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Original Article

Pathology Section

Determining the Oestrogen and Progesterone Receptor Expression in Cases of Endometrial Carcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Endometrial carcinoma is the second most common female genital tract malignancy in India with a incidence rising globally. Hormone receptors are positive in 35-90% of endometrial carcinomas. Hormone therapy can be given to patients with hormone receptor positive tumours.

Aim: To determine whether Progesterone and Oestrogen Receptors (PR and ER) are most often expressed in endometrial cancer cases, and to correlate this expression with histopathologic features in these cases.

Materials and Methods: A cross-sectional study was conducted in the Department of Pathology, Government Medical College, Thrissur, Kerala, India, on 37 cases of endometrial carcinoma. ER and PR expression were assessed and correlated with histopathologic parameters in carcinoma endometrium.

Results: 75.6% of the patients were in the 51-70 age range. Grade I endometrioid cancer accounted for 24 (77.42%) of the 31 cases, grade II for 5 (16.13%) and grade III for 2 (6.45%). 19 (51.4%) of cases had ER positivity and 21 (56.8%) had PR positivity. While all grade III tumours were PR and ER negative, grade I tumours had 70.83% and 79.17% ER and PR positivity, respectively. While ER expression did not correlate negatively with grade (p-value=0.076), PR expression did (p-value=0.043). In 29.73% of patients, lymphocytic infiltrates were seen, and they had a strong correlation with the expression of ER and PR. All cases of papillary serous carcinomas (100%), mucinous carcinomas (100%), and clear cell carcinomas (100%), showed ER negative. Hormone receptor status did not significantly correlate with FIGO (The International Federation of Gynecology and Obstetrics) stage, lymphovascular emboli, or myometrial invasion.

Conclusion: Most of the endometrioid endometrial carcinomas showed ER and PR positivity, while all of the non endometrioid endometrial carcinomas were negative for both ER and PR. ER and PR were positive in most of the grade I tumours, whereas in the high-grade tumours, they were often negative. Immunoreactivity for PR had a stronger association with tumour grade, when compared to ER.

Keywords: Endometrial neoplasms, Hormone therapy, Uterine neoplasms

INTRODUCTION

Endometrial carcinoma is the most common malignancy of the female genital system in developed countries. In India, mainly in Kerala, it ranks as the second most common genital malignancy among women [1,2]. Bokhman JV, categorised endometrial carcinoma into two major types: type I (endometrioid) and type II (non endometrioid), based on endocrine and metabolic factors [3]. Subsequent studies have revealed distinct molecular genetic differences between these types [4]. Endometrioid carcinoma often arises from prolonged oestrogen exposure and is typically preceded by a premalignant lesion known as Endometrial Intraepithelial Neoplasia (EIN) or atypical endometrial hyperplasia [5]. Potischman N et al., found elevated serum oestrogen levels in patients with endometrioid carcinoma [6]. This type generally occurs in women aged 40-60 years and has a favourable prognosis postsurgery [7]. In contrast, type II endometrial carcinoma typically occurs in older women, without prior hyperestrogenism or EIN precursor. These tumours are usually poorly differentiated and have a poorer prognosis [8,9]. Serous Endometrial Intraepithelial Carcinoma (serous EIC) is a rare precursor to non endometrioid adenocarcinomas, like serous carcinoma [10,11]. Endometrioid carcinoma is the most common form of endometrial carcinoma, accounting for 80% of cases [12]. They are termed endometrioid due to their similarity to proliferative endometrium, while non endometrioid carcinomas include subtypes like serous, mucinous, clear cell, neuroendocrine, mixed, undifferentiated, and dedifferentiated carcinomas.

Similar to breast carcinomas, endometrioid carcinomas express hormone receptors. These receptors are positive in 35-90% of cases, with their absence potentially indicating advanced disease [13]. Oestrogen regulates endometrial carcinogenesis, countered by progesterone's differentiating effects via PR, promoting apoptosis and inhibiting invasion. Loss of ER-alpha and PR positivity correlates with decreased survival in endometrial carcinoma patients [3].

