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ORIGINAL RESEARCH

Evaluating the Nottingham Prognostic Index Plus (NPI+) as a Histopathological Predictor Against Standard NPI and Bloom-Richardson Grading in Breast Cancer

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ABSTRACT

Background and Aim: Breast carcinoma represents a heterogeneous group of tumors with varied genotypic and phenotypic features.Biological characteristics of breast carcinoma are important for deciding clinical management and incorporation into the NPI could significantly improve the delivery of personalized medicine in BC patients. **Material and Methods:** The present study was a retrospective analytical study of 145 patients and carried out in Department of Pathology, Jawaharlal Nehru Medical College, Sawangi. Patients who were diagnosed and operated cases of breast carcinomas 5 years back were included in the present study. Histopathological sections from these resected specimens were studied and tumor tissue was grade as per BR grade. Further NPI score was evaluated.The detailed clinical history and results of relevant investigations done were collected from the patient case files. Specimens were received in the Pathology Department in 10% formalin. In every case the standard protocol for surgical grossing of specimen was followed. **Results:** Maximum of 42(28.97%) cases were in Luminal A Biological classes.There is significant association between NPI+ biological classes with NPI prognostic groups and BR grading.BR grading does not consider tumor size and lymphnode stage which are known clinicopathological parameters included in conventional NPI. **Conclusion:** Pertaining to immunohistochemical biomarker newer elaborated categorization of breast carcinoma have evolved for better understanding of tumor behaviour, hormonal status, luminal and basal characteristics, local and distant metastasis and thereby reflect on survival of breast carcinoma patients.

Key Words: Bloom Richardson Grading, Breast Carcinoma, Nottingham Prognostic Index Plus, Tumor

INTRODUCTION

Breast cancer (BC) is one of the most common cancers and the second leading cause of cancer related death in women.[1] It's incidence and prevalence is rapidly increasing throughout the world. According to GLOBOCAN 2018, there is an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018. [2]

The development of breast cancer is a multi-step process which involves multiple cell types.[3] Breast carcinoma represents a heterogeneous group of tumors with varied genotypic and phenotypic features.Various genetic and acquired risk factors have been associated with breast cancer. These risk factors are non-modifiable and modifiable. Non-modifiable factors include female gender, increasing age, race and ethnicity, early attainment of menarche, late menopause, nulliparity, genetic predisposition like BRCA1 and BRCA2 mutation, history of radiation exposure, and history of breast cancer in family.Modifiable risk factors are parity, absence of breastfeeding, use of hormone replacement therapy, decreased physical activity, obesity, alcohol consumption, and smoking.[2]

BRCA1 associated breast carcinomas are poorly differentiated and have medullary features and do not

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express hormone receptors or overexpression of HER2/neu. BRCA2-associated breast carcinomas are also poorly differentiated, but are ER positive than BRCA1 cancers.[4]

The diagnosis of breast cancer is based on clinical, radiological and histopathological examination. Clinical examination includes detailed physical examination and establishment of clinical staging of the disease. Radiological evaluation includes ultrasonography, mammography, or magnetic resonance imaging. Histopathological evaluation is performed by fine needle aspiration cytology (FNAC) and core biopsy. Histopathological evaluation is considered as the gold standard method of diagnosis. Complete evaluation of patients with breast cancer also includes work metastatic work up, to determine if disease has spread to distant organs. The investigations used in metastatic workup are chest X-ray, bone scan, ultrasound of the abdomen and pelvis, and computed tomography of abdomen and thorax.[4]

There are increasing number of treatment options available for BC patients, among them deciding the most appropriate choice remains challenging. However, accurate personalized breast carcinoma treatment requires robust and accurate risk stratification based on both outcome prediction and biology of tumour.[5] Several Methods have been developed to assist in predicting patient outcome and to support clinical decision making in breast carcinoma management. The most widely used method for prognostification is the Nottingham prognostic index (NPI),which incorporates tumor size, lymph node stage and histological grade.[6]

The NPI accuracy has been confirmed using long term patient follow-up, validated in large independent multi-centre studies revised in order to stratify patients into five prognostic groups, and is currently adopted in clinical practice in the UK and other parts of Europe and Australia.[7-9] Prognosis worsens as the NPI numerical value increases and by using cutoff points patients may be stratified into good, moderate and poor prognostic group. However, the NPI does not consider the biological heterogeneity of BC.

