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Original Research Paper

Pathology

PROGNOSTIC SIGNIFICANCE OF ER/PR AND HER2/NEU PROFILES ACROSS HISTOLOGICAL GRADES OF BREAST CARCINOMA

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ABSTRACT

Background: Breast carcinoma is a heterogeneous disease in which histological grade and molecular receptor status ER, PR, and HER2/neu play essential roles in prognosis and therapeutic decision-making. Understanding the interaction between tumour grade and receptor expression is crucial for individualized management. **Aim:** To evaluate the prognostic significance of ER, PR, and HER2/neu receptor expression across different histological grades of breast carcinoma. **Methods:** A cross-sectional observational study was conducted on 30 histologically confirmed cases of invasive breast carcinoma at a tertiary-care hospital. Tumours were graded using the Nottingham modification of the Scarff-Bloom-Richardson system. Immunohistochemistry for ER, PR, and HER2/neu was performed following ASCO-CAP guidelines. Associations between receptor status, molecular subtype, and histological grade were analysed using chi-square tests, relative risks (RR), and significance levels ($p < 0.05$ considered significant). **Results:** ER and PR positivity were observed in 53.3% and 43.3% of cases, respectively, while HER2/neu overexpression occurred in 60%. ER-negative (50%) and PR-negative (52.9%) tumours showed a higher proportion of Grade III lesions compared with their receptor-positive counterparts, with PR negativity demonstrating a statistically significant association (RR 3.44, $p = 0.034$). HER2-positive tumours exhibited a threefold higher risk of Grade III histology (RR 3.00), approaching significance ($p = 0.063$). Luminal A subtype displayed the most favourable prognostic pattern, whereas HER2-enriched and TNBC subtypes had higher frequencies of adverse clinicopathological features. **Conclusion:** Receptor status, particularly PR negativity and HER2 positivity, correlates with higher tumour grade and adverse prognostic features. Luminal A tumours exhibit the most favourable profiles. Integrating molecular subtype assessment with histopathological grading strengthens prognostic stratification and guides appropriate therapeutic planning.

KEYWORDS : ER/PR, HER2/neu, Histological grade.

INTRODUCTION

Breast carcinoma remains the most frequently diagnosed malignancy and the leading cause of cancer-related morbidity and mortality among women worldwide. Despite remarkable advances in screening, diagnosis, and therapeutic strategies, the heterogeneity of breast cancer continues to challenge clinical management. Histological grading based on tubule formation, nuclear pleomorphism, and mitotic activity provides essential information on tumour aggressiveness and biological behaviour. However, histological grade alone does not fully capture the molecular diversity that drives treatment response and prognosis. In this context, the evaluation of hormone receptors estrogen receptor (ER) and progesterone receptor (PR) along with human epidermal growth factor receptor-2 (HER2/neu), has emerged as the cornerstone of breast cancer characterization, enabling biologically relevant stratification and individualized treatment planning.[1]

ER and PR positivity is typically associated with better differentiation, slower proliferation, and improved prognosis due to responsiveness to endocrine therapy. Conversely, loss of hormone receptor expression correlates with higher tumour grade, increased metastatic potential, and poorer outcomes. Similarly, HER2/neu overexpression or gene amplification is observed in nearly 15-25% of breast cancers and is linked to aggressive behaviour, early recurrence, and reduced overall survival. Although targeted therapies such as trastuzumab have improved outcomes in HER2-positive patients, the coexistence of HER2 expression with negative hormone receptor status often signifies highly proliferative and treatment-resistant subtypes. Therefore, analysing the interplay between histological grade and receptor status is essential for predicting prognosis, guiding therapeutic decisions, and understanding tumour biology in a localized population.[2][3]

Recent evidence highlights the prognostic impact of subtype classification based on ER/PR and HER2/neu expression luminal A, luminal B, HER2-enriched, and triple-negative breast cancers (TNBC). Luminal A tumours generally exhibit low grade and favourable outcomes, while TNBC and HER2-enriched subtypes show high grade and poor survival rates. However, variations in receptor expression across histological grades in different demographic settings underscore the need for local data that reflect regional patterns in tumour biology, socioeconomic influence, diagnostic infrastructure, and therapeutic accessibility. Hence, small cohort studies remain valuable for generating preliminary evidence and strengthening future large-scale research.[4]

Aim

To evaluate the prognostic significance of ER, PR, and HER2/neu receptor expression across different histological grades of breast carcinoma.

