



Nottingham Prognostic Index with IHC-Based Biological Subgroups in Invasive Ductal Carcinoma: A 6-Month Retrospective Observational Study

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Abstract

Background: The Nottingham Prognostic Index (NPI) integrates tumour size, histological grade and lymph-node status to provide a clinicopathological assessment of prognosis in breast carcinoma, whereas immunohistochemical (IHC) assessment of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) provides complementary information about tumour biology. This study evaluated the distribution of NPI in relation to IHC-based biological subgroups in invasive ductal carcinoma.

Materials and Methods: A retrospective 6-month observational study was performed on invasive ductal carcinoma cases identified between January and June 2026. NPI was recalculated from tumour size, histological grade and lymph-node status where eligible data were available. ER, PR and HER2 results were used for IHC-based biological subgrouping. Associations were assessed using Fisher's exact test. A secondary analysis dichotomised NPI at 3.4.

Results: The study presentation identified 182 invasive ductal carcinoma cases. Of these, 35 were NPI-assessable because tumour size, histological grade and lymph-node status were available for NPI calculation; the remaining 147 cases did not have complete information required for NPI assessment. Four of the 35 NPI-assessable cases could not be assigned a definitive IHC-based biological subgroup, leaving 31 cases for the final NPI-IHC analytical cohort. In the 35-case cohort, the NPI range was 2.4–7.0. In the final 31-case analytical cohort, 17 (54.8%) were HR-positive/HER2-negative, 11 (35.5%) were triple-negative and 3 (9.7%) were HR-negative/HER2-positive. At an NPI threshold of 3.4, 7/17 (41.2%) HR-positive/HER2-negative cases had NPI ≤ 3.4 compared with 1/14 (7.1%) in the combined HR-negative group; 13/14 (92.9%) of the latter had NPI > 3.4 . Fisher's exact test showed an association ($p=0.045$).

Conclusion: Higher NPI values were more frequently observed in the combined HR-negative group in this exploratory cohort. The finding is exploratory and does not establish independent prognostic significance, causation or survival prediction. Larger cohorts with complete clinicopathological data and follow-up are required for validation.

Keywords: breast carcinoma; IHC-based biological subgroup; HER2; immunohistochemistry; Nottingham Prognostic Index; prognostic index

Introduction

Breast carcinoma is a biologically heterogeneous disease in which conventional histopathological parameters and biomarker-defined tumour biology provide complementary information for clinical assessment. The Nottingham Prognostic Index (NPI) was developed as a clinicopathological prognostic tool incorporating tumour size, histological grade and lymph-node status [1]. Subsequent work established NPI categories for prognostic stratification in primary breast carcinoma [2].

Tumour size, grade and nodal involvement capture major components of pathological tumour burden and aggressiveness. In contrast, immunohistochemical assessment of ER, PR and HER2 characterises important biological features relevant to classification and treatment. Current ASCO/CAP recommendations provide standardized approaches to ER/PR and HER2 testing [3,4]. IHC-based surrogate groups are useful in routine pathology, but they should not be equated directly with molecular intrinsic subtypes.

Previous work has demonstrated differences in immunohistochemical marker expression across NPI groups [5], supporting the concept that clinicopathological prognostic indices and tumour biology may show meaningful relationships. NPI and IHC-based biological subgrouping, however, describe different dimensions of breast carcinoma: NPI is derived from tumour size, histological grade and lymph-node status, whereas IHC grouping is derived from biomarker expression.

The present study evaluated the distribution of NPI in relation to IHC-based biological subgroups in invasive ductal carcinoma and explored the relationship using a secondary NPI threshold of 3.4.

Materials And Methods

Study Design And Setting

This was a retrospective 6-month observational study conducted in the Department of Pathology, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India, covering cases identified between January and June 2026.

Study Cohort And Data Selection

The study presentation identified 182 invasive ductal carcinoma cases. Cases were screened for the availability of the variables required for NPI

assessment: tumour size, Nottingham histological grade and lymph-node status. The presentation defined 35 cases as NPI-assessable and 31 cases as the final cohort with both NPI and interpretable IHC-based biological subgrouping. Cases with incomplete or indeterminate ER, PR or HER2 information were not assigned a definitive IHC-based subgroup.

