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RESEARCH ARTICLE
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PROGNOSTIC IMPLICATIONS OF THE NOTTINGHAM INDEX: CORRELATING WITH HORMONAL AND MOLECULAR MARKERS IN BREAST CANCER

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Abstract

Background: The Nottingham Prognostic Index (NPI), developed in the 1980s, is a widely recognized tool used to assess breast cancer prognosis. It is based on three key parameters: tumor size, lymph node status, and histological grade. The NPI categorizes patients into distinct risk groups, facilitating tailored treatment strategies and informed clinical decision-making. The relationship between the NPI, hormonal receptors, and molecular subtypes raises essential questions about the potential for enhanced prognostic accuracy.

Material & Methods: Representative sections from both lumpectomy and mastectomy specimens were submitted for histopathological analysis. The pathological features evaluated included tumor size, histologic type, histologic grade, and lymph node status. The immunohistochemical status of ER, PR, HER2/Neu, and Ki-67 was assessed using standard techniques. Tumor grading was performed according to the Elston-Ellis modification of the Scarff-Bloom-Richardson (SBR) grading system. An H-score was utilized to evaluate ER and PR status, while HER2/Neu was graded based on the intensity of membrane staining. Subsequent to the assessment of pathological features, the Nottingham Prognostic Index (NPI) was calculated using a specific formula.

Results: The analysis of the Nottingham Prognostic Index (NPI) in relation to various pathological parameters revealed that only the modified Scarff-Bloom-Richardson (SBR) grade demonstrated a statistically significant association with NPI, achieving a significance level of 5% ($p < 0.001$). In contrast, there was no substantial agreement observed between the NPI and the values for estrogen receptor (ER), progesterone receptor (PR), HER-2/Neu, or Ki-67.

Conclusion: The findings suggest that reliance on the NPI alone may not provide a comprehensive understanding of patient prognosis. Therefore, integrating independent assessments of both the NPI and other prognostic markers is essential for enhancing the accuracy of prognostic evaluations and optimizing treatment strategies for breast cancer patients.

Keywords: Nottingham Index, Prognostic Implications, Hormonal Markers, Molecular Markers, Breast Cancer

INTRODUCTION

Breast cancer remains a critical global health concern, representing one of the most prevalent malignancies affecting women worldwide. According to the World Health Organization, **1** breast cancer accounts for approximately 12% of all new cancer cases annually. The heterogeneity of breast cancer, characterized by various histological types, molecular subtypes, and clinical behaviors, poses challenges for prognosis and treatment decisions. As our understanding of breast cancer biology has evolved, the need for comprehensive prognostic tools that integrate clinical, pathological, and molecular data has become increasingly important.[1]

The Nottingham Prognostic Index (NPI), developed in the 1980s, is a widely recognized tool used to assesses three critical factors: pathological tumor size, lymph node status, and histologic grade of the tumor. These factors are combined to create a prognostic index, where a higher total score indicates a worse prognosis for the patient. The NPI is primarily designed to predict the clinical outcomes for individuals diagnosed with breast cancer. [2] The NPI categorizes patients into distinct risk groups, facilitating tailored treatment strategies and informed clinical decision-making.

Prognostic Group Classification: Patients are categorized into three groups based on their NPI scores, using established cut-off values of 3.4 and 5.4 (Table 1)

- ***Group 1****:* Represents a good prognosis (score up to 3.4) with an estimated five-year survival rate of 80%.
- ***Group 2****:* Indicates a moderate prognosis (score between 3.4 and 5.4) with a five-year survival rate of 42%.
- ***Group 3****:* Reflects a poor prognosis (score greater than 5.4) with a five-year survival rate of 13%.

Hormonal receptor status, particularly the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), plays a crucial role in determining prognosis and guiding treatment. Studies have shown that ER-positive tumors generally exhibit better outcomes and respond favorably to hormone therapies, whereas HER 2-positive tumors can benefit from targeted therapies like trastuzumab. [3,4] Thus, integrating these hormonal markers with established prognostic indices like the NPI may enhance the precision of breast cancer prognostication.

Furthermore, advancements in molecular profiling techniques have led to the identification of distinct breast cancer subtypes, including luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC). These subtypes exhibit varied biological behaviors, treatment responses, and outcomes. [5, 6] For instance, luminal A tumors are generally associated with a more favorable prognosis, while TNBC and HER2-enriched tumors are associated with a more aggressive clinical course. By correlating the NPI with these molecular subtypes and their respective markers, we can gain valuable insights into patient outcomes and refine risk stratification.

