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Research article

Morphology and Nottingham prognostic index in triple-negative breast carcinomas

Jyothi A Raj[1], Anisha Tirumala Sudarshan*[1], Naveen Shivappa[2], Santhi[1], Anusha[1]

[1] Department of Pathology, Raja Rajeswari medical college, and hospital, Mysore Road, Bangalore, Karnataka, India
[2] Department of Surgery, Raja Rajeswari medical college, and hospital, Mysore Road, Bangalore, Karnataka, India

ABSTRACT

Triple-negative breast carcinomas are defined by a lack of expression of the steroid hormone receptors i.e., Estrogen Receptor, Progesterone Receptor, and Human epidermal growth factor Receptor-2. They are characterized by distinct molecular, histological, and clinical features. With higher mortality and early relapse, management of these tumors relies on clinicopathologic prognostic factors. Nottingham's prognostic index is a widely used prognostic tool that integrates three independent prognostic factors, namely tumor size, lymph node status, and histologic grade. It is a sensitive index of clinical aggressiveness in breast carcinomas. This study aims to evaluate morphologic features of Triple negative breast carcinomas and correlate them with Nottingham prognostic index. 22 modified radical mastectomies with triple-negative status were considered for this study. Tumor size, histologic type, grade, node involvement, necrosis, lymphovascular invasion, and Nottingham prognostic index were assessed. All 22 Triple negative breast carcinomas were invasive ductal carcinomas [NOS]. One involved skin and six were larger than 5cms. 10 cases (45%) were histologic grade III, and 9 cases (41%) were grade II. 2 cases had more than 10 positive nodes. Nottingham's prognostic index ranged from 2 to 9.4. Lymphovascular invasion and necrosis in 16 cases (73%) and perineural invasion in 3 cases were noted. Prognostication of breast carcinomas using Nottingham prognostic index helps clinicians in decision-making, stratifying risks, and tailoring individual treatment plans. Including Nottingham's prognostic index routinely in breast carcinoma reporting offers a meaningful integrated indicator for clinicians to assess tumor behavior and aggressiveness.

Keywords: Triple-negative breast carcinoma, Prognostic factors, Nottingham prognostic index.

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Correspondence: Anisha Tirumala Sudarshan ✉ anishats@gmail.com, **Orcid Id**: 0000-0002-4420-1440

Department of Pathology, Raja Rajeswari Medical College and Hospital, Bangalore, Karnataka, India.

INTRODUCTION

Breast carcinoma is the second most common carcinoma in women and accounts for 22% of all female cancer, which is more than twice the prevalence of cancer in women at any other site [1]. It is a heterogeneous disease and it encompasses a variety of entities with distinct morphological appearances and clinical behaviors [2]. The incidence of breast cancer has increased globally over the last several decades; the greatest increase has been in Asian countries as in Asia, breast cancer incidence peaks among women in their forties, whereas in the United States and Europe, it peaks among women in their sixties [1].

The clinical management of this tumor relies on various prognostic factors, most importantly lymph node stage, tumor size, and histologic grade. Numerous other features have been independently shown to have prognostic value. Hence, there have been attempts to integrate these factors into meaningful indices. The most widely used of these is the Nottingham prognostic index (NPI), first described in 1982, which incorporates tumor size, lymph node stage and histologic grade [3]. The analysis of gene expression data has suggested that breast cancers can be divided into molecular subtypes which have distinct clinical features, with markedly differing prognoses and clinical outcomes [2]. These subtypes consist of two ER-positive types (Luminal A and Luminal B), and three ER-negative types (HER-2 expressing, basal-like and normal breast-like). NPI, in various studies, has been shown to yield a continuum of clinical aggressiveness of breast carcinoma with differing patient survival rates [3], indexing the outcome likelihood of invasive breast cancer patients.

Triple Negative Breast Cancers (TNBC) are defined as tumors that are negative for estrogen and progesterone receptors as assessed by Immunohistochemistry (IHC), combined with a lack of over-expression of HER2 when tested by IHC or absence of its gene amplification when tested by fluorescence in situ hybridization technique [4]. The prognosis of breast carcinoma has been associated with many variables like age, histological type, tumor grade, tumor size, lymph node status, and receptor status [1]. The above-mentioned

variables have prognostic significance but receptor status has been proved repeatedly to be one of the most important prognostic factors which affect five-year survival rates and also mortality and disease-free survival rates hence TNBCs are associated with the worst prognosis [1]. TNBC patients lack the benefit of routinely available target therapy,which explains the undeniable growing attention of both pathologists and oncologists as an easily recognizable group of breast cancer with aggressive behavior and poor therapeutic options[5].

