Original Article

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Pathology Section

A Cross-sectional Study of Prognostic Implications of Survivin Expression in Combination with Nottingham Prognostic Index and Immunohistochemical Techniques in Patients with Breast Cancer

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ABSTRACT

Introduction: Breast Cancer (BC) is a malignant multivariant disease associated with premature death in women. BC exhibits variable morphological and biological features in women from developing countries.

Aim: The primary aim of this study is to analyse the nuclear and cytoplasmic expression of survivin in various molecular types of BC and to compare it with other prognostic indices, such as the Nottingham Prognostic Index (NPI) and the Immunohistochemical (IHC4) score.

Materials and Methods: This was a retrospective cross-sectional study of 50 primary BC cases conducted in a PSG Institute of Medical Science and Research, a tertiary care hospital in Coimbatore, Tamil Nadu, over a period of three years (January 2016 to December 2018). All study materials were collected from the patients' archives, including tissue blocks and slides for IHC studies, which included Oestrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), and Ki-67. An individual assessment of NPI, IHC4, and survivin expression for the cases was conducted. Additionally, the correlation between NPI and IHC4, NPI and survivin expression, and IHC4 and survivin expression was analysed statistically using Pearson's Chi-square test with Statistical Package for the Social Sciences (SPSS) software (version 16.0, Chicago, IL, USA).

Results: The NPI analysis showed that 50% of the cases were graded as grade II. The number of positive axillary lymph nodes in the cases varied from 0 to 19; however, most cases presented with zero lymph metastasis, resulting in an overall NPI score ranging from 2.4 to 7. The IHC4 score indicated that there were 37 high-risk cases, along with 3 low-risk and 10 intermediate-risk cases. The majority of cases belonged to the luminal B subtype (40%), followed by HER2 (30%), luminal A (20%), and Triple Negative Breast Cancer (TNBC) (10%). The expression of survivin peaked in the luminal B subtype, with high cytoplasmic and nuclear expression noted in grade II NPI and IHC4 tumours. However, a weak correlation was established between survivin expression and NPI (r-value=0.1) and between survivin and IHC4 (r-value=0.1), while a negative correlation was observed between NPI and IHC4 (r-value=-0.1).

Conclusion: The combined use of these surrogate prognostic tools will aid in better predicting the prognosis of patients with BC and in planning adjuvant therapies aimed at improving the survival and quality of life of patients.

Keywords: Cancer prognosis, Multivariant disease, Oestrogen receptor, Premature death

INTRODUCTION

Breast Cancer (BC) accounts for 14% of cancers in Indian women, with about one million Indian women expected to develop BC during their lifetime [1]. There have been significant advances in BC management over the last few decades, resulting in significant decline in cancer-related deaths [2]. BC is no longer viewed as a single disease; it is considered a multifaceted condition with distinct biological subtypes and a wide-ranging spectrum that includes clinical, pathological, and molecular features, manifesting different prognostic and therapeutic implications [3]. Prognostic indices that combine several clinicopathological factors have been available for many years [4]. The most widely applied index is the Nottingham Prognostic Index (NPI), established in 1982, which assesses tumour size, histological grade, and lymph node stage to prognostically stratify patients with invasive BC [5,6].

Immunohistochemical (IHC) classification provides valuable therapeutic and prognostic information [7]. A combination of several IHC markers, including ER, PR, HER2, and Ki-67, is used to derive the IHC4 score, which has been clinically validated to evaluate distant recurrence in BC patients and the response to adjuvant therapy [8,9].

Survivin belongs to the family of apoptotic inhibitors and also regulates cell division. The expression pattern of survivin has been extensively analysed in various cancers, including breast cancer, where positive expression has been found to predict a significantly higher risk of disease recurrence and is associated with the occurrence of metastases. There has been a vast expansion of knowledge regarding the treatment options for BC in recent years; however, despite significant therapeutic efforts, the outcomes for BC have not improved dramatically. The prognosis of BC is predicted based on clinicopathological factors and IHC marker expression [10]. Nevertheless, it is noted that tumours within the same group can behave differently, thereby altering responses to treatment. Consequently, it is crucial to detect prognostic markers that can enhance prognostic predictions and potentially target these markers with their respective antagonists.

