ORIGINAL ARTICLES

NOTTINGHAM PROGNOSTIC INDEX IN DIFFERENT AGE GROUPS OF NEWLY DIAGNOSED BREAST CARCINOMA PATIENTS AND ITS ASSOCIATION WITH ER, PR AND HER-2-NEU RECEPTOR STATUS

Faryal Zafar, Tariq Sarfraz, Humaira Tariq*, Saleem Ahmed Khan, Syed Raza Jaffar, Aiza Saadia

Army Medical College/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To calculate Notingham Prognostic Index in all newly diagnosed patients of breast carcinoma from histopathological analysis, to compare the mean Notingham Prognostic Index between different age groups and to determine the association between Notingham Prognostic Index and ER, PR, HER2 expression.
Study Design: Cross-sectional study.
Place and Duration of Study: Department of Pathology, Army Medical College, Rawalpindi, Jan to Sep 2018.
Methodology: A total of 138 diagnosed cases of breast cancer with age >20 years were enrolled. Notingham Prognostic Index was calculated from histopathology report and Immunohistochemistry was performed for ER, PR and HER-2-neu status. Mean Notingham Prognostic Index was measured and compared within different age groups. Association of NPI with receptor status was assessed.
Results: Mean age of the study participants was 52.2 ± 12.2. Family history was positive in 40 (29%) of cases. ER expression was positive in 67 (48.6%) of patients, PR expression was positive in 44.9% 62 of patients and HER-2-neu expression was positive in 78 (56.5%) of cases. In overall study sample, mean Notingham Prognostic Index was found to be 5.53 ± 1.29 SD (95% CI; 5.32-5.75). In age group 21-30 years it was 7.56 ± 0.83 (95% CI; 6.53-8.59) and showed decreasing trend with increasing age (p=0.04). No significant difference was observed in mean Notingham Prognostic Index between receptor positive and negative cases (p>0.05).
Conclusion: A statistically significant difference was found in mean Notingham Prognostic Index values across age groups. Mean Notingham Prognostic Index was significantly higher in younger age group with decreasing trend in older age groups. The finding was remarkable and prognostic implications of these measurements following conventional therapy need to be confirmed by observing these patients for longer periods of follow up.

Keywords: Breast cancer, Estrogen receptor, Immunohistochemistry, Notingham prognostic index, Progesterone receptor.

INTRODUCTION

Breast carcinoma is the commonest cancer in women worldwide and is associated with high mortality rates. It accounts for 23% of all the cancers and 14% of all deaths related to cancers[1]. In the developing countries incidence of breast cancer is reportedly rising due to numerous factors. These include lifestyle modifications, behavioral patterns like and improvement in diagnostic facilities[2]. The trends are similar in Pakistan where breast carcinoma is also the commonest cancer among females, generally presented at later stages and with higher grades at the time of diagnosis, likely due to unavailability of awareness and screening programs across the country[3]. The age of the patient at presentation is considered to be an independent prognostic factor and several studies reported age at presentation as a significant predictor of long term survival in breast cancer patients[4]. The estima-ted "risk of developing breast cancer" rises with age, however, more aggressive biological beha-vior has been reported in breast cancer develops at a younger age in comparison with the disease in older females[5]. The genotype, phenotype, behavioral features of breast cancer are remark-

Correspondence: Dr Faryal Zafar, Department of Pathology, Army Medical College, Rawalpindi Pakistan
Email: faryal.zafa.fz@gmail.com
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ably heterogeneous as well as the response to treatment. Clinical decision making for managing breast carcinoma is individually focused and it needs robust and accurate risk stratification, which should be based on biological characteristics and outcome prediction. Tumour size, pathological stage, lymph nodes positivity, and histological grades are other prognostic factors predicting survival. The Nottingham prognostic index (NPI) is a tool which takes into account the histologic features of the tumor, which helps in the prediction of outcomes and supports clinical decision making while managing these females with breast cancer. The NPI combines nodal status, tumour size and histological grade in a simple formula. Numerous studies reported the advantages of using NPI as a prognostic tool and recommend its use in clinical practice. In a recent study, Peiris, *et al*. 2015 determined the association between age at presentation and NPI. They reported that NPI ≤3.40 was found in 9% of younger age group (<35 years of age) as compared to the older age groups 14% in 35-60 years of age and 18% in >60 years of age. It has been realized that hormonal receptors particularly estrogen and progesterone (ER and PR) and HER2 receptors are present in the tumor tissue and is considered as an important advancement in the evaluation of breast cancer. The presence of these hormonal receptors correlated well with outcome of therapy andthey are now routinely evaluated in the clinical practice to gather prognostic information[8].