Management of breast carcinoma depends on numerous prognostic factors, including morphologic features [3]. The most widely used histologic grading system is the Nottingham (Elston-Ellis) modification of the Scarff- Bloom- Richardson grading system, also known as the Nottingham Grading System (NGS), recommended by international professional bodies [6].

Grading of invasive breast carcinomas is based on the evaluation of three tumor characteristics: tubule formation/ glandular differentiation, nuclear pleomorphism, and mitotic count. Each of these factors is assessed independently and scored 1 to 3. The glandular formation is assessed under low- power over the whole tumor. Structures with clear central lumina and surrounded by polarized neoplastic cells only are counted as tubules and acini. Nuclear pleomorphism is evaluated in the most pleomorphic area. Nuclear size and shape, irregular outlines, and number and size of nucleoli are considered. Mitoses are counted in the tumor area with the most proliferation. Only definite mitotic figures in the peripheral leading edge of the tumor are scored, ignoring hyperchromatic and pyknotic nuclei. Optimally fixed and well-prepared tissue sections are prerequisites for assessing mitotic figures. Total mitoses per 10 HPF is recorded [7].

Table 1: Each of the features is scored as follows

Tubule and gland formation • Majority of tumors (> 75%) • Moderate degree (10- 75%) • Little or none (< 10%)		1 2 3
Nuclear pleomorphism • Small, regular uniform cells • The moderate increase in size and variability • Marked variation		1 2 3
Mitotic counts Dependent on the microscope field area		1-3
Final grading Add scores for gland formation, nuclear pleomorphism and count, to produce scores of 3 to 9, to which the grade is assigned as follows:		
Total score, 3- 5	Grade 1	well-differentiated
Total score, 6 or 7	Grade 2	moderately differentiated
Total score, 8 or 9	Grade 3	poorly differentiated

The histological grade is a powerful prognostic factor and studies have shown a significant association between histological grade and survival of patients with breast carcinoma.

TNM system published by the American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC) is the most widely used system for staging breast carcinoma.

Pathological classification of T and N depends on the gross and microscopic examination of excised specimens. T is based on the size of the invasive carcinoma. It is based on the largest focus when multiple areas of invasion are present. Smaller tumors may be measured on glass slides. Axillary lymph node status is the single most important prognostic factor, which correlates strongly with tumor size [8]; more the nodes are involved,the worse the prognosis [5].

The Nottingham prognostic index (NPI) was first described in 1982 and is among the most widely used [3]. It is a scoring system developed to assist risk stratification and clinical decision-making in breast cancer management and prognostication and has found validation in large multicentre studies [6]. This formula assembles histopathological examination of tumor size, lymph node stage, and tumor grading, into an index- score, reflecting metastatic potential, growth rate, and genetic instability. It assigns a numerical value to tumors along a continuum of clinical aggressiveness, allowing a straightforward correlation of tumor progression [6]. It is a sensitive model for prognostication of breast cancers [5].

NPI is calculated using the equation: NPI = 0.2 × tumor size (cm) + grade (1-3) + lymph node status (1-3) [6]. Most studies stratify patients into three prognosis groups using NPI: good (≤3.4), moderate (3.41-5.4), and poor (>5.4) [5]. Some studies **[6]** grouped patients into four prognostic categories: I (excellent) ≤ 2.4; II (good) >2.4 but ≤3.4; III (moderate) >3.4 but ≤5.4; IV (poor) >5.4.

NPI combined with predictive factors such as hormone receptors and HER-2 status can be used for patient selection for adjuvant therapy. Factors like vascular invasion can further improve its potential [9]. The present study was designed to evaluate the NPI in a group of Triple-negative breast cancer patients in our Institute and to correlate NPI with other clinical and histomorphology features.

MATERIALS AND METHODS

Source and Method of Collection of Data

This is a cross-sectional study. A total of 22 Modified radical mastectomies with triple-negative status received over 3 years were considered for this study. The mastectomy specimens were received in the Histopathology section of the Department of Pathology, in our institute.

