

Categorization of the Nottingham Prognostic Index in Breast Carcinoma: A Retrospective Study of 473 Female Patients

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ABSTRACT

Background: The Nottingham prognostic index (NPI) combines lymph node status, tumor size, and histological grade, reflecting breast cancer's metastatic behavior, growth rate, and genetic instability. NPI is a commonly used, clinically relevant, and internationally validated system for classifying early and locally advanced breast cancer cases [TNM (tumor, lymph nodes, and metastasis) stages I, II, and III] into three or more prognostic groups. NPI is important for patients and clinicians to decide whether to undergo adjuvant chemotherapy following surgery.

Objectives: To determine the prevalence of various categories of NPI in breast cancer patients in Duhok, Iraqi Kurdistan and to establish a correlation between NPI and a variety of clinical, pathological, and immunohistochemical parameters.

Materials and methods: This retrospective cross-sectional study was conducted in the Oncology Clinic at Azadi Teaching Hospital, Duhok, Iraq. The data included age, side of the breast involved, multi-centricity of cancer, histological type, NPI category, surgery type, and excision margins. The histopathological data included the type of carcinoma, lympho-vascular invasion (LVI), dermal invasion, and nipple involvement. IHC profile included ER, PR, Her2-neu and ki67 index. These data were expressed in frequencies and percentages, and the NPI was correlated with the previous parameters using appropriate statistical tests, and a P-value < 0.5% is considered a statistically significant difference.

Results: There was no statistically significant association between NPI and age, focality, and ER status (P-value = 0.93, 0.55, and 0.64, respectively). Significant correlations exist with, dermal involvement, surgical margins involvement, and PR status (P-value = 0.03, 0.029, 0.046, and 0.011, respectively). The correlation is highly significant when the NPI is considered against the stage, Ki-67, and Her2-neu (P-value = 0.001 for all).

Conclusion: Most cases that were examined belonged to the moderate and poor numerical NPI categories, and these NPIs show significant associations with the stage, Ki-67, and Her2-neu.

Keywords: Carcinoma; Breast; Nottingham prognostic index; Duhok.

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INTRODUCTION

Numerous worldwide studies have demonstrated the top ranking of breast cancer in females and its huge contribution to cancer mortality rates [1], and even surpassed lung cancer as the leading

cause of cancer incidence globally in 2020, representing 11.7% of all cancer cases with an estimated 2.3 million new cases. Globally, breast cancer accounts for fifth among other cancers, with 685,000 deaths reported. For every 4 women with cancer, one has breast cancer, ranking first for incidence in most countries (159 out of 185 countries) [2]. Iraqi cancer registration showed that the total number of breast cancer was 7515, which also ranks first (22.2%), while the deaths due to breast cancers were 3019 and also ranks first (15.3%) among other malignancies [2]. A registration performed in Erbil and

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Duhok governorates in Iraqi Kurdistan during the seven years 2013-2019 showed that 3406 (39.4%) females and 105 (1.2%) males had breast cancer in Erbil city, and 1025 (18.1%) female breast cancer and 17 (0.3%) male breast cancers in Duhok city [3].

Many improvements and advancements have been made over the last 20 years in managing breast cancer due to the identification of prognostic factors capable of providing information on the progression of the disease. These survival-related factors are indicators of growth, invasion, and metastatic potential [4]. These prognostic factors include tumor size, lymph nodes, histologic grade, stage, estrogen and progesterone receptors, ki67 expression, and HER2/neu (erB-2) oncogene alteration [5]. One of these survival-related parameters is the Nottingham prognostic index (NPI), which combines lymph node status, tumor size, and histological grade and reflects metastatic behavior, growth rate, and genetic instability in breast cancer [6]. This index is commonly applied, internationally validated, and clinically relevant to the patient's outcome and is used for classifying early and locally advanced breast cancer cases (excluding metastatic disease) and dividing such cases into three or more prognostic groups. NPI has an active role in clinical practice and research. Clinically, NPI provides a guide for adjuvant chemotherapy after surgery and represents an example of precision medicine [7]. The NPI is not applied to patients with distant metastases; such patients will usually die from their disease, and an alternative metastatic index can be used to guide treatment in this group [8].

The index is calculated using the formula: $NPI = [0.2 \times S] + N + G$. Where S is the size of the index lesion in centimeters, N is the node status 0 nodes = 1, 1-3 nodes = 2, > 3 nodes = 3, and G is the grade of tumor Grade I = 1, Grade II = 2, Grade III = 3 [[8].

NPI correlates with the 5 years of survival: 1) For a score of $\geq 2,0$ to $\leq 2,4$, the 5-year survival was 93%; 2) For a score of $> 2,4$ to $\leq 3,4$, the 5-year survival was 85%; 3) For a score of $> 3,4$ to $\leq 5,4$, the 5-year survival was 70%; 4) For a score of $> 5,4$ the 5-year survival was 50% [9].

