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A Better Perspective of Nuclear Atypia in Nottingham Prognostic Index: Study on Breast Carcinoma Patient Cohort from Eastern India

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Authors' contributions

This work was carried out in collaboration between all authors. Author DRS designed the study and wrote the manuscript. Author SNS managed the literature searches, analyses of the study. Author TKS involved in designing the study and writing the manuscript. Author PK involved in analyzing the data. Author SM involved in writing the manuscript and literature search. Author SS involved in analyzing data. Author RNM involved in study literature search and analyzing data. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This paper uses the parameter-based correlation to Nottingham prognostic indexwith specific attempt for histologic grade/ nuclear atypia.
Place and Duration of the Study: The retrospective analysis was conducted at Acharya Harihar Regional Cancer Research Centre and Hospital, Cuttack, Odisha within a period of 6 years starting from 2008 to 2013.
Methodology: In this paper we have done retrospective analysis of the histopathological data of 1372 breast carcinoma patients from eastern India and subjected to different regimens of therapy and patient health constitution driven treatment outcome. This paper uses the parameter-based correlation to NPI with specific attempt for histological grade/ nuclear atypia.
Statistical Methods: SPSS version 22.
Results: The results of the study gives a impression that the correlation of NPI and histologic grade bears statistical significance and especially nuclear atypia and mitotic activity are two of those parameters with higher significance of correlation with NPI.
Conclusion: Nuclear atypia as seen from multivariate analysis and correlation study can be a better prognostic marker for a range of values with most the confidence interval being up to 3.71.

Keywords: Nuclear atypia; histological grade; Nottingham prognostic index; breast cancer; tumor size; nodal involvement.

1. INTRODUCTION

Clinical management of breast cancer depends on various clinical and pathologic prognostic and predictive factors to support clinical and patient decision making for suitable treatment options. It has been largely accepted by the clinicians that there is no exact generalization of an effective breast cancer treatment. The common modalities of treatment involve surgery, radiotherapy, chemotherapy, hormone therapy and biological treatment [1]. A modern and effective approach has been adopting a combinatorial approach for treatment of breast cancer based on the clinicopathological parameters involved and patient history along with bimolecular signatures associated with the disease manifestation [2]. Therefore, it is imperative to identify and characterize the commonly associated parameters of breast cancer like type of breast cancer; size of tumor; stage of tumor; grade of tumor; whether the patient had menopause, general patient health constitution and the status of cancer cell sensitive to receptor targeted therapy (trastuzumab) [3,4]. Although these parameters are mostly identified but the characterization along with correlation of these parameters with the most widely adopted prognostic index has been negligible in the scientific community leading to a broad prognostic score generation with limited applicability to treatment or early treatment options [5].

The Nottingham Prognostic Index (NPI), a continuous variable based index uses retrospective factors like tumor size [6], nodal involvement [7] and tumor histologic grade for determining the likelihood outcome of breast cancer patients [8]. NPI has been recognized as the only appropriately validated prognostic index in breast cancer [9]. The brief review of NPI gets clearer with the correlation summary of NPI scores and the predicated survival rates (Table 1). Higher the NPI score lower is the survival rate and higher is the aggressiveness of breast cancer.

Table 1. Correlation between NPI scores and survival rate

NPI score	Survival rate (in %)
>/=2.0 to </= 2.4	93
>/=2.4 to </= 3.4	85
>3.4 to </= 5.4	70
>5.4	50

The prognostic index has not only facilitated stratification of treatment strategies but also has been linked with the typical and significant molecular changes involved in breast cancer. These molecular markers with stage specific expression patterns have been developed using immunohistochemistry method for different clinical samples of different stages of breast cancer (pre and post-surgery conditions) [10]. This improvised version of correlating the clinicopathological factors with that of the molecular markers involved in progression of breast cancer has led to the development of NPI-Plus (NPI+) [11,12]. In addition to predicting the treatment outcome and deciding for next course

of treatment it also aids in sensitive modeling of treatment stage, patient health constitution and aggressiveness of cancer [13]. This bioinformatics modeling along with biological and clinical analysis has been the basis of improvised prognostic index development for breast cancer [14].

Understanding the clinic-pathological factors involved in breast cancer has aided the contemporary clinical management practices. One of the major outcomes of has been categorical identification of individual factors and their summative and independent correlation to prognostic index [15,16]. The three strongest prognostic determinants in operable breast cancer used in routine clinical practice internationally are lymph node (LN) stage, primary tumor size, and tumor histologic grade, which constitute Nottingham prognostic index [17,18]. In 1957, Bloom and Richardson proposed a simplified system, which utilized only three of Greenough's variables: gland-formation (tubularity) degree of variation in nuclear size and shape (pleomorphism) [19], and 'hyperchromatic figures' as an estimate of proliferation to form the histological grade [20]. Though lymph node, which has traditionally been regarded as the most powerful prognostic factor in breast cancer, all the other factors are potentially regarded as prognostic factor.