Many recent studies [11-13] have highlighted the importance of survivin expression in BC and suggested that using survivin antisense oligonucleotides can increase sensitivity to chemotherapy. Research reports on the correlation between survivin expression and other clinicopathological prognostic indices, like NPI, are currently lacking

in the literature. Furthermore, in this era of molecular diagnostics, a more affordable alternative to expensive genomic-based molecular tests, such as Oncotype Dx and Mammaprint, is essential, especially considering the financial impact on patients diagnosed with BC. Hence, this study, which involves the correlation (r-value) of survivin expression with NPI and IHC4 scores, is not only novel but may also provide new insights into the cost-effective management of primary BC. Hence, the objective of the present study was to evaluate the implications of survivin expression in the prognosis of breast cancers and to correlate survivin expression with other prognostic indices like NPI and IHC4 scores.

MATERIALS AND METHODS

A retrospective cross-sectional study of 50 primary BC patients was conducted at the PSG Institute of Medical Science and Research, a tertiary care hospital in Coimbatore, Tamil Nadu,India. The subjects had undergone modified radical mastectomy and were receiving treatment during the period from January 2016 to December 2018 (IHEC no. PSG/IHEC/2018/Appr/Exp/295).

Inclusion criteria: Cases of BC diagnosed in the pathology laboratory with available paraffin blocks/slides from the tumour, as well as BC cases for which IHC for ER, PR, Her2, and Ki-67 had been previously performed, were included. Additionally, BC patients who were receiving treatment post-mastectomy and those with complete clinicopathological data and follow-up data for a period of at least 12 months were incorporated into the study.

Exclusion criteria: Patients with metastatic disease at the time of diagnosis, those treated with neoadjuvant chemotherapy or radiotherapy, and cases with irregular follow-up were excluded from the study.

Study Procedure

Relevant clinical and pathological parameters were collected for patients diagnosed with invasive carcinoma, No Special Type {World Health Organisation (WHO) classification of breast tumours, 2019} [14]. This included details of age, tumour size, lymph node status, postoperative follow-up, and tumour stage, which were retrieved from the patients' records in the archives. Blocks and slides of tumour tissues were also obtained to assess the status of biomarkers.

Nottingham Prognostic Index (NPI): The tumours were graded using the Modified Scarff-Bloom-Richardson grading system, or Nottingham Combined Histologic Grade [15], and were grouped into three grades based on the following parameters: tubule formation, mitosis, and nuclear pleomorphism. The NPI was calculated as follows [5]:

NPI=Tumour Size (cm)×0.2+Grade+Lymph Node Points

{Negative nodes=1 point; 1-3 positive=2 points; >3 positive nodes= 3 points}

NPI can define three subsets of patients with different survival probabilities from BC: Good (<3), Moderate (3.41-5.4), and Poor (>5.4) prognostic subgroups [16].

IHC4 score: The IHC4 score was calculated using algorithms proposed by Cuzick J et al., [8]. ER, PR, Her2/NEU, and Ki-67 slides of the respective cases were taken and reviewed for calculating the IHC4 score using the formula:

$IHC4=94.7\times\{-0.100ER_{10}-0.079\ P_gR_{10}+0.586HER2+0.240\ln(1+4\times Ki\text{-}67)\}$

According to the expression of the IHC markers, the cases were divided into four molecular subtypes: Luminal A, Luminal B, HER2 overexpressing and TNBC.

Immunohistochemistry (IHC) for survivin expression: Survivin IHC was performed on representative slides for each case using rabbit monoclonal antibody PRO72 (PathnSitu Biotechnologies). Human gastric malignancy sections were used as positive controls, with duplicate sections without exposure to primary antibodies serving as negative controls.