The grading system which is most commonly used is Bloom Richardson Grading (Scharf–Bloom-Richardson Grading System) and has a potent predictive value. BR grading is done when it is combined with lymph node stage and size of tumor to form prognostic indices. It is also incorporated in algorithm to determine the use of adjuvant chemotherapy. Moreover, it is easy and cheap.[10]

According to 12th International St. Gallen Breast Cancer Conference in March 2011, 5 subtypes of breast cancer were defined using IHC to analyse the expression of four markers ER, PR, HER2 neu, and Ki-67.[11] Also, Gene expression profile measures the quantity of mRNA for every gene. It identified 5 patterns of gene expression and these are luminal A, luminal B, basal-like, and HER2 positive. These molecular classes correlate with the prognosis and response to therapy.[12]

Biological characteristics of breast carcinoma are important for deciding clinical management and incorporation into the NPI could significantly improve the delivery of personalized medicine in BC patients. Nottingham prognostic index plus (NPI+) is biomarker-based prognostic index incorporates a comprehensive panel of biomarkers of immunophenotypic origin with relevance to BC. NPI+ is based on the well-established clinicopathologic variables which includes Bloom Richardson grading used in the NPI but has been redefined to integrate with tumour biology.

MATERIAL AND METHODS

The present study was a retrospective analytical study of 145 patients and carried out in Department of Pathology, Jawaharlal Nehru Medical College, Sawangi. Patients who were diagnosed and operated cases of breast carcinomas 5 years back were included in the present study. Histopathological sections from these resected specimens were studied and tumor tissue was grade as per BR grade. Further NPI score was evaluated.

Estrogen receptor and progesterone receptor immunohistochemical reactivity was determined by Allred scoring system.For HER2, the American Society of Clinical Oncology/College of American Pathologists Guidelines Recommendations were used. Biological Classes were determined by the evaluation ofbreast carcinoma-related biomarkers using immunohistochemistry and a fuzzy rule induction algorithm[5] to classify the breast tumours into seven NPI+ biological classes- Luminal A, Luminal N,LuminalB,basal p53 altered, basal p53 normal, HER2+ER+, HER2+ER-.

Inclusion criteria

- Patients confirmed as breast carcinoma on histopathology.
- Female patient of all ages with breast carcinoma
- Patients who had undergone modified radical mastectomy

Exclusion criteria

- Patients with benign breast diseases and mesenchymal tumors
- Recurrent carcinoma
- Patient on chemotherapy
- Biopsy, simple mastectomy, lumpectomy will be excluded.

The detailed clinical history and results of relevant investigations done were collected from the patient case files. Specimens were received in the Pathology Department in 10% formalin. In every case the standard protocol for surgical grossing of specimen was followed.

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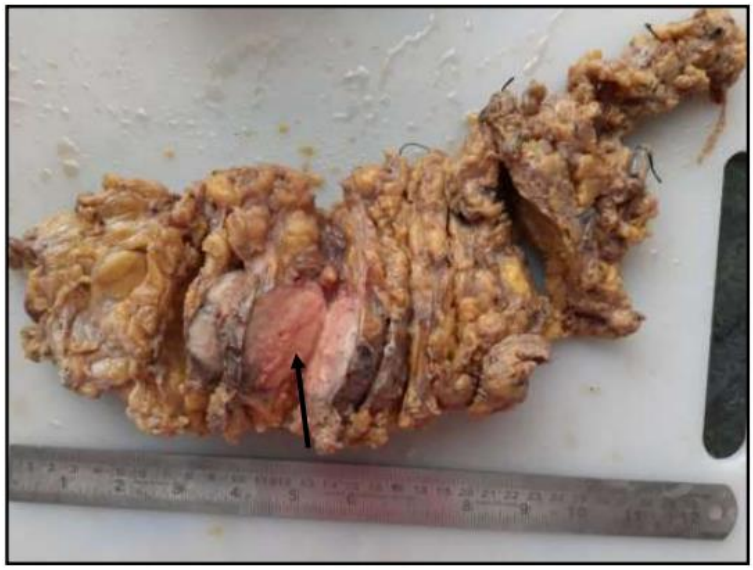

