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Immunoexpression of hormonal receptors in phyllodes tumors

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Abstract

Background: Phyllodes tumor (PT) is a rare fibroepithelial neoplasm of the breast characterized by biphasic proliferation of epithelial and stromal components. The role of hormonal receptors such as estrogen receptor (ER) and progesterone receptor (PR) in PT remains unclear, particularly in relation to tumor grade and stromal behavior. **Objective**: This study aimed to evaluate the immunoexpression of ER and PR in both stromal and epithelial components of phyllodes tumors and analyze their correlation with histologic grade (benign, borderline, and malignant). **Methods:** A retrospective cross-sectional study was conducted on 49 archived FFPE samples of phyllodes tumors diagnosed at the Department of Pathology, Universitas Jambi Hospital. Two samples were excluded due to poor tissue quality, leaving 47 cases for immunohistochemical (IHC) evaluation. ER and PR expression were assessed semi-quantitatively in epithelial and stromal cells, and correlations with tumor grade were analyzed using Chi-square and Spearman tests. **Results:** Among 47 evaluable cases, 28 (59.6%) were benign, 12 (25.5%) borderline, and 7 (14.9%) malignant. ER and PR were expressed predominantly in epithelial cells, with low positivity in stromal cells. No significant correlation was found between ER/PR expression and histologic grade ($p > 0.05$). **Conclusion:** Hormonal receptor expression does not correlate significantly with histologic grade of phyllodes tumors, suggesting a limited role of ER and PR in tumor progression.

Keywords: immunoexpression; horomonal receptors; pyhllodes tumors.

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INTRODUCTION

Phyllodes tumors (PTs) are uncommon fibroepithelial breast neoplasms characterized by a biphasic proliferation of epithelial and stromal components. They account for less than 1% of all breast tumors and approximately 2–3% of all fibroepithelial lesions worldwide. Reported incidence varies geographically, with higher proportions noted in Asian populations compared to Western cohorts. In Indonesia, PTs are sporadically reported, mostly from tertiary centers, but often underrecognized in national registries due to coding overlap with fibroadenomas.

Histologically, PTs are graded as benign, borderline, or malignant based on stromal cellularity, atypia, mitotic activity, stromal overgrowth, and tumor margins. Their clinical behavior depends largely on the stromal component; while benign PTs behave indolently, malignant forms may recur or metastasize. Surgery with wide excision remains the mainstay of treatment.1

The role of hormonal receptors such as ER and PR in PT pathogenesis is not clearly established. Unlike in breast carcinoma, where ER/PR serve as major predictive markers for endocrine therapy, their expression in PTs has shown inconsistent patterns—typically high in epithelial cells but low in stromal cells.2,3

Understanding hormonal receptor expression in PT is crucial to elucidate possible involvement in tumor biology, particularly through epithelial–mesenchymal transition (EMT), a process in which epithelial cells acquire mesenchymal features and increased motility. The crosstalk between ductal epithelium and stromal fibroblasts may, through hormonal signaling, contribute to stromal overgrowth and progression from benign to malignant PTs.

Clinically, identifying hormonal receptor status could support prognostic stratification and guide future therapeutic considerations, particularly for recurrent or metastatic PTs where systemic options remain limited.4-6 This study aimed to evaluate the immunoexpression of ER and PR in both stromal and epithelial components of phyllodes tumors and analyze their correlation with histologic grade (benign, borderline, and malignant).

METHODS

Study design and setting

A retrospective cross-sectional study analyzed 49 formalin-fixed paraffin-embedded (FFPE) phyllodes tumor samples diagnosed at the Department of Pathology, Universitas Jambi Hospital were obtained from the Pathology Laboratory archives (2020–2025) Two samples were excluded for poor preservation, leaving 47 samples for analysis.