A subset of patients with advanced or recurrent endometrial cancer often does not respond to standard therapies, which are associated with significant side-effects. Many of these patients are elderly with co-morbidities, complicating treatment and increasing morbidity and mortality. There is significant potential to improve treatment outcomes by using prognostic and predictive markers to individualise therapy. Reliable biomarkers could help identify patients who might benefit from aggressive treatment versus those who could avoid toxic therapies, like approaches in breast cancer treatment [3].

This study aims to assess the histomorphological types of endometrial carcinoma, evaluate ERR and PR expression in these cases, and correlate ER and PR expression with histopathologic parameters.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Pathology at Government Medical College, Thrissur, Kerala, India on 37 cases. The study period spanned 18 months, from February 1, 2014, to July 31, 2015. The study was approved by Institutional Ethics Committee (IEC). All procedures followed were in accordance with the ethical standards of the responsible committee. The study population consisted of all hysterectomy specimens of carcinoma endometrium received in the Department of Pathology during the study period.

Inclusion criteria: All hysterectomy specimens of carcinoma endometrium were included in the study.

Exclusion criteria: Endometrial curetting samples of carcinoma endometrium and hysterectomy specimens with other pathological conditions were excluded from the study.

Study Procedure

Gross examination of the hysterectomy specimens of endometrial carcinoma was performed, and the findings were documented. Tissue samples were taken and routinely fixed, processed, and embedded in paraffin. Four-micron thick sections were cut and stained with Haematoxylin and Eosin (H&E) for microscopic assessment. Histological grading, myometrial and lymphovascular invasion, and prominent lymphocytic infiltrates were evaluated. The FIGO grading [14] system for endometrial cancer was the classification scheme utilised for grading in this study. Immunohistochemical analysis was performed on serial sections using an immunoenzymatic soluble complex method. The antibodies used were Monoclonal Mouse Antihuman ER Alpha (Clone 1D5, Ready to Use, Dako Autostainer/ Autostainer Plus) and Monoclonal Mouse Antihuman PR (Clone PgR 636, Ready to Use, Dako Autostainer/Autostainer Plus). The immunostaining of ER and PR was determined by calculating the positivity index (PI), representing the percentage of positive cells per 1000 cells counted on a 40× power field.

Cases with more than 10% of neoplastic cells showing nuclear positivity were considered positive. The results were scored accordingly. The expression of ER and PR and their association with histopathologic parameters, such as tumour type, histologic grade, mitosis, prominent lymphocytic infiltrate, lymphovascular emboli, myometrial invasion, and FIGO stage, were analysed. Several clinical and pathological features were evaluated, such as the tumour's grade, age distribution, myometrial invasion, lymphovascular invasion, and FIGO staging. The study included immunohistochemical analysis with antibodies against PR and ER. The staining intensity was categorised using the ER and PR expression grading system.

Scoring of ER, PR Expression [15]

Score 0: Negative ≤10% of neoplastic cells show nuclear positivity

Score 1: 11-25% of neoplastic cells show nuclear positivity

Score 2: 26-50% of neoplastic cells show nuclear positivity

Score 3: 51-75% of neoplastic cells show nuclear positivity

Score 4: >75% of neoplastic cells show nuclear positivity

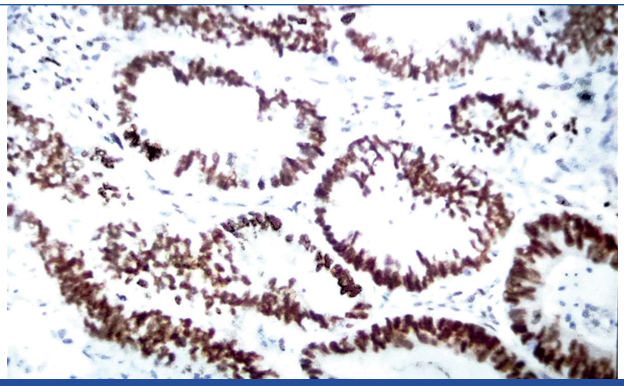
STATISTICAL ANALYSIS

Data were collected and entered a Microsoft Office Excel 2007 sheet. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 16.0 The tests used included the Chi-square test, Kendall's tau-b correlation coefficient, and Spearman's correlation coefficient.