Figure 1: Cut Surface from Mastectomy Specimen shows grayish White Infiltrative Growth with Irregular Peripheral Edges, Size of Tumor 2 cm - 5 cm

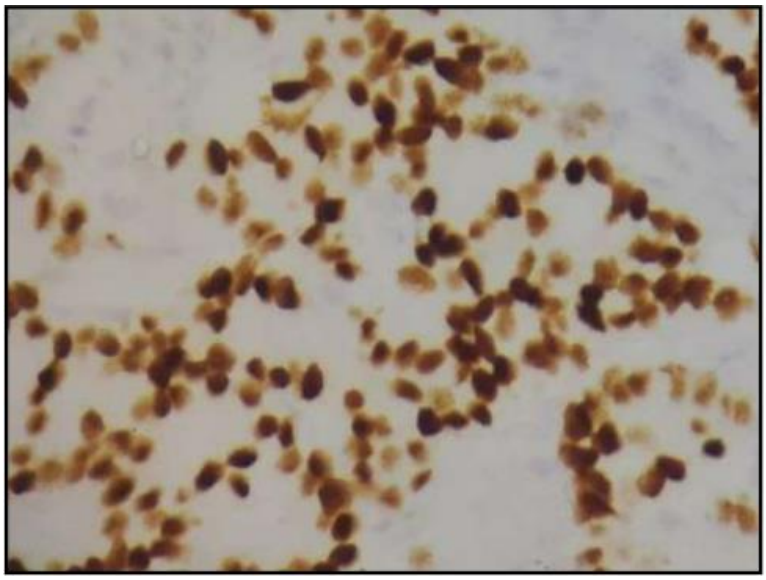

Figure 2: Photomicrograph shows Immunohistochemistry-stained section (×40 view) from breast tissue mass shows intense brown color-stained nuclei signifying progesterone receptor positive

STATISTICAL ANALYSIS

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2019) and then exported to data editor page of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described as means and standard deviations or median and interquartile range based on their distribution. Qualitative variables were presented as count and percentages.For all tests, confidence level and level of significance were set at 95% and 5% respectively.

RESULTS AND DISCUSSION

The present study was a retrospective analytical study of 145 patients and carried out in Department of Pathology, Jawaharlal Nehru Medical College, Sawangi. Patients who were diagnosed and operated cases of breast carcinomas 5 years back were included in the present study.

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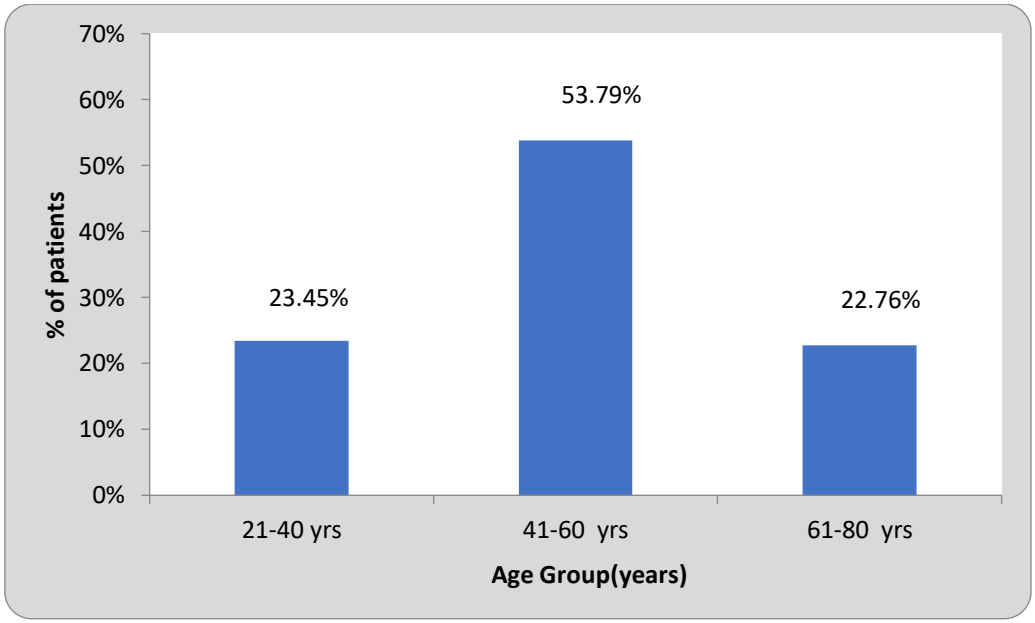

