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Original Research Article

PROGNOSIS OF MODIFIED NOTTINGHAM PROGNOSTIC INDEX IN RELATION TO AGE, ER, PR, HER2NEU AND KI67

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Abstract: ***Objectives:*** To determine the grading of the Modified Nottingham Prognostic Index (MNPI) among patients with breast cancer and to compare the frequency of ER, PR, HER2neu, and Ki67 expression between patients with good, moderate, and poor prognosis. ***Study Design and Setting***: A cross-sectional study conducted in the Department of General Surgery, Liaquat National Hospital, Karachi. ***Methodology***: A total of 236 female patients aged 20–70 years with histopathologically diagnosed breast cancer were enrolled between 15th September 2019 and 16th March 2020. Patients who underwent neoadjuvant chemotherapy or had a history of other malignancies were excluded. Modified Nottingham Prognostic Index was calculated using tumor size, nodal status, and histological grade. Immunohistochemical expression of ER, PR, HER2neu, and Ki67 was analyzed. Data were evaluated using SPSS v25. **Results:** The mean age was 51.08 ± 13.45 years. ER, PR, and HER2neu were positive in 68.6%, 58.9%, and 48.6% cases, respectively, while Ki67 was high in 72.5%. According to MNPI, 23.7% had good, 31.4% moderate, and 44.9% poor prognosis. Good MNPI scores were significantly associated with ER positivity (82.1%), PR positivity (71.4%), and low Ki67 (33.9%). ***Conclusions:*** MNPI remains a valuable prognostic indicator in breast cancer. Patients with ER and PR positivity and low Ki67 expression demonstrated a better prognosis. Incorporating MNPI in clinical practice can improve risk stratification and treatment planning.

Keywords: Breast Neoplasms; Estrogen Receptor; Ki-67 Antigen; Prognosis; Progesterone Receptor; Receptor, erbB-2.

INTRODUCTION

Breast cancer is the most common malignant tumor among women worldwide and represents a major public health challenge. It accounts for nearly **one in four cancer diagnoses in women** and is the leading cause of cancer-related deaths in females globally. According to GLOBOCAN 2020 estimates, more than **2.3 million new cases** of breast cancer were diagnosed worldwide, with approximately **685,000 deaths** attributable to the disease.[1] This burden is expected to increase in coming decades, especially in developing countries, where screening programs are limited and diagnosis is often delayed.[2]

The epidemiology of breast cancer varies across different regions. In developed countries, early detection through widespread mammographic screening and better access to treatment has led to improved survival rates.[3] In contrast, in South Asian countries such as Pakistan, India, and Bangladesh, breast cancer is often diagnosed at advanced stages due to lack of awareness, stigma, and socioeconomic barriers to healthcare.[4] Pakistan, in particular, has one of the **highest incidences of breast cancer in Asia**, with estimates suggesting that one in nine women will develop the disease during her lifetime.[5] In such a high-burden setting, reliable and cost-effective prognostic tools are urgently required to stratify

patients, predict outcomes, and guide therapeutic decisions.

Breast cancer is also by definition a heterogeneous disease. It has extensive molecular subtypes, biological behavior, and clinical outcome.[6] It is prognosticated by both established pathological characteristics, including tumor size, histologic grade, and nodal involvement, and by molecular markers that affect tumor biology and response to therapy, including expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/neu), and proliferation index (measured by Ki67). These biomarkers together offer a good prognostic data and are the must-have when treating breast cancer in the modern world.

Breast Cancer Prognostic Indexes

Various scoring systems have been developed to combine these multiple prognostic variables. One of them, the Nottingham Prognostic Index (NPI), has been highly acceptable since its publication in the 1980s. The NPI involves three parameters of critical account:

- **Tumor size**,
- **Lymph node stage**, and
- **Histological grade (Scarff-Bloom-Richardson system)**.