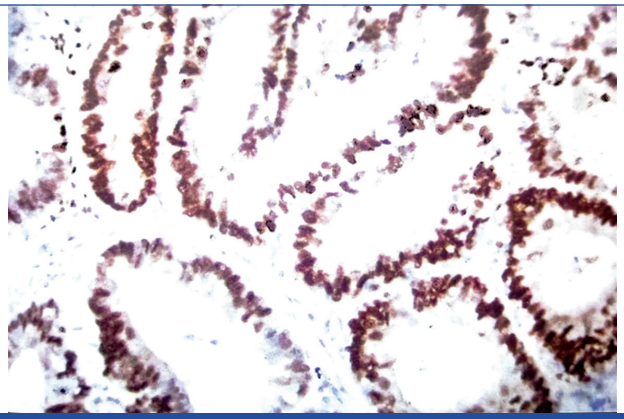
RESULTS

The patients' ages ranged from 38 to 85 years, with a mean age of 56.65 for endometrioid carcinomas and 59.17 for non endometrioid carcinomas. Immunohistochemical staining of the tissue sections revealed Endometrioid EC grade 1 ER and PR positivity (score 4) [Table/Fig-1,2]; grade 3 ER and PR negativity (score 0) [Table/Fig-3,4]. In clear cell carcinoma endometrium the IHC staining was seen to be negative for both ER and PR (score 0) [Table/Fig-5,6].

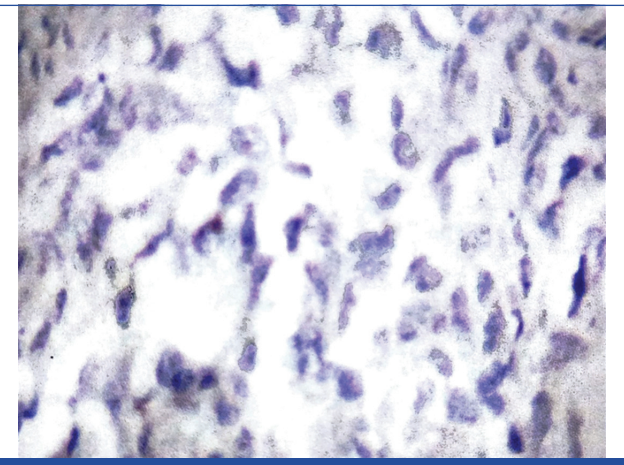
Most patients (75.6%) were in the 51-70 age group [Table/Fig-7]. Among the 31 cases of endometrioid carcinomas, 24 (77.42%) were grade I tumours, 5 (16.13%) were grade II tumours, and 2 (6.45%) were grade III tumours. Lymphocytic infiltrates, lymph vascular emboli and myometrial invasion are shown in [Table/Fig-8]. The pattern of ER and PR staining in 37 cases of endometrial cancer is shown in [Table/Fig-9]. Out of the 37 cases, the distribution of score (0-4) for ER and PR is shown in [Table/Fig-10]. The distribution of ER staining across various tumour types in 37 endometrial cancer