The formalin-fixed specimens were grossly examined and tissue bits were taken. The tissue bits were processed by an automated tissue processor and sections were stained with routine eight-step Hematoxylin and Eosin (H&E) staining procedure.

Analysis method

Prognosis implication on ER, PR, and HER-2/neu was assessed using Nottingham prognostic index (NPI).

Hormone receptor status was determined with these antibody clones: the estrogen receptor (Pathnsitu-rabbit monoclonal, EP1), the progesterone receptor (Pathnsitu-rabbit monoclonal, EP2), and HER – 2(Pathnsitu-rabbit monoclonal, EP3). Tumors with more than 10% nuclear positivity for ER or PR were considered positive for that particular hormone receptor. Tumor size, histologic type, grade, node involvement, necrosis, lymphovascular invasion, and NPI [NPI=0.2xtumor size(cm) +lymph node stage(I/II/III) +tumour grade (1/2/3)] were assessed and tabulated, in all cases of triple-negative breast carcinomas.

Inclusion Criteria

All breast biopsies which were reported as invasive carcinoma were considered for the study.

Exclusion criteria

Metastatic carcinomas and male breast carcinomas were excluded from the study.

Sampling technique used

Stratified sampling technique.

RESULTS AND DISCUSSION

A total of 22 Modified radical mastectomies with triple-negative status obtained over three years in the Department of Pathology, were considered for this study.

Table 2: Radical mastectomies with triple-negative status

Clinicopathological variables		No. Of cases
Tumor	T1	6(27%)
	T2	9(41%)
	T3	6(27%)
	T4	1(5%)
Histologic Type	Invasive ductal carcinoma-nst	22(100%)
Tumor Grade	I	3(14%)
	II	9(41%)
	III	10(45%)
Lymph Node Involvement	Present	11(50%)
	Absent	11(50%)
Tumor Necrosis	Present	16(73%)
	Absent	6(27%)
Margins	Uninvolved	14(64%)
	Involved	8(36%)

In our study, the age of the patients ranged from 29 to 70 years and the majority of the patients were in the age group of 40-49 years (41%) with the side affected or the tumor laterality being the right side (54%). All 22 cases with triple-negative status were histologically diagnosed as Invasive Ductal Carcinoma, No Special Type (DC-NST) (100%).

By using the TNM stage, most of the tumors belonged to T2(41%) i.e. tumor size between 2-5cms in the greatest dimension, and by using Nottingham Histologic Scores, most tumors belonged to Grade 3(45%) i.e. Scores of 8 or 9 of the 22 cases of TNBC studied, 11 of them (50%) had involvement of lymph nodes, and the surgically resected margins were involved in 8 cases (36%), and the overlying skin and the Nipple were involved only in 1 case (5%). Tumour necrosis and Lymphovascular invasion were seen in 16 of the 22 cases (73%) and perineural invasion was noted in 4 cases (18%). Features of DCIS were seen in 10 cases (45%). NPI was applied to all the 22 TNBC studied, of the 22, the majority i.e.,13 cases were group II (59%), 4 were group III (18%) and 5 were group I (23%).

Table 3: TNM stage

Clinicopathological variables		Number of cases
Lympho-Vascular Invasion	Present	16(73%)
	Absent	6(27%)
Perineural Invasion	Present	4(18%)
	Absent	18(82%)
Skin Involvement	Present	1(5%)
	Absent	21(95%)
Nipple Involvement	Present	1(5%)
	Absent	21(95%)
Dcis	Present	10(45%)
	Absent	12(55%)
Nottingham Prognostic Index	I	5(23%)
	II	13(59%)
	III	4(18%)
Peri Tumoural And Intra-Tumoural Lymphocytic Infiltrate	Present	21(95%)
	Absent	1(5%)

Breast carcinoma is one of the leading causes of cancer-related mortality in women [3]. They are complex diseases, with morphological and molecular heterogeneity. Histologically similar tumors may show different clinical behaviors, reflecting distinct molecular aberrations [5].

Triple Negative Breast Cancers (TNBC) are a subset of breast cancers with different molecular subtypes, defined by lack of expression of estrogen and progesterone receptors (IHC) and lack of over-expression of human epidermal growth factor receptor 2 (HER2) or gene amplification (IHC/ FISH). TNBC accounts for 10-20% of all breast cancers worldwide. Studies in India have reported a higher range of up to 31.9% [4].