The histologic grade of tumor is primarily determined by nuclear atypia (nuclear pleomorphism), nodal involvement and mitotic activity [21]. Broadly, the histologic grade for breast cancer range from: Grade 1 (Low grade)-> Grade 2 (Intermediate grade)-. Grade 3 (High grade) [22]. Cancers with lower grade profile tend to grow slowly and respond much efficiently to surgery and other treatment regimens (radiotherapy, chemotherapy, hormone therapy, biological treatments) [23]. This ensures higher survival rate, which thus can be deduced to be inversely related to NPI.

It is understood that the factors contributing to histologic grade have a correlation to the NPI. However, there has been no direct evidence of correlation of each of these factors or as independent parameters to NPI [24]. The Nottingham prognostic index, which has histologic grade as one of the constituting factors can be reasoned to have some significant and more indicative correlation to either of the factors making of histologic grade or a combination of those [25]. Nuclear atypia, nodal involvement and mitotic activity are three parameters making up the histologic grade [26,27] and more or less subjected to individual or contextual bias during observation or scoring [28,29]. However, the gap in this knowledge has limited our understanding and earlier prediction of treatment outcome or more clearly poorer prognosis.

This paper tries to identify the correlation of the factors making up histologic grade of tumors to that of the calculated Nottingham prognostic score [30,31]. The long-term aim of the work is to establish a better perspective to these factors other than mere calculation of histologic grade [32] and thereby develop any such significant factor for early prognosis in cases of breast carcinomas.

2. METHODS

2.1 Patient Selection

The samples were collected from 1372 primary invasive breast cancer patients for a period of 6 years starting from 2008 to 2013 from Acharya Harihar Regional Cancer Research Centre and Hospital, Cuttack, Odisha. A series of histopathological analysis and data collection was subsequently followed up. The histopathological data was subjected to univariate, multivariate and parametric statistical analysis using IBM SPSS software version 22 (SPSS Inc., Chicago, IL, USA) [33,34].

The age of patients considered for the study ranged from 20 to 82 (Fig. 1) years old of which most were subjected to surgery/radiotherapy/ chemotherapy and/or a suitable combination of these treatment options. The detailed patient characteristics and the parameter range used for this study has been summarized in Table 2. The sample processing involved initial clinical review of formalin fixed histological sections embedded with paraffin. This study was conducted under the regulations of Indian council of medical research. The handling of biological specimens from tumor banks, being the samples available for research and clinical purposes in retrospective studies.

The histological diagnoses were cross-verified by trained pathologists. The tumor samples were categorical characterized for parameters like tumor size, nodal status, histologic grade, surgical margin, nuclear atypia, mitotic activity, (Table 2). In samples with valid data for all the parameters, NPI was calculated using the standard equation:

$$NPI = 0.2 \times \text{tumor size (cm)} + \text{grade (1-3)} + \text{lymph node status (1-3)}$$

