NOTTINGHAM PROGNOSTIC INDEX AND ITS CORRELATION WITH IMMUNOHISTOCHEMICAL MARKERS IN INVASIVE BREAST CARCINOMA: A PROSPECTIVE STUDY

Original Research Article

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Abstract

Background: The Nottingham Prognostic Index (NPI) combines tumour size, histological grade and lymph-node status to stratify patients with invasive breast carcinoma into prognostic groups. This study assessed the distribution of NPI categories and their association with estrogen receptor (ER), progesterone receptor (PR), HER2/neu and Ki-67 expression.

Methods: This observational study included 100 female patients with invasive ductal carcinoma, not otherwise specified (IDC-NOS), who underwent modified radical mastectomy at Thanjavur Medical College during 2017–2020. Histological grade was assigned using the Nottingham modification of the Scarff–Bloom–Richardson system. NPI was calculated from lymph-node score, grade and maximum tumour diameter. Immunohistochemistry (IHC) results were abstracted for ER, PR, HER2/neu and Ki-67. Available marker-specific denominators varied.

Results: The most frequent age group was 50–59 years (35/100, 35%), and 70/100 cases (70%) were histological grade 2. NPI categories comprised 22/100 (22%) good, 60/100 (60%) moderate and 18/100 (18%) poor prognosis. ER was positive in 52/87 cases (59.8%), PR in 39/87 (44.8%), and HER2/neu in 32/87 (36.8%); Ki-67 was below 10% in 20/55 cases (36.4%), 10–20% in 21/55 (38.2%), and above 20% in 14/55 (25.5%). The study reported significant associations of PR and Ki-67 with NPI category, and an association of HER2/neu with NPI score and tumour size.

Conclusion: Most cases were grade 2 and belonged to the moderate-prognosis NPI group. The study concluded that the original three-tier NPI correlates with expression of prognostic immunohistochemical markers in invasive breast carcinoma, not otherwise specified.

Keywords: breast carcinoma; Nottingham Prognostic Index; estrogen receptor; progesterone receptor; HER2/neu; Ki-67; immunohistochemistry

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Introduction

Breast carcinoma is biologically heterogeneous, and its clinical course is influenced by tumour size, histological grade, regional lymph-node involvement and biomarker expression. Histological grading using the Nottingham modification of the Scarff–Bloom–Richardson system evaluates tubule formation, nuclear pleomorphism and mitotic activity, providing an established morphologic measure of tumour differentiation [1,2].

The Nottingham Prognostic Index (NPI) combines tumour diameter, histological grade and lymph-node status to classify patients into prognostic groups [3]. Immunohistochemical assessment of estrogen receptor (ER), progesterone receptor (PR), HER2/neu and Ki-67 adds information relevant to tumour biology and treatment selection. ER and PR are markers of hormone-receptor status; HER2 identifies a therapeutically relevant molecular subgroup; and Ki-67 is used as an indicator of tumour-cell proliferation [4–7].

The present study examined 100 cases of invasive breast carcinoma of no special type (IDC-NOS) managed at Thanjavur Medical College. The objectives were to describe the distribution of NPI categories and assess their association with ER, PR, HER2/neu and Ki-67 expression.

The present study was undertaken in a tertiary-care pathology department and focused on women undergoing modified radical mastectomy. This surgical cohort may differ from populations diagnosed through screening or managed with breast-conserving surgery. The study's practical contribution is therefore descriptive: it reports the distribution of NPI and IHC findings in this local cohort and examines whether the available marker results vary across NPI categories. It does not provide survival follow-up or a direct comparison of treatment outcomes.

Immunohistochemistry is widely used to characterize breast carcinoma in routine diagnostic practice [9]. ER and PR are assessed by nuclear staining, whereas HER2 interpretation depends on the pattern and completeness of membrane staining and, for equivocal cases, may require in-situ hybridization according to current testing algorithms. Ki-67 is assessed by nuclear staining in tumour cells. Thresholds and scoring protocols can vary between laboratories and over time, which limits direct comparisons across studies when the same methods are not used. In this present study, Ki-67 was grouped into less than 10%, 10–20% and greater than 20%, so findings should be interpreted within those categories rather than treated as a universal classification.