This study was conducted due to the significance of NPI in relation to the prognosis and treatment of breast cancer and the absence of any previous local research in Duhok City. The objective of this study was to ascertain the frequency of different classifications of the NPI among female breast carcinoma patients in Duhok, Iraqi Kurdistan. Additionally, we sought to establish a correlation between NPI and a range of clinical, pathological, and immunohistochemical parameters.

MATERIALS AND METHODS

This is a retrospective cross-sectional study conducted in Duhok city, registered in the Department of Surgery Duhok College of Medicine, and approved by the scientific committee of the college and the ethical committee of the directorate of Health in Duhok (reference number: 08032023-2-17, issued on March 8, 2023). The patient data were retrieved from the oncology clinic at Azadi Teaching Hospital. The inclusion criterion included patients with complete clinical, surgical, and histopathological records. The exclusion criteria were patients with deficient records (about half of the cases), patients in stage IV since NPI is not applied to stage IV cases, and male patients with breast carcinoma. A total of 473 cases of breast carcinoma were enrolled in this study from 2016-2021.

Patients were grouped according to their ages by admin-

istering a ten-year interval, the side of the breast, multicentricity of cancer, histological type, NPI, types of surgery, and excision margins.

Histopathological data included the type of carcinoma, lympho-vascular invasion, dermal invasion, nipple involvement, and surgical margin freedom. IHC profiles included: ER, PR, Her-2neu, and Ki-67 indexes.

The data were entered and analyzed using SPSS (Statistical Package for the Social Sciences) version 25. The continuous variables were expressed as mean \pm SD. While the categorical variables were presented in figures and tables as frequencies and percentages. The NPI was correlated with the previous parameters using the Chi-square and Fisher exact tests. A P-value $< 0.05\%$ is considered a statistically significant difference.

RESULTS

This study included 473 female patients with breast carcinoma. The age was ranged from 23 to 90 year with a mean age of 49.44 years \pm 0.57. The highest incidence (n = 109) was in the fifth decade of life. NPI of 3.4-5.4 was the highest category. There was no statistically significant association between the NPI categories and age groups (P-value = 0.93) as shown in Table 1.

The left breast was involved in 253 (53.48%) cases, the right one in 218 (46.08%) cases with a left: right ratio of 1.16:1, and two cases (0.44%) had bilateral breast carcinomas. The majority of the cases (n = 330, 69.77%) underwent a modified radical mastectomy, while the other 143 (30.23%) had conservative surgery like lumpectomy, wide local excision, or quadrantectomy.

The majority of the cases were with free margins (n = 437, 92.4%), no skin involvement (n = 454, 96%), unifocal lesion (416 (87.9%), and stage 2 (n = 229, 48.4%). There was no statistically significant association between the NPI categories and the focality of carcinoma (P-value = 0.055). While, the NPI categories had statistically significant association with the dermal and surgical margin involvement (P-value < 0.05) and highly significant association with the stage (P-value = 0.001) as shown in Table 2. Besides, Paget's disease was found in 24 (5.07%) cases.

The lympho-vascular invasion was reported in 103 (21.78%) cases, the majority in stage III (Figure 1).

Histopathologically speaking, most cases were with ductal carcinomas (n = 442, 93.5%) and Table 3 illustrates the various histopathological types of breast carcinoma.

The majority of the cases were with high Ki67 (n = 333, 70.4%), positive Estrogen Receptors (n = 347, 74.4%), positive Progesterone Receptors (n = 331, 70%), and no expression of the HER2-neu (n = 191, 40.39%). There was no statistically significant association between the NPI categories and the Estrogen Receptor (P-value = 0.064). While, the association was significant with the other above-mentioned variables (P-value < 0.05) as shown in Table 4.

DISCUSSION

In the present work, the mean age of the included patients is 49.44 years \pm 0.57. This result is comparable to many other studies [16-18]. Mastectomy still surpasses conservative surgery despite the running educational programs that fight against people's desperation, famines, wars, and natural disasters that overwhelm these eras. All these negative impacts

Table 1. The relationship between the Nottingham prognostic index (NPI) and age groups in 473 patients with breast cancer. P-value = 0.93.