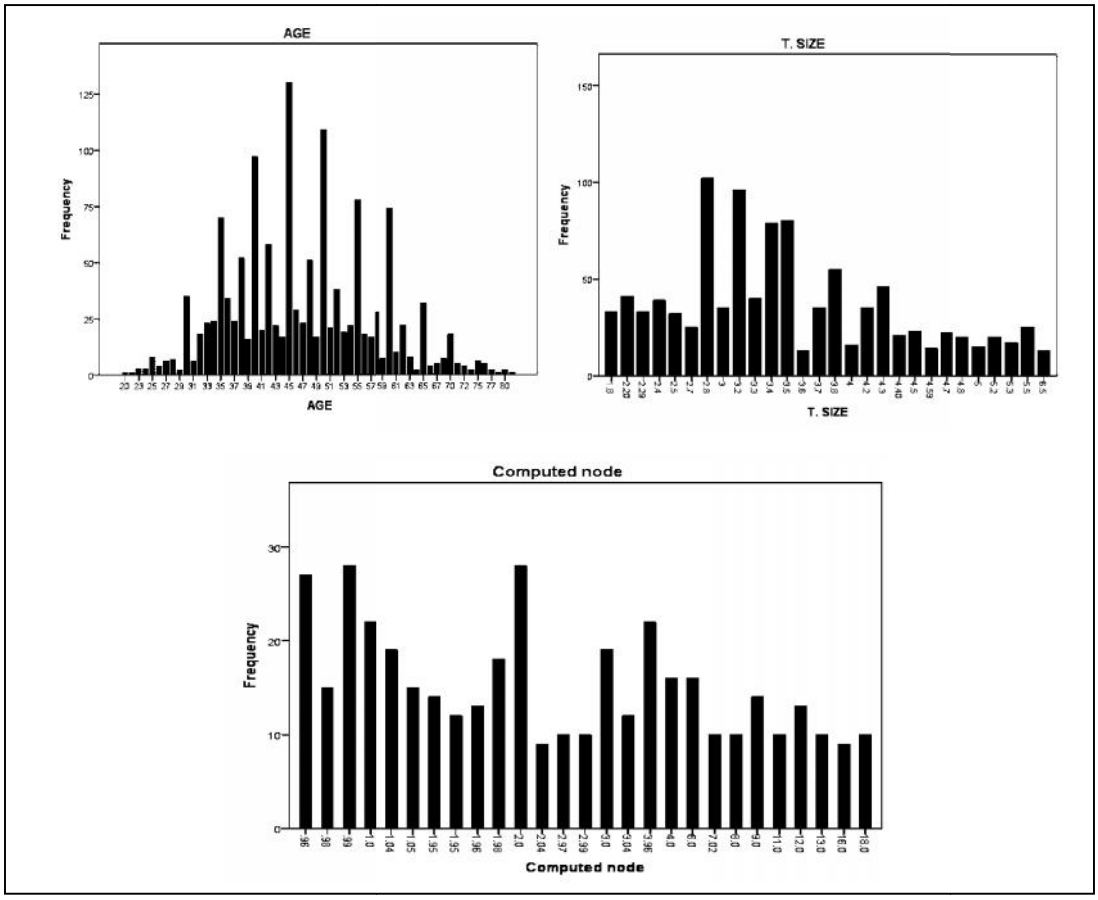


Fig. 1. Distribution of the patient characteristics involved in the study of correlation of histologic grade parameters with NPI in 1372 breast cancer patients

In addition, patient history and medical related information were collected like age, sex, spread of breast cancer and their geographical origin (broadly defined in this paper as belonging to eastern India). Tumor size, histologic grade and the corresponding NPI are most frequent for their respective median values. The most frequent tumor size was 2-5 cm (86.7%) with the mean being 3.83 cm±2.00 cm (Fig. 1). Similarly, histologic grade of tumors was mostly reported for grade 2 tumors (60%) indicating moderately severe aggressiveness of tumors among the cohort of patients.

The calculated NPI was most frequent for the range "3.4 ≤ NPI ≤ 5.4 and NPI > 5.4" (Fig.1) indicating intermediate to poor survivability rates post treatment of the patients under consideration. With reference to the standard correlation of NPI with survivability rates (Table 1) it is assumed to be between 50-70% for the patient cohort under focus.

2.2 Statistical Analysis

The histological data collected from the 1372 breast cancer patients was subjected to statistical analysis using IBM SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA). The convention used in the data representation (Table 2) is: continuous variables have been represented in form of mean standard deviation and category-based variables have been represented as percentages.

The data was subjected to distribution analysis to ensure comparison uniformity among different parameters being used in this study, namely NPI; histologic grade; nuclear atypia; mitotic activity; nodal involvement and tumor size. An unpaired T-test with 95% confidence interval was used for generating the mean differences for continuous variables. The above specified parameters were subjected to univariate, multivariate and parameter bias analysis using SPSS. In addition

to develop a predictive model for determining the range of NPI that can be predicted with the constituent factors making up histologic grade we performed a predictive analysis where the scores with 95% confidence was considered significant for our study. In this paper we have used Pearson correlation and chi-squared tests to determine the associativity of the parameters with NPI (Fig. 1).

Table 2. Showing patient characteristics and tumour parameters

Variable (N = 1372)	Data
Age at diagnosis, years	
Mean and standard deviation	47.06±10.714
Range	62 (Min 20; Max 82)
Tumor size (cm)	
Mean and standard deviation	3.83 cm±2.00 cm
Range	16.2 (Min 0.8; max 17)
T1: < 2 cm	94 (7.67%)
T2: 2-5 cm	1092 (86.7%)
T3: > 5 cm	469 (38.3%)
Not assessed	148
Lymph node invasion	
Present	657 (48.59%)
Absent	695 (51.40%)
Not assessed	20
Histological grade	
Grade I	33 (2.50%)
Grade II	767 (60.10%)
Grade III	471 (37.0%)
Not assessed	101
Nottingham prognostic index	
NPI < 3.4	50 (4.14%)
3.4 ≤ NPI ≤ 5.4	566 (46.90%)
NPI > 5.4	589 (48.80%)

3. RESULTS

3.1 Correlational Analysis

The study focuses on understanding the correlation of the Nottingham prognostic index (NPI) along with that of histologic grade as well as the factors contributing to it. However, the approach to deduce the correlation of the factors making up histologic grade independently to that of NPI has been an unique and over searching attempt of this paper to understand for any clinical/ biological parameter that holds significant correlation to NPI and thus can be developed as an aid for early prognosis of breast cancer prior to standardization of NPI scores. The parameters giving rise to NPI like tumor size, lymph node involvement and histologic grade have also been attempted for finding any intuitive correlation. For the purpose of higher accuracy we have adopted the significance threshold to be at 0.01 level (2-tailed).

