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СРАВНИТЕЛЬНАЯ ОЦЕНКА ПРОГНОСТИЧЕСКОЙ ЗНАЧИМОСТИ МОЛЕКУЛЯРНЫХ МАРКЕРОВ ОПУХОЛИ (РЕЦЕПТОРЫ ЭСТРОГЕНОВ И ПРОГЕСТЕРОНА, HER-2/NEU) И НОТТИНГЕМСКОГО ПРОГНОСТИЧЕСКОГО ИНДЕКСА ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ

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ВВЕДЕНИЕ. Ноттингенский прогностический индекс (НПИ) – это инструмент, который на основании количественных гистологических характеристик опухоли позволяет оценить прогноз заболевания и выработать оптимальную тактику лечения больных, страдающих раком молочной железы (РМЖ). Уровень рецепторов эстрогенов и прогестерона (ЭР/ПР), а также экспрессия рецепторов HER-2/neu являются важными параметрами молекулярной оценки данной опухоли.

ЦЕЛЬ. Рассчитать НПИ у первичных больных РМЖ и сравнить прогностическую эффективность молекулярных маркеров (ЭР/ПР) с Ноттингемским прогностическим индексом.

МЕТОДЫ И МАТЕРИАЛЫ. В исследование включены 125 больных с ранним РМЖ. Ноттингемский прогностический индекс рассчитан на основании данных патоморфологических заключений, а уровни молекулярных маркеров получены путем иммуногистохимического анализа. Выполнено сравнение прогностической эффективности молекулярных маркеров с НПИ.

РЕЗУЛЬТАТЫ. По данным иммуногистохимического анализа ЭР-позитивные опухоли выявлены у 66 (53 %) больных, ПР-позитивные – у 55 (44 %), высокий уровень экспрессии рецепторов HER-2/neu зарегистрирован в 22 (18 %) случаях. Среднее значение НПИ составило 4,99±1,23. Было обнаружено, что молекулярные маркеры, соответствующие отличному прогнозу, согласно Ноттингемскому прогностическому индексу были отнесены к группе умеренного прогноза. При сравнении молекулярных маркеров с Ноттингемским прогностическим индексом не было обнаружено статистически значимых результатов, которые помогли бы в оценке прогноза ($p>0,05$).

ЗАКЛЮЧЕНИЕ. При раке молочной железы Ноттингемский прогностический индекс является более точным инструментом для оценки прогноза, чем иммуногистохимические маркеры.

Ключевые слова: *Ноттингенский прогностический индекс, рецепторы эстрогенов и прогестерона, HER-2/neu*

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COMPARATIVE EVALUATION OF THE PROGNOSTIC SIGNIFICANCE OF MOLECULAR TUMOR MARKERS (ESTROGEN AND PROGESTERONE RECEPTORS, HER-2/NEU) AND THE NOTTINGHAM PROGNOSTIC INDEX IN BREAST CANCER

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INTRODUCTION. The Nottingham prognostic index (NPI) is a tool that, based on quantitative histological features of the tumor, allows optimal treatment tactics for patients suffering from breast cancer (BC). The level of estrogen and

progesterone receptors (ER/PR), as well as the expression of HER-2/neu receptors are important parameters in the molecular evaluation of this tumor.

The OBJECTIVE was to calculate the NPI in newly diagnosed patients with BC and to compare the prognostic efficacy of molecular markers (ER, PR) and Nottingham prognostic index.

METHODS AND MATERIALS. The study included 125 patients with early BC. The Nottingham prognostic index was calculated based on the data of pathomorphological conclusions, and the levels of molecular markers were obtained by immunohistochemical analysis. Prognostic efficacy of molecular markers and Nottingham prognostic index was compared.

RESULTS. According to immunohistochemical analysis, ER-positive tumors were detected in 66 (53%) patients, PR-positive – in 55 (44%) patients, a high level of expression of HER-2/neu receptors was registered in 22 (18%) cases. The mean NPI was 4.99±1.23. We found out that molecular markers corresponding to an excellent prognosis and by the Nottingham prognostic index were assigned to the moderate prognostic group. No statistically significant results was observed between the Nottingham prognostic index and molecular markers that would help in assessing the prognosis ($p>0.05$).

CONCLUSION. In breast cancer, the Nottingham prognostic index is the best tool for prognosis determination than immunohistochemical markers.

Keywords: *Nottingham prognostic index, estrogen and progesterone receptors, HER-2/neu*

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Introduction. Breast carcinoma is the commonest cancer in women worldwide with associated high mortality rates. It accounts for 23 % of all cancers and 14 % of all deaths related to cancers [1]. The incidence rates in India begin to rise in the early thirties and peak at age 50–64 years [2]. Overall, chances of developing breast cancer during lifetime are 1 in 28 women. Women in urban areas have a higher risk of developing breast cancer and chances are as high as 1 in 22 women compared to 1 in 60 women in rural areas [3].