Evaluation of Immunohistochemistry (IHC): Survivin expression was calculated as the percentage of cells demonstrating nuclear and/or diffuse cytoplasmic reaction. At least 10 high-power fields were assessed separately at 40X magnification to determine the nuclear and cytoplasmic tumour cell immune reactivities.

The tumour cells were graded as follows: 0=<5%, 1=5-20%, 2=21-50%, 3=51-75%, 4=>76%. A cut-off value of >20% was considered positive, with results of 0 and 1 deemed negative [3].

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS software package (version 16.0, Chicago, IL, USA). Two tailed p-values of <0.05 were considered significant. The independent Chi-square test was used to calculate the relationship between the NPI score, IHC4 score, and the nuclear/cytoplasmic immunoreactivity of survivin. Descriptive statistics were employed to summarise the clinicopathological parameters.

RESULTS

A total of 50 cases of BC were included in our study based on the established inclusion and exclusion criteria. The baseline clinicopathological features considered were age, size, histological subtype, and recurrence.

The age of the patients varied between 29 and 82 years, with the mean age being 55 years. All cases were of the histological type invasive carcinoma, No Special Type (WHO, 2019 classification of breast tumours). All these patients underwent mastectomy. In the study cohort, no patient received chemotherapy prior to surgery. Among the patients, 6% developed recurrence or distant metastasis. The histopathological reports of all these cases were retrieved from the archives, and the maximum dimensions of the breast tumours were recorded. The size of the tumours varied from 1.5 to 9 cm, with a mean size of 3.9 cm. In the study cohort, 6% of the patients developed recurrence or distant metastases.

In our study, the majority of the cases (25 cases) exhibited histological grade II (50%). The gross and microscopic descriptions for each of these cases were noted, and the number of axillary lymph nodes with metastatic tumour deposits from the primary BC was recorded. The number of positive axillary lymph nodes varied from 0 to 19.

All cases were grouped into three categories [Table/Fig-1] based on NPI score:

Category I: ≤3.4

Category II: >3.4 and ≤5.4

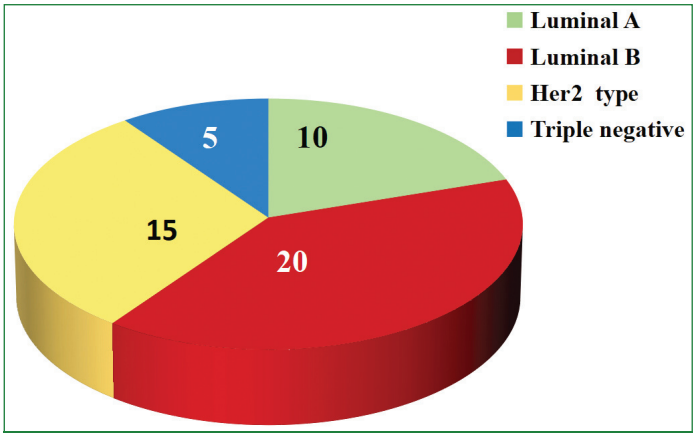
Category III: >5.4

NPI category	Number of cases
I	5
II	29
III	16

[Table/Fig-1]: Distribution of cases between the three NPI categories.

The IHC slides were retrieved from the archives, and the ER, PR, Her2 and Ki-67 statuses were analysed. Based on these parameters, the cases were divided into four molecular subtypes: Luminal A, Luminal B, HER2 overexpressing, and TNBC. In our study, the majority of the cases belonged to the Luminal B subtype (40%). The Luminal A subtype accounted for 20% of the cases, while the HER2 overexpressing and triple-negative molecular subtypes had 30% and 10%, respectively [Table/Fig-2].

Using the IHC4 score, the patients were categorised into three prognostic groups, with cases distributed as stated below [Table/Fig-3]. The cases tabulated in [Table/Fig-4] based on NPI were compared with the IHC4 score.