Based on these, patients are categorized into prognostic groups: good, moderate, or poor. This simple calculation has been validated in numerous studies and remains an important tool for risk stratification in breast cancer.[9]

However, limitations were observed with the original NPI, especially regarding histological grading, which lacked consistency. To address this, the **Modified Nottingham Prognostic Index (MNPI)** was developed. The MNPI replaces the original Scarff-Bloom-Richardson grading system with the **Modified Scarff-Bloom-Richardson (MSBR) system**, which evaluates nuclear variation, tubular differentiation, and mitotic activity with more reproducibility.[10] Studies have shown that MNPI provides more reliable prognostic discrimination and is applicable across different subtypes of breast cancer.[11]

Role of Molecular Markers

Modern oncology emphasizes the role of **molecular subtyping** in breast cancer. The St. Gallen International Expert Consensus has categorized breast cancer into molecular subtypes based on ER, PR, HER2, and Ki67 expression: luminal A, luminal B, HER2-enriched, and triple-negative breast cancers.[12] These classifications not only predict prognosis but also guide targeted therapies such as endocrine therapy for ER/PR-positive cancers and trastuzumab for HER2-positive cancers.[13]

Despite their prognostic and therapeutic value, molecular markers are not universally available or affordable in all clinical settings, especially in low- and middle-income countries.[14] This makes integrated tools such as MNPI, which combine histopathological features with selective biomarker analysis, highly valuable in routine clinical practice.

Local Context

In Pakistan, breast cancer is frequently diagnosed at advanced stages, with large tumor size and nodal involvement being common.[15] Limited access to molecular testing means that many patients cannot benefit from advanced prognostic assays or gene-expression profiling tools, which are widely used in high-income countries.[16] Therefore, there is a strong rationale for utilizing cost-effective, histology-based indices such as MNPI, complemented by basic immunohistochemistry (ER, PR, HER2, and Ki67), to provide prognostic guidance.

Previous studies have demonstrated that MNPI correlates well with established prognostic markers. Patients with ER/PR-positive tumors generally have better MNPI scores, while HER2 positivity and high Ki67 expression are associated with poorer outcomes.[17] Research also shows that MNPI has predictive value in aggressive subtypes such as triple-negative breast cancer, where treatment options remain limited.[18]

Rationale of the Study

While MNPI has been validated in various populations, there is limited data from South Asian settings, particularly Pakistan. Given the high incidence and late-stage presentation of breast cancer in this region, it is crucial to assess the applicability of MNPI in local clinical practice. Furthermore, the relationship between MNPI and immunohistochemical markers such as ER, PR, HER2, and Ki67 has not been comprehensively studied in our patient population.

Objectives:

1. To determine the grading of MNPI among patients with breast cancer.
2. To compare ER, PR, HER2neu, and Ki67 expression between different MNPI prognostic categories.

Methodology

This **cross-sectional study** was conducted at the Department of General Surgery, Liaquat National Hospital, Karachi, between **15th September 2019 and 16th March 2020**.

Ethical Approval: The study was approved by the **Ethical Review Committee of Liaquat National Hospital (REU No: 40531)** and CPSP. Written informed consent was obtained from all participants.

Sample Size and Sampling: A sample size of 236 was calculated using WHO software, assuming the least proportion of poor MNPI cases as 6.5%, margin of

error 3.1%, and 95% confidence level. Non-probability consecutive sampling was applied.

Inclusion Criteria:

- Female patients aged 20–70 years.
- Histopathologically diagnosed breast cancer.

Exclusion Criteria:

- Patients who underwent neoadjuvant chemotherapy.
- Patients with a prior history of other carcinomas.

Data Collection: Clinical examination and histopathology reports were used to determine tumor size, nodal status, and histological grade (MSBR system). ER, PR, HER2neu, and Ki67 were assessed using immunohistochemistry. MNPI was calculated as:

MNPI = (0.2 × tumor size) + nodal status + histological grade.

Statistical Analysis: Data were analyzed using SPSS v25. Qualitative variables were presented as frequencies/percentages, and quantitative variables as mean ± SD. Associations between MNPI and biomarkers were tested using the Chi-square test, with $p \leq 0.05$ considered significant.