Graph 1: Distribution of patients according to their age in years

Table 1: Correlation between tumor size(cm) and biological class

Tumor Size(cm)	Luminal A	Luminal N	Luminal B	Basal p53 altered	Basal p53 normal	HER2+/ ER+	HER2 +/ER-	Total
<4 cm	19 (38.78%)	4 (8.16%)	7 (14.29%)	4 (8.16%)	5 (10.20%)	4 (8.2%)	6 (12.24%)	49 (33.79%)
≥4 cm	23 (23.96%)	12 (12.50%)	22 (22.92%)	13 (13.54%)	7 (7.29%)	6 (6.3%)	13 (13.54%)	96 (66.21%)
Total	42 (28.97%)	16 (11.03%)	29 (20%)	17 (11.72%)	12 (8.28%)	10 (6.9%)	19 (13.10%)	145 (100%)
Cramer's V (p-value	0.47, Significant							

Table 2: Correlation between BR Grading and biological class

BR Grading	Luminal A	Luminal N	Luminal B	Basal p53 altered	Basal p53 normal	HER2 +/ER+	HER2 +/ER-	Total
Grade I	10 (45.45%)	5 (22.73%)	5 (22.73%)	1 (4.55%)	1 (4.55%)	0 (0%)	0 (0%)	22 (15.17%)
Grade II	24 (27.27%)	9 (10.23%)	18 (20.45%)	9 (10.23%)	7 (7.95%)	9 (10.2%)	12 (13.64%)	88 (60.69%)
Grade III	8 (22.86%)	2 (5.71%)	6 (17.14%)	7 (20%)	4 (11.43%)	1 (2.9%)	7 (20%)	35 (24.14%)
Total	42 (28.97%)	16 (11.03%)	29 (20%)	17 (11.72%)	12 (8.28%)	10 (6.9%)	19 (13.10%)	145 (100%)
Cramer's V(p-value	0.10, Significant							

Table 3: Correlation between NPI prognostic groups and biological class

NPI prognostic group	Luminal A	Luminal N	Luminal B	Basal p53 altered	Basal p53 normal	HER2+/ER+	HER2 +/ER-	Total
Good	7 (63.64%)	3 (27.27%)	0(0%)	1 (9.09%)	0(0%)	0(0%)	0(0%)	11 (7.59%)
Moderate	24 (32%)	8 (10.67%)	15 (20%)	7 (9.33%)	8 (10.67%)	4 (5.3%)	9(12%)	75 (51.72%)
Poor	11 (18.64%)	5 (8.47%)	14 (23.73%)	9 (15.25%)	4 (6.78%)	6 (10.2%)	10 (16.95%)	59 (40.69%)
Total	42	16	29 (20%)	17	12	10 (6.9%)	19	145

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	(28.97%)	(11.03%)		(11.72%)	(8.28%)		(13.10%)	(100%)
Cramer's V(p-value	0.081, Significant							

Table 4: Correlation between Lymph Node Stage and biological class

Lymph Node Stage	Luminal A	Luminal N	Luminal B	Basal p53 altered	Basal p53 normal	HER2+/ER+	HER2 +/ER-	Total
Stage I	25(44.64%)	6(10.71%)	9(16.07%)	6(10.71%)	3(5.36%)	2(3.6%)	5(8.93%)	56(38.62%)
Stage II	6(16.67%)	6(16.67%)	7(19.44%)	4(11.11%)	6(16.67%)	2(5.6%)	5(13.89%)	36(24.83%)
Stage III	11(20.75%)	4(7.55%)	13(24.53%)	7(13.21%)	3(5.66%)	6(11.3%)	9(16.98%)	53(36.55%)
Total	42(28.97%)	16(11.03%)	29(20%)	17(11.72%)	12(8.28%)	10(6.9%)	19(13.10%)	145(100%)
Cramer's V(p-value	0.099, Significant							

DISCUSSION

Various prognostic factors associated with breast carcinoma are age, size of tumor, lymph node involvement, histological grade, molecular subtypes etc. Prognosis depends upon the grade of the tumor. The grading system which is most commonly used is Bloom Richardson Grading (Scharf –Bloom-Richardson Grading System) and has a reliable prognostic value.[1]

In present study, out of 145 patients 15.2% showed grade 1,60% showed grade 2 and 24.8% showed grade 3 BR grade which is comparable to study done by Green et.al[8] that concluded in Nottingham series,14.7% showed grade 1 ,32.4% showed grade 2 and 52.8% showed grade 3 and in Edinbergh series 22% showed grade 1 ,40.8% showed grade 2 and 37.2% showed grade 3.