Of the parameters making up histologic grade only nuclear atypia and mitotic activity hold significantly high correlation (0.079 and 0.076 respectively) with that of NPI in contrast to tubule formation (Table 3). Thus, we build on our hypothesis that among three factors contributing to histologic grade, mitotic activity and nuclear atypia hold stronger correlation and thus can be potential candidate for independent early prediction of treatment outcome in breast cancer patients. This correlational analysis or associativity study helps to build a more objective hypothesis that nuclear atypia or mitotic activity can be a better prognostic marker in contrast to tubule formation. In addition, the positively significant correlation also establishes a retrospective link of “not just histologic grade but factors making histologic grade can be better prognostic markers”. This adds higher prognostic power to the less explored parameters like nuclear atypia and mitotic activity.

3.2 Sample Distribution Study and Range Homogenization

Considering the ample number of sample, i.e. 1372 samples from eastern Indian cohort of patients, it is imperative to understand that the difference in sample exposure to climate, genetic make-up, epigenetic influencers as well as the experimental bias do not significantly mask the correlation outcome. So, it was hypothesized that identification of the frequency distribution patterns (Fig. 2) and the correlation of the various categories with that of histologic grade and the parameter of focus i.e. “nuclear atypia” will enable us to confirm the applicability of our data to clinical set up and to homogenize the differential missing data for each parameters among all the samples.

The NPI as well as the inherent factors like tumor size and nodal involvement have a similar pattern of distribution with the most of the samples being crowded around the median case for each. With respect to histologic grade there is a significant mismatch of the range of sample

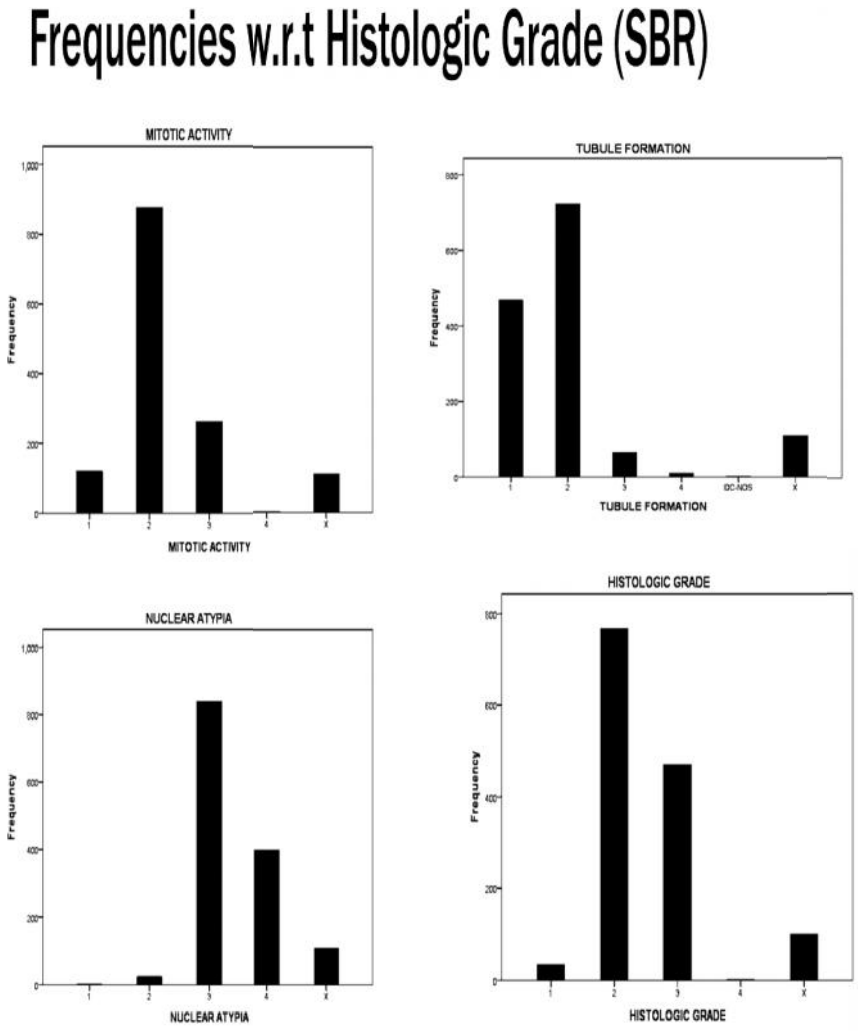
distribution of NPI and histologic grade where histologic grade is mostly accumulate within grade I and grade II tumors. So the applicability of NPI for prognosis forecasting might lead to erroneous assumption and clinical bias during treatment.