The NPI is calculated by combining the histological grade, tumour diameter and a score for lymph-node involvement. Its appeal is practical: the required variables are routinely available from surgical pathology, and the resulting score provides a concise summary of several important features. However, the index does not include all factors that influence prognosis, including age, comorbidity, molecular subtype, treatment received and response to treatment. Nor does an association between NPI and a biomarker necessarily show that the biomarker adds independent prognostic information. Such a claim would require a model that evaluates incremental value, ideally with follow-up outcomes.

Prognostic and predictive information should be distinguished. Prognostic factors describe the likely course of disease independent of a particular treatment, whereas predictive factors help estimate the likelihood of benefit from a treatment. Tumour size, nodal status and histological grade are central clinicopathological prognostic variables. ER and PR status inform the likelihood of response to endocrine therapy, and HER2 status may identify patients eligible for HER2-directed treatment. Ki-67 reflects cellular proliferation, although its interpretation is affected by pre-analytic conditions, scoring methods and the cut-off selected. These markers are complementary rather than interchangeable.

Materials and Methods

Study design and setting

This prospective study included 100 modified radical mastectomy specimens diagnosed as invasive ductal carcinoma, not otherwise specified (IDC-NOS), received at the Department of Pathology, Thanjavur Medical College, during 2017–2020.

Eligibility and specimen processing

The inclusion criteria were female patients older than 15 years who underwent MRM and had a diagnosis of invasive ductal carcinoma, not otherwise specified. Patients who had received chemotherapy or radiotherapy before surgery were excluded. Specimens were fixed in 10% neutral buffered formalin, grossly examined, sampled, processed and embedded in paraffin. Four-micrometre sections were stained with haematoxylin and eosin and examined histopathologically. Clinical details were obtained from hospital records and pathology requisition forms.

Histological grading and NPI

Tumours were classified according to the WHO system and graded using the Nottingham modification of the Scarff–Bloom–Richardson system, based on tubule/gland formation, nuclear pleomorphism and mitotic count. The study reports the NPI calculation as: NPI = lymph-node score (1–3) + histological grade (1–3) + [maximum tumour diameter in cm × 0.2]. Lymph-node scores were 1 for no nodal metastasis, 2 for 1–3 positive nodes, and 3 for more than 4 positive nodes in the source description. NPI was categorized as good (≤3.4), moderate (reported as 3.41–5.4 or 3.5–5.4 in different tables) and poor (>5.4). The category cut-off wording requires author confirmation before submission.

Immunohistochemistry

Representative paraffin sections were stained for ER, PR, HER2/neu and Ki-67. The study states that interpretation followed ASCO/College of American Pathologists guidance. ER and PR were considered positive when at least 1% of tumour cells showed immunoreactivity. HER2/neu was classified using membrane-staining criteria described in the study. Ki-67 was assessed by counting at least 500 malignant cells and expressing the percentage of positive tumour-cell nuclei; categories were below 10%, 10–20% and above 20%. Marker-specific denominators were lower than the overall sample size and are reported as available-case analyses.

Ethics and statistical analysis

Ethical approval was obtained from the Institutional Ethical Committee, Thanjavur Medical College (approval number 571; dated 22 November 2018). Statistical analysis in this study included chi-square/Fisher's exact tests for categorical associations and non-parametric tests for continuous variables, with $p<0.05$ considered statistically significant.

Results

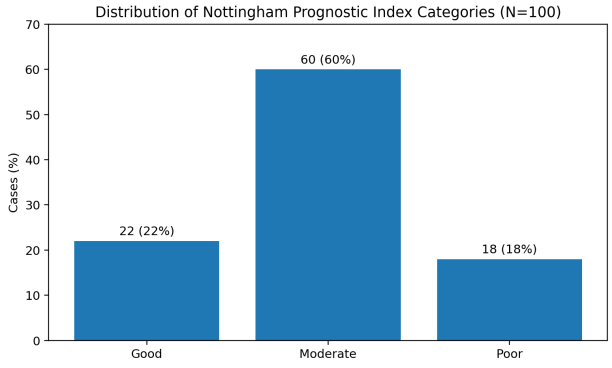
A total of 100 modified radical mastectomy specimens with IDC-NOS were studied. The largest age group was 50–59 years (35%), and the mean age was 51 years. The left breast was involved in 55 cases (55%). Histological grade 2 was the most common grade (70%), followed by grade 1 (20%) and grade 3 (10%). Tumour size had a mean of 4.26 ± 2.11 cm, median 4 cm (IQR 3–5), and range 1–11 cm. Axillary lymph-node metastasis was present in 48 cases (48%).

