9	29.03%	3	37.50%	1	25.00%	2	100.00%	
Grade 3	17	54.84%	1	12.50%	2	50.00%	0	0.00%	

The results show that the majority of serous cystadenocarcinoma cases were classified as Grade 3 (54.84%), followed by Grade 2 (29.03%) and Grade 1 (16.13%). For mucinous cystadenocarcinoma, Grade 1 and Grade 2 had similar frequencies (50% and 37.50%, respectively), while only one case was classified as Grade 3 (12.50%). In endometrioid carcinoma,

50% of cases were classified as Grade 3, 25% as Grade 1, and 25% as Grade 2. For clear cell carcinoma, all cases were classified as Grade 2 or Grade 3. The P value for the overall distribution of WHO grading in the different tumor types was 0.115, indicating no significant difference in the distribution of tumor grades among these types.

**Table 6:** Correlation of estrogen receptor (ER) expression with WHO grading of the tumors (n=45).

WHO Grading	Positive ER (n=22)		Negative ER (n=23)		P value
	N	%	N	%	
Grade 1	4	18.18%	6	26.09%	0.032
Grade 2	4	18.18%	11	47.83%	
Grade 3	14	63.64%	6	26.09%	

The highest percentage of positive ER expression was found in Grade 3 tumors (63.64%), followed by Grade 2 (18.18%) and Grade 1 (18.18%). The difference in ER positivity between the three grades was statistically significant

(P=0.032). The highest percentage of negative ER expression was found in Grade 2 tumors (47.83%), followed by Grade 1 (26.09%) and Grade 3 (26.09%).

**Table 7:** Correlation of progesterone receptor (PR) with grading of the tumors (n=45).

WHO Grading	Positive PR (n=9)		Negative PR (n=36)		P value
	n	%	n	%	
Grade 1	7	77.78%	3	8.33%	0.001
Grade 2	1	11.11%	14	38.89%	
Grade 3	1	11.11%	19	52.78%	

The highest percentage of positive PR expression was observed in Grade 1 tumors (77.78%), followed by Grade 2 tumors (11.11%), and Grade 3 tumors (11.11%). On the other hand, the highest percentage of negative PR expression was observed in Grade 3 tumors (52.78%), followed by Grade 2 tumors (38.89%), and Grade 1 tumors (8.33%). The statistical analysis indicates a significant association between PR expression and tumor grade (P=0.001).

#### IV. DISCUSSION

The present study was conducted with a total of 45 patients with malignant epithelial ovarian tumor, to observe any possible correlation between ER and PE with WHO grading of tumors. The distribution of the participants by baseline characteristics showed that the majority of the participants were in the age range of 41-60 years (73.33%), with a mean age of 51.29 years, ranging from 35 to 70 years. This was similar to previous studies, confirming the general belief that old age is



a significant risk factor of ovarian tumor.(20,21)Additionally, the study found that 24.44% of the participants were post-menopausal. The mean age at menarche was 10.86 years, with 71.11% of participants reporting an age of >10 years at menarche. These findings were also supported by multiple previous studies, that observed a higher incidence of ovarian tumors occurring in post-menopausal women and in multiparous women.(22–24)The majority of participants (86.67%) were nulliparous, while only 13.33% reported being multiparous. The mean CA-125 level was 149.51, with 88.89% of the participants having a level in the range of 101-299. This high mean CA levels were also observed in a previous study by Chen et al.(25)Furthermore, the study found that among the participants, 37.78% had a family history of malignant ovarian tumor, while 62.22% had no such family history. Family history of tumor is considered a significant risk factor, as observed by previous studies, and reinforced by the findings of the present study.(4) Histopathological diagnosis of the study participants revealed that out of the total number of cases, 31 (68.89%) were diagnosed with serous cystadenocarcinoma, 8 (17.78%) with mucinous cystadenocarcinoma, 4 (8.89%) with endometrioid carcinoma, and 2 (4.44%) with clear cell carcinoma. Serous neoplasm is considered a rather aggressive form of ovarian tumor, and has been observed in higher prevalence in few other studies.(26–28)The prevalence of positive estrogen receptor (ER) expression among the participants was 51.11%, while the prevalence of positive progesterone receptor (PR) expression was 80.00%. The study observed that grade 3 tumor had the highest prevalence among participants at 44.44%. Grade 1 tumor was observed in 22.22% of participants, while grade 2 tumor was observed in 33.33% of the participants. This high prevalence of Grade 3 tumor was consistent with the high prevalence of serous epithelial tumors in the present study, and this finding was also supported by another older study.(29)Regarding the correlation of ER and PR expression with WHO grading of tumors, the study found that among the 31 cases of serous cystadenocarcinoma, 20 (64.52%) had a positive ER status, while none of the 8 cases of mucinous cystadenocarcinoma were positive for ER. Out of the 4 cases of endometrioid carcinoma, 2 (50.00%) were positive for ER, and none of the 2 cases of clear cell carcinoma were positive for ER. The difference in ER positivity between serous and mucinous cystadenocarcinoma, as well as other subtypes, was found to be statistically significant with a P-value of 0.001. In

conclusion, it was observed that ER positivity had a higher association with Grade 3 tumors. This correlation was supported by the findings of previous studies, where similar significant association (<0.05) was observed between ER positive expression and high grades of tumor.(19,29)In the context of PR expression, the study observed that the expression of PR was highest in grade 1 tumors, with 7 out of 10 cases (77.8%) expressing the protein. Meanwhile, only one patient each in the grade 2 and grade 3 categories (11.1% each) expressed PR. The statistical analysis revealed that this difference in PR expression between tumor grades was significant ( $p=0.001$ ), consistent with previous research findings.(19,30,31) The data from these studies provide compelling evidence that PR expression is strongly associated with low-grade tumors.Overall, these findings suggest that ER expression was significantly associated with serous carcinoma and high grade of diseases. PR was expressed in all tumors except clear cell carcinoma in variable numbers and was significantly associated with low grade tumors.

#### Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

## V. CONCLUSION

The study found that old age, post-menopausal status, higher CA-125 levels, and family history of malignant ovarian tumor were significant risk factors for the development of ovarian tumors. Serous cystadenocarcinoma was the most common histopathological diagnosis, and it was observed to be associated with ER positivity. The study also observed that Grade 3 tumors had a higher association with ER positivity. In contrast, PR expression was found to be associated with low-grade tumors, with the highest expression observed in Grade 1 tumors. The study provides valuable insights into the correlation between ER and PR expression with the WHO grading of ovarian tumors, and the results could be useful in devising targeted treatment strategies for patients with ovarian cancer.

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**Conflict of interest:**None

**Ethical approval:**The study was approved by the Institutional Ethics Committee



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