However, nuclear atypia has a much similar frequency distribution pattern in comparison to NPI as well as other parameters like tumor size, nodal involvement and tubule formation.

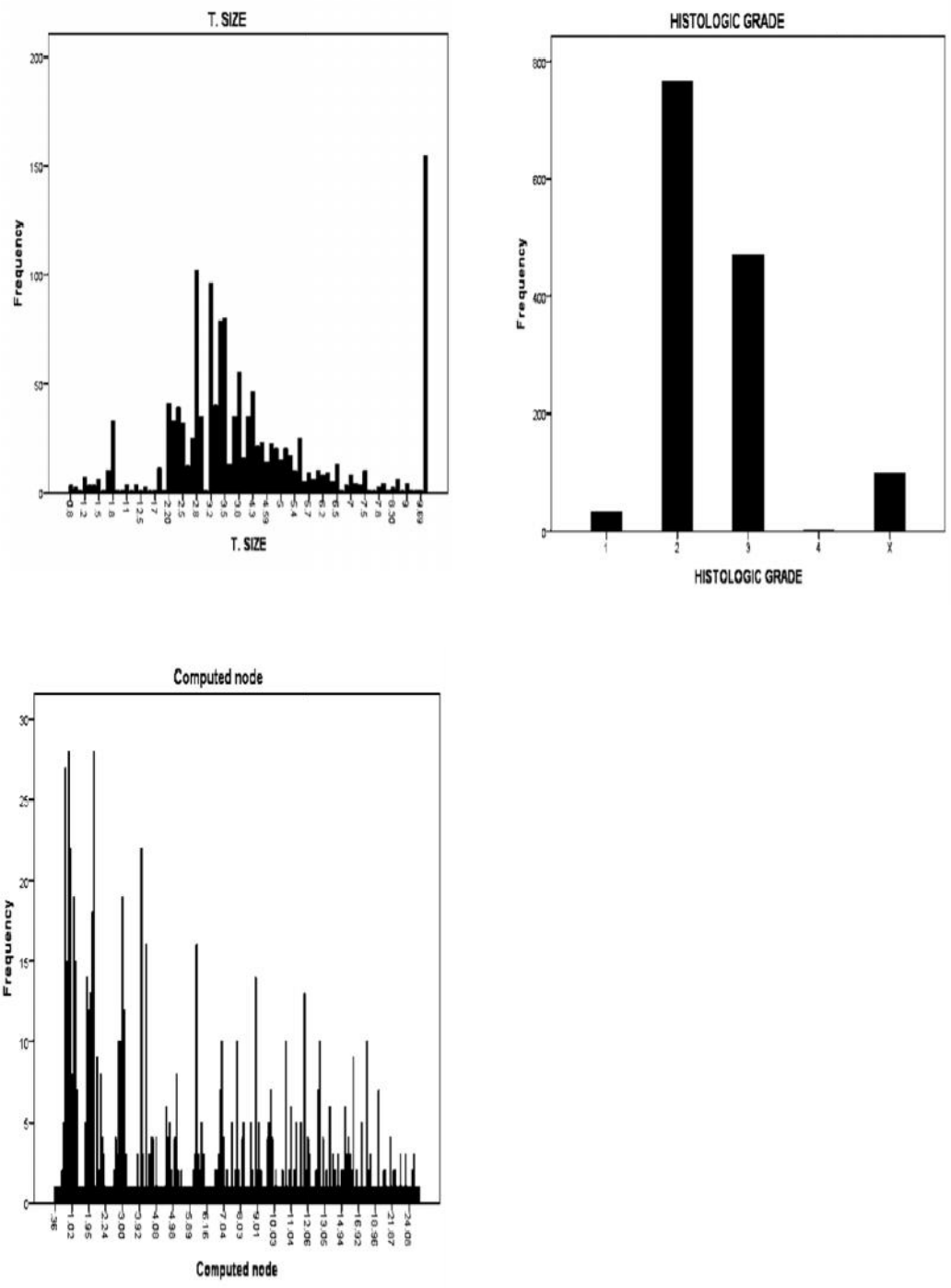
3.3 Histologic Grade and the Role of Contributing Parameters

Histologic grade of tumors is the summation of three parameters observed in tumors like nuclear atypia, tubule formation and mitotic activity. As deciphered from the correlation analysis (Table 3) nuclear atypia and mitotic activity have higher significance and independent correlation to that of NPI and thus characterizing the pattern of this categorical variable for the continuous variable (NPI) is important to deduce a meaningful relationship.

Nuclear atypia and mitotic activity as like NPI also hold their most frequent observation in the median range, which means a case of intermediate nuclear pleomorphism oratypia and mitosis. This suggests that nuclear atypia or mitotic activity or both can have a stronger predictive correlation depending how significant is their univariate/ multivariate analysis.