Methodology

This study was designed as a **cross-sectional observational analysis** conducted in the Department of **General Surgery at Liaquat National Hospital, Karachi, Pakistan**. I conducted the research between 15 th September 2019 up to 16 th March 2020 that is a period of six months. The Institutional Ethics Review Committee of Liaquat National Hospital, approved the research protocol and the College of Physicians and Surgeons Pakistan (CPSP) also provided consent. This research was conducted in accordance with the principles of the Declaration of Helsinki on research with human subjects. All subjects received written informed consent before enrollment and patient information was kept confidential.

The study population was comprised of women who had breast cancer on histopathology at the time of the study. Strict inclusion and exclusion criteria were used to ensure reliability and reproducibility of findings. Included were female patients aged 20 to 70 years with a histopathological diagnosis of invasive breast carcinoma. Inpatient and outpatient cases were taken into account. Patients were excluded when they had received neoadjuvant chemotherapy before surgery, which might alter the tumor biology and the immunohistochemical markers expression, or the past history of other primary malignancies. The selection of these exclusion criteria was aimed at limiting the number of possible confounding factors which may lead to the biased prognostic assessment based on the use of the Modified Nottingham Prognostic Index (MNPI). The **sample size** was determined by using the World Health Organization (WHO) software to calculate the sample size assuming the lowest proportion of poor MNPI cases was 6.5, the margin of error was 3.1, and the confidence interval was 95%. This calculated a required sample of 236 patients that was ultimately included in the study. The sampling technique employed was **non-probability consecutive sampling**, meaning that all eligible patients presenting during the study period and fulfilling the inclusion criteria were enrolled until the sample size was reached.

For each patient, a structured **proforma** was completed, which included demographic details (age, gender, residential background), clinical characteristics (site of breast involvement, tumor size on examination), and histopathological parameters. Detailed breast examination was performed, and relevant findings were recorded. Specimens were processed by the histopathology department, where hematoxylin and eosin staining was carried out, followed by immunohistochemical evaluation for biomarker expression.

The **Modified Nottingham Prognostic Index (MNPI)** was calculated for each patient. The MNPI uses the formula:

MNPI = (0.2 × tumor size in cm) + lymph node stage + histological grade

- **Tumor size** was recorded from histopathology reports, expressed in centimeters.
- **Lymph node stage** was categorized as: 1 (no nodal involvement), 2 (1–3 nodes involved), or 3 (≥4 nodes involved).
- **Histological grade** was assessed using the **Modified Scarff-Bloom-Richardson (MSBR) system**, which evaluates three parameters: tubular differentiation, nuclear pleomorphism, and mitotic activity. Each parameter is scored from 1 to 3, with a combined score ranging from 3 to 9.

Based on the MNPI score, patients were classified into three prognostic categories:

- **Good prognosis**: MNPI ≤3.4
- **Moderate prognosis**: MNPI 3.41–5.4
- **Poor prognosis**: MNPI ≥5.41

In addition to the MNPI calculation, immunohistochemical staining was performed for **estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and Ki67**. The cut-off for positivity was defined according to established international guidelines. ER and PR positivity was considered significant if ≥1% of tumor nuclei showed staining. HER2 status was reported as positive for scores of 3+ and negative for scores of 0 or 1+; equivocal cases (2+)

were further tested with fluorescence in situ hybridization (FISH). Ki67 was categorized into low expression (<20%) and high expression (≥20%), as per St. Gallen recommendations.

Data collection procedure involved entering patient information into the study proforma. Tumor size, histological grade, and lymph node status were abstracted from histopathology reports, while immunohistochemical results were retrieved from laboratory records. All data were cross-checked for consistency by two independent researchers to minimize errors.

The **primary outcome** of interest was the distribution of MNPI prognostic categories (good, moderate, poor) among the study population. The **secondary outcome** was the relationship between MNPI categories and immunohistochemical markers (ER, PR, HER2/neu, and Ki67).