Present study was planned to calculate NPI in all newly diagnosed breast cancer patients at our settings and to compare mean NPI in different age groups. We also aimed to determine the association between NPI and ER, PR, HER2 receptors. Expectedly, the gathered data would have useful prognostic implication, which could help the clinician in choosing best individualized therapeutic options.

METHODOLOGY

This cross-sectional study was conducted out at the department of pathology, Army Medical College, Rawalpindi, from January to September 2018 after obtaining approval from the Institutional Review Board. A total of 138 histopathologically diagnosed cases of breast cancer with age 20 years were enrolled in the study by non-probability convenience sampling. Sample size was calculated by using WHO sample size calculator by taking Confidence level: 95%, Anticipated population proportion I (P1): 9%, Anticipated population proportion II (P2): 18%, Precision (d): 8%, sample size, 138[9]. Patients with a history of taking neoadjuvant chemotherapy, history of prior surgery to the same breast and patients with inflammatory breast lesions were excluded from the study. NPI was calculated from histopathology report, "NPI = [0.2 x S] ± N ± G (where S is the size of the index lesion in centimeters, N is the node status: 0 nodes = 1, 1-4 nodes = 2, >4 nodes = 3 and G is the grade of tumor: Grade 1, Grade 2, Grade 3)". Immunohistochemistry analysis was performed on formalin fixed and paraffin embedded sections for ER, PR and HER-2-neu status. Specimen collection, handling and pathological examination was done as per NHSBSP guidelines. All the patients were divided into 5 groups. "Group I: age 21-30 years, Group II: 31-40 years, Group III: 41-50 years, Group IV: 51-60 years and Group V: >60 years". Data were entered on computer software Statistical Package for the Social Sciences (SPSS) version 22. Quantitative variables like age and NPI were measured as mean ± SD. Qualitative variables like Gender, marital status, family history of CA Breast, ER, PR and HER-2 status were measured as frequency and percentages. Mean NPI was measured in each age group and compared with other age groups using students-test. *p*-value ≤0.05 was considered as significant. Association with receptor status was assessed by comparing mean NPI with ER, PR and HER-2 status (positive/negative). Student t-test was used and $p \leq 0.05$ was taken as significant.

RESULTS

A total of 138 histopathologically diagnosed cases of breast cancer with age more than 20 years were finally analyzed. Mean age of the

study participants was 52.2 years ± 12.2 SD. In overall study sample, mean NPI was found to be 5.53 ± 1.29 SD (95% CI; 5.32-5.75). In age group 21-30 years it was 7.56 ± 0.83 SD (95% CI; 6.53-8.59) and showed decreasing trend with increasing age (p=0.04, table-I). ER expression was positive in 67 (48.6%), PR expression was positive in 62 (44.9%) and HER2 neu expression was positive in 78 (56.5%) of cases (table-II). No significant difference was observed in mean NPI between and receptor (ER/PR/HER2-NEU) status (p= 0.915, 0.888 and 0.340 respectively, table-II).

Table-I: Mean Notingham Prognostic Index and comparison in different age groups.

Age groups	N	Mean NPI	Std. Dev	Std. Error	95% CI for mean		*p*-value
					Lower	Upper	
21-30 Years	5	7.56	0.83	0.37	6.53	8.59	0.04
31-40 Years	25	5.73	1.10	0.22	5.28	6.18	
41-50 Years	38	5.39	1.30	0.21	4.97	5.83	
51-60 Years	40	5.50	1.21	0.19	5.11	5.89	
>60 Years	30	5.25	1.34	0.24	4.75	5.75	
Total	138	5.53	1.29	0.11	5.32	5.75	

Table-II: Association of Notingham Prognostic Index with ER/PR/HER2-NEU status.