(a)



(b)

Fig. 2. (a) and (b): Frequency distribution of breast cancer parameters like NPI, tumour size, tubule formation, mitotic activity and nodal involvement with that of histologic grade/nuclear atypia

Table 3. Correlation analysis of NPI with that of its constituent parameters (tumour size, nodal involvement and histologic grade)

	Correletions						
	Prognostic score	**T. size**	**Tubule formation**	**Nuclear atypia**	**Mitotic activity**	**Computed node**	**Histologic grade**
Prognostic score	1	.022	.007	.076	.079	.034	.079
		.456	.819	.009	.006	.234	.006
	1202	1147	1184	1185	1184	1200	1185

***. Correlation is significant at the 0.01 level (2-tailed)*
**. Correlation is significant at the 0.05 level (2-tailed)*

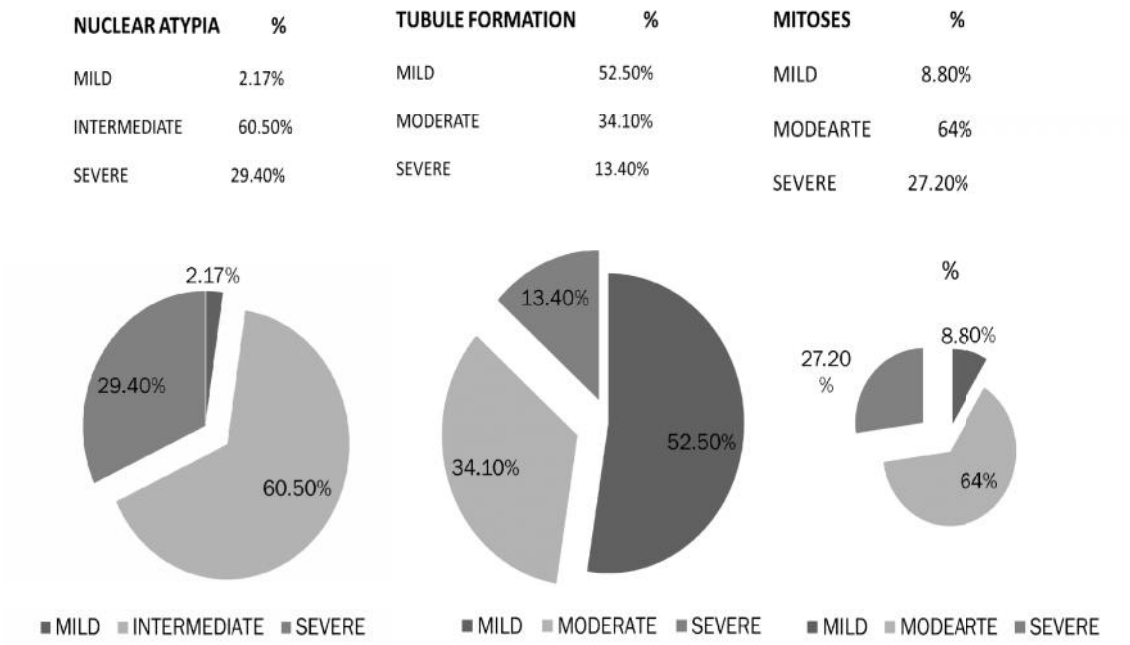


Fig. 3. Frequency distribution of breast cancer parameters like NPI, tumor size, tubule formation, mitotic activity and nodal involvement with that of histologic grade/nuclear atypia

3.4 Univariate Analysis

Univariate analysis with NPI as the dependent variable subjected to parametric variations highlight histologic grade to the better prognostic marker in comparison to other parameter like nuclear atypia, tubule formation and mitotic activity (Table 4). NPI has a high significant correlation with histologic grade 0.864 in comparison to nuclear atypia (0.421) and tubule formation (0.439). The result of univariate analysis supports the contemporary convention that the "histologic grade itself can be an early prognostic factor than that of inherent factors like nuclear atypia and mitotic activity". However, modeling the prognostic index using univariate analysis limits the variability of the multiple parameters and doesn't resemble or recreate the practical influence of multiple parameters on NPI. Therefore, we proceed with multivariate analysis.

3.5 Multivariate Analysis

A multivariate analysis of NPI with that of histologic grade and nuclear atypia reveals a contradictory or more suggestive explanation to the univariate analysis result (Table 5). Here nuclear atypia is more significantly related to NPI score than that of histologic grade but the confidence interval for histologic grade runs higher than that for nuclear atypia. Nuclearatypia for the sample of this study mostly range in the intermediate range (Fig. 3) therefore a confidence threshold of 3.711 permits only type 1 and type 2 cases of nuclear atypia. However, histologic grade with confidence threshold of

4.095 accounts for most of the reported tumor grades, which range among grade1/2/3 and most frequently in this study for grade 2.Thus, in a way histologic tumor grade has a wider window for accommodating higher number and variety of samples for better prognosis for most of the breast cancer patients whereas nuclear atypia, is limited by the specific confidence limit for up to 3.711.