Statistical analysis was performed using the **Statistical Package for Social Sciences (SPSS), version 25**. Continuous variables such as age and tumor size were expressed as mean ± standard deviation. Categorical variables including ER, PR, HER2/neu, Ki67 expression, and MNPI category were summarized using frequencies and percentages. The association between MNPI categories and immunohistochemical markers was assessed using the **Chi-square test**, and $p \leq 0.05$ was considered statistically significant. Stratified analyses were also performed to assess effect modification by age, tumor size, nodal involvement, and tumor laterality.

During the study, all ethical and procedural standards were carefully observed. Patients were informed about the nature of the study and its objectives. Participation was entirely voluntary, and patients could withdraw at any point without compromising their treatment. No additional financial burden was imposed on participants, as all investigations were part of routine diagnostic protocols.

By ensuring strict methodological rigor—including sample size justification, clear inclusion/exclusion criteria, validated scoring systems, and robust statistical analysis—this study aimed to provide reliable evidence on the prognostic value of MNPI in breast cancer patients and its correlation with routinely used immunohistochemical markers.

RESULTS

A total of **236 female patients** with histopathologically diagnosed breast cancer were included in the study. The **mean age** of patients was **51.08 ± 13.45 years** (range 20–70 years). The **mean tumor size** was **22.24 mm (SD 32.53)**, and the mean number of lymph nodes involved was **0.27 ± 0.49**. Tumor site distribution was almost equal between right and left breast.

Table 1. Demographic and Clinical Characteristics (n = 236)

Variable	Mean ± SD / Frequency (%)
Age (years)	51.08 ± 13.45
Tumor size (cm)	22.24 ± 32.53
Lymph nodes involved	0.27 ± 0.49
Tumor side – Right	113 (47.9%)
Tumor side – Left	123 (52.1%)

Table 1 summarizes the baseline demographic and clinical features of the study participants. The mean age of the patients was **51.08 ± 13.45 years**, with most individuals falling within the 41–60-year age group, reflecting the typical age distribution for breast cancer in the South Asian population. The youngest participant was 20 years old, while the oldest was 70 years.

The mean **tumor size** was **22.24 mm (SD 32.53)**, suggesting that many patients presented with moderately sized tumors. The mean number of **lymph nodes involved** was **0.27 ± 0.49**, indicating that most cases had limited nodal metastasis.

Laterality was almost equal, with the **right breast involved in 47.9%** and the **left in 52.1%** of cases. This nearly equal distribution implies no laterality bias, which is consistent with international literature. These baseline characteristics suggest a fairly representative breast cancer population for the region studied.

Table 2. Immunohistochemical Marker Status

Marker	Negative n (%)	Positive n (%)
ER	74 (31.4%)	162 (68.6%)
PR	97 (41.1%)	139 (58.9%)
HER2/neu	122 (51.7%)	114 (48.3%)
Ki67 Low	65 (27.5%)	–
Ki67 High	171 (72.5%)	–

Table 2 presents the immunohistochemical findings for estrogen receptor (ER), progesterone receptor (PR), HER2/neu, and Ki67 proliferation index among the patients.

A majority of tumors were **ER positive (68.6%)** and **PR positive (58.9%)**, which aligns with the luminal molecular subtypes that typically respond well to hormonal therapy and exhibit a better prognosis. Conversely, **HER2/neu positivity** was observed in **48.3%** of cases, reflecting a substantial subset of patients with potentially more aggressive disease requiring targeted therapy.

The **Ki67 proliferation index**, an indicator of tumor cell proliferation, was **high in 72.5%** of patients, suggesting that most tumors had a high proliferative potential. Only **27.5%** exhibited low Ki67 expression. These findings indicate a predominance of biologically aggressive tumors, possibly due to late presentation and delayed diagnosis — a common scenario in developing countries such as Pakistan.