Population, samples and sampling

The study population consisted of all patients diagnosed histologically with phyllodes tumor of the breast whose specimens were archived at the Department of Histopathology, Faculty of Medicine and Health Sciences, Universitas Jambi, between 2018 and 2024. A total of 49 cases were identified from pathology records. Two cases were excluded due to inadequate tissue preservation or incomplete immunohistochemical data, resulting in 47 eligible cases included in the analysis. The sampling technique used was total sampling (consecutive sampling), including all cases meeting the diagnostic and quality criteria during the study period.

Instruments and criteria
The primary instrument used in this study was the immunohistochemical (IHC) staining method, employed to evaluate the expression of estrogen receptor (ER) and progesterone receptor (PR) in both epithelial and stromal components of phyllodes tumors.

Procedure and data collection
After confirmation, representative tissue blocks containing both epithelial and stromal areas were selected for immunohistochemical (IHC) staining. Sections of 4 μm thickness were cut and mounted on poly-L-lysine-coated slides, followed by deparaffinization, rehydration, and antigen retrieval. Primary antibodies against ER (clone 1D5) and PR (clone PgR 636) were applied according to standardized protocols, and detection was performed using the avidin–biotin–peroxidase complex (ABC) method. Positive (normal breast tissue) and negative controls were included in each staining run to ensure reliability. The stained slides were then examined under a light microscope at ×400 magnification. The percentage of positively stained nuclei was determined separately for epithelial and stromal components in each tumor. Data were entered into a database and grouped by histologic grade.

Statistical analysis
Statistical analysis was conducted using Spearman's rank correlation test to assess the relationship between ER/PR expression and tumor grade. Results were expressed as correlation coefficients (ρ) with corresponding p-values, and significance was determined at $p < 0.05$.

*Ethical concideration*s
This study was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Universitas Jambi, under Ethical Clearance No. 2552/UN.21.8/PT.01.04/2025.

RESULTS
A total of 47 patients with histologically confirmed phyllodes tumors were included in this study (table 1). The mean age of patients was 37.10 ± 11.06 years (range 15–57 years). The majority of tumors were located in the left breast (56.1%), with an average tumor size of 12.5 cm (range 3.01–27.0 cm). Most cases were benign (59.6%), followed by borderline (25.5%) and malignant (14.9%).

Table 1. Clinicopathologic characteristic.

Variable	N=47
Age (yrs)	
Mean±Std	37.10±11.06
Median	40.21
Range (min-max)	15.00-57.00
Location	
Right	18(39.3%)
Left	29 (56.1%)
Size (cm)	
Mean±Std	12.29±6.257
Median	12.5
Range (min-max)	3.10-27.00

Variable	N=47
Tumor Type	
Soliter	40(85.1%)
Multiple	7(14.9%)
Diagnosis	
Malignant PT	7(14.9%)
Borderline PT	12(25,5%)
Benign PT	28(59.6%)

The immunohistochemical analysis demonstrated that estrogen receptor (ER) and progesterone receptor (PR) expression were predominantly localized within the epithelial component of phyllodes tumors, while the stromal component showed much lower positivity rates (table 2). Among the benign group (n = 28), epithelial ER positivity was observed in 75.0% of cases, whereas stromal ER expression was noted in only 21.4%. Similarly, epithelial PR positivity was detected in 64.3%, while stromal PR was found in 17.9%. In the borderline group (n = 12), ER expression remained relatively high in the epithelial component (75.0%) but decreased in stromal cells (16.7%). PR positivity in epithelial cells reached 66.7%, compared to only 8.3% in stromal cells. In malignant cases (n = 7), epithelial ER and PR expression were 71.4% each, whereas stromal ER and PR were both 14.3%.

Table 2. Stromal component.

Tumor Grade	ER Positive (Epithelial)	ER Positive (Stromal)	PR Positive (Epithelial)	PR Positive (Stromal)
Benign (n=28)	75.0%	21.4%	64.3%	17.9%
Borderline (n=12)	75.0%	16.7%	66.7%	8.3%
Malignant (n=7)	71.4%	14.3%	71.4%	14.3%

Statistical analysis using Spearman's rank correlation showed no significant association between ER or PR immunoexpression and histologic grade of phyllodes tumors in both epithelial and stromal components ($p > 0.05$) (table 3).