The relationship between the NPI, hormonal receptors, and molecular subtypes raises essential questions about the potential for enhanced prognostic accuracy. Can the NPI retain its predictive value when applied to patient subgroups defined by specific hormonal and molecular characteristics? Does the incorporation of these markers significantly alter the prognostic landscape? This study aims to address these questions by evaluating the prognostic implications of the Nottingham Index in correlation with hormonal and molecular markers in breast cancer.

We hypothesize that integrating hormonal receptor status and molecular subtype information with the NPI will provide a more comprehensive understanding of patient prognosis, ultimately facilitating personalized treatment approaches. Previous research indicates that combining traditional prognostic factors with molecular markers may enhance predictive accuracy and lead to better patient outcomes. [7, 8.]

This study seeks to build upon these findings by analyzing a cohort of breast cancer patients with extensive clinical, pathological, and molecular data. Moreover, this investigation carries significant clinical implications. A robust correlation between the NPI and hormonal or molecular markers could lead to more tailored therapeutic strategies that align with the unique biological characteristics

of each tumor. In practice, this could optimize treatment regimens, minimize overtreatment in low-risk populations, and improve survival rates for high-risk patients. [9]
The purpose of this study is to evaluate various prognostic markers in breast carcinomas. These include the modified Scarff-Bloom-Richardson (SBR) grade, estrogen receptor (ER) status, progesterone receptor (PR) status, HER2/Neu status, and cell proliferation activity as measured by Ki-67. Additionally, the study aims to explore the statistical correlations between these prognostic markers and the NPI score.

MATERIALS AND METHODS

This study was conducted in the Department of Pathology at a tertiary care hospital in Western Uttar Pradesh, over a period of 1 year. It is a prospective study that includes 60 cases of primary breast carcinoma, with data collected between September 2023 to August, 2024. A total of 60 cases of infiltrating ductal carcinomas of the breast were included in the study based on purposive sampling The focus was on breast cancers diagnosed as infiltrating ductal carcinoma of no special type through lumpectomy and mastectomy procedures.
Histopathological Examination: Representative sections from both lumpectomy and mastectomy specimens were submitted for histopathological analysis. These samples were stained using hematoxylin and eosin (H&E) for general examination, and immunohistochemical assessments for estrogen receptors (ER), progesterone receptors (PR), HER2/Neu, and Ki-67 were routinely performed as part of the protocol for breast carcinoma cases. The pathological features evaluated included tumor size, histologic type, histologic grade, and lymph node status.
Immunohistochemical Evaluation: The immunohistochemical status of ER, PR, HER2/Neu, and Ki-67 was assessed using standard techniques. Tumor grading was performed according to the Elston-Ellis modification of the Scarff-Bloom-Richardson (SBR) grading system. An H-score was utilized to evaluate ER and PR status, while HER2/Neu was graded based on the intensity of membrane staining.
Statistical Grouping: For statistical analysis, cases were categorized into ER-negative and ER-positive groups. Tumors with weak, moderate, or strong ER positivity were grouped as ER positive, and a similar classification was applied for PR status. Cases with equivocal HER2/Neu status were excluded from the study. To differentiate between high and low proliferative tumors, a cut-off of 14% for Ki-67 was utilized, following the 2011 St. Gallen International Expert Consensus guidelines.
Subsequent to the assessment of pathological features, the Nottingham Prognostic Index (NPI) was calculated using a specific formula. This calculation incorporates tumor grade, the number of involved lymph nodes and the size of the primary tumor.

The formula for calculating the NPI is as follows:
NPI = (tumor size in cm × 0.2) + histologic grade [1−3] + number of positive lymph nodes

Parameter Definitions

- **Tumor Size**: Measured in centimeters.
- **Histologic Grade**: Scored on a scale of 1 to 3.
- **Number of Positive Lymph Nodes**: Scored as follows:
  - 1:- 0 nodes involved
  - 2:- 1-3 nodes involved
  - 3:- More than 3 nodes involved

Data Analysis

The data was analyzed using various statistical methods, including mean, standard deviation, frequency percentage, cross-tabulation of scores, the Chi-Square test, and Kappa statistics. A significance level of 5% was established for the analysis. Kappa statistics were employed to assess

the level of agreement between the Nottingham Prognostic Index (NPI) and the modified Scarff-Bloom-Richardson (SBR) grade, as well as the statuses of ER, PR, HER2/Neu, and Ki-67.