NPI Category	Age groups per year						Total
	20–29 N (%)	30–39 N (%)	40–49 N (%)	50–59 N (%)	60–69 N (%)	≥ 70 N (%)	
< 2.4	1 (7.1%)	8 (9.0%)	15 (10.3%)	15 (13.8%)	4 (4.9%)	5 (15.2%)	48 (10.1%)
2.4–3.4	2 (14.3%)	10 (11.2%)	18 (12.3%)	18 (16.5%)	13 (15.9%)	4 (12.1%)	65 (13.7%)
3.4–5.4	6 (42.9%)	38 (42.7%)	57 (39.0%)	40 (36.7%)	36 (43.9%)	14 (42.4%)	191 (40.4%)
> 5.4	5 (35.7%)	33 (37.1%)	56 (38.4%)	36 (33.0%)	29 (35.4%)	10 (30.3%)	169 (35.7%)
Total	14 (100%)	89 (100%)	146 (100%)	109 (100%)	82 (100%)	33 (100%)	473 (100%)

Table 2. The relationship between the Nottingham prognostic index (NPI) and clinical findings in 473 patients with breast cancer.

Variables	NPI Category					P-value
	< 2.4 N (%)	2.4–3.4 N (%)	3.4–5.4 N (%)	> 5.4 N (%)	Total N (%)	
Margins						0.046
Free	43 (89.6%)	56 (86.2%)	183 (95.8%)	155 (91.7%)	437 (92.4%)	
Involved	5 (10.4%)	9 (13.8%)	8 (4.2%)	14 (8.3%)	36 (7.6%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	
Skin involvement						0.029
No	48 (100%)	64 (98.5%)	186 (97.4%)	156 (92.3%)	454 (96.0%)	
Yes	0(100%)	1 (1.5%)	5 (2.6%)	13(7.7%)	19 (4.0%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	
Lesion						0.055
Unifocal	47 (97.9%)	83.1 (100%)	171 (89.5%)	144 (85.2%)	416 (87.9%)	
Multifocal	1 (2.1%)	11 (16.9%)	20 (10.5%)	25 (14.8%)	57 (12.1%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	
Stage						0.001
In situ	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	
Stage 1	23 (47.9%)	27 (41.5%)	12 (6.3%)	1 (0.6%)	63 (13.3%)	
Stage 2	20 (41.7%)	31 (47.7%)	144 (75.4%)	34 (20.1%)	229 (48.4%)	
Stage 3	4 (8.3%)	7 (10.8%)	35 (18.3%)	134 (79.3%)	180 (38.1%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	

Table 3. The histopathology of breast carcinoma in 473 cases.

Histopathological type		Number	Percentage
Ductal	In situ	1	0.2
	Invasive		
	Subtype		
	NOS	419	88.6
	Comedo	5	1.1
	Mucinous	7	1.5
	Neuroendocrine features	2	0.4
	Mucinous and neuroendocrine	1	0.2
	Papillary	1	0.2
	Micropapillary	1	0.2
	Tubular	1	0.2
	Medullary features	3	0.63
	Metaplastic	1	0.2
Lobular	Classical	24	5.1
	Pleomorphic	1	0.2
Mixed		6	1.27
Total		473	100

enhance the late presentation of cancer patients and necessitate mastectomy over conservative surgery. In this study, 330 patients (69.77%) underwent a modified radical mastectomy, while the other 143 (30.23%) had conservative surgery like lumpectomy, wide local excision, or quadrantectomy. Anal-

ysis of 20.000 breast cancer patients from large Turkish research revealed comparable findings regarding the type of surgery. According to the authors, mastectomy rates were 60.7% and 39.3%, respectively, for breast-conserving surgery. A study of breast cancer that included Syrian immigrants

Table 4. The association of the Nottingham prognostic index (NPI) with Ki67, Estrogen Receptors, progesterone Receptors, and HER2-neu in 473 patients with breast cancer.

Variables	NPI Category					P-value
	< 2.4 N (%)	2.4–3.4 N (%)	3.4–5.4 N (%)	> 5.4 N (%)	Total N (%)	
Ki67						0.001
High	14 (29.2%)	27 (41.5%)	152 (79.6%)	140 (82.8%)	333 (70.4%)	
Low	34 (70.8%)	38 (58.5%)	39 (20.4%)	29 (17.2%)	140 (29.6%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	
Estrogen receptors						0.064
Negative	10 (20.8%)	13 (20.0%)	46 (24.1%)	57 (33.7%)	126 (26.6%)	
Positive	38 (79.2%)	52 (80.0%)	145 (75.9%)	112 (66.3%)	347 (74.4%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	
Progesterone receptors						0.011
Negative	10 (20.8%)	12 (18.5%)	56 (29.3%)	64 (37.9%)	142 (30%)	
Positive	38 (79.2%)	53 (81.5%)	135 (70.7%)	105 (62.1%)	331 (70%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	
HER2-neu						0.001
No expression	31 (64.6%)	34 (52.3%)	68 (35.6%)	58 (34.3%)	191 (40.39%)	
Mild	6 (12.5%)	12 (18.5%)	27 (14.1%)	22 (13.0%)	67 (14.17%)	
Moderate	4 (8.3%)	6 (9.2%)	49 (25.7%)	45 (26.6%)	104 (21.98%)	
Strong	7 (14.6%)	13 (20.0%)	47 (24.6%)	44 (26.0%)	111 (23.46%)	
Total	48 (100%)	65 (100%)	191 (100%)	169 (100%)	473 (100%)	

Table 5. Comparison of NPI in different studies.