3.6 Non-parametric Analysis

In order to account for and eliminate the bias of any parameter towards NPI and the model of multivariate analysis with NPI as the dependent variable and histologic grade and nuclear atypia as the parameters is subjected to Friedman's Two-way analysis of variance by ranks. The result indicates that no significant parametric bias exists in the multivariate analysis model used above (Table 5) and thus the null hypothesis, i.e. "NPI, Tumor Size and Histologic grade" are the same for nuclear atypia stands rejected.

3.7 Predictive Analysis of NPI w.r.t to Histologic Grade / Nuclear Atypia

The correlational analysis and variable study of NPI with that off histologic grade and nuclear atypia suggests for possible methods for early prognosis of breast cancer from clinical data. Therefore, modeling in retrospective manner will help to generate a predictive model for estimating the treatment outcome of patient and thereby deciding how reliable can the nuclear atypia based prognosis can be in face of the 95% confidence interval being exerted upon.

Table 4. Univariate correlation analysis of NPI with that of its constituent parameters (tumour size, nodal involvement, histologic grade, nuclear atypia and mitotic activity)

Tests of between – subject effects Dependent variable: Prognostic score		
Source	**Mean square**	**Sig.**
Tubule formation	108.141	0.439
Nuclear atypia	310.858	0.421
Mitotic activity	32.491	0.190
T. size	5.312	0.671
Histologic grade		0.864
Computed node	242.327	0.234

***. Correlation is significant at the 0.01 level (2-tailed)*

Table 5. Multivariate analysis of NPI, tumour size, nodal involvement, mitotic activity and tubule formation with that of histologic grade and nuclear atypia

Parameter estimates					
Dependent variable	**Parameters**	**Std. error**	**Sig.**	**95% confidence Interval**	
				Lower bound	**Upper bound**
Prognostic score	Intercept	2.760	.878	-5.839	4.991
	Histologic grade	1.398	.337	-1.401	4.085
	Nuclear atypia	1.454	.555	-1.995	3.711
T. size	Intercept	.319	.000	2,377	3.627
	Histologic grade	.161	.004	.145	.778
	Nuclear atypia	.168	.617	-.413	.245
Computed node	Intercept	1.217	.005	1.034	5.808
	Histologic grade	.604	.248	-.487	1.882
	Nuclear atypia	.634	.849	-1.365	1.123
Mitotic activity	Intercept	.083	.000	.844	1.171
	Histologic grade	.042	.000	.843	1.008
	Nuclear atypia	.044	.000	-.407	-.235
Tubular formation	Intercept	.118	.000	1.822	2.286
	Histologic grade	.060	.000	-.494	-.259
	Nuclear atypia	.062	.013	.033	.277

***. Correlation is significant at the 0.01 level (2-tailed)*

Table 6. Non-parametric analysis of NPI, histologic grade and nuclear atypia using Friedman's Two-way Analysis of variance by ranks

Hypothesis test summary			
Null hypothesis	**Test**	**Sig.**	**Decision**
The distributions of prognostic scores, T. size and histologic grade are the same	Related samples Friedman's two-way analysis of variance by ranks	.000	Reject the null hypothesis

Asymptomatic significances are displayed. The significance level is .05

The confidence co-efficient (CCF) of NPI with respect to histologic tumor grade and nuclear atypia help in a developing a reference based model for predicting the treatment outcome. The model as shown in Fig. 4 represents the table of NPI correlation to histologic grade or nuclear atypia and the reliability of the prediction using 95% confidence interval as the filter.

4. DISCUSSION

The Nottingham prognostic index has been the most widely accepted and used prognosis index for primary operable breast cancers around the world. Several experimental data arising from different geographical coordinates of the world have confirmed the validity of NPI and simultaneously few of these have added exceptions or newer possibilities to the NPI. In this paper, we tried to understand how histologic grade (considered to be an independent prognostic parameter in comparison to tumor size and node status) correlates to NPI. Precisely, we have explored the patterns of possible correlation of parameters making up histologic tumor grade and NPI.