In the developing countries, the incidence is reportedly rising due to numerous factors. These include lifestyle modifications, behavioral patterns and improvement in diagnostic facilities [4]. The estimated «risk of developing breast cancer» rises with age; however, more aggressive biological behavior has been reported in breast cancer developing at a younger age in comparison with the disease in older females [5].

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. Tumor 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 histological grade, tumor size and nodal status in a simple formula, which helps in the prediction of outcomes and supports clinical decision making while managing females with breast cancer. The NPI combines numerous studies reported the advantages of using NPI as the prognostic tool and recommend its use in clinical practice. In a recent study, Peiris et al. [6] 2015 determined the association between the age at presentation and the NPI. They reported that the NPI ≤3.40 was found in 9 % of younger age group (<35 years of age) as compared to the older age groups, 14 % aged in 35–60 years of age and 18 % aged in >60 years of age. It has been realized that hormonal receptors, in particular estrogen, 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 and they are now routinely evaluated in the clinical practice to gather prognostic information.

The present study was planned to calculate the NPI and Immunohistochemistry markers (ER, PR and HER-2/neu) status in all newly diagnosed breast cancer patients. We also aimed to determine prognostic efficacy of molecular markers ER, PR, HER-2/neu expression in comparison with Nottingham prognostic index. Expectedly, the gathered data would have useful prognostic implication, which could help the clinician in choosing best individualized therapeutic options.

The **objective** was to calculate Nottingham Prognostic Index in newly diagnosed patients of breast carcinoma and to compare the prognostic efficacy of molecular markers ER, PR, HER-2/neu expression with Nottingham prognostic index.

Methods and materials. The present study was conducted on 125 patients diagnosed of breast carcinoma in the Department of General Surgery at Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar, during the period of 1st April 2021 to 31th July 2022 after obtaining approval from the Institutional Research and Ethical Committee.

A total of 125 histopathologically diagnosed cases of breast cancer were randomly enrolled in the study, patients with breast abscess and pregnant women were excluded from the study. The NPI was calculated from histopathology report, «NPI =[0.2 × S] + N + G (where S is the size of the index lesion in centimeters, N is the node status:0 nodes=1,1–3 nodes =2,≥4nodes =3 and G is the grade of tumor: Grade 1, Grade 2, Grade 3)». All patients were divided into four prognostic groups: excellent (NPI<or=2.4), good (NPI<or=3.4), moderate (NPI<or=4–5.4) and poor (NPI>5.4).

Immunohistochemistry analysis was performed on formalin fixed and paraffin embedded sections for ER,PR and HER-2/neu status and all patients were divided into four prognostic groups: excellent (ER/PR+, HER-2/neu-) , good (ER/PR+/-, HER-2/neu-) , moderate (ER/PR-, HER-2/neu+) and poor (ER/PR/ HER-2-neu-).

Table 1

Demographic and histopathological data

Age group	No. of cases	Percent
≤40	20	16.0 %
41–50	36	28.8 %
51–60	41	32.8 %
61–70	23	18.4 %
>70	5	4.0 %
Total	125	100.0 %
	Frequency	Percent
Menopausal age		
≤45year	56	62.9 %
>45year	33	37.1 %
Total	89	100.0 %
Tumor grade		
Grade 1	1	0.8 %
Grade 2	79	63.2 %
Grade 3	45	36.0 %
Total	125	100.0 %
χ^2 Value	29.35	
p value	<0.001	
Age of menarche		
12year	24	19.5 %
13year	43	35.0 %
14year	55	44.7 %
15year	1	0.8 %
Total	123	100.0 %
Gender		
Female	123	98.4 %
Male	2	1.8 %
Tumor size		
<2 cm	14	11.2 %
2–5 cm	99	79.2 %
>5 cm	12	9.6 %
χ^2 Value	29.350	
p value	<0.001	
Family history		
Present	123	98.4 %
Absent	2	1.6 %
Clinical stage		
Stage 1	19	15 %
Stage 2	72	58 %
Stage 3	34	27 %

All the data were entered in a Microsoft Excel sheet and statistical analysis was performed on computer software IBM Statistical Package for the Social Sciences (SPSS) version 26. Mean value, frequency and percentages of the NPI and Immunohistochemistry markers were measured in each group and compared with each other. P-value≤0.05 was considered as significant. Prognostic efficacy of ER, PR and HER-2/neu status compared with the NPI.