Nottingham Prognostic Index

NPI was calculated using the formula: $NPI = 0.2 \times \text{tumour size (cm)} + \text{histological grade} + \text{lymph-node score}$. Lymph-node score was assigned as 1 for no positive nodes, 2 for 1–3 positive nodes and 3 for more than 3 positive nodes. NPI categories were defined as good (≤ 3.4), moderate ($>3.4-5.4$) and poor (>5.4).

Immunohistochemical Classification

ER and PR were interpreted using Allred scoring. HER2 was interpreted according to the ASCO/CAP framework, with 3+ considered positive; equivocal HER2 results requiring ISH/FISH clarification were not forced into a definitive subgroup. For the primary three-group analysis represented in the study dataset, cases were classified as HR-positive/HER2-negative, triple-negative, or HR-negative/HER2-positive. A case with HR-positive/HER2-positive status was not included in this three-group comparison. This definition is important for reproducing the reported 31-case analysis.

Statistical Analysis

Categorical data were summarized as frequencies and percentages. Because of the small analytical cohort, Fisher's exact test was used. In the secondary analysis, NPI was dichotomised into ≤ 3.4 and >3.4 and compared between HR-positive/HER2-negative cases and the combined HR-negative group comprising HR-negative/HER2-positive and triple-negative cases. A p value <0.05 was considered statistically significant.

Ethical Considerations

Ethics approval/waiver: [Insert the applicable Institutional Ethics Committee approval number or formal waiver statement before submission, in accordance with institutional and journal requirements.]

Results

Study Cohort

A total of 182 invasive ductal carcinoma cases were identified, of which 35 were considered NPI-assessable after data-quality screening. Four of these 35 cases could not be assigned a definitive IHC-based biological subgroup because of incomplete or indeterminate biomarker information. The final NPI-IHC analytical cohort therefore comprised 31 cases.

The case-selection pathway and the relationship between clinicopathological NPI assessment and IHC-based biological subgrouping are shown in Figure 1.

Cohort selection pathway: Of 182 invasive ductal carcinoma cases identified during the study period, 35 (19.2%) had complete tumour size, histological grade and lymph-node information required for NPI calculation. The remaining 147 cases were not NPI-assessable because the required NPI variables were incomplete. Among the 35 NPI-assessable cases, 4 lacked sufficient or definitive ER, PR and/or HER2 information for assignment to the predefined IHC-based biological subgroups, resulting in a final NPI-IHC analytical cohort of 31 cases.

NPI distribution

Among the 35 NPI-assessable cases reported in the study presentation, NPI values ranged from 2.4 to 7.0, with a mean of 4.54 ± 1.22 and a median of 4.50. The presentation reported 9 cases (25.7%) in the good category, 18 (51.4%) in the moderate category and 8 (22.9%) in the poor category. Thus, 26/35 (74.3%) were reported as moderate or poor NPI. The distribution is shown in Table 1&2 and Figure 2.