In present study, 7.59% showed Good NPI score(<3.4), 51.72% showed moderate NPI score(3.4-5.4) and 40.69% showed poor NPI Score(>5.41) which is comparable to study done by Green et al8 that concluded 10.3% showed good NPI score, 53.1% showed moderate NPI score and 36.6% showed poor NPI score in Nottingham series and in Edinbergh series 15.5% showed good NPI score, 48.1% showed moderate NPI score and 36.3% showed poor NPI score.

In present study there is significant association between NPI+ biological classes with NPI prognostic groups and BR grading [p value (<0.05)] which is comparable to Edinbegh series, which also concluded significant association between NPI + biological classes and NPI prognostic groups and BR grading.

Limitation of the study were

- Limited sample size.
- The procedure of immunohistochemistry is expensive.
- Inter-observer bias may affect the result.

CONCLUSION

There is significant association between NPI+ biological classes with NPI prognostic groups and BR grading.BR grading does not consider tumor size and lymphnode stage which are known clinicopathological parameters included in conventional NPI. However, presently conventional NPI is not included in reporting format as core data and is much underutilized. Pertaining to immunohistochemical biomarker newer elaborated categorization of breast carcinoma have evolved for better understanding of tumor behaviour, hormonal status, luminal and basal characteristics, local and distant metastasis and thereby reflect on survival of breast carcinoma patients.

REFERENCES

1. Juan Rosai. Breast. In: Rosai and Ackerman's Surgical Pathology. 10th ed. Milan, Italy: 2011 Elsevier; p. 1686–701.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Sun Y-S, Zhao Z, Yang Z-N, Xu F, Lu H-J, Zhu Z-Y, et al. Risk Factors and Preventions of Breast Cancer. Int J Biol Sci. 2017;13(11):1387–97.
4. Kumar A. The Breast. In: Robbins and Cotran Pathologic Basis of Diseases. South Asian edition. Philadelphia: Saunders Elsevier; p. 1046,1051-1054,1057.
5. Soria D, Garibaldi JM, Green AR, Powe DG, Nolan CC, Lemetre C, et al. A quantifier-based fuzzy classification system for breast cancer patients. ArtifIntell Med 2013; 58: 175–184.
6. Rakha EA, El-Sayed ME, Lee AH, Elston CW, Grainge MJ, Hodi Z, et al. Prognostic significance of Nottingham histologic grade in invasive breast carcinoma. J Clin Oncol. 2008;26(19):3153-8.
7. Green AR, Soria D, Stephen J, Powe DG, Nolan CC, Kunkler et al (2016) Nottingham prognostic index plus: validation of clinicaldecision making tool in breast cancer in an independent series. J Pathol: Clin Res 2(1):32–40
8. Rakha EA, Soria D, Green AR, Lemetre C, Powe DG, Nolan CC et al (2014) Nottingham prognostic index

DOI: 10.69605/ijlbpr_13.10.2024.168

plus (NPI+): a modern clinical decision making tool in breast cancer. Br J Cancer 110(7):1688–16975.
9. Lee AH, Ellis IO. The Nottingham prognostic index for invasive carcinoma of the breast. Pathol Oncol Res. 2008;14(2):113-5.
10. Rakha EA, Reis-Filho JS, Baehner F, Dabbs DJ, Decker T, Eusebi V, et al. Breast cancer prognostic classification in the molecular era: the role of histological grade. Breast Cancer Res. 2010 Jul 30;12(4):207.
11. Hu H, Liu Y, Xu L, Zhao J, Duan X, Ye J, et al. Clinicopathological classification and individualized treatment of breast cancer. Chin Med J (Engl). 2013 Oct;126(20):3921–5.
12. O'Toole SA, Selinger CI, Millar EKA, Lum T, Beith JM. Molecular assays in breast cancer pathology. Pathology (Phila). 2011 Feb;43(2):116–27.