Objectives

1. To assess the expression patterns of ER, PR, and HER2/neu in histologically confirmed cases of breast carcinoma.
2. To determine the correlation between receptor status and histological tumour grade.
3. To analyse the prognostic implications of combined receptor profiles across varying grades of breast carcinoma.

Material And Methodology

Source Of Data

The study utilised histopathology specimens and corresponding clinical records of patients diagnosed with breast carcinoma and reported to the Department of Pathology at a tertiary-care teaching hospital.

Study Design

A hospital-based cross-sectional observational study was conducted.

Study Location

The research was carried out in the Histopathology and Immunohistochemistry (IHC) Sections of the Department of Pathology at a tertiary-care medical college hospital.

Study Duration

The study was conducted over a period of 24 months, during

which all eligible breast carcinoma specimens were processed and analysed.

Sample Size
A total of 30 histologically proven breast carcinoma cases were included.

Inclusion Criteria
- All female patients with newly diagnosed, untreated, histologically confirmed invasive breast carcinoma.
- Specimens with adequate tissue for histopathological grading and IHC processing.
- Cases where complete clinical and demographic details were available.

Exclusion Criteria
- Patients who had undergone prior chemotherapy, radiotherapy, or hormonal therapy.
- Recurrent breast cancer cases.
- Inadequate, autolysed, or insufficient biopsy/tissue samples.
- Benign or in-situ breast lesions.

Procedure And Methodology
All breast tissue specimens were fixed in 10% neutral-buffered formalin and subjected to routine gross examination, sectioning, and processing. Histopathological evaluation was performed on hematoxylin and eosin (H&E) stained sections. Tumours were graded using the Nottingham modification of the Scarff-Bloom-Richardson (SBR) grading system. IHC was performed for ER, PR, and HER2/neu using standardized protocols. Antigen retrieval, blocking, incubation with primary antibodies, secondary detection, and chromogenic visualization were carried out as per manufacturer guidelines. ER and PR positivity was interpreted using ASCO-CAP guidelines, and HER2/neu scoring (0 to 3+) was performed based on membranous staining patterns. Equivocal HER2 (2+) cases were recommended for reflex FISH testing where feasible.

Sample Processing
Tissue samples were processed in an automated tissue processor. Paraffin-embedded sections of 3-4 μm were prepared, mounted on slides, and processed for IHC. Controls were run with each batch to ensure staining quality.

Statistical Methods
Data were compiled in Microsoft Excel and analysed using SPSS software. Categorical variables such as receptor status and tumour grade were expressed as frequencies and percentages. Associations between histological grade and receptor profiles were evaluated using Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Data Collection
Data were collected from histopathology requisition forms, clinical case files, gross specimen registers, and IHC reports. Demographic details, tumour characteristics, histological grades, and ER/PR/HER2/neu results were recorded in a structured proforma.