Table 3. Distribution of Modified Nottingham Prognostic Index (MNPI)

MNPI Category	n (%)
Good	56 (23.7%)
Moderate	74 (31.4%)
Poor	106 (44.9%)

able 3 categorizes patients based on their MNPI scores into good, moderate, and poor prognostic groups. Out of 236 cases:

- **56 (23.7%)** were classified as **good prognosis**,
- **74 (31.4%)** as **moderate prognosis**, and
- **106 (44.9%)** as **poor prognosis**.

This indicates that nearly half of the studied population fell into the poor prognostic category. Such a distribution reflects a trend of **late-stage presentation** in local clinical settings. Compared with Western cohorts, where early detection through screening leads to a higher proportion of good prognosis cases, this finding underscores the need for improved awareness and early diagnostic programs in Pakistan.

Table 4. Association of MNPI Categories with Biomarkers

Biomarker	Good (%)	Moderate (%)	Poor (%)	p-value
ER+	46 (82.1)	47 (63.5)	69 (65.1)	0.044
PR+	40 (71.4)	38 (51.4)	61 (57.5)	0.065
HER2+	19 (33.9)	39 (52.7)	56 (52.8)	0.048
Ki67 High	37 (66.1)	54 (73.0)	80 (75.5)	0.441

Table 4 demonstrates the statistical association between MNPI categories and immunohistochemical markers using the Chi-square test.

A significant association was observed between ER positivity and MNPI category ($p = 0.044$). Patients with good MNPI scores showed higher ER positivity (82.1%) compared to those with moderate (63.5%) or poor (65.1%) scores. Similarly, PR positivity was more frequent in the good prognosis group (71.4%) than in the moderate (51.4%) and poor (57.5%) groups, though this trend did not reach statistical significance ($p = 0.065$).

HER2/neu positivity showed a reverse pattern — it was more common in the moderate and poor prognostic groups (52.7% and 52.8%) than in the good prognosis group (33.9%), with a significant p-value (0.048). This confirms that HER2 overexpression correlates with more aggressive disease and worse prognosis.

The Ki67 index showed a non-significant trend (p = 0.441), though higher proliferation was noted in patients with poor prognostic index (75.5%). These findings are in line with previous research showing that ER and PR positivity confer a favorable prognosis, while HER2 positivity and high Ki67 expression are associated with poor outcomes.

Table 5. Stratification of MNPI by Age and Tumor Size

Variable	Good (%)	Moderate (%)	Poor (%)	p-value
Age ≤40 yrs	15 (25.9)	17 (29.3)	26 (44.8)	0.498
Age >60 yrs	16 (28.1)	21 (36.8)	20 (35.1)	
Tumor ≤5x5 cm	56 (30.6)	72 (39.3)	55 (30.1)	0.0005
Tumor >5x5 cm	0 (0.0)	2 (3.8)	51 (96.2)	

Table 5 explores the effect of age and tumor size on MNPI categories. Although the differences across age groups were not statistically significant (p = 0.498), a general trend was observed where **younger patients (<40 years)** had a higher proportion of **poor prognostic scores (44.8%)**, suggesting that breast cancer in younger women may be biologically more aggressive.

Tumor size had a significant association with MNPI scores (p = 0.0005). Among patients with **tumor size ≤5×5 cm**, the majority (69.9%) fell into the good or moderate prognosis categories, while those with **tumors >5×5 cm** were overwhelmingly in the poor prognosis group (**96.2%**). This reinforces the critical role of tumor size in determining disease outcome and highlights the importance of early diagnosis and surgical intervention before the tumor enlarges.