Age distribution in TNBC

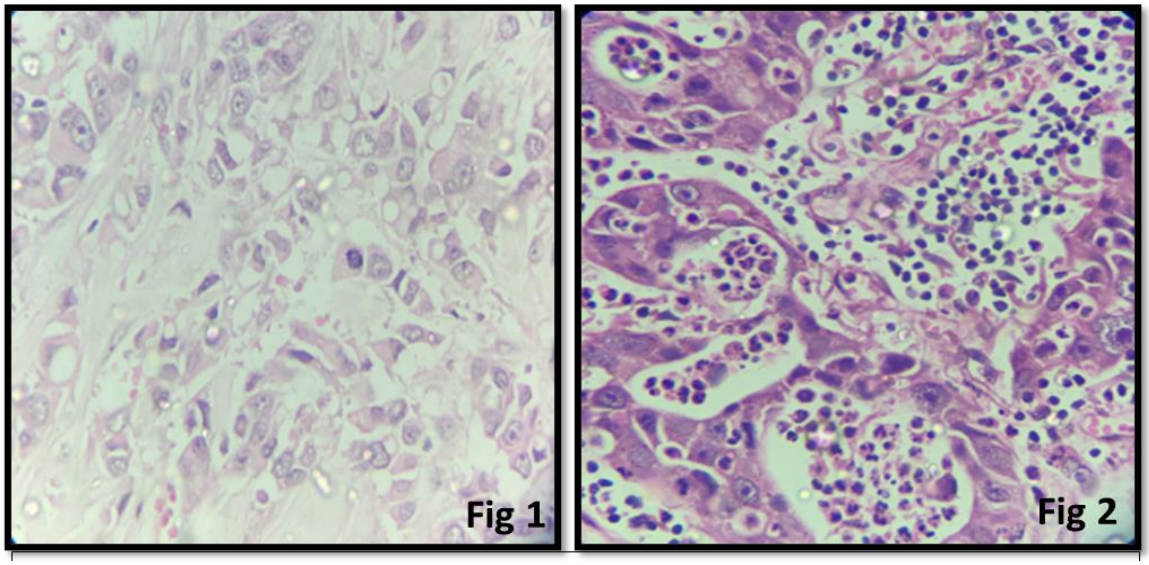
In our study, the 22 cases with triple-negative status were histologically diagnosed as Invasive Ductal Carcinoma, No Special Type (IDC-NST) (100%). The age group in our study ranged from 29 years to 73 years with a mean age of 36.9 years.

Priyanka Kumari et al [1] studied 60 diagnosed cases of carcinoma breast, of which triple negative breast cancer cases were 12 (20%) and they were 25 to 84 years of age, maximum number of patients being in the age group of 45-54 years.

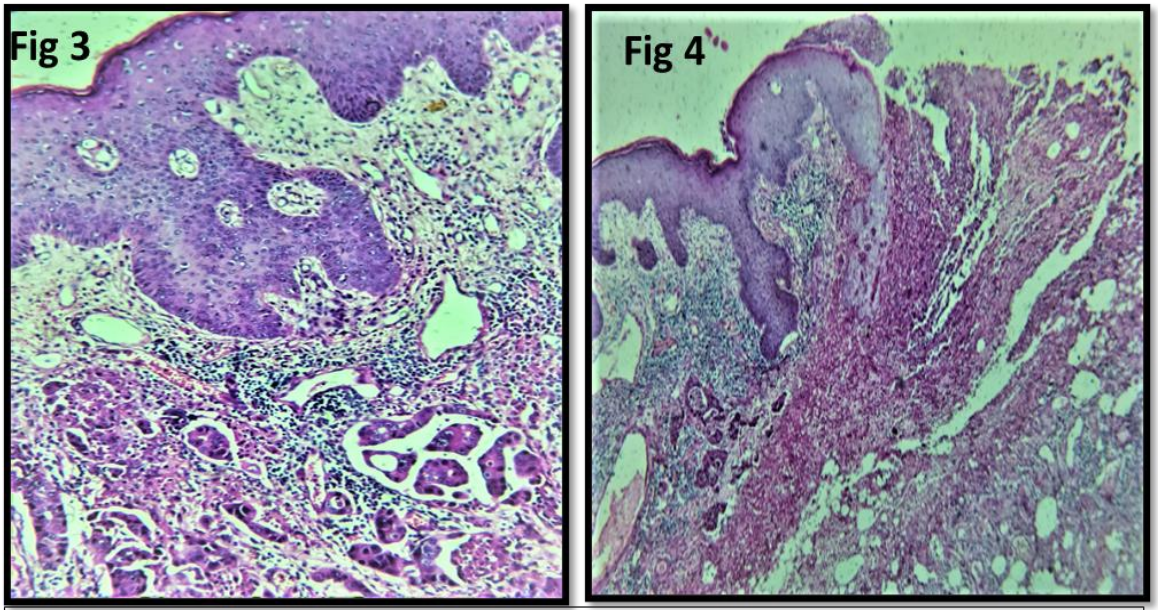
Chandrika Rao et al [2] included 50 female patients with triple-negative primary invasive breast carcinoma in their study. The patients were in the age range of 37- 58 years, with a mean age of 46.8 years.