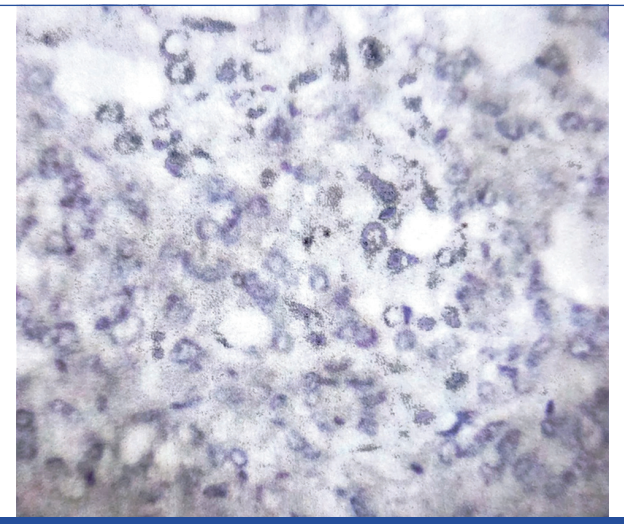
[Table/Fig-1]: Endometrioid endometrial carcinoma grade 1 showing ER positivity, score 4 (400x).



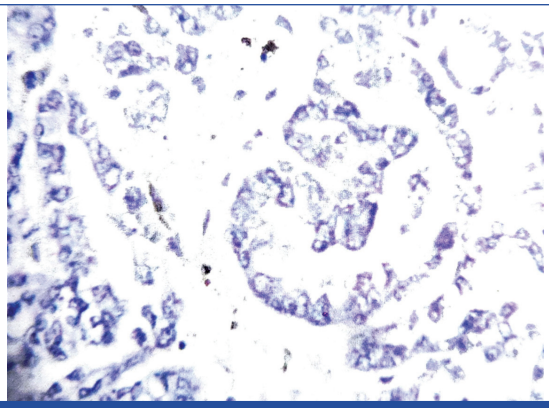
[Table/Fig-2]: Endometrioid endometrial carcinoma grade 1 showing PR positivity, score 4 (400x).



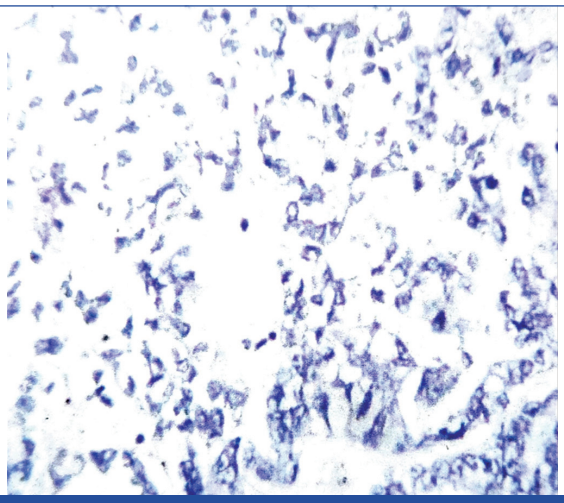
[Table/Fig-3]: Endometrioid endometrial carcinoma grade 3 showing ER negativity, score 0 (400x).



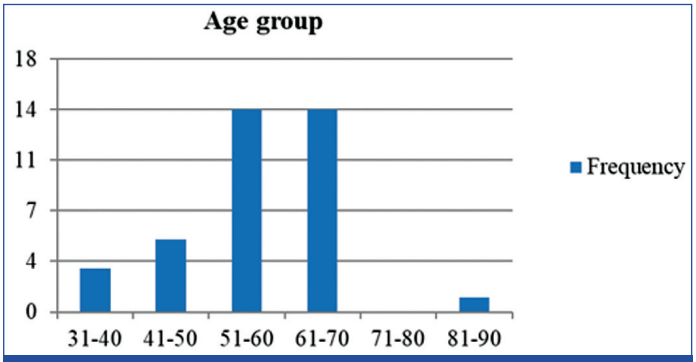
[Table/Fig-4]: Endometrioid endometrial carcinoma grade 3 showing PR negativity, score 0 (400x).



[Table/Fig-5]: Clear cell carcinoma endometrium (IHC; (400x) showing ER negativity.