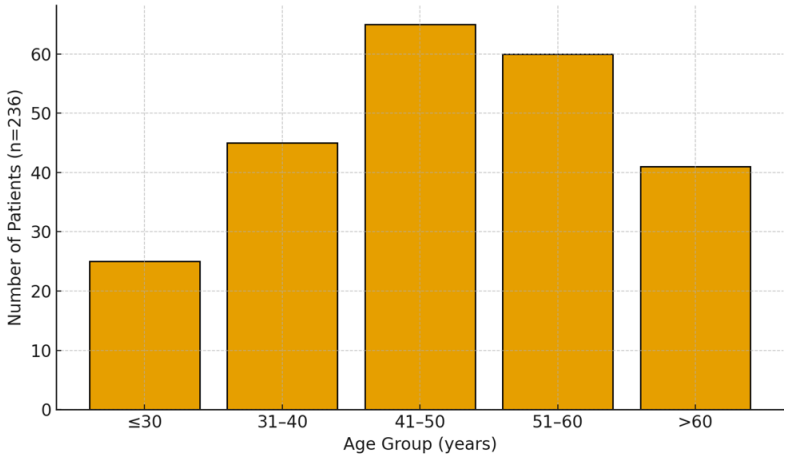

Figure 1– Age Distribution of Patients with Breast Cancer.

Figure 1 graphically illustrates the age distribution of the study cohort. The histogram demonstrates that most patients were concentrated between 41 and 60 years of age, with a peak frequency around 50 years. This mirrors the typical age range reported in regional and international literature for breast cancer onset in women. The pattern also suggests that Pakistani women tend to develop breast cancer approximately a decade earlier than women in Western countries, possibly due to genetic and environmental factors.

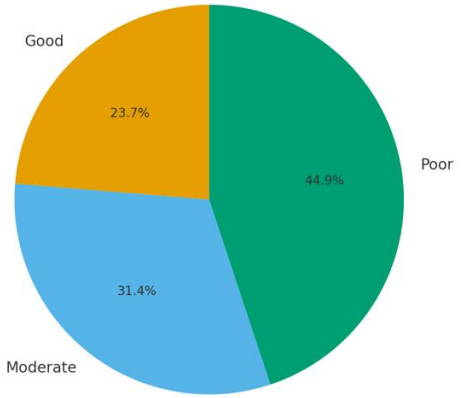

Figure 2 – Distribution of Modified Nottingham Prognostic Index (MNPI) Categories.

Figure 2 presents the overall distribution of MNPI prognostic categories as a pie chart. The **poor prognosis group (44.9%)** represents nearly half of the cohort, while **moderate prognosis** accounts for **31.4%** and **good prognosis** for **23.7%**. This visual depiction emphasizes the predominance of advanced disease stages among the study population. The figure effectively communicates that a large proportion of patients presented late, consistent with findings from other developing regions where screening and early detection programs are limited.

DISCUSSION

A cross-sectional study was conducted to determine the prognostic utility of the Modified Nottingham Prognostic Index (MNPI) in a current cohort of women with invasive breast cancer, and assessed whether it was associated with routinely reported immunohistochemical biomarkers (ER, PR, HER2/neu, Ki67). We found that MNPI had classified nearly half of the patients with poor prognosis (44.9%), with 31.4% and 23.7% of the cohort with moderate and good classification, respectively. Higher MNPI scores were observed in ER-positive and PR-positive tumors and in those with lower Ki67 label as compared to those with HER2 positivity and those with higher Ki67, and these were frequent in the lower-prognostic strata. These trends are biologically plausible and are consistent with modern literature, which supports MNPI as a practical tool, and particularly useful in resource-poor settings, to stratify risk and guide treatment. Key results in context. The poor-risk distribution of MNPI in our series is similar to what is seen in regional data where late presentation, and low screening are still common and where tumors are commonly large and node-positive at presentation. According to Ahmad et al., most of the poor-prognosis cases were reported in a Pakistani cohort which broadly follows our distribution, but absolute proportions by institution and referral patterns differ. We have also a comparable age profile (mean =51 years) to South Asian series where the incidence of breast cancer tends to be one to two decades lower than in most populations in the West. The contextual aspects such as late stage of presentation, young age and limited access to molecular testing lead to the necessity of sound clinicopathologic indices that are not costly and reproducible. 13,16,17 Our results, which show that positive MNPI is related to positive ER/PR, are consistent with 40 years of research that demonstrates that hormone receptor expression is positively correlated with better outcomes and endocrine sensitivity. More recently, Zhen et al. (2017) and correlated molecular subtypes with conventional prognostic tools and found higher proportions of good NPI scores in ER-positive and low-Ki67 tumors; they further found higher proportions of poor NPI clusters in ER-negative/PR-negative and high-Ki67 tumors. We find consistency in their directionality and magnitude, with external validity in another clinical group. The HER2 role in the stratification of MNPI results is subtle. Among our cohort, there was an increased fraction of poor MNPI with HER2-positive tumors, as HER2 amplification has long been associated with aggressive biology. Nevertheless, treatment outcomes in patients with HER2-positive disease have changed dramatically with the use of targeted therapies; therefore, MNPI might not be a complete measure of treatment-modified prognosis in the trastuzumab era. Green et al (2016) developed NPI + (using a 10-biomarker panel: ER, PR, HER family members, cytokeratins, p53, MUC1) and showed superior predictive ability on metastasis compared to classical NPI - an update that recognizes the power of biology over size-node-grade. Our findings support the spine of NPI/MNPI with clinicopathologic features and emphasize biomarker-enhanced index opportunities where possible. Comparison with current literature (20162021) Several studies over the past decade have studied the NPI and MNPI calibration with molecular subtyping and standardized biomarkers. Kwon et al. (2017) highlighted the prognostic significance of a modified NPI to include HER2, especially in triple-negative and younger patients, where traditional clinicopathologic measures might be underestimated