Anna M. Badowska-Kozakiewiczet al [7], subtyped 111 triple-negative breast cancers and identified 89.1% invasive ductal carcinomas of no special type and 10.9% other special types of cancers. The mean age of patients was 47.8 years.

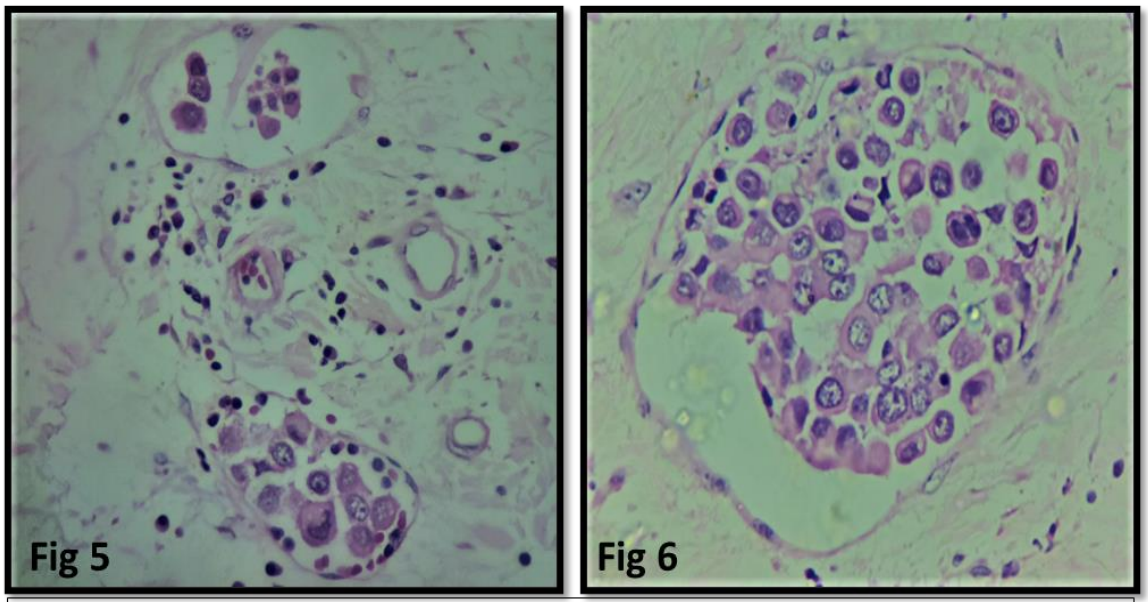
Figure 1&2: Showing high-grade Infiltrating Ductal Carcinoma-Nos (H&E, 40X)



Figures 3 & 4: Showing high-grade Infiltrating Ductal Carcinoma-Nos with skin (H&E, 10X)



Figures 4 & 5: Showing high-grade Infiltrating Ductal Carcinoma-Nos with Lymphovascular invasion (H&E, 10X)



André Albergaria et al [5] studied 467 primary invasive breast carcinomas. Patients' ages ranged from 28 to 92 years.