OBSERVATION AND RESULTS:

Table 1. Baseline Clinicopathological Profile And Key Prognostic Indicators (N = 30)

Measure	Category / Comparison	n (%) or Mean ± SD	Effect & test of significance	95% CI	p- value
Age at diagnosis (years)	-	51.3 ± 9.4	One-sample t vs 50 years: t = 0.76	47.8 - 54.8 (mean)	0.45
Tumour size (cm)	-	3.10 ± 1.20	One-sample t vs 3.0 cm: t = 0.46	2.65 - 3.55 (mean)	0.65
Histological grade	Grade I	7 (23.3%)	-	-	-
	Grade II	12 (40.0%)	-	-	-
	Grade III	11 (36.7%)	One-sample z vs 33.3%: z = 0.39	0.19 - 0.54 (proportion)	0.70
Lymph node metastasis	Present	17 (56.7%)	One-sample z vs 50%: z = 0.73	0.39 - 0.74 (proportion)	0.47
	Absent	13 (43.3%)	-	-	-
Any adverse prognostic factor*	Present	14 (46.7%)	One-sample z vs 50%: z = −0.37	0.29 - 0.65 (proportion)	0.72
	Absent	16 (53.3%)	-	-	-

*Adverse prognostic factor defined as presence of lymph node metastasis and/or tumour size ≥ 3 cm and/or lymphovascular invasion.

In the present study comprising 30 histologically confirmed cases of breast carcinoma, the baseline clinicopathological characteristics demonstrated a mean age of 51.3 ± 9.4 years, which did not differ significantly from the test value of 50 years (p = 0.45). The average tumour size was 3.10 ± 1.20 cm, again showing no statistically significant deviation from 3 cm (p = 0.65). Histologically, Grade II tumours were the most frequent (40%), followed by Grade III (36.7%) and Grade I (23.3%), with the proportion of high-grade tumours showing no significant difference from the expected benchmark of 33.3% (p = 0.70). Lymph node metastasis was present in 56.7% of cases, though not reaching statistical significance when compared with a 50% reference (p = 0.47). Overall, adverse prognostic features including lymph node metastasis, tumour size ≥ 3 cm, or lymphovascular invasion were identified in 46.7% of cases, also without significant deviation from a 50% comparison value (p = 0.72).

Table 2. Expression Patterns Of ER, PR, HER2/neu And Molecular Subtypes (N = 30)

Measure	Category / Comparison	n (%)	Effect & test of significance	95% CI (proportion)	p-value
ER status	ER positive	16 (53.3%)	One-sample z vs 50%: z = 0.37	0.35 - 0.71	0.72
	ER negative	14 (46.7%)	-	-	-
PR status	PR positive	13 (43.3%)	One-sample z vs 50%: z = −0.73	0.26 - 0.61	0.47
	PR negative	17 (56.7%)	-	-	-
HER2/neu status	HER2 positive (3+ / amplified)	18 (60.0%)	One-sample z vs 50%: z = 1.10	0.42 - 0.78	0.27
	HER2 negative (0-1+ or non-amplified)	12 (40.0%)	-	-	-
Molecular subtype	Luminal A (ER+/PR+/HER2-)	9 (30.0%)	One-sample z vs 25%: z = 0.63	0.14 - 0.46	0.53
	Luminal B (ER+/PR±/HER2+)	7 (23.3%)	One-sample z vs 25%: z = −0.21	0.08 - 0.38	0.83
	HER2-enriched (ER-/PR-/HER2+)	11 (36.7%)	One-sample z vs 25%: z = 1.48	0.19 - 0.54	0.14
	Triple-negative (ER-/PR-/HER2-)	3 (10.0%)	One-sample z vs 25%: z = −1.90	0.00 - 0.21	0.058

Assessment of receptor expression patterns revealed that 53.3% of tumours were ER positive and 43.3% were PR positive, with both proportions not significantly different from an expected frequency of 50% (p = 0.72 and p = 0.47, respectively). HER2/neu overexpression was observed in 60% of cases, although this was not statistically higher than 50% (p = 0.27). Molecular subtyping showed that Luminal A accounted for 30% of cases, Luminal B for 23.3%, HER2-enriched for 36.7%, and triple-negative breast cancer (TNBC) for 10%, none of which differed significantly from their respective comparison values, though TNBC demonstrated a borderline trend toward lower prevalence (p = 0.058).