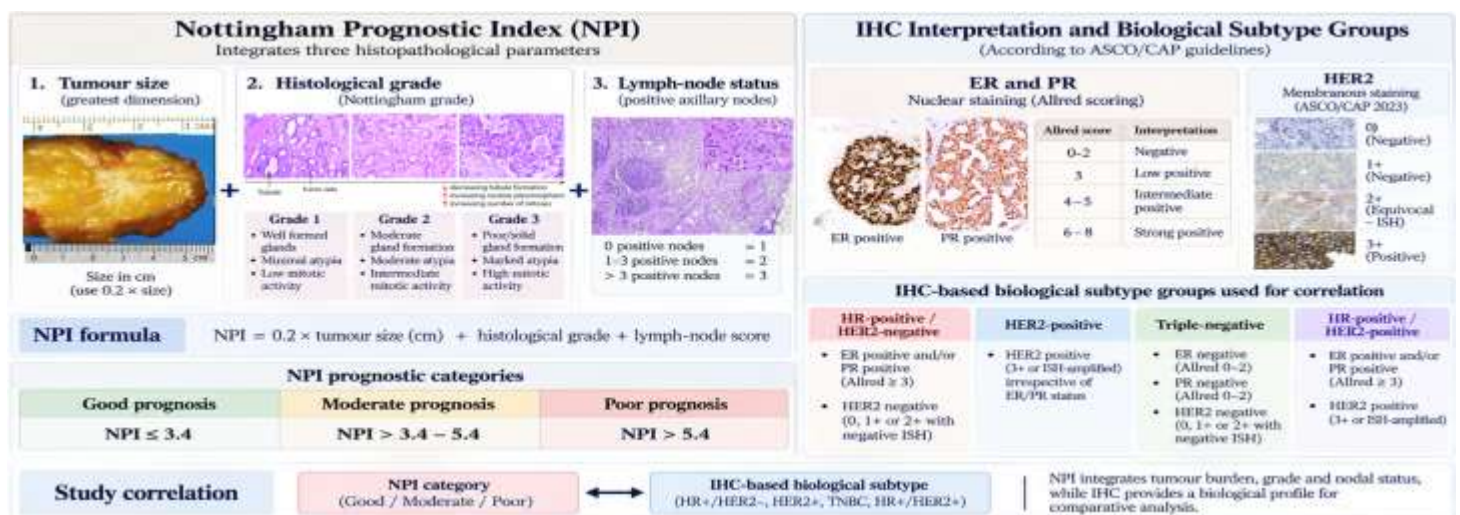
IHC-based biological subgroup distribution

Among the 31 cases included in the primary NPI-IHC analysis, HR-positive/HER2-negative tumours constituted the largest subgroup, with 17 cases (54.8%). Triple-negative tumours accounted for 11 cases (35.5%), while HR-negative/HER2-positive tumours accounted for 3 cases (9.7%). These figures reproduce the final analytical grouping shown in the study presentation and are supported by the corresponding case-level dataset after exclusion of indeterminate/unassigned cases and the HR-positive/HER2-positive case from the three-group comparison.

Association between NPI and IHC-based biological subgrouping

When NPI was dichotomised at 3.4, 7/17 (41.2%) HR-positive/HER2-negative cases had $\text{NPI} \leq 3.4$ and 10/17 (58.8%) had $\text{NPI} > 3.4$. In the combined HR-negative group of 14 cases, 1 (7.1%) had $\text{NPI} \leq 3.4$ and 13 (92.9%) had $\text{NPI} > 3.4$. Fisher's exact test demonstrated a statistically significant association ($p=0.045$). The contingency table is shown in Table 3 and Figure 4.

Thus, higher NPI values were more frequently observed in the combined HR-negative group in this exploratory cohort. This association does not establish that IHC-based biological subgroup independently determines NPI, nor does it demonstrate an effect on survival or treatment outcome