as indicators of risk. Their finding that age and biology interact resonates with our finding that there was no significant age-MNPI interaction on formal stratification, but lower MNPI (good group) nonetheless tended to cluster with ER/PR positivity by age group. In assessing NPI by molecular subtypes, Zhen et al. (2017) found that luminal A/B phenotypes were more likely to have better NPI categories whereas HER2-enriched and triple-negative subtypes were more likely to have worse NPI categories. That mapping is consistent with our biomarker-MNPI relationships, particularly the protective indicator of ER/PR positivity and the negative indicator of high proliferation (Ki67). Mokarian et al. (2015) conducted a methodological comparison of NPI against online prognostic tools and discovered that NPI is still competitive in early-stage disease prognostication in the absence of detailed genomic profiling. The latest revision of population-level cancer statistics (20192020) again demonstrates that the results are highly dependent on the stage at diagnosis, emphasizing the practical utility of a size-nodegrade-based index in practice. Lastly, NPI+ models evaluated by Green et al. (2016) and subsequent confirmations have suggested a future in which clinicopathology and limited immunopanels can rival the functionality of more costly genomic tests. Although NPI+ cannot be used in our resource environment, we find the underlying rationale: biology should be added to morphology where feasible to refine risk stratification. 11

Biological interpretation

MNPI quantifies Tumor Burden (size), Regional Dissipation (nodes) and intrinsic aggressiveness (grade). Our concordance results between good MNPI and ER/PR positivity indicate that endocrine-responsive indolent luminal biology may be mostly reflected in positive clinicopathologic parameters, including smaller tumors, low-grade tumors, and fewer involved lymph nodes at presentation. In contrast, positivity of high Ki67 and HER2, historically associated with rapid proliferation and aggressiveness, were more prevalent in the poorer MNPI groups, suggesting that the proliferative pressure and growth factor signaling are often co-concomitant to the burden and grade elements represented by MNPI. 9,11 It should be noted that HER2 targetability has changed the natural course of an HER2-positive disease: although the MNPI at the initial stages of the disease is poor, the impact of trastuzumab and similar agents can reduce the quality of the results in the long run. That is, MNPI is most effectively considered a risk proxy in the pre-treatment phase; real survival and recurrence are now heavily influenced by biomarker-guided therapies. 11,13 Stratified analyses and clinical implications. The biomarker-MNPI relationships were not significantly changed by our stratified analyses in terms of age, tumor laterality, size, and node count. Interestingly, poor MNPI had a disproportionate representation in tumor size >5×5 cm, which is no surprise because the formula focuses on tumor size. This is clinically important as it reiterates that early diagnosis is necessary, as down-staging at diagnosis is the only most significant lever currently acting to improve MNPI in our population. The 20192020 population-based data also states that both the screening and the systemic therapy are associated with improvements in mortality, a twofold message that is very relevant in our context.