Table 3. Correlation between ER/PR immunoexpression and histologic grade.

Variable	Spearman's ρ	p-value
ER (Epithelial) vs Grade	−0.12	0.76
ER (Stromal) vs Grade	−0.28	0.41
PR (Epithelial) vs Grade	0.10	0.81
PR (Stromal) vs Grade	−0.16	0.68

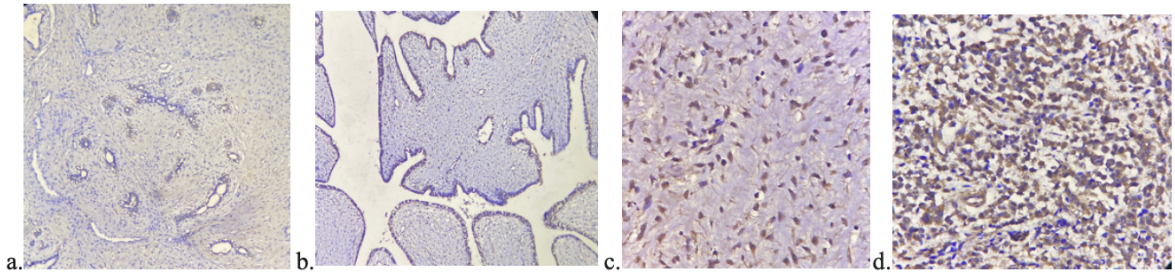

Figure 1. Immunohistochemical staining for estrogen receptor (ER) and progesterone receptor (PR) in phyllodes tumors.(A) Stromal component showing weak or absent ER staining (×100). (B) Epithelial

PR-positive nuclei with diffuse brown nuclear reactivity (×100). C) Epithelial ER-positive nuclei showing strong brown nuclear staining (×400). (D) Epithelial ER-positive nuclei showing strong brown nuclear staining (×400).