Table 1: Prognostic classification based on the Nottingham Prognostic Index (NPI)

Group	Value
Group 1	≤3.4
Group 2	3.41-5.4
Group 3	>5.4

RESULTS

The study involved 60 cases of infiltrating ductal carcinoma of the breast, selected through purposive sampling. Participants' ages ranged from 34 to 71 years, with a mean age of 54.5 years.

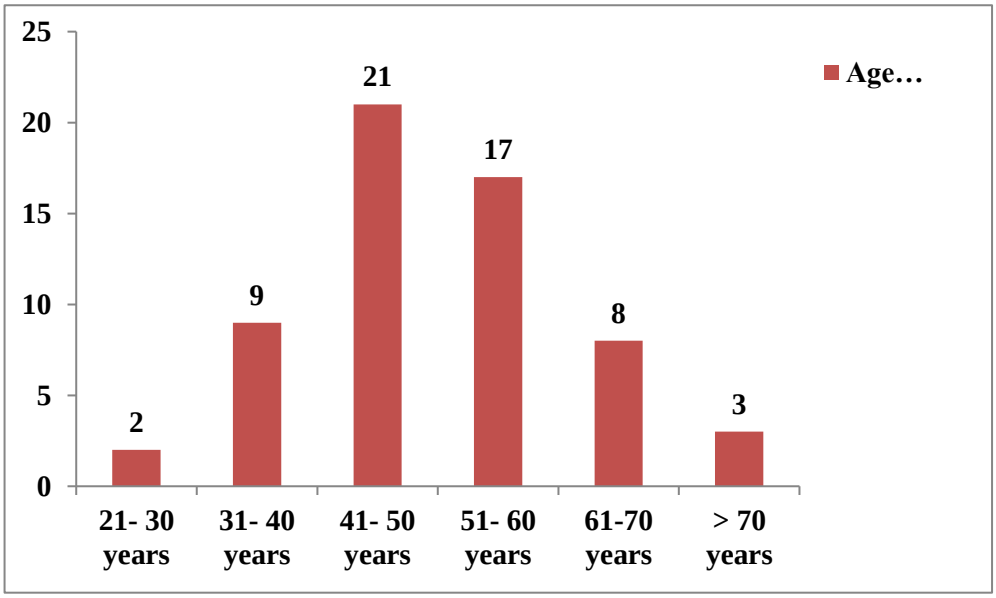

Fig 1: Age distribution of study subjects

Tumor Characteristics:

Out of the total patients studied, a significant majority (34, 56.7%) exhibited right breast involvement. The upper outer quadrant was the most commonly affected area, accounting for 41% of cases.