Gunadala Ishitha et al [4] reported fifty-three (22.2%) TNBC among 238 cases of primary invasive breast carcinomas, and 96% of TNBC cases were classified as invasive ductal carcinoma (NOS). The mean age of TNBC patients in their study was 46±12 years. The youngest patient with TNBC was 23-year-old and the oldest patient was 79 years old.

The majority of the triple-negative tumor patients were in the age group of 20-50 years. The results of our study correlated with the studies by André Albergaria et al [5], Rebecca Dent et al [10], Emad A Rakha et al [11], Jorge S Reis-Filhoet al [12], and Aye Thikeet al [13].

Size, grade, and lymph node status in TNBC

The majority of the tumors in our study measured 5 cm and above in size, showing frequent high tumor grade, lymphovascular invasion, lymph node involvement seen in 11% of the cases, and tumor necrosis. All the cases (100%) were invasive ductal carcinomas [NOS] and the majority were grade II (41%) and grade III (45%) in the present study which was consistent with the studies conducted by Kwatra A et al[3] and Chandrika Rao et al[2].

The study done by Chandrika Rao et al [2] showed that the predominant histopathological type was infiltrating ductal carcinoma of no special type (44 of 50, 88%). In most of the patients, the tumor size was between 2.1 to 5cm (34 of 50, 68%), Histopathological evaluation showed poorly differentiated high-grade tumors in 38 of the 50 patients (76%), tumor necrosis in 56% (28 of the 50 patients), lymphovascular invasions were 20% of the patients (10 of the 50 patients) respectively. Chandrika Rao et al [2] observed that focal/come do- necrosis was an important morphological factor in triple-negative breast cancer. Lymph node metastases were noted in 37 of the 50 patients, (74% tumors). Their study showed higher node-positive TNBC cases and a decreasing incidence of axillary lymph node metastasis with enlarging tumor sizes. Similar results were obtained by Anna M. Badowska-Kozakiewiczet al [7] and Gunadala Ishitha et al [4].

The study done by Gunadala Ishitha et al [4] used Modified Bloom-Richardson histological grading in 49 cases and were classified as grade II or III and none were of grade 1. The average size of the tumor was 4.3 ± 2.56 cm and 53% of cases presented with stage III and IV disease. Lymphovascular invasion was seen in 69% of cases in their study.

André Albergaria et al [5] studied 467 primary invasive breast carcinomas. Tumour size ranged from 0.4 to 16 cm, with T1[< 2 cm]: 101 (24.7%), T2[2-5 cm]: 245 (59.9%), and T3[>5 cm]: 63 (15.4%). Histological grade was Grade I in 81 (18.3%), Grade II in 135 (30.5%), Grade III in 227 (51.2%), and not assessed in 24 patients. Lymph node invasion was present in 207 (56.6%), absent in 159 (43.4%), and not assessed in 101 cases.

Anna M. Badowska-Kozakiewiczet al. [7], subtyped 111 triple-negative breast cancers. TNBC was most commonly G2 and G3 (52.2%; 45.1%), pT1 and pT2 (34.2%; 62.1%), and pN1, pN2 (45%; 41.4%). Necrosis was more common (36%; 19.6%) in TNBC than in non-TNBC. Lymph node status in their study was as follows: 50 (45.0) were pN1, 46 (41.4) were pN2 and 15 (13.8) were pN3. They found no association between tumor size and the presence of lymph node metastasis in patients with TNBC.

James S Michaelson et al [14], found an increasing fraction of lymph node involvement with growth in tumor size.

Marco Colleoni et al [15], found a linear relationship between lymph node involvement and increasing tumor size. By using the TNM stage, most of the tumors belonged to T2(41%) i.e., tumor size between 2-5cms in the greatest dimension, and by using Nottingham Histologic Scores, most tumors belonged to Grade 3(45%) i.e., Scores of 8 or9.

Dinesh Chandra Doval et al **[16]**, in their study, showed that a strong statistical association was observed with premenopausal women (51.5%), tumor grade 3 (73.1%), tumor size >20 mm (91.5%), negative lymph node status (58.7%), cancer stage II (72.5%) and invasive ductal carcinoma (98.4%) among the patients with triple-negative tumors.

NPI in breast carcinomas

In our study, the NPI was applied to all the 22 TNBCs studied. Of the 22, the majority i.e.,13 cases were group II (59%), 4 were group III (18%) and 5 were group I (23%).