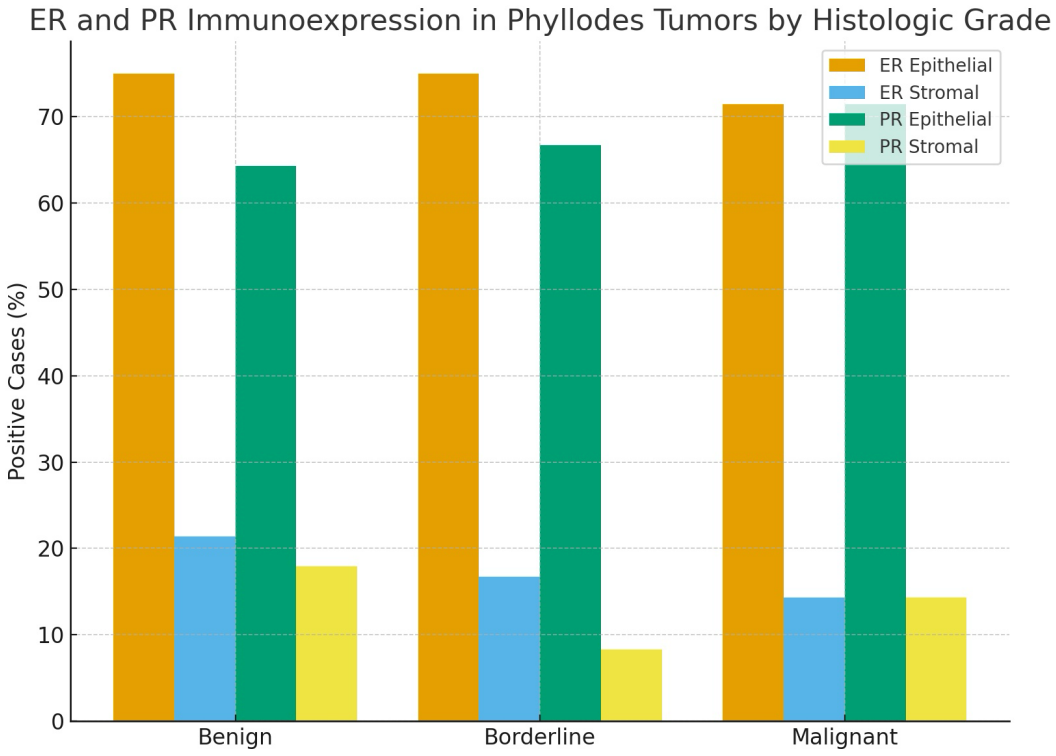

Figure 2. ER and PR immunoexpression in phyllodes tumors by histologic grade.

DISCUSSION

This study investigated the immunoexpression of estrogen receptor (ER) and progesterone receptor (PR) in both epithelial and stromal components of phyllodes tumors and examined the statistical correlation between hormonal receptor status and histologic grade (benign, borderline, malignant). Overall, ER and PR positivity was consistently higher in the epithelial component than in the stromal component across all tumor grades, and there was no statistically significant correlation between ER or PR expression and histologic grade based on Spearman correlation analysis (all $p > 0.05$). These findings indicate that classical hormonal signaling, as measured by ER and PR immunohistochemistry, is unlikely to be a key driver of stromal progression or grade escalation in phyllodes tumors.

Our findings are aligned with multiple studies published in the last decade that have evaluated hormonal receptor expression in phyllodes tumors and its clinicopathological significance. Several studies have consistently shown that ER and PR are usually expressed in the benign ductal epithelium entrapped within the tumor, while the neoplastic stromal compartment—which actually determines the histologic grade—often shows weak, focal, or even absent expression of these receptors.7,8 In particular, Wang et al. (2021) reported that while epithelial ER/PR expression is common, stromal ER and PR staining tends to be low and does not stratify tumors into benign, borderline, or malignant categories in a clinically meaningful way.9 Similarly, Karim et al. (2021) found that hormonal receptor immunoprofiles did not reliably predict local recurrence or aggressive histologic behavior, even in malignant phyllodes tumors.10

In our dataset, epithelial ER was positive in approximately 71–75% of cases across all grades, and epithelial PR was positive in roughly 64–71%. By contrast, stromal ER and PR expression was much lower (mostly in the range of ~14–21% for ER stromal and ~8–18% for PR stromal, depending on grade), and this stromal expression did not significantly increase or decrease in a stepwise fashion from benign to borderline to malignant. These proportions are in close agreement with recent series describing that the stromal component of phyllodes tumors is generally hormone-receptor poor, even in higher-grade lesions. The lack of a monotonic trend across grades in our cohort was confirmed quantitatively: Spearman's ρ for ER (stromal) vs grade was −0.28 ($p = 0.41$), and for PR (stromal) vs grade was −0.16 ($p = 0.68$), indicating only a weak, non-significant inverse tendency. This weak, statistically non-significant association supports the interpretation that increasing histologic grade is not simply the result of progressive loss or gain of ER/PR-driven signaling in stromal cells.

The implication of this pattern is biologically important. The malignant potential of phyllodes tumors is thought to reside predominantly in the stromal (mesenchymal) compartment, which is graded based on stromal cellularity, atypia, mitotic activity, stromal overgrowth, and tumor margins. High-grade (malignant) phyllodes tumors demonstrate sarcomatous stromal proliferation that can recur locally and, in some cases, metastasize hematogenously. If ER/PR signaling were a major driver of stromal transformation, one might expect a strong correlation between stromal ER/PR expression and tumor grade, or at least a distinct shift in receptor status between benign and malignant categories.11-15 Our results did not show such a relationship. This is in line with more recent molecular studies over the past 10 years, which increasingly suggest that stromal progression in phyllodes tumors is driven primarily by genetic and proliferative alterations—such as MED12 mutations, TERT promoter mutations, increased Ki-67 index, p53 overexpression, and EGFR pathway activation—rather than by classical estrogen/progesterone signaling.16-18