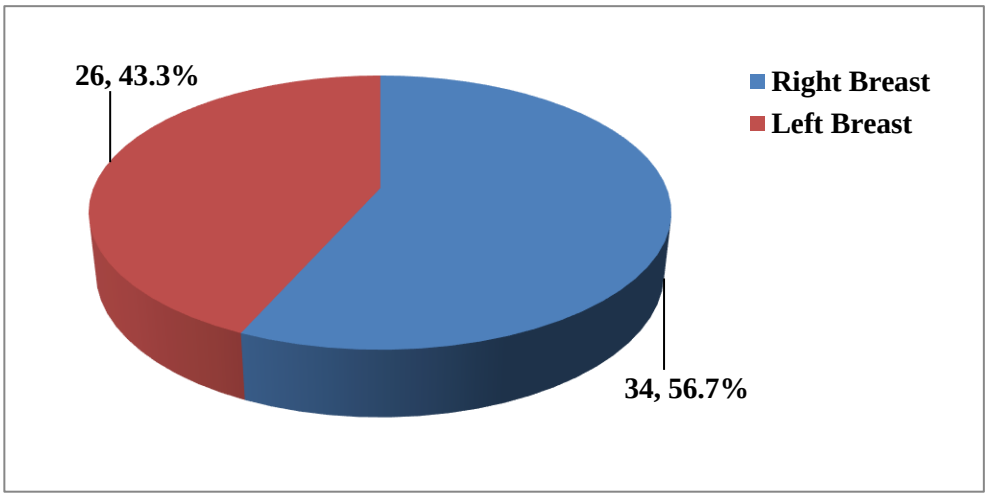

Fig 2: Breast involvement of study subjects

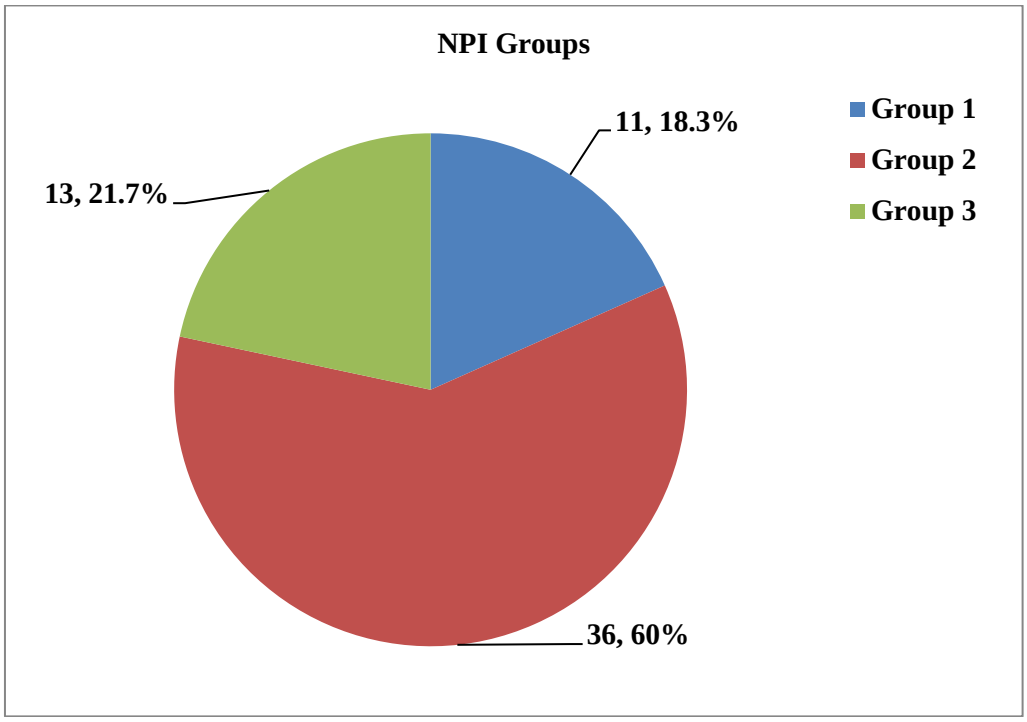

Fig 3: Distribution of study subjects according to Nottingham Prognostic Index (NPI)

Lymph Node Involvement and Staging:
A considerable proportion of the cases demonstrated lymph node involvement, with 56% presenting with this characteristic. Most patients were classified as T2 stage (62%).

Histological Grading:
The modified Scarff-Bloom-Richardson (SBR) grade 2 was the predominant histological grade observed, seen in (27, 45%) of the tumors.