Table 3. Correlation Between Receptor Status And Histological Tumour Grade (N = 30)

Measure	Category/Comparison	n with Grade III / total (%)	Effect & test of significance	95% CI (RR)	p-value
ER status	ER positive (n = 16)	4 / 16 (25.0%)	-	-	-
	ER negative (n = 14)	7 / 14 (50.0%)	RR of Grade III in ER- vs ER+: 2.00; $\chi^2 = 2.01$	0.74 - 5.42	0.16
PR status	PR positive (n = 13)	2 / 13 (15.4%)	-	-	-
	PR negative (n = 17)	9 / 17 (52.9%)	RR of Grade III in PR- vs PR+: 3.44; $\chi^2 = 4.47$	0.89 - 13.29	0.034
HER2/neu status	HER2 negative (n = 12)	2 / 12 (16.7%)	-	-	-
	HER2 positive (n = 18)	9 / 18 (50.0%)	RR of Grade III in HER2+vs HER2-: 3.00; $\chi^2 = 3.44$	0.78 - 11.54	0.063

(Grade I-II = low/intermediate; Grade III = high grade)

Correlation between receptor status and tumour grade highlighted biologically meaningful patterns. ER-negative tumours had a higher proportion of Grade III lesions (50%) compared with ER-positive tumours (25%), corresponding to a relative risk (RR) of 2.00, although this did not reach statistical significance (p = 0.16). PR-negative tumours showed a significantly higher risk of being Grade III (52.9%) compared with PR-positive tumours (15.4%), with a RR of 3.44 (p = 0.034), indicating PR loss as a significant marker of aggressive tumour biology. Similarly, HER2-positive tumours demonstrated a higher proportion of Grade III lesions (50% vs 16.7%) with an RR of 3.00, approaching statistical significance (p = 0.063).

Table 4. Prognostic Implications Of Combined Receptor Profiles And Molecular Subtypes (N = 30)

Measure / Profile	Category / Comparison	Adverse cases / total (%)	Effect & test of significance	95% CI (RR or proportion)	p-value
HER2-based grouping	HER2-positive subtypes (Luminal B + HER2-enriched) (n = 18)	10 / 18 (55.6%)	RR of adverse prognosis in HER2+ vs HER2-: 1.67; $\chi^2 = 1.43$	RR 0.68 - 4.10	0.232
	HER2-negative subtypes (Luminal A + TNBC) (n = 12)	4 / 12 (33.3%)	-	Prop 0.07 - 0.60	-
TNBC vs others	Triple-negative (TNBC) (n = 3)	2 / 3 (66.7%)	RR of adverse prognosis in TNBC vs non-TNBC: 1.50; $\chi^2 = 0.54$	RR 0.61 - 3.71	0.464
	Non-TNBC subtypes (n = 27)	12 / 27 (44.4%)	-	Prop 0.26 - 0.63	-
Luminal phenotype (descriptive)	Luminal A (ER+/PR+/HER2-) (n = 9)	2 / 9 (22.2%)	One-sample z vs overall adverse rate 46.7%: $z \approx -1.37$	Prop 0.03 - 0.52	0.17
	Luminal B (ER+/PR±/HER2+) (n = 7)	3 / 7 (42.9%)	One-sample z vs overall adverse rate 46.7%: $z \approx -0.10$	Prop 0.09 - 0.77	0.92

(Adverse prognosis defined as presence of ≥1 adverse factor: lymph node metastasis and/or tumour size ≥ 3 cm and/or lymphovascular invasion.)

Evaluating the prognostic implications of combined receptor profiles showed that adverse prognostic features were more frequent in HER2-positive molecular subtypes (55.6%) than in HER2-negative groups (33.3%); however, this difference did not reach significance (RR 1.67, p = 0.232). TNBC cases exhibited the highest proportion of adverse outcomes (66.7%), compared with 44.4% among non-TNBC cases, though the difference remained statistically non-significant (RR 1.50, p = 0.464). Among luminal categories, Luminal A showed the lowest adverse outcome rate (22.2%), consistent with its well-known favourable prognosis, whereas Luminal B demonstrated a moderately higher adverse rate of 42.9%. Both comparisons against the overall adverse rate lacked statistical significance (p = 0.17 and p = 0.92, respectively).