Parameter	n (%)	Mean NPI	Std. Dev	*p*-value Student t-test	
ER	Positive	67 (48.6)	5.52	1.12	0.915
	Negative	71 (51.4)	5.55	1.43	
PR	Positive	62 (44.9)	5.55	1.11	0.888
	Negative	76 (55.1)	5.52	1.44	
HER2-NEU	Positive	78 (56.5)	5.44	1.15	0.340
	Negative	60 (43.5)	5.65	1.46	

DISCUSSION

Present study results showed that mean age of the enrolled patients was 52.2 years ± 12.2 SD. In overall study sample, mean NPI was found to be 5.53 ± 1.29 SD (95% CI; 5.32-5.75). In age group 21-30 years it was 7.56 ± 0.83 SD (95% CI; 6.53-8.59) and showed decreasing trend with increasing age (p=0.04). No significant difference was observed in mean NPI between receptor positive and negative cases. p-value independent sample t-test was 0.915, 0.888 and 0.340 respectively. Our study results showed that the NPI became lesser with older age at presentation. This means that with increasing age the pathological factors, which are predictive of poor prognosis, become less prevalent. The results of the present study and their biological nature in younger age group are in concordance with other studies[10-15]. A study done in India stated the in breast cancer patients with younger age, tumors were of high grade with extensive lymph node involvement were not positive for hormone receptors (ER and PR)[16,17]. A study done in the USA, reported that a remarkable proportion of breast cancer patients (40.9%) with age >65 years were undertreated due other concomitant morbidities, due to refusal from treatment or due to favorable tumor pathology. The authors further reported that even if those elderly patients were treated effectively, the prognosis remained worse in younger age group (<35 years) due to biologically aggressive tumors in younger age group[18-21]. Our results are similar with a study conducted by Pierse *et al*[18]. They enrolled around one thousand females and grouped them according to their age; "≤35 years (7%), 36-60 years (70%) and >60 years (23%)". They found a significant difference between the age groups and the younger females demonstrated higher tumor grades when compared witholder age groups and only 3% of the younger females had grade 1 tumors (p=0.043). In all age groups, T2 (20-50mm) tumor was the most frequent. Nonetheless, T3 (>50mm) tumor was more prevalent in the youngest age group (13%) while the prevalence of T1 (≤20mm) tumours was higher in the oldest age group (40%). They further demonstrated that a progressive reduction in the prevalence

of lymph node metastases was noted with increasing age ($p \leq 0.05$). The prevalence of lymph node metastases was least in patients who were >60 years of age. The age group ≤35 years had the highest prevalence (52%) of NPI >5.4. Similar to present study results they also found a reduction in NPI with increase in the age ($p<0.05$, $\chi 2$ trend =0.001). In the presents study, we did not measure survival in these patients, as the study was time bound and was requirement of M. Phil thesis. Nonetheless, we suggest continuation of the study for long term follow in order to determine the prognostic implications of NPI measured in the present study. Rakha *et al* in their study applied a wide range of biomarker panel related tobreast cancer to a large and well-characterized series of breast cancer and combined several variables to estimate known as the "Nottingham Prognostic Index Plus (NPI ±)" and applied it to predict outcome in different molecular classes[16]. They reported that higher NPI was associated with poorer outcomes. In the presents study, we did not measure outcomes or development of distant metastases as the study was time bound.

In summary, present study has revealed that patients in younger age groups demonstrated poor prognostic features when compared with older age groups. The NPI was significantly higher in younger age group. We observed that the NPI is a reproducible tool that may provide improved individualized clinical decision making for females with breast carcinoma by refining clinical prediction. The implications of these measurements following conventional therapy need to be confirmed by observing these patients for longer periods of follow up.

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CONCLUSION

A statistically significant difference was found in mean NPI values across age groups. Mean NPI was significantly higher in younger age group with decreasing trend with increasing age. The finding was remarkable and prognostic implications of these measurements following conventional therapy need to be confirmed by observing these patients for longer periods of follow up.

CONFLICT OF INTEREST

There was no conflict of interest to be declared by any author.

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