[Table/Fig-6]: Clear cell carcinoma endometrium (IHC; (400x) showing PR negativity.



[Table/Fig-7]: Age distribution of the cases in the study (total n=37).

Parameters	n (%)
Grade I tumours	24 (77.42)
Grade II tumours	5 (16.13)
Grade III tumours	2 (6.45)
Lymphocytic infiltrates	11 (29.73)
Lymphovascular emboli	4 (10.8)
Myometrial invasion	
• Less than half of myometrium	19 (51.4)
• More than half of myometrium	18 (48.6)

[Table/Fig-8]: Summary of findings in endometrioid carcinomas analysis.

Parameters	ER staining n (%)	PR staining n (%)
Negative	18 (48.6)	16 (43.2)
Positive	19 (51.4)	21 (56.8)

[Table/Fig-9]: Comparison of ER and PR staining in endometrioid carcinomas.

cases is shown in [Table/Fig-11]. Twelve instances (38.7%) of the endometrioid carcinomas were ER negative, whereas nineteen cases (61.3%) were ER positive. Interestingly, ER negative was present in every case of mucinous, clear cell, and papillary serous carcinoma. In general, endometrioid carcinomas tended to be ER positive. The distribution of PR staining across different tumour types in 37 endometrial cancer cases is shown in [Table/Fig-12]. Ten instances (32.3%) of endometrioid carcinomas were PR negative, whereas 21 cases (67.7%) were PR positive. Remarkably, PR negativity was present in every case of mucinous, clear cell, and papillary serous carcinomas. Most PR positive cases were found in endometrioid carcinomas. The ER and PR positivity rates for various stages of endometrial cancer are shown in [Table/Fig-13]. 17 cases (70.83%) and 19 cases (79.17%) of the Grade I cancers (n=24) were ER positive and PR positive, respectively. Forty percent of the Grade II tumours (n=5) were PR and ER positive. Remarkably, every Grade III tumour (n=2) exhibited negative ER and PR results. This suggests a possible correlation between the expression of hormone receptors and tumour grade. The scatter plot [Table/Fig-14] shows a weak negative correlation (R^2=0.103) between ER score and grade in endometrioid carcinomas, suggesting higher ER scores are slightly associated with lower grades. However, there was no statistically significant correlation between grade and ER score (Kendall's tau_b correlation coefficient=1.000, p-value=0.076), indicating ER score alone is not a strong predictor of carcinoma grade. In endometrioid carcinomas, the scatter plot demonstrates a negative connection (R^2=0.136) between the PR score and grade, suggesting that lower grades are linked to higher PR scores. As demonstrated in [Table/Fig-15], this correlation was statistically significant (Kendall's tau_b correlation coefficient=1.000, p-value=0.043), indicating that PR score is a useful predictor of carcinoma grade. As can be seen in [Table/Fig-16], out of 26 cases where there is no lymphocytic infiltration, 16 are ER negative and 15 are PR negative. There are 11 patients with a lymphocytic infiltration, of which 10 are PR positive and 9 are ER positive. There are 37 cases in all, 18 of which are ER

Score	ER frequency n (%)	PR frequency n (%)
0	18 (48.7)	16 (43.2)
1	3 (8.1)	3 (8.1)
2	4 (10.8)	2 (5.4)
3	1 (2.7)	4 (10.8)
4	11 (29.7)	12 (32.4)

[Table/Fig-10]: Comparison of ER and PR scores in endometrioid carcinomas.