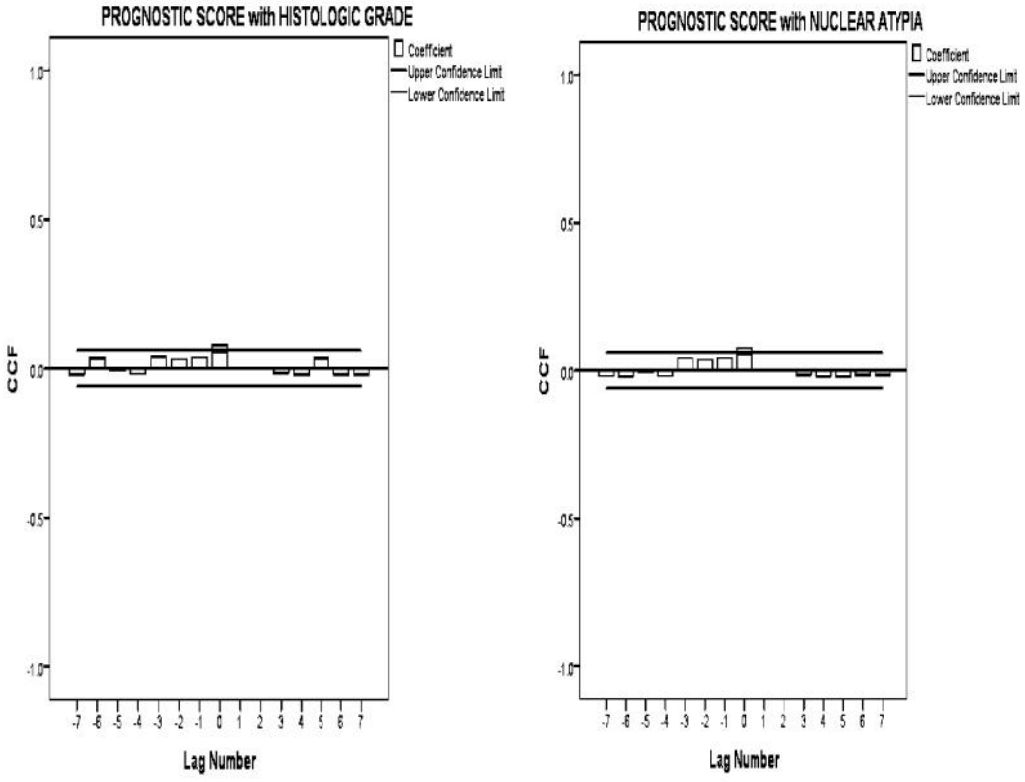


Fig. 4. Predictive analysis model of NPI using histologic grade/ nuclear atypia as significant parameter estimates

From the correlational analysis the results gave a clear indication that indeed the correlation of NPI and histologic grade bears statistical significance and especially nuclear atypia and mitotic activity (factors constituting histologic grade) are two of those parameters with higher significance of correlation with NPI. Further since the data set for the study consisted to heterogeneous valid data for each parameters, it was necessary to compare the distribution and frequency of the parameters including NPI to eliminate experimental error and input / output mismatch. The data of 1372 breast cancer patients suggested that most of the data remained in the median distribution range and the nature of tumor under study ranged from intermediate to severely aggressive ones with lesser survivability rates and poorer treatment outcomes.

Associativity analysis using univariate and multivariate analysis models suggest that nuclear atypia than the overall histologic grade holds significance in early and better prognosis of breast cancer patients but the confidence levels with which NPI can be predicted using either of these as parameters varies. Histologic grade has a wide range of grade values for which NPI can be predicted with more than 95% confidence score whereas nuclear atypia experiences a lower threshold cut-off at just 3.711 for predicting NPI. This suggests practical limitation of nuclear atypia in predicting prognosis for intermediate and severely aggressive breast cancers where the survival rates are low. In other words, nuclear atypia as an independent prognostic marker serves good when used for predicting grade 1/ grade 2 tumors with NPI ranging 5.4 or less. Since, most of the cases of less aggressive breast cancers are hard to detect and less reported the clinical appreciation of nuclear atypia, as an important prognostic factor has been less. In addition the non-parametric analysis suggested there is no statistical parametric based bias as nuclear atypia recognizes NPI, tumor size and histologic grade to be independent parameters and correlates differentially with each of these.

5. FUTURE PERSPECTIVE

It would be expected in the scientific and clinical domain that any prognostic tool developed must be applicable to all the known forms of breast carcinomas. However, one of the major limitations to developing NPI is the inability or the paradoxical applicability to triple negative breast cancer patients (insensitive to estrogen, progesterone and trastuzumab targeted therapy). The existing results of triple negative breast cancer suggest that there is a prevalence of lymph node metastasis at the time of diagnosis. In contradiction few other literatures suggest that the metastasis and spread of cancer cells in triple negative breast cancer have a heterogeneous preference and doesn't always spread to lymph nodes. Breast cancer in general is characterized by heterogeneity of patient outcome in terms of response to treatment and their health constitution. However, this heterogeneity is further complicated in triple negative breast cancer patients.

6. CONCLUSION

A future perspective of developing NPI is to identify and characterize the prognostic patterns associated with triple negative breast cancers and specifically characterize for cases with lymph node metastasis and those without. This retrospective analysis will allow for a more widely accepted form of NPI with better applicability to triple negative breast cancer patients.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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