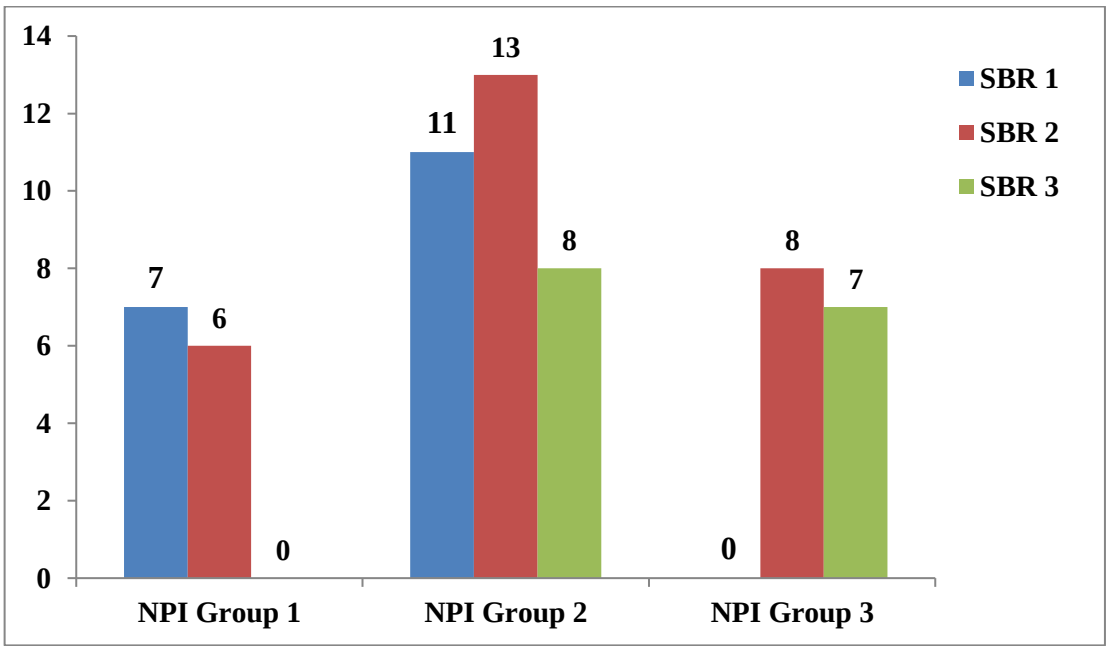

Fig 4: Scarff-Bloom-Richardson (SBR) grading in different NPI Groups

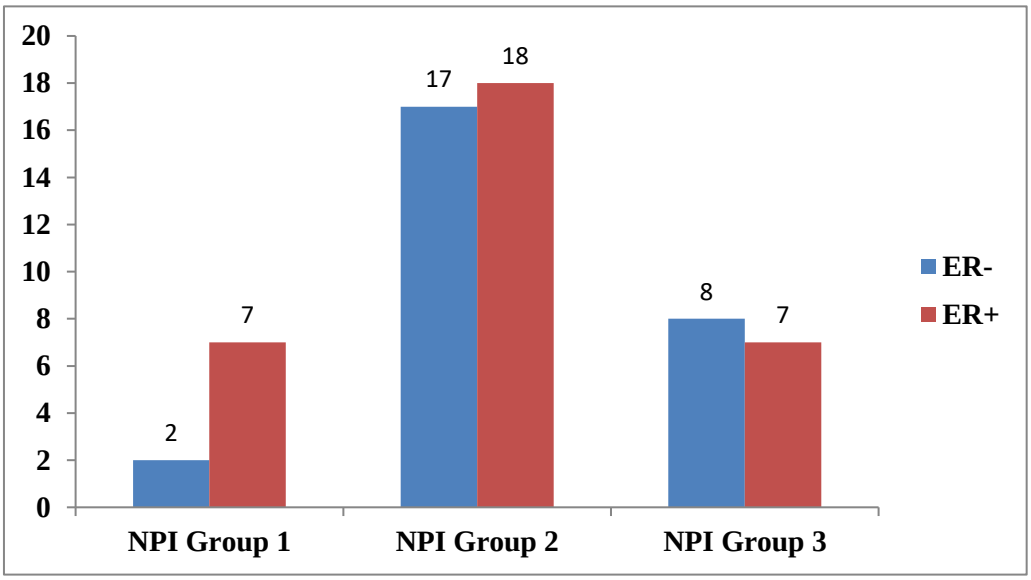

Fig 5: Expression of ER in different NPI Groups

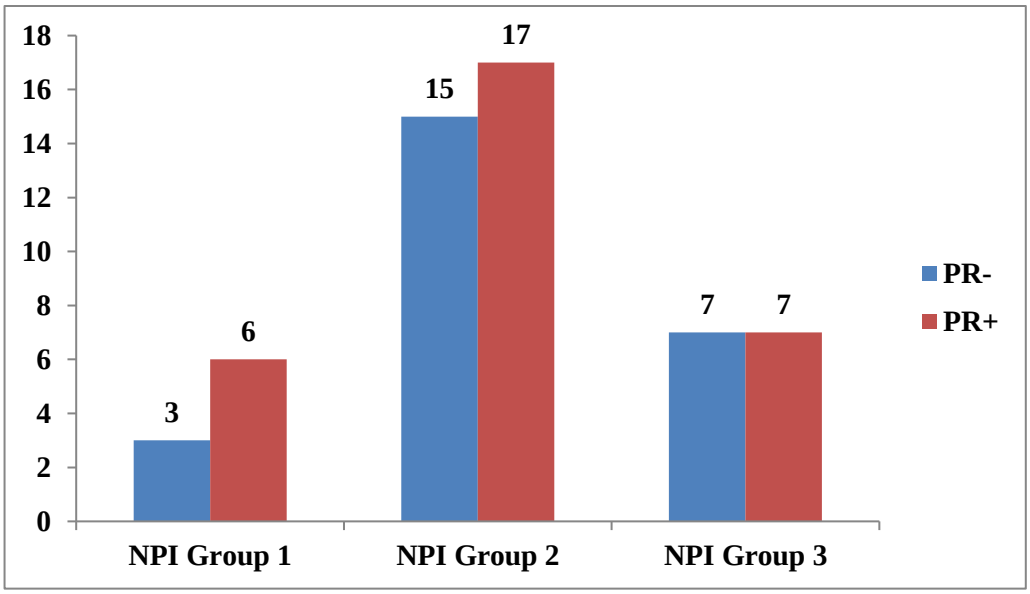

Fig 6: Expression of PR in different NPI Groups