Characteristic	n (%) or summary
Age 20–29 years	2 (2.0%)
Age 30–39 years	10 (10.0%)
Age 40–49 years	31 (31.0%)
Age 50–59 years	35 (35.0%)
Age 60–69 years	14 (14.0%)
Age 70–79 years	6 (6.0%)
Age 80–89 years	2 (2.0%)
Left-sided tumour	55 (55.0%)
Right-sided tumour	45 (45.0%)
Histological grade 1	20 (20.0%)
Histological grade 2	70 (70.0%)
Histological grade 3	10 (10.0%)
Tumour size, mean ± SD	4.26 ± 2.11 cm
Tumour size, median (IQR)	4 (3–5) cm
Nodal metastasis present	48 (48.0%)
Nodal metastasis absent	52 (52.0%)

Table 1. Clinicopathological characteristics of the study cohort (N=100).

The NPI distribution was 22% good prognosis, 60% moderate prognosis and 18% poor prognosis. The study reported a significant correlation of NPI prognostic groups with histological grade, tumour size and lymph-node metastasis.

Figure 1. Distribution of NPI categories.



NPI category	Cases, n (%)
Good (≤3.4)	22 (22.0%)
Moderate (reported as 3.5–5.4)	60 (60.0%)
Poor (>5.4)	18 (18.0%)
Total	100 (100%)

Table 2. Distribution of Nottingham Prognostic Index categories.

Immunohistochemical results were available for 87 cases for ER, PR and HER2/neu, and for 55 cases for Ki-67, as reported in the study. ER positivity was reported in 52/87 cases (59.8%) and PR positivity in 39/87 (44.8%). HER2/neu was positive in 32/87 (36.8%). The Ki-67 distribution was 20/55 (36.4%) below 10%, 21/55 (38.2%) at 10–20%, and 14/55 (25.5%) above 20%.

aFigure 2. ER, PR and HER2/neu positivity among cases with recorded results.

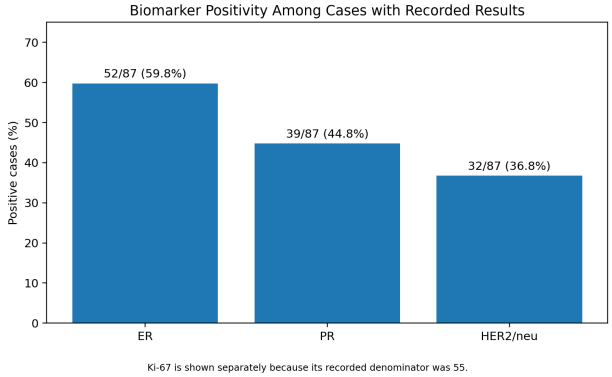


Table 3. Available immunohistochemical results. Percentages are as sorted out from the clinical data records.

Marker	Positive / category	Negative / other categories	Available / missing
ER	52 (59.8%) positive	35 (40.2%) negative	87 / 13
PR	39 (44.8%) positive	48 (55.2%) negative	87 / 13
HER2/neu	32 (36.8%) positive	55 (63.2%) negative	87 / 13
Ki-67	<10%: 20 (36.4%); 10–20%: 21 (38.2%); >20%: 14 (25.5%)	—	55 / 45

Table 4. Biomarker findings by Nottingham Prognostic Index category.

Biomarker/result	Good NPI (≤3.4)	Moderate NPI (3.5–5.4)	Poor NPI (>5.4)	Available n	Missing n
ER positive	14	31	7	52	13
ER negative	5	23	7	35	—
PR positive	14	19	6	39	13
PR negative	5	35	8	48	—
HER2/neu positive	3	22	7	32	13
HER2/neu negative	16	32	7	55	—
Ki-67 <10%	6	13	1	20	45
Ki-67 10–20%	5	11	5	21	—
Ki-67 >20%	0	13	1	14	—

Values are counts reported in the study for cases with recorded immunohistochemical results. ER, PR and HER2/neu results were available for 87 cases and Ki-67 results for 55 cases.