[Table/Fig-2]: Distribution of different molecular subtypes of Breast Cancer (BC).

IHC4 score groups	Number of cases
Low-risk	3
Intermediate-risk	10
High-risk	37

[Table/Fig-3]: Distribution of cases between the IHC4 score groups.
≤ -30: Low-risk; -30 to 30: Intermediate-risk; >30: High-risk

Prognostic indices	IHC4 1	IHC4 2	IHC4 3
NPI 1	20%	40%	40%
NPI 2	10%	10%	80%
NPI 3	0	30%	70%

[Table/Fig-4]: Comparison between the different groups of NPI and IHC4 score.

Survivin expression in different molecular subtypes was studied and is summarised below [Table/Fig-5]. The nuclear expression of survivin was observed in 45% of Luminal A cases and 42% of Luminal B cases. In the HER2 overexpressing and triple-negative subtypes, positive expression was found in 20% and 40%, respectively. The cytoplasmic survivin expression for Luminal A, Luminal B, HER2, and TNBC was 72%, 42%, 53%, and 40%, respectively.

The expression of survivin, the NPI [Table/Fig-6], and the IHC4 score [Table/Fig-7] were plotted separately, and the results are presented as follows: the observations indicated that patients with a higher NPI score belonged to higher IHC4 risk groups. The majority of the cases belonged to the Luminal B subtype (20 cases). The expression of survivin, both nuclear and cytoplasmic, was high in cases grouped under NPI category II (25 cases). Similarly, survivin expression, both nuclear and cytoplasmic, was also high in cases grouped under IHC4 group II (intermediate-risk group) (25 cases). Furthermore, it was found that survivin expression was higher in the Luminal B molecular subtype. Patients' medical records were obtained from the archives of the Medical Oncology Department, and treatment and follow-up details were all recorded.

Survivin grade	Nuclear	Cytoplasmic
0	17	11
1	16	16
2	13	16
3	1	1
4	3	6

[Table/Fig-5]: Nuclear and cytoplasmic grades of survivin.

Survivin	Nuclear		Cytoplasm	
	Positive	Negative	Positive	Negative
NPI Group 1	20%	80%	0	100%
NPI Group 2	66.6%	33.3%	50%	50%
NPI Group 3	66.6%	33.3%	50%	50%

[Table/Fig-6]: Relationship between NPI as well as nuclear and cytoplasmic expressions of survivin.

Survivin	Nuclear		Cytoplasm	
	Positive	Negative	Positive	Negative
IHC4 Class 1	20%	80%	0	100%
IHC4 Class 2	66.6%	33.3%	50%	50%
IHC4 Class 3	66.6%	33.3%	50%	50%

[Table/Fig-7]: Relationship between IHC4 score as well as nuclear and cytoplasmic expressions of survivin.

DISCUSSION

The BC is a malignant, multivariate disease, displaying variable morphology and biological features, which contribute to high mortality rates among women. The heterogeneity of BC has led to an explosion of research in this field. With the existing published research, we understand that BC is no longer a single disease but rather a group of diseases comprising molecularly distinct subtypes that respond differently to hormonal therapy, conventional chemotherapy, and targeted therapies. A personalised treatment approach for BC requires the integration of clinical, histopathological, and biological information, thereby effectively stratifying patients based on their expected outcomes and response to applicable treatment options.

Prognostic index like NPI play a crucial role in the assessment of BC as they evaluate tumour grade and stage. Grading is based on histological subtype, while staging is based on size, nodal status, and the presence of distant metastasis. Axillary lymph node metastasis is the most important predictor of overall recurrence and survival in patients with BC. Hence, the accurate assessment of axillary lymph node status is critically important for staging and for guiding multidisciplinary treatment decisions.