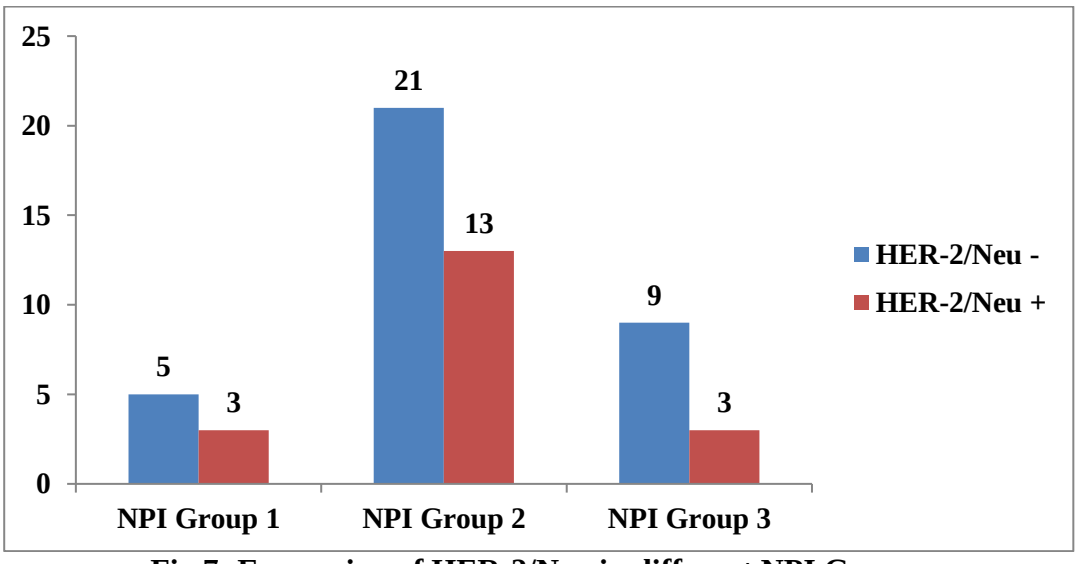

Fig 7: Expression of HER-2/Neu in different NPI Groups

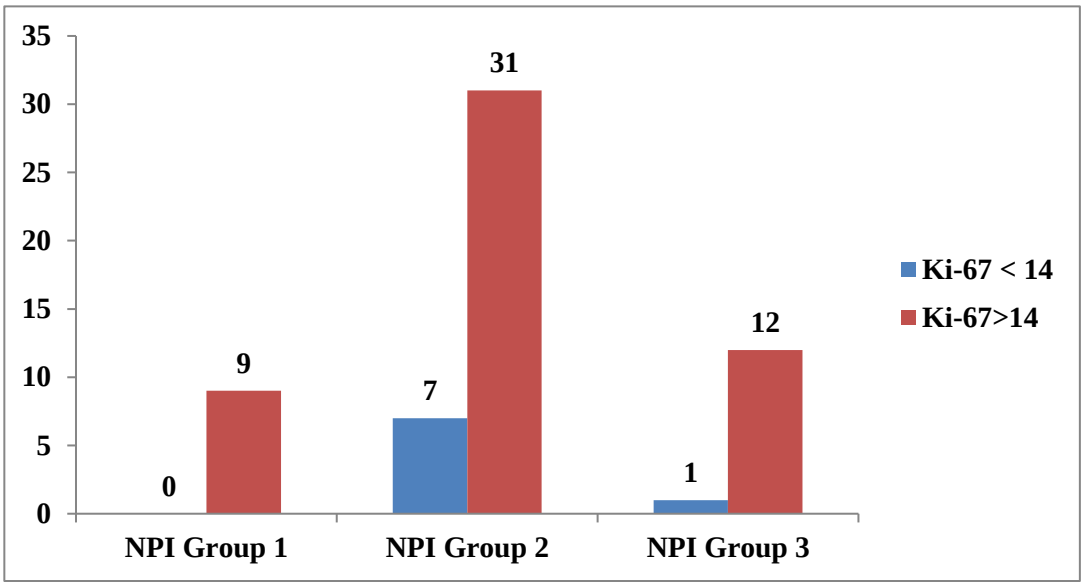

Fig 9: Expression of Ki-67 in different NPI Groups

Table 2: Summaryof expression of various Hormonal and Molecular Markers in different groups of NPI