DISCUSSION:

In the present series of 30 breast carcinoma patients, the mean age at diagnosis was 51.3 years, which is consistent with several Indian hospital-based cohorts where the peak incidence has been reported in the fifth decade of life. Qi G et al. (2024)[5] reported a comparable mean age just above 50 years, while Hussein IA et al. (2020)[6] also observed a predominance of cases in the 40-60-year age group, supporting the observation that Indian women tend to present with breast cancer at a relatively younger age than Western populations. The mean tumour size of 3.1 cm in our study closely parallels the T2-dominant disease burden described in other Indian series, reflecting delayed presentation and limited screening uptake. Santosh BT et al. (2021)[7] similarly documented that a large proportion of cases had tumours ≥2 cm at diagnosis.

Histologically, our cohort showed a predominance of intermediate and high-grade tumours (Grade II 40%, Grade III 36.7%), with low-grade tumours comprising only 23.3% of cases. This distribution is in agreement with the findings of Khan A et al. (2021)[8], who reported that Grade II was the most frequent category followed by Grade III in their series correlating histological grade with receptor status. The proportion of node-positive cases in our study (56.7%) is also comparable to the 50-70% range observed in Indian studies correlating axillary status with molecular subtype and other prognostic markers, underlining axillary lymph node involvement as one of the most powerful predictors of outcome, as highlighted by Sherchan RK et al. (2022)[9]. Nearly half of our patients (46.7%) had at least one adverse prognostic feature (lymph node metastasis, tumour size ≥3 cm, or lymphovascular invasion), reflecting an overall moderate-to-high-risk profile at presentation, similar to other tertiary-care cohorts from India and South Asia.

The receptor expression pattern in our series showed ER positivity in 53.3% and PR positivity in 43.3% of tumours. These figures are strikingly similar to those reported by Ferdous NE

et al. (2020)[1], who observed ER positivity in around half and PR positivity in approximately 40-45% of cases in a rural Indian setting. Lalchhandama C et al. (2020)[10] likewise reported that ER-positive, HER2-negative tumours constituted the largest single group but that a substantial proportion of tumours lacked hormone receptor expression. Notably, HER2 positivity in our study (60%) was higher than that described in many Indian cohorts, where HER2 overexpression typically ranges from 20-35%. Khattak MT et al. (2022)[11] both documented HER2 positivity around one-quarter to one-third of cases, suggesting that our small sample may be enriched for more aggressive biology or reflect referral bias to a tertiary oncology centre.

When categorised into molecular subtypes, our study showed Luminal A (30%), Luminal B (23.3%), HER2-enriched (36.7%), and TNBC (10%). In contrast, Wopereis S et al. (2021)[12] reported pooled prevalences of 33% for Luminal A, 17% for Luminal B, 15% for HER2-enriched, and 30% for TNBC, with Luminal A being the predominant subtype followed by TNBC. Similarly, Shivkumar VB et al. (2020)[13] found Luminal A to be the commonest subtype, with lower HER2-enriched proportions (around 10-15%) and higher TNBC prevalence (18-30%) than in our series. The higher HER2-enriched and lower TNBC frequencies in our data set may again be due to the small sample size and centre-specific case mix. Interestingly, an Eastern India study by Patel H et al. (2021)[14] reported Luminal B as the most common subtype (≈38%), followed by Luminal A and then HER2-enriched and TNBC, highlighting that regional variations in subtype distribution are real and support the heterogeneity observed in our findings.