Author	NPI score%			
	Excellent	Good	Moderate	Poor
Zaimi et al. [10]	0.00%	5.1%	55.1%	39.8%
Pradhan et al. [11]	6.45%	16.1%	61.29	16.13%
Ahmad et al. [12]	0.00%	2.8%	41.1	58.1%
Gite et al. [13]	0.00%	4.44%	45.66	48.88%
NIAZI et al. [14]	0.00%	11.42%	53.57	35%
Akhtar et al. [15]	0.7%	7.3%	44.5%	47.4%
Present study	10.14%	13.74%	40.38%	35.72%

produced comparable findings [19, 20].

Although laterality has a limited clinical impact, this study found a modest left breast preponderance over a right breast, consistent with prior studies [19]. While Amer MH reported a bilaterality rate of 3.0%, only two bilateral instances in our

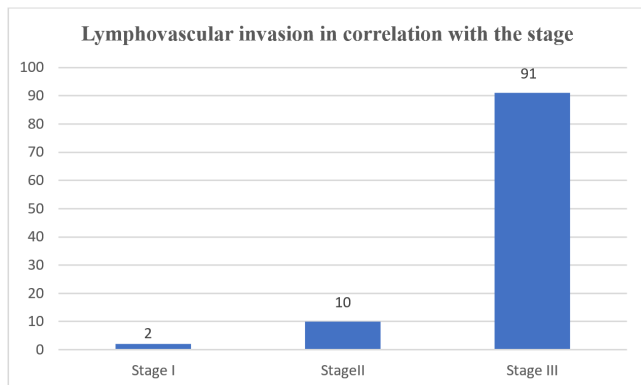


Figure 1. The distribution of lympho-vascular invasion in correlation with the stage.

analysis, accounted for just 0.42% of the included cases [21]. Multifocality has a negative impact on patient survival; in one large Italian series, it was detected in 11.3% of their patients, a very approximate figure compared to the result of our study (12%) [22]. Surgical margin involvement is associated with increased distant metastases and local recurrence rates. In the present study, surgical margins were free from a tumor in 437 (92.4%) cases and involved by tumor cells in 36 (7.6%) cases. In contrast, in a meta-analysis of 68 studies, surgical margin involvement was reported in 9.4% of cases [23].

In our study, the dermal invasion was detected in 52 (10.1) cases, while Uwe et al. reported a rate of 7.2% [24]. Although Paget’s disease does not affect the prognosis, it is reported variably in various studies [25, 26]. Our study detected it in 24 (5.07%) cases. The lympho-vascular invasion was detected in 103 (21.78%) cases, the majority in stage III. A higher rate of 59% was reported in one Turkish study [19]. Histopathologically speaking, most cases, as expected, were ductal carcinomas (93.5%). This is a well-known histological fact proven by many other studies [19].

The relationship between NPI and various tumor biomarkers is not well agreed upon. The well-known statement that tumors with low NPI showed high ER and PR expression; hence a good prognosis, seems to be a non-inevitable rela-

tion. Some authors found no correlation between good NPI scores and various biomarkers [25, 26], others reported positive correlation [27]. In this study, there is no correlation between numerically low NPI scores and ER status, while the correlation is significant with PR, Her2-neu, and Ki-67 status. Accordingly, it is better to consider the NPI score as a separate prognostic indicator from the biomarkers status. In this study, NPIs with high values, especially those with poor prognosis, constituted 35.7%. The finding can be explained based on late presentation, high stage, or lymph node metastases in our patients. Table 5 illustrates the results of NPI scores in different studies [10].

This study included a large number of patients (473) over a six-year period, but unfortunately, about an equal number of patients were excluded due to a lack of clinical or immunohistochemical data. This is considered a limitation of the current study.

CONCLUSION

Most of the included cases (40.38% and 35.72%, respectively) fell into the moderate and poor numerical NPI categories, and these NPIs show highly significant correlations with the stage, Ki-67, and Her2-neu reflecting advanced disease, mitotically active cancer, or cancer with an adverse immunohistochemical pattern.

ETHICAL DECLARATIONS

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Ethics Approval and Consent to Participate

The written agreement had been obtained from the Scientific Committee of the Duhok Medical College-Iraq. Ethical approval was gained from the ethical committee of the Directorate of Health in Duhok (reference number: 08032023-2-17, issued on March 8, 2023). Consent to participate is not applicable because it is a retrospective study performed on data without violating patients privacy.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Data generated during this study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Authors' Contributions

All stated authors contributed significantly, directly, and intellectually to the work and consented it to be published.

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