		NPI						p value
		Group 1		Group 2		Group 3		
		Frequency	%	Frequency	%	Frequency	%	
ER	Negative	2	22.2%	17	48.5%	8	53.3%	0.376
	Positive	7	77.8%	18	51.5%	7	46.7%	
PR	Negative	3	33.3%	15	46.8%	7	50%	0.412
	Positive	6	66.7%	17	53.2%	7	50%	
HER-2/Neu	Her2-	5	62.5%	21	61.8%	9	75%	0.396
	Her2+	3	37.5%	13	38.2%	3	25%	
Ki-67	<14	0	0%	7	18.4%	1	7.7%	0.214
	>14	9	100%	31	81.6%	12	92.3%	
SBR	Grade 1	7	53.8%	11	34.4%	0	0%	<0.001*
	Grade 2	6	46.2%	13	40.6%	8	53.3%	
	Grade 3	0	0%	8	25%	7	46.7%	

significant p value

Cross Tabulation of NPI with Pathological Parameters:

The analysis of the Nottingham Prognostic Index (NPI) in relation to various pathological parameters revealed that only the modified Scarff-Bloom-Richardson (SBR) grade demonstrated a statistically significant association with NPI, achieving a significance level of 5% ($p < 0.001$).

Agreement with Hormonal Receptors and Ki-67:

In contrast, there was no substantial agreement observed between the NPI and the values for estrogen receptor (ER), progesterone receptor (PR), HER-2/Neu, or Ki-67.

DISCUSSION

The Nottingham Prognostic Index (NPI) has been a pivotal tool in assessing the prognosis of breast cancer patients since its inception. It is a composite score derived from three key parameters: tumor size, lymph node involvement, and histological grade. Although the NPI has proven effective in

stratifying patients into prognostic groups, advances in our understanding of breast cancer biology necessitate a more nuanced approach to prognostication.

The Role of Hormonal Markers

Hormonal receptor status, specifically the presence of estrogen receptors (ER) and progesterone receptors (PR), has profound implications for both prognosis and treatment strategy in breast cancer. ER-positive tumors are generally associated with a more favorable prognosis and are responsive to endocrine therapies, such as tamoxifen and aromatase inhibitors as found in study done by Harvey et al. in 2009. [10] The NPI does not factor in hormonal receptor status, but integrating this data can enhance risk stratification. Study done by Nitzkorski et al. in 2020. [11] has shown that among patients with the same NPI score, those with ER-positive tumors tend to exhibit better survival outcomes compared to their ER-negative counterparts similar to our study findings. For instance, in a cohort study, ER-positive patients classified as high-risk by NPI still demonstrated a relatively favorable prognosis, emphasizing the importance of hormonal status in determining treatment strategies. [12] This finding suggests that the NPI should be viewed as part of a broader prognostic framework, where hormonal receptor status can modulate risk assessment.

Molecular Markers and Their Relevance

The introduction of molecular profiling has added another layer of complexity to breast cancer prognostication. Assays such as Oncotype DX and MammaPrint evaluate gene expression patterns to predict recurrence risk and response to chemotherapy. [13, 14] These molecular tests have proven particularly valuable for patients with early-stage, ER-positive breast cancer. When comparing molecular markers with the NPI, findings indicate that patients with a high NPI score are often more likely to present with aggressive tumor characteristics, including high Ki-67 indices or HER2 positivity in line with our study results done by Loi et al. in 2014. [15] These factors indicate a higher likelihood of poor outcomes and often necessitate more aggressive treatment strategies. Conversely, a patient classified as low-risk by NPI and with a low Oncotype DX score may avoid unnecessary chemotherapy, underscoring the potential for personalized treatment approaches. A recent study done by Duffy et al. in 2021 [16] examined the prognostic value of combining the NPI with molecular profiling, demonstrating that patients with an intermediate NPI score and favorable molecular markers had significantly better outcomes than those with similar NPI scores but adverse molecular features. This suggests that integrating molecular data can lead to more precise risk stratification, informing treatment decisions and optimizing patient management.