In the current management practices for BC, there are two main types of modalities used to estimate the risk of recurrence and prognosis for individual patients. The first set of modalities consists of risk calculators and scoring systems, such as PREDICT and the NPI. These scoring systems incorporate clinicopathological features such as age at diagnosis, lymph node status, tumour size, and histological grade. The NPI generates a five- and ten-year survival score. These scoring systems are readily available online and free of charge. The NPI is an applicable prognostic tool in non metastasising BC and is more accurate in predicting disease-free survival rates and mortality in younger patients. The NPI was created by combining important prognostic parameters such as tumour size, lymph node status, and histological grade. The NPI was calculated using the formula stated above, resulting in three prognostic groups as follows:

- Score <3.4: Good
- Score 3.4 to 5.4: Moderate
- Score >5.4: Poor

In our study, most of the cases (29 out of 50) belong to NPI category II, followed by 16 out of 50 patients in category III. Out of these, two of four patients who had metastasis or recurrence belong to NPI category II, while two cases belong to category III. A generalised conclusion cannot be derived as the sample size is inadequate, and there was a significant number of treatment defaulters. However, based on the available data, it is understood that the NPI alone is not sufficient to accurately predict prognosis, given the heterogeneity of BC.

Gene expression profiling has had a considerable impact on our understanding of the biology of BCs [17,18]. Over the last 15 years, extensive research has led to the categorisation of BCs into five intrinsic molecular subtypes: Luminal A, Luminal B, HER2-enriched, Basal-like, and Claudin-low. These entities exhibit significant differences in their incidence, risk factors, prognosis, and treatment sensitivity.

The identification of targets, such as ER, PR, and HER2, as well as quantifying the cellular proliferation rate using the Ki-67 index, has been pivotal [19]. The consensus from the 2011 St. Gallen meeting recommended the use of the differential expression of the IHC4 panel in various BCs as a surrogate for the molecular classification of BCs. The IHC4 prognostic signature is an algorithm based on a combination of biomarkers evaluated in IHC using the formula stated above.

Barton S et al., assessed the contribution of the IHC4 score in decision-making in clinical practice for BC and found that the application of the IHC4 score may substantially improve decision-making regarding adjuvant chemotherapy [20]. Lakhanpal R et al., reported a significant association between the IHC4 score and the risk of local recurrence and metastasis in BC patients who did not receive adjuvant therapy [21]. Patients were categorised into three grades based on their IHC4 score, as per the recommendations by Cuzick J et al., ≤ -30: Low-risk; -30 to 30: Intermediate-risk; >30: High-risk [8].

In present study, three, ten, and twenty-seven patients belonged to categories I, II, and III, respectively. Authors compared the IHC4 scores with NPI scores. There was a clear relationship between the IHC4 categories and NPI scores; most breast tumours falling into NPI category III also exhibited higher IHC4 scores. However, a significant proportion of NPI category II tumours also expressed higher IHC4 scores. Upadhyay AK and Prakash A, reported that the overall distant metastasis-free survival in intermediate- and high-risk groups was 91.3%, compared to 96.88% in the low-risk group [22].

In current study, all tumours that metastasised or recurred belonged to a higher IHC4 score category. Consequently, the IHC4 score provides significant independent prognostic value, and its ability to re-stratify luminal subtypes certainly adds value as a risk stratification tool. It is an affordable and accurate prognostic and risk stratification tool for patients with BC.

The expression status of a protein with antiapoptotic potential is believed to enhance the tumour cell's resistance to programmed cell death, and overexpression of these proteins leads to chemotherapy resistance and aggressive biological features in tumour cells.

Survivin, an inhibitor of apoptotic proteins, functions by interfering with caspases 3, 7, and 9, and is located on chromosome 17q25 [23]. It binds to mitotic spindle microtubules, thereby controlling the G2/M phase of the cell cycle. Survivin is present as both a cytoplasmic and nuclear protein in various embryonic tissues, as well as in malignancies of the lung, colon, breast, stomach, and prostate [24]. However, survivin is either undetectable or expressed at very low levels in differentiated adult cells. Tumours that express survivin exhibit shortened survival, which is associated with adverse disease progression markers, increased recurrence rates, and therapy resistance [25]. In present study, the relationship between survivin expression and clinicopathological factors, NPI, and IHC4 score were analysed.