Tumour type	ER negative	ER positive	Total
Endometrioid	12	19	31
Papillary serous	4	0	4
Clear cell	1	0	1
Mucinous	1	0	1
Total	18	19	37

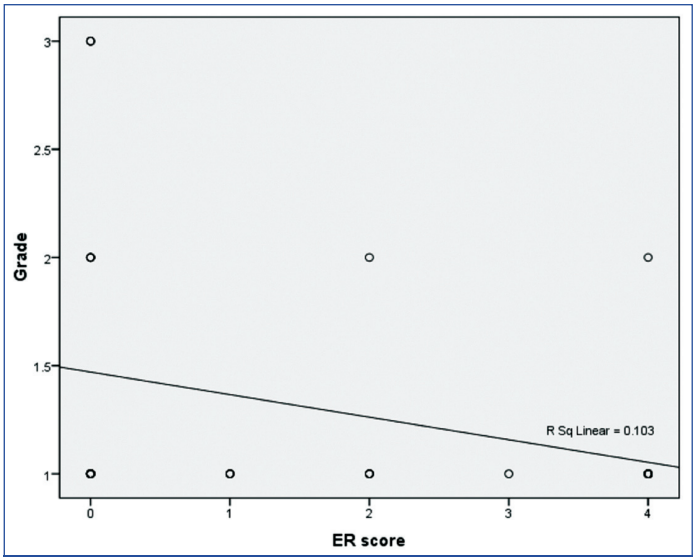
[Table/Fig-11]: Distribution of ER staining by tumour type.

Tumour type	PR negative	PR positive	Total
Endometrioid	10	21	31
Papillary serous	4	0	4
Clear cell	1	0	1
Mucinous	1	0	1
Total	16	21	37

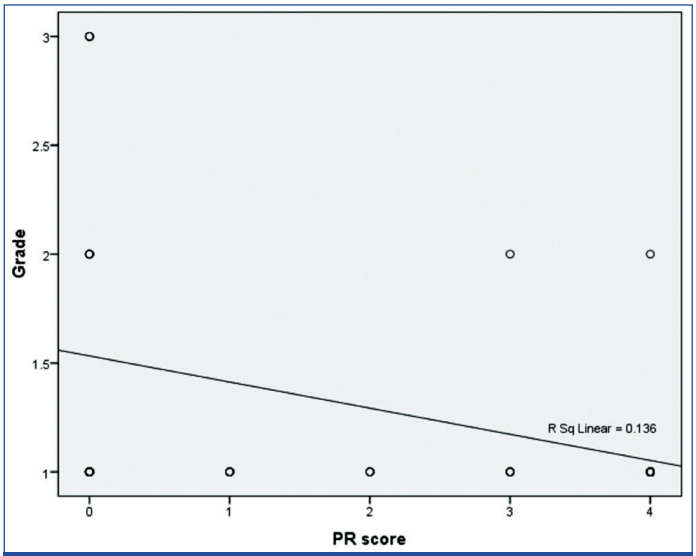
[Table/Fig-12]: Distribution of PR staining by tumour type.

Grade	ER negative	ER positive	PR negative	PR positive	Total
1	7	17	5	19	24
2	3	2	3	2	5
3	2	0	2	0	2
Total	12	19	10	21	31

[Table/Fig-13]: Grade of endometrial carcinoma and ER and PR staining.



[Table/Fig-14]: Scatter plot and linear regression analysis of ER score and grade in endometrioid carcinomas (Kendall's tau_b Correlation).



[Table/Fig-15]: Scatter plot and linear regression analysis of PR score and grade in endometrioid carcinomas (Kendall's tau_b Correlation)

Prominent lymphocytic Infiltrate	ER negative	ER positive	PR negative	PR positive	Total
Absent	16	10	15	11	26
Present	2	9	1	10	11
Total	18	19	16	21	37

[Table/Fig-16]: Association between lymphocytic infiltrate and hormone receptor status in endometrioid carcinomas.