André Albergaria et al [5] studied 467 primary invasive breast carcinomas. They reported NPI ranging from 2-8.4 (mean 4.8). Nottingham Prognostic Index: < 3.4- 99 (24.4%); 3.4 to ≤ 5.4- 188 (46.4%); > 5.4- 118 (29.2%); and not assessed in 62 cases. They noted that TNBC disseminates to axillary lymph nodes as frequently as HER2+ tumors, they are larger compared with other subtypes and almost all grade 3. They concluded that NPI retained the ability to predict survival, remaining a useful prognostic tool in TNBC.

O Al Jarroudi et al **[6]** did a retrospective study on 98 patients with TNBC, to evaluate the prognostic value of NPI. Patients were grouped into four categories according to the NPI score: I (excellent) ≤ 2.4; II (good) >2.4 but ≤3.4; III (moderate) >3.4 but ≤5.4; IV (poor) >5.4. NPI score ranged from 3-7 (Mean 4.75). It stratified the patients into Good (5.1%), Moderate (55.1%), and poor prognosis (39.8%). None of the cases was scored as NPI <3.4 (classed in the Excellent prognosis group), reinforcing the poor prognosis of this breast cancer subtype,48.9% of the patients had positive lymph nodes. This study found a significant association between tumor size, histological grade, and lymph node status in TNBC to high scores of NPI (> 5.4). O Al Jarroudi et al **[6]** observed

that NBC does not obey the "size-node" rule, with no association between tumor size and lymph node status in these cases. O Al Jarroudi et al [6] and André Albergaria et al [5], found NPI to be a reliable and reproducible tool in TNBC tumors, with increasing NPI related to poor outcomes and short survival. Their studies confirmed NPI as a practicable prognostic tool even for the TNBC subtype, with high-score NPI (> 5.4) independently predicting overall and disease-free survival in these patients. Improving NPI (iNPI), extended NPI, and NPI plus are evolving concepts to modernize the prognostic methods by applying the biological characteristics of breast cancer to NPI, to improve risk stratification and management in these patients.

DCIS component in TNBC

Ductal Carcinoma in Situ (DCIS) components were seen in 10 cases (45%) in our study. DCIS component was reported in 17 of the 52 cases (33.3%) of TNBC by Gunadala Ishitha et al [4]. Dinesh Chandra Doval et al [16], studied1,284 women with breast carcinoma, of which 306 (23.8%) tumors were triple negative. DCIS was present in 103 (35.6%) of TNBC cases. Chandrika Rao et al [2] included 50 female patients with triple-negative primary invasive breast carcinoma in their study of which DCIS was seen in 42% (21 of the 50 patients) which was similar to the percentage seen in our study. Aye Aye Thike et al. [17] studied DCIS component of 241 TNBC and concluded that triple negative ductal carcinoma in situ is the precursor of the corresponding invasive counterpart

Lymphocytic infiltrate

Most TNBC cases have a dense intra-tumoral or peri-tumoral lymphocytic infiltrate. In our study, the majority of the cases (21 of the 22 cases) showed moderate intra-tumoral and peri-tumoral lymphocytic infiltrates. In the study by Gunadala Ishitha et al [4], 98% of cases showed lymphocytic infiltrate, of which 54% had mild infiltrate, 33% had moderate infiltrate and 11% had a marked infiltrate. A study by Chandrika Rao et al [2] showed lymphocytic infiltrates in 44% (22 of the 50 patients). A study done by Özgecan Dülgar et al[18] on 167 patients of TNBC concluded that tumor lymphocyte infiltration was found to have a statistically significant better prognostic effect on disease-free survival but not on overall survival of patients with operated TNBC

CONCLUSION

Triple-negative breast carcinomas encompass a heterogeneous group of tumors with distinct clinicopathological features. Prognostication using Nottingham Prognostic Index helps clinicians in decision-making, stratifying risks, and tailoring individual treatment plans. Including NPI routinely in breast carcinoma reporting offers a meaningful integrated indicator for clinicians to assess tumor behavior and aggressiveness. With lower disease-free survival, higher predisposition for metastases, and poorer outcomes among triple-negative breast cancers, further workup with the use of additional markers to identify basal-like subtypes can help identify a worse outcome group in these tumors.

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