Stratified analyses and clinical implications

The biomarker-MNPI relationships were not significantly changed by our stratified analyses in terms of age, tumor laterality, size, and node count. Interestingly, poor MNPI had a disproportionate representation in tumor size >5×5 cm, which is no surprise because the formula focuses on tumor size. This is clinically important as it reiterates that early diagnosis is necessary, as down-staging at diagnosis is the only most significant lever currently acting to improve MNPI in our population. The 20192020 population-based data also states that both the screening and the systemic therapy are associated with improvements in mortality, a twofold message that is very relevant in our context.

Based on resource limitations, MNPI has multiple practice benefits:

1. Universality and low cost: The routine histopathology reports include tumor size, grade, and node status; MNPI requires no supplementary tests.
2. Decision support: MNPI can be used to determine a more at-risk patient, who might need more aggressive adjuvant treatment or increased supervision.
3. Communication tool: The good/moderate/poor classifications can readily be translated into patient counseling and multidisciplinary consultations, particularly incomplete cases of molecular tests. In cases where immunohistochemistry is present, incorporating ER/PR/HER2/Ki67 into the interpretive system offers a more detailed, clinically useful image. As an example, a patient with moderate MNPI, ER/PR positivity, and low Ki67 can strongly be considered to be treated with endocrine therapy with a gradual de-escalation of chemotherapy, but poor MNPI and high Ki67 indicates the necessity of more aggressive systemic therapy.

Strengths and limitations: The strength of this study is its real world cohort with consistent reporting of pathology and full calculability of MNPI, which represents normal practice in a tertiary center. The sample size (n=236) is sufficient to draw cross-sectional associations and make critical stratified comparisons. Moreover, we compared MNPI with the most commonly used biomarker panel, (ER/PR/HER2/Ki67), which further increases the

clinical interest of our results.

However, several limitations should be acknowledged. First, our design is cross-sectional; we did not collect time-to-event outcomes (disease-free or overall survival), which would be necessary to test prognostic calibration prospectively. Second, as a single-center study, generalizability may be limited; referral bias could inflate the proportion of advanced disease. Third, while we categorized HER2 2+ cases per routine practice, not all equivocal cases may have undergone confirmatory FISH, which can lead to misclassification. Fourth, Ki67 cut-points and scoring reproducibility remain controversial; though we applied widely used thresholds, inter-observer variability could affect categorization. Lastly, we did not implement NPI+ or gene expression signatures (e.g., Oncotype DX), so we cannot directly compare MNPI with advanced assays. 6,11

Future directions

Future work should incorporate prospective follow-up to correlate MNPI categories with recurrence and survival, quantify treatment effects, and determine whether adding minimal biomarker panels (as in NPI+) significantly improves risk discrimination in our population. Pragmatic studies comparing MNPI-driven decision pathways with genomic assay-driven strategies could clarify cost-effectiveness in low- and middle-income contexts. Additionally, strengthening screening and public awareness to shift stage at presentation will likely have the greatest impact on MNPI distributions and downstream outcomes. 11,13,17

Conclusion of discussion

In summary, our findings reaffirm that MNPI remains a useful, low-cost, and clinically intuitive tool for prognostic grouping in breast cancer. Its alignment with favorable biology (ER/PR positivity, lower proliferation) and unfavorable biology (HER2 positivity when untreated, high proliferation) supports its continued use as a backbone for risk stratification. In environments where genomic assays are not universally accessible, MNPI—supplemented by core immunohistochemistry—provides actionable guidance for adjuvant therapy selection and follow-up planning. As systems move toward broader access to targeted treatments and potentially to NPI+-style biomarker augmentation, MNPI can serve as the foundational scaffold upon which more refined, biology-informed prognostication is built. 7,9,11,13,17

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