negative and 21 of which are PR positive.The association between hormone receptor status (PR and ER) and lymphovascular emboli in endometrioid carcinomas is shown in [Table/Fig-17]. It is noteworthy that out of 33 cases without lymphovascular emboli, 18 have PR positive and 15 have PR negative results. Conversely, of the four cases involving lymphovascular emboli, three are ER positive and one is ER negative. The relationship between myometrial invasion and hormone receptor status (ER and PR) in endometrioid carcinomas is shown in [Table/Fig-18]. Remarkably, eight of the 19 instances with less than half of the myometrial invasion are PR negative and 11 are PR positive. Eight of the 18 cases with over half of the myometrial invasion, however, are ER negative, while the remaining 10 are ER positive. The association between the FIGO stage and the hormone receptor status (ER and PR) in endometrioid carcinomas is shown in [Table/Fig-19]. Notably, distinct patterns in hormone receptor expression appear at different FIGO stages. For example, in stage Ia, there are nine ER positive cases and 11 PR positive instances; in stage II, there are five ER negative cases

Lymphovascular emboli	ER negative	ER positive	PR negative	PR positive	Total
Absent	17	16	15	18	33
Present	1	3	1	3	4
Total	18	19	16	21	37

[Table/Fig-17]: Association between lymphovascular emboli and hormone receptor status in endometrioid carcinomas.

Myometrial invasion	ER negative	ER positive	PR negative	PR positive	Total
<half of myometrium	10	9	8	11	19
>half of myometrium	8	10	8	10	18
Total	18	19	16	21	37

[Table/Fig-18]: Association between myometrial invasion and hormone receptor status in endometrioid carcinomas.

FIGO stage	ER negative	ER positive	PR negative	PR positive	Total
Ia	4	9	2	11	13
Ib	5	6	5	6	11
II	5	1	5	1	6
IIIa	2	0	2	0	2
IIIb	2	2	2	2	4
IVa	0	1	0	1	1
Total	18	19	16	21	37

[Table/Fig-19]: Association between FIGO stage and hormone receptor status in endometrioid carcinomas.

and five PR negative cases. There was no statistically significant correlation between FIGO stage and ER score (Kendall's correlation coefficient=1.000, p value=0.360) and between FIGO stage and PR score (Kendall's correlation coefficient=1.000, p value=0.120).

DISCUSSION

Endometrial Carcinoma (EC) is a prevalent gynaecological malignancy with rising incidence and decreasing age of onset. It is more common in developed countries but has similar mortality rates worldwide. EC is classified into oestrogen-dependent (type I, mostly endometrioid) and non oestrogen-dependent (type II, including serous and clear cell) carcinomas [16]. EC is a major cancer worldwide, where the status of hormone receptors is a key factor in the characterisation and prognosis of the tumour. Oestrogen is seen as playing a role in the development of endometrial cancer, emphasising the need to assess the expressions of ER and PR. The present study found that 51.4% of EC cases were ER positive, while 56.8% were PR positive. The results align with the study done by Kounelis S et al., where ER positive cases were found in 54.1% and PR positive cases in 54.9%, suggesting a comparable pattern of hormone receptor expression in EC [17]. This constancy strengthens the trustworthiness of ER and PR as indicators in endometrial cancer. Stoian SC al., found higher rates of ER positivity (86.3%) and PR positivity (81.1%) as compared to present study. This variation might be due to differences in the study groups, such as the ratios of endometrioid to non endometrioid and low to high-grade tumours [18]. These variances highlight the importance of standardised criteria and study populations when evaluating hormone receptor status in EC. A study done by Giuffrè G et al., investigated the expression of hormone receptors and discovered strong correlations between lactoferrin expression and ER, PR, as well as proliferation markers such as Ki-67 and AgNOR. This research highlighted the importance of hormone receptor status in predicting outcomes for endometrial carcinomas [19].