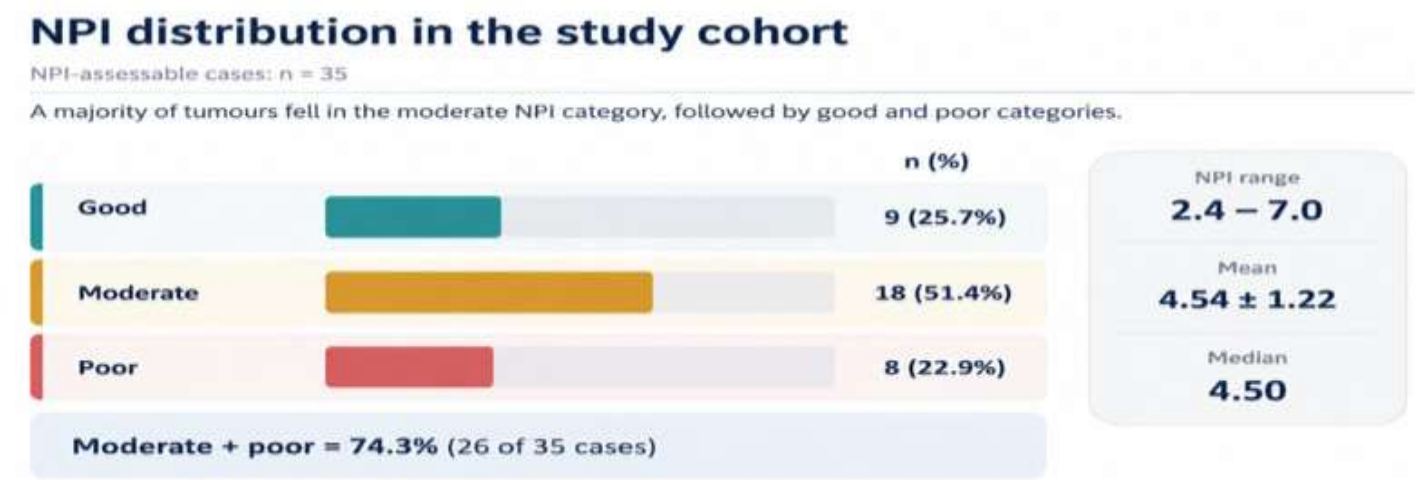


Figure 2. Distribution of IHC-based biological subgroups among the 31 cases in the primary NPI–IHC analysis.

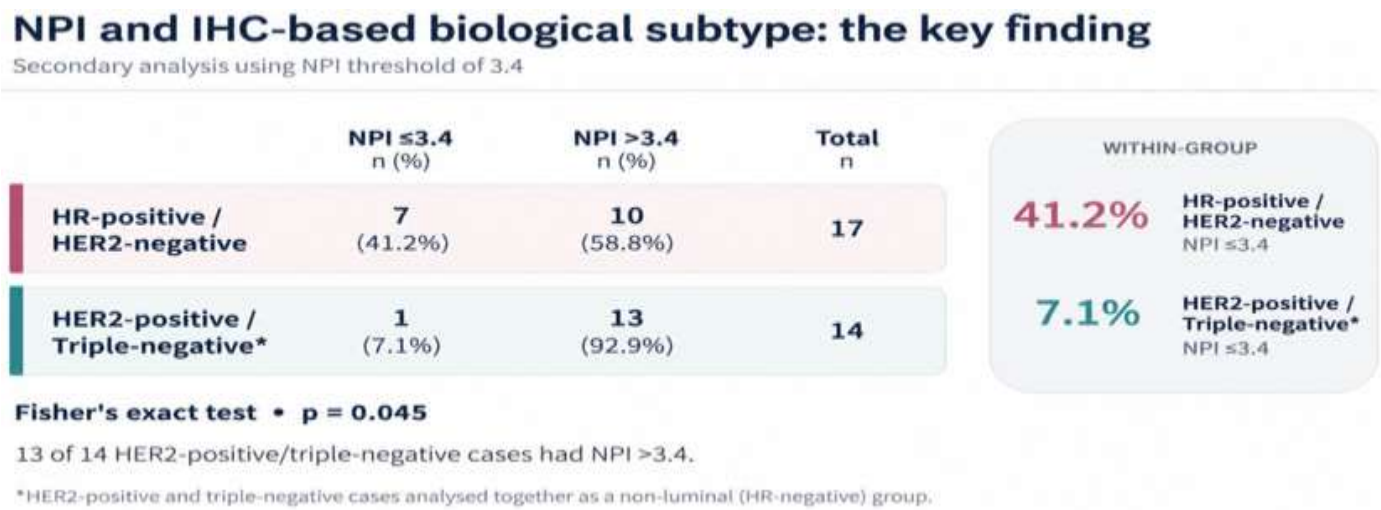


Figure 3. Secondary analysis using an NPI threshold of 3.4, showing the distribution of NPI ≤3.4 and >3.4 across the two biological groups and Fisher’s exact test result.

Discussion

The present study examined the relationship between a conventional clinicopathological prognostic index and IHC-based tumour biology in invasive ductal carcinoma. The principal observation was that higher NPI values were more frequently represented in the combined HR-negative group in this exploratory cohort. In the final 31-case analytical cohort, 13 of 14 cases in the combined HR-negative group had NPI >3.4, compared with 10 of 17 HR-positive/HER2-negative cases. Fisher’s exact test yielded p=0.045.