Marker	Reported test statistic	p value	Interpretation reported in study
ER	$\chi^2 = 2.211$	0.331	No significant association with NPI category
PR	$\chi^2 = 8.449$	0.015	Significant association with NPI category
HER2/neu	W = 1141.000	0.022	Significant association with NPI score; positivity more frequent in moderate/poor groups
Ki-67	As reported in study	0.043	Significant association with NPI category

Table 5. Associations between NPI category and immunohistochemical markers

Figure 3. Ki-67 distribution among cases with recorded results.

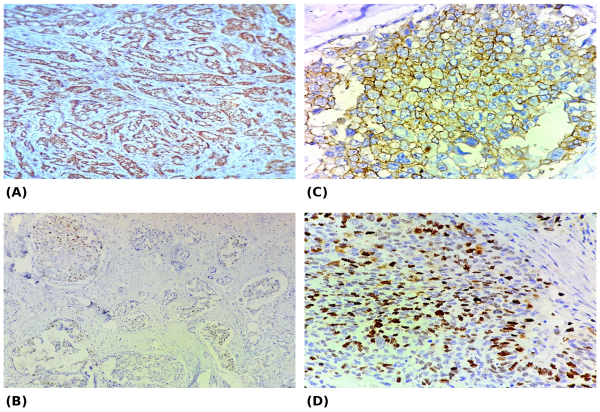
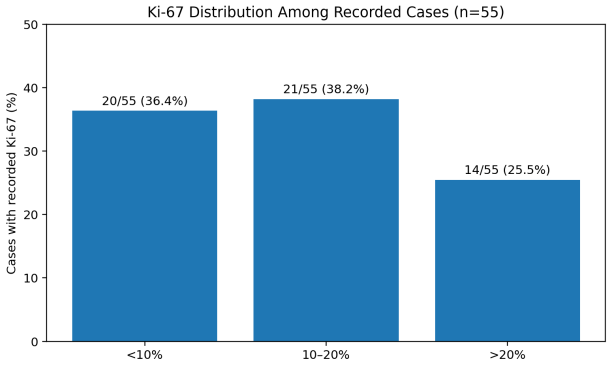


Figure 4. Representative immunohistochemical images. (A) nuclear ER positivity; (B) nuclear PR positivity; (C) HER2/neu membrane positivity; (D) Ki-67 labeling index >20%.



In the clinical analysis, ER distribution did not differ significantly across NPI categories (χ^2=2.211, p=0.331), although ER positivity decreased with increasing NPI category. PR distribution differed significantly across NPI categories (χ^2=8.449, p=0.015). The PR-positive group had a larger proportion of good-prognosis cases, whereas PR-negative cases were more frequent in the moderate- and poor-prognosis groups.

The study reported that 48 patients (48%) had lymph-node metastasis and 52 (52%) did not. Nodal involvement increased across NPI prognostic categories, consistent with the role of lymph-node status in the NPI score.

Grade 2 tumours accounted for 70% of the cohort, while grade 1 and grade 3 tumours accounted for 20% and 10%, respectively. Mean tumour size was 4.26 cm (SD 2.11), the median was 4 cm (IQR 3–5), and the range was 1–11 cm. The study reported increasing tumour size across NPI categories.

The mean age at presentation was 51 years, and the largest age group was 50–59 years (35%). The study reported no significant difference in age distribution across NPI categories.

Discussion

In this cohort of 100 women with IDC-NOS, grade 2 tumours predominated and the moderate NPI category was the most frequent. This distribution is broadly consistent with the role of NPI as a composite clinicopathological index used to stratify patients according to tumour size, grade and nodal status [3,8]. Studies describing NPI and clinicopathological features of breast carcinoma provide relevant context for interpreting such distributions [11,12]. However, comparisons with other cohorts should be interpreted cautiously because case mix, treatment setting and NPI grouping can differ.

The available IHC data showed ER positivity in 59.8% and PR positivity in 44.8% of tested cases. PR status was associated with NPI category in the study's cross-tabulation, whereas the ER association was not statistically significant. These analyses use the 87 cases with reported ER/PR/HER2 results; the NPI subgroup denominators in those tables are 19, 54 and 14 rather than the full cohort's 22, 60 and 18. The reason for this pattern of missing marker data is not provided. Therefore, these cross-tabulations are available-case analyses and may be affected by selection or missing-data bias.