In EC cases, ER positivity was seen in 61.3% and PR positivity in 67.7% in the present study. Maniketh I et al., reported similar rates, with ER positivity found in 73.3% and PR positivity in 84.4% of endometrioid carcinoma cases [13]. These findings indicate that endometrioid ECs may be more inclined to show these hormone

receptors, potentially influencing treatment choices and prognostic evaluations. This study showed that ER and PR were absent in all non endometrioid EC cases which was found to be in concordance with previous study done by Deligdisch L et al., demonstrating negative hormone receptor status in non endometrioid ECs [20]. This highlights the unique biological characteristics of non endometrioid ECs and their absence of hormone receptor expression, affecting potential treatment strategies.The present study found that 70.83% of Grade I tumours were ER positive, whereas all Grade III tumours were ER negative when it comes to tumour grade. In Grade I tumours, 79.17% tested positive for PR, while all Grade III tumours tested negative. This pattern indicates a negative correlation between tumour grade and hormone receptor positivity. Stoian SC et al., also discovered that tumours of a lower grade showed increased ER and PR positivity, but their research revealed a significant correlation between grade and receptor positivity, in contrast to the present study [18]. This variation could suggest that other factors also play a role in determining hormone receptor expression, apart from just tumour grade.

In the present study, a strong correlation was found between the presence of prominent lymphocytic infiltrate and higher ER (81.8%) and PR (90.9%) positivity. Jung IK et al., [21] corroborated this discovery by associating high lymphocytic infiltrate with lower histologic grade, while Stoian SC et al., [19] found higher ER and PR immunoreactivity in low-grade tumours. These findings indicated that a potent immune response might be associated with more positive tumour features and increased hormone receptor levels. In relation to lymphovascular invasion, the present research did not discover a notable connection with ER or PR positivity, which was consistent with the results of Maniketh I et al., who similarly found no significant correlation between lymphovascular invasion and hormone receptor status [13]. This suggests that although lymphovascular invasion is important for the spread of tumours and for predicting outcomes, it may not have a direct effect on hormone receptor levels. In the current study, there was also no notable association observed between myometrial invasion and ER or PR positivity, aligning with the outcomes of a study by Maniketh I et al., that showed similar results. This implies that hormone receptor expression is not greatly affected by myometrial invasion, underscoring the importance of considering other pathological factors when assessing hormone receptor status.

Mylonas I highlighted the importance of ERα and ERβ in predicting the prognosis of endometrioid adenocarcinomas, showing that increased ER levels are linked to improved clinical results [22]. This was consistent with the finding of the present study that lower-grade tumours, which usually have a better prognosis, tend to have higher ER positivity. A study in a Nigerian tertiary hospital by Odetola SS et al., reported ER and PR positivity rates of 29.5% and 18.2%, respectively. Their research did not establish a noteworthy link between hormone receptor expression and tumour grade, aligning with the conclusions of the current study [23]. This highlights the differences in hormone receptor expression among various populations and emphasises the importance of conducting studies specific to each region to gain a better understanding of these trends. van Weelden J al., suggested certain thresholds for ER and PR expressions to categorise EC into high-risk (0-10% positivity), intermediate-risk (20-80% positivity), and low-risk (90-100% positivity) groups in terms of clinical outcomes [24]. This categorisation emphasises the significance of accurately establishing hormone receptor threshold values for predicting disease-specific and disease-free survival in patients with EC.

Hence, the levels of ER and PR expression in endometrial cancer can differ greatly due to various factors like tumour characteristics and the extent of lymphocytic infiltration. Establishing universal thresholds for hormone receptor positivity can improve the assessment and treatment of EC. Further studies are needed to confirm the results in bigger groups and investigate the molecular pathways that regulate hormone receptor expression in EC. Also, creating standardised thresholds for hormone receptor positivity will improve the practicality of using these biomarkers to treat EC.

Limitation(s)

The small sample size was the limitation of the study.

CONCLUSION(S)

The study highlights the varying hormone receptor expression and its potential prognostic importance, specifically focusing on ER and PR positivity. Accurate identification of hormone receptor status in EC is essential for treatment decisions and prognostic assessments in a clinical setting. Acknowledging varied ER and PR expression profiles among various tumour grades and histological subtypes underscores the importance of tailored treatment approaches.

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