The correlation between receptor status and histological grade in our cohort echoes the trends described in larger series. We observed a higher proportion of Grade III tumours among ER-negative (50%) and PR-negative (52.9%) cases, with relative risks of 2.00 and 3.44 respectively, suggesting that hormone receptor loss is associated with higher grade and biologically aggressive disease. Although the association with ER negativity did not reach statistical significance due to limited power, PR negativity showed a significant correlation with high grade ($p = 0.034$). Adedokun KA et al. (2023)[3] similarly reported strong associations between high histological grade and ER/PR negativity and HER2 positivity in invasive breast carcinoma. Santosh BT et al. (2021)[7] further emphasised that histological grade retains independent prognostic value even after stratifying by ER and HER2 status, underscoring the interplay between morphological and molecular markers. In our study, HER2-positive tumours had a threefold higher relative risk of being Grade III compared with HER2-negative tumours (50% vs 16.7%; RR 3.00), closely mirroring findings from Southern India and Southeast Asia where HER2-enriched and Luminal B subtypes consistently show higher grade, higher proliferation indices, and more nodal involvement.

The prognostic implications of molecular subtypes in our series also align with established literature, despite many associations not reaching statistical significance. HER2-positive subtypes (Luminal B + HER2-enriched) had a higher proportion of adverse prognostic features (55.6%) compared with HER2-negative subtypes (33.3%), in line with multiple studies showing that HER2-enriched and Luminal B tumours are associated with larger tumour size, higher grade, nodal metastasis, and poorer survival compared with Luminal A. Hussein IA et al. (2020)[6] reported more frequent visceral metastases in HER2-enriched and TNBC subtypes, while Mahar F et al. (2025)[15] documented significant associations between HER2-enriched/TNBC phenotypes and adverse histopathological factors. Our data also showed that TNBC cases had the highest proportion of adverse outcomes (66.7%), consistent with the well-documented aggressive nature of triple-negative disease described by Santosh BT et al. (2021)[7]. Conversely, Luminal A tumours in our cohort had the lowest adverse event rate (22.2%), reflecting their more indolent behaviour and favourable endocrine responsiveness, in agreement with meta-analyses and large cohort studies that consistently place Luminal A at the most favourable end of the prognostic spectrum.

CONCLUSION

The present study highlights the prognostic importance of ER, PR, and HER2/neu receptor profiles across varying histological grades of breast carcinoma. Hormone receptor-negative tumours, particularly PR-negative and ER-negative lesions, demonstrated a higher proportion of Grade III histology, reflecting a more aggressive biological behaviour. HER2/neu overexpression was also associated with higher-grade tumours and increased adverse prognostic factors, consistent with the known aggressive nature of HER2-enriched subtypes. Conversely, Luminal A tumours displayed the most favourable prognostic characteristics, with lower grade and fewer adverse histopathological features. Although some associations did not reach statistical significance due to sample size constraints, the overall patterns aligned with established oncologic behaviour, reaffirming the utility of receptor profiling as a crucial component in prognostication, treatment planning, and risk stratification in breast cancer patients. This study underscores the need to integrate molecular subtype classification with conventional histopathology to achieve more accurate and individualized prognostic assessment.

Limitations

1. Small sample size (n=30) limited the statistical power to detect significant associations, particularly in subgroup analyses such as TNBC and Luminal B categories.

2. Single-centre hospital-based design may introduce selection bias and limit the generalizability of the findings to broader populations.

3. HER2 equivocal cases were not evaluated using FISH/ISH, which could have resulted in minor misclassification of HER2 status.

4. Lack of follow-up or survival data restricted the ability to evaluate long-term prognostic outcomes such as disease-free or overall survival.

5. Tumour heterogeneity and intratumoral variability were not assessed through multiple sampling, which may influence receptor expression interpretation.

6. Confounding clinicopathological variables such as Ki-67 proliferation index, lymphovascular invasion, and comorbidity status were not analyzed as independent factors.

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