Ki-67 results were available for 55 cases: 20 had an index below 10%, 21 had an index of 10–20%, and 14 had an index above 20%. The study reported a significant association between Ki-67 index and NPI category (p=0.043), with low Ki-67 associated with the good-prognosis group and higher Ki-67 categories associated with moderate and poor prognosis.

Limitations include the single-centre design, restriction to women undergoing modified radical mastectomy, incomplete immunohistochemical records and absence of survival or recurrence follow-up.

Limitations include the single-centre design, restriction to modified radical mastectomy specimens, incomplete immunohistochemical records, and absence of survival or recurrence follow-up.

Strengths include a defined hospital-based cohort of 100 cases, review of histopathology, use of a recognized grading framework and collection of multiple routinely used biomarkers. The study also provides a master chart, allowing discrepancies to be investigated rather than relying only on a narrative summary. The availability of an institutional ethics certificate is another important strength, although the manuscript must reproduce the approval details and consent status accurately.

Clinical implications should remain modest. NPI provides a compact summary of tumour size, grade and nodal status, while IHC markers add biologically and therapeutically relevant information. The current study does not show that NPI can replace IHC, nor that any marker can be inferred reliably from NPI category. In clinical practice, each marker should be reported from the tumour specimen according to validated laboratory procedures. The study's findings may help describe

patterns in the local cohort but should not be used to alter individual patient management.

ER and PR findings require careful interpretation. The overall ER positivity rate was approximately 60% among cases with available results, while PR positivity was approximately 45%. These proportions reflect the study's testing and reporting practices and may not match other centres; published Indian data have also described hormone-receptor status in breast tumours [10]. The ER cross-tabulation did not reach statistical significance. Although the PR cross-tabulation did, it remains an unadjusted comparison based on 87 available cases, with subgroup totals that differ from the full cohort. The source data do not permit determination of whether the PR association remains after adjustment for histological grade, tumour size, nodal burden, age or HER2 status. Therefore, PR should be described as associated with NPI category in this unadjusted table, not as an independent prognostic factor established by this study.

The observed increase in tumour size across NPI categories is not an independent finding because tumour size is one of the index components. Likewise, the increasing frequency of nodal involvement across NPI groups is inherent to the scoring method. Such results can describe the cohort and help check whether the data are internally coherent, but they cannot be presented as validation that NPI predicts tumour size or nodal status. A validation study would require an independent endpoint, such as recurrence or survival, and adequate follow-up.

The predominance of grade 2 disease is clinically plausible in a hospital-based sample of invasive breast carcinoma, but it should not be generalized to all breast cancer patients. Referral patterns, access to screening, age distribution and surgical selection can influence the histological spectrum. The analysis reports a mean age close to 51 years and a concentration of cases in the fifth and sixth decades. The absence of a statistically significant association between age group and NPI category is not evidence that age has no prognostic relevance; the study may have lacked power to detect differences, and age is not a component of the NPI formula.

The principal findings were that grade 2 tumours and the moderate NPI category predominated. ER and PR positivity was more frequent in the good-prognosis group, whereas ER and PR negativity was more frequent in the moderate- and poor-prognosis groups. HER2/neu expression was associated with moderate and poor NPI categories and increasing tumour size. Low Ki-67 index was associated with good prognosis, while moderate and poor NPI categories were associated with higher Ki-67 index.

Conclusion

Among the 100 cases studied, the largest age group was 50–59 years (mean age 51 years), and most tumours were histological grade 2. The moderate-prognosis NPI group was the most common category. A significant correlation of NPI prognostic groups with histological grade, tumour size and lymph-node metastasis was observed. Cases in the good-prognosis group showed increased ER and PR positivity, whereas ER and PR negativity was more frequent in the moderate- and poor-prognosis groups. HER2/neu expression was associated with the moderate- and poor-prognosis groups and with increasing tumour size. Low Ki-67 index was significantly associated with the good-prognosis group, while moderate- and poor-prognosis groups were associated with high Ki-67 index. Overall, the study supports the conclusion reported in the clinical findings that the original three-tier Nottingham Prognostic Index correlates with the expression of prognostic immunohistochemical markers in invasive breast carcinoma, not otherwise specified.

Ethics approval

Approval was granted by the Institutional Ethical Committee, Thanjavur Medical College (approval number 571; dated 22 November 2018),

Informed consent

Written informed consent was taken from the patient and the privacy was maintained.

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There is no funding for this study.

Conflict of interest

There is no conflict of interest known.

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