Survivin immunoreactivity was observed in the cytoplasm and/or nucleus of tumor cells [26]. Immunostaining for survivin was recorded according to both staining intensity and the percentage of tumour cells that stained positively. The percentage of stained cells and staining intensity were multiplied to produce a weighted score for each case, ranging from 0 (for <5% positive cells) to 12 (for >75% of tumour cells with intense staining). Cases with a survivin score of <1 were considered negative, while scores of ≥1 were considered positive.

The association between survivin expression and clinicopathological parameters was analysed. Survivin was not expressed in any tumours measuring <2 cm. In the second category, which comprised 39 cases with tumour sizes between 2 and 5 cm, nuclear positivity was observed in 16 cases, while cytoplasmic positivity was noted in 21 cases. Among the nine cases in the third category, where tumour size was >5 cm, only one case demonstrated nuclear positivity, whereas three cases exhibited cytoplasmic positivity.

The expression of survivin was tabulated against the categories of NPI and it was found that in category II, out of 29 cases, 10 showed nuclear positivity and 15 showed cytoplasmic positivity. In contrast, only one case out of five in category I exhibited nuclear positivity. Among the 16 cases in category III, six cases showed nuclear expression, while nine cases displayed cytoplasmic positivity. A possible explanation for these findings is that survivin induces angiogenesis through interactions with vascular endothelial growth factor, angiopoietin, and basic fibroblast growth factor. Thus, tumours expressing a high level of survivin may be more associated with prominent lymph node and distant metastases.

Survivin can be regarded as a diagnostic marker and may also serve as a suitable target for tumours [27,28]. In current study, the expression of survivin was significantly higher in larger tumours, HER2-positive tumours, and triple-negative tumours. However, a statistically significant relationship between survivin expression and the NPI score could not be established.

Survivin is localised in two subcellular locations (cytoplasmic and nuclear), which relates to its function in the regulation of either cell viability or cell division [29,30]. The nuclear localisation of survivin is involved in cell mitosis, whereas its cytoplasmic localisation participates in regulating apoptosis [31].

In the present investigation, it was reported that the expression of survivin in the nucleus and cytoplasm separately and observed no significant difference in the nuclear or cytoplasmic expression of survivin.

Molecular classification of BC is an important factor for detecting prognosis and clinical outcomes. In this current study, authors assessed whether survivin expression was related to the molecular subtypes of BC. Very few researchers have investigated survivin protein expression among different molecular BC subtypes.

Yakirevich E et al., reported that high expression of survivin was associated with the basal subtypes of breast tumours and represented an individual predictive factor for patients' overall survival rates [32]. These findings are clinically relevant, as IHC staining of primary breast tumours for survivin may assist in risk-stratifying patients and may also help identify those who could benefit from existing survivin-targeted therapies.

Limitation(s)

A major limitation of our study is the small number of cases. The histological type considered was only invasive carcinoma, with no special types included. Consequently, the expression of survivin could not be studied in other histological subtypes of BC. Additionally, these breast tumours were not included in molecular studies such as Oncotype Dx and Mammaprint, which makes comparisons with survivin expression arbitrary. Many studies have examined the expression of survivin in cases following neoadjuvant chemotherapy, which is not applicable to present study. A significant number of cases were defaulted, rendering it impossible to trace the history of recurrence and metastasis. Another major limitation of our study is that the quantification of survivin expression was not performed for all these breast tumours.

CONCLUSION(S)

A better understanding of patients' clinical characteristics and pathological behaviour can alter the management of BC. In summary, we propose that NPI, IHC4, and survivin expression complement one another and should always be used in combination to effectively prognosticate, predict response to therapy, and provide hope for every BC patient.

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