Limitations of the NPI

Despite its utility, the NPI has inherent limitations. It primarily relies on histopathological features and does not encompass the full spectrum of molecular heterogeneity seen in breast cancer. This lack of molecular consideration may result in underestimating the risk for some patients or overestimating it for others, particularly in cases with discordant NPI and molecular marker findings. [17] As our understanding of breast cancer biology evolves, future prognostic models should aim to incorporate a broader array of biomarkers to enhance predictive accuracy. Another limitation is the variability in clinical practices and treatment approaches across different healthcare settings, which may impact the application of the NPI. Factors such as access to hormonal therapies and molecular profiling can create disparities in outcomes. To address these challenges, ongoing research should focus on developing standardized protocols that incorporate both the NPI and molecular markers into routine clinical practice.

The integration of the NPI with hormonal and molecular markers represents a promising direction for future research. Establishing algorithms that combine these factors could enable more accurate prognostication and personalized treatment planning.

For example, future studies could explore the development of a composite score that incorporates the NPI, hormonal receptor status, and molecular profiling results to create a more comprehensive

risk stratification tool. Moreover, the incorporation of emerging biomarkers, such as tumor-infiltrating lymphocytes (TILs) and genomic alterations, into prognostic models could further enhance their predictive power. Recent evidence suggests that TILs can serve as an independent prognostic factor in breast cancer, particularly in triple-negative and HER2-positive subtypes in study done by Pérez-García et al. in 2019. [18] Incorporating such markers into prognostic frameworks may yield insights into tumor microenvironment interactions and improve treatment strategies.

Recommendations

- **Comprehensive Marker Evaluation**: Regularly assess hormonal markers (ER, PR) and molecular markers (HER2/Neu, Ki-67) alongside NPI to provide a more holistic view of tumor biology and patient prognosis.
- **Tailored Treatment Approaches**: Utilize NPI scores in conjunction with hormonal and molecular markers to develop personalized treatment strategies, potentially improving patient outcomes.
- **Regular Training for Pathologists**: Ensure that pathologists are trained in the application and interpretation of NPI and related markers to promote consistency and accuracy in diagnostic assessments.
- **Multidisciplinary Collaboration**: Foster collaboration among oncologists, pathologists, and other healthcare professionals to ensure a comprehensive approach to breast cancer management based on NPI and biomarker profiles.
- **Standardize Reporting**: Establish standardized reporting protocols for NPI and associated hormonal and molecular markers to facilitate comparison across studies and enhance the quality of care.
- **Conduct Further Research**: Encourage ongoing research to explore the relationship between NPI and emerging biomarkers, which may refine prognostic capabilities and lead to the discovery of novel therapeutic targets.

Limitations

- **Sample Size Constraints**: Small sample sizes in certain studies can affect the statistical power and reliability of the correlations between NPI and hormonal/molecular markers.
- **Variability in Marker Assessment**: Differences in techniques and criteria for evaluating hormonal and molecular markers (e.g., ER, PR, HER2/Neu, Ki-67) can lead to inconsistencies in results across different laboratories.
- **Dynamic Nature of Tumors**: Breast cancer can evolve over time, and a single assessment of NPI and biomarkers may not fully capture the tumor's biological behavior throughout the course of the disease.
- **Exclusion of Other Factors**: The NPI primarily focuses on three factors (tumor size, lymph node status, histologic grade), potentially overlooking other important prognostic factors such as patient genetics, lifestyle, and comorbidities.
- **Technological Advancements**: Rapid advancements in genomic and molecular profiling techniques may render traditional methods, including NPI, less relevant over time if not regularly updated.

CONCLUSION

In conclusion, this study highlights the lack of correlation between the Nottingham Prognostic Index (NPI) and various hormonal and molecular markers in breast cancer, emphasizing the importance of evaluating these factors separately. The findings suggest that reliance on the NPI alone may not provide a comprehensive understanding of patient prognosis. Therefore, integrating independent assessments of both the NPI and other prognostic markers is essential for enhancing the accuracy of prognostic evaluations and optimizing treatment strategies for breast cancer patients. Further

research is warranted to explore the potential interactions and implications of these markers in clinical practice.

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