NPI combines tumour size, histological grade and lymph-node status into a single numerical measure [1,2]. Its practical value lies in summarizing several conventional pathological prognostic variables. In the present study, the reported NPI distribution was

predominantly moderate, with a substantial proportion of cases in the poor category. This distribution reflects the composition of the available retrospective cohort and should not be interpreted as a population-level estimate.

HR-positive/HER2-negative tumours formed the largest IHC-based subgroup, followed by triple-negative and HR-negative/HER2-positive tumours. The classification used in this analysis is explicitly IHC-based. Although ER, PR and HER2 are clinically important biomarkers and their assessment is standardized by ASCO/CAP recommendations [3,4], IHC surrogate groups do not reproduce genomic intrinsic subtypes exactly.

The observed relationship between higher NPI and the combined HR-negative group is plausible because NPI

incorporates pathological features associated with tumour burden and aggressiveness. However, the present dataset cannot establish which individual NPI component contributed most to the observed association. It also cannot determine whether the IHC-based subgroup remains independently associated with NPI after adjustment for tumour size, grade and nodal status.

The findings are conceptually related to previous work demonstrating differences in immunohistochemical marker expression across NPI categories [5]. The present study specifically evaluates the distribution of IHC-based biological subgroups across NPI-defined risk categories in a short retrospective institutional series. The small sample size and retrospective nature make the result hypothesis-generating rather than confirmatory.

A major strength is the attempt to reconstruct NPI from underlying pathological variables rather than treating the index as an unexplained recorded value. The use of Fisher's exact test is appropriate for the small analytical cohort. The study also avoids forcing equivocal HER2 results into a definitive biological subgroup. Nevertheless, incomplete clinicopathological information substantially reduced the eligible cohort, and no survival, recurrence or treatment-response data were available.

Future studies should use a prospectively defined dataset with complete tumour size, grade, nodal status and biomarker results, clearly prespecified handling of HR-positive/HER2-positive tumours, and clinical follow-up. Larger cohorts would also permit multivariable analysis to determine whether biological subgroup contributes independently beyond the components already incorporated into NPI.

Conclusion

In this retrospective institutional cohort, higher NPI values were more frequently observed among the combined HR-negative group comprising triple-negative and HR-negative/HER2-positive tumours. The association reached statistical significance in the exploratory secondary analysis using an NPI threshold of 3.4 (Fisher's exact test, $p=0.045$). The finding should be regarded as exploratory and does not establish independent prognostic significance, causation or survival prediction. Larger studies with

complete clinicopathological data and outcome follow-up are required for validation.

Strengths And Limitations

The strengths of the study include reconstruction of NPI from underlying pathological variables where eligible data were available, use of Fisher's exact test for the small analytical cohort, and avoidance of definitive classification of equivocal HER2 cases. Limitations include the retrospective pathology-derived dataset, incomplete tumour size/grade/nodal information in many records, the small final analytical cohort, absence of survival or treatment follow-up, and the use of IHC-based surrogate groups rather than genomic intrinsic subtypes.

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TABLES

Table 1. NPI distribution among the 35 NPI-assessable cases.

NPI category	NPI range	n (%)
Good	≤ 3.4	9 (25.7)
Moderate	$> 3.4-5.4$	18 (51.4)
Poor	> 5.4	8 (22.9)

Table 2. IHC-based biological subgroup distribution in the 31-case analytical cohort

IHC-based biological subgroup	n	%
HR-positive / HER2-negative	17	54.8
Triple-negative	11	35.5
HR-negative / HER2-positive	3	9.7

Table 3. Association between dichotomised NPI and IHC-based biological subgrouping.

Biological group	NPI ≤ 3.4 , n (%)	NPI > 3.4 , n (%)	Total
HR-positive / HER2-negative	7 (41.2)	10 (58.8)	17
HR-negative (HER2-positive / triple-negative)	1 (7.1)	13 (92.9)	14
Total	8	23	31

Note: HR-negative group comprises HR-negative/HER2-positive and triple-negative cases. Fisher's exact test, $p=0.045$.