This concept links directly to epithelial–mesenchymal transition (EMT) biology. Contemporary models of phyllodes tumor progression propose that the stromal compartment undergoes a form of "activation," acquiring more aggressive, sarcomatous features and proliferative capacity that underlie the borderline and malignant categories. EMT-like stromal remodeling has been hypothesized to result from paracrine signaling and genomic instability within the stromal cells, rather than direct hormonal stimulation.15,19,20 Our findings reinforce that view: although ER and PR are present in the epithelial component (which morphologically resembles benign breast ducts), they are not strongly and consistently expressed in the stromal component that dictates grade. Therefore, ER/PR status in the epithelium may simply reflect baseline breast parenchymal biology, whereas stromal transformation toward borderline or malignant phenotype appears to be governed by non-hormonal, proliferation-related, and genetic mechanisms.

Several studies in the last decade have also explored whether hormonal receptor status could have therapeutic or prognostic value in phyllodes tumors. Clinical management of phyllodes tumors, including malignant phyllodes tumors, remains primarily surgical: wide local excision with clear margins is the standard of care for all grades, and margin status is still considered one of the most important predictors of local recurrence.21,22 While small case reports have speculated about the use of anti-estrogen (endocrine) therapy in metastatic malignant phyllodes tumors, these attempts are not supported by consistent stromal ER/PR expression or by robust outcome data. Our present results support the cautious consensus from recent literature: because the stromal compartment (the clinically relevant driver) is largely

ER/PR negative or only weakly positive, routine endocrine therapy targeting ER/PR cannot currently be recommended as an evidence-based adjuvant or systemic treatment in phyllodes tumors, even in malignant cases. Another relevant point is prognostication. Some authors in the past decade have attempted to propose risk stratification schemes for malignant phyllodes tumor that incorporate histologic grade, stromal overgrowth, margin status, and sometimes proliferative markers such as Ki-67 or p53.22 In these models, ER/PR expression does not consistently emerge as an independent predictor of recurrence or metastasis. Our findings are concordant with that trend: ER and PR were not significantly associated with tumor grade, suggesting limited utility as standalone prognostic biomarkers.23

Taken together, the results of this study confirm and extend what has been reported in the last 10 years: ER and PR are mainly epithelial, not stromal, in phyllodes tumors; stromal ER/PR expression is generally low and does not correlate significantly with histologic grade ($p > 0.05$); the biological "escalation" from benign to malignant phyllodes tumor likely reflects stromal genomic alterations, high proliferative index, and features consistent with EMT-like stromal activation, rather than a shift in estrogen/progesterone signaling; and clinically, surgical excision with adequate margins remains the most reliable management strategy, and endocrine manipulation based purely on ER/PR status is not supported by current evidence.

Despite some limitations, including retrospective design and sample size, our findings contribute additional evidence from an Indonesian academic center to the international body of literature from the last decade, reinforcing the conclusion that hormonal receptor immunoexpression is not a reliable marker of grade or aggressiveness in phyllodes tumors. In combination with recent molecular work, this supports a biologic model in which stromal evolution and EMT-like transformation rather than hormone receptor driven signaling drive the malignant potential of phyllodes tumors.24,25

CONCLUSIONS

These findings indicate that hormonal receptor activity, as reflected by ER and PR immunostaining, does not play a major role in stromal transformation or malignant progression of phyllodes tumors. Instead, tumor behavior is likely governed by molecular and proliferative mechanisms rather than classical hormonal pathways.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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DECLARATION OF ARTIFICIAL INTELLIGENCE USE

We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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