Results. A total of 125 histopathologically diagnosed cases of breast cancer were analyzed. In overall study sample, demographic and histopathological data was represented (*table 1*). Patients presented with chief complaint of breast lump – 65 (52 %). Histopathologically infiltrating ductal carcinoma breast was most common – 113 (90.4 %). ER, PR and HER-2/neu expression was represented (*table 2)*. Molecular markers groups were determined and distributed and was represented (*table 3)*. Then patients were distributed on the basis of prognostic

Table 2

ER/PR/ HER-2/NEU frequency and percent

ER	Frequency	Percent	PR	Frequency	Percent	HER-2/NEU	Frequency	Percent
+	66	33 %	+	55	44 %	+	22	18 %
–	59	47 %	–	70	56 %	–	103	82 %
Total	125	100 %	Total	125	100 %	Total	125	100 %

Table 3

Distribution of patients on the basis of Molecular Marker Group

Hormone status	No. of patients	Percent
ER+PR+HER+	5	4 %
ER+PR-HER-	11	8.8 %
ER+PR+HER-	49	39.2 %
ER-PR-HER+	15	12 %
ER-PR+HER-	0	0
ER-PR+HER+	1	0.8 %
ER+PR-HER+	1	0.8 %
ER-PR-HER-	43	34.4 %
Total	125	100 %

Table 4

Distribution of patients on the basis of Prognostic Group of Molecular Marker Groups

Prognosis (Molecular Markers)	Frequency	Percent
Excellent (ER/PR+, HER-2/NEU–)	54	43 %
Good (ER/PR+/–, HER-2/NEU–)	11	9 %
Moderate (ER/PR–, HER-2/NEU+)	17	14 %
Poor (ER/PR/HER-2/NEU–)	43	34 %
Total	125	100 %

Table 5

Distribution of patients on the basis of Nottingham Prognostic Index Status

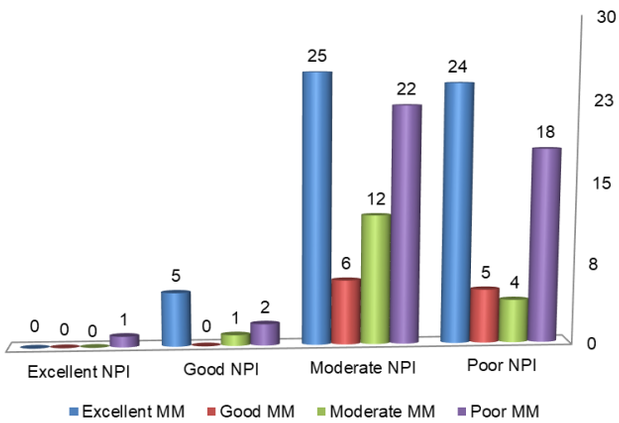
Prognosis (NPI)	Frequency	Percent
Excellent (<or=2.4)	1	1 %
Good (<or=3.4)	8	6 %
Moderate (<or=4.4–5.4)	65	52 %
Poor (>5.4)	51	41 %
Total	125	100 %

Table 6

Prognostic Association of Nottingham prognostic index and Molecular Markers

Prognostic group (ER/PR/HER-2/NEU)	Prognostic group (Nottingham prognostic index)				Total
	Excellent	Good	Moderate	Poor	
Excellent	0	5	25	24	54
Good	0	0	6	5	11
Moderate	0	1	12	4	17
Poor	1	2	22	18	43
Total	1	8	65	51	125
χ^2 Value	6.489				
p value	0.668				

groups of molecular markers (*table 4)*. Patients were distributed on the basis of Nottingham prognostic index *(table 5)*. Mean Nottingham prognostic index was found to be 4.99±1.23SD. The majority of cases of the molecular markers were found to be excellent prognosis – 54 (43 %). The majority of cases of the Nottingham prognostic index were moderate prognosis – 65 (52 %). Prognosis was compared and no significant difference was observed between Nottingham prognostic index and molecular markers (ER/PR/ HER-2/neu) status (χ^2 Value=6.489, p=0.668, *table 6, figure)*.



Distribution of patients on the basis of Molecular Markers prognosis according to Nottingham prognostic index

Discussion. The resent study results showed that mean age of the enrolled patients was 52.42 years ±10.93 SD. The majority of studies found similar results, there was no significant difference in the mean age of presentation, which were comparative to our study. Out of 125 patients studied, we found that the majority of 65(52 %) presented with lump in the breast, S. Bhattacharya et al. [11], J. Donnely [13], P. Newton et al. [12], D. S. Sandhu et al. [14] and O. Hallberg et al. [15] also found similar results in there studies.

In current study, a majority of 49 (39.2 %) cases were ER+, PR+, HER-2/neu- and 43 (34.4 %) cases

Table 7

Discussion between present and other studies

	Our study	Y. Fong et al. [7]	D. B. R. Hungund et al. [8]	P. Mehta et al. [9]
Mean age	52.42 years	57 years	54 years	47 years

	Our study	C. Rudlowski [10]
Gender	98.4 % Females	99 % Females
	1.6 % Males	1 % Males

Presenting complaint	Our study	P. Newton et al. [12]
Breast lump	52 %	81 %

Tumour grade	Our study	Azizun Nisa et al. [19]	M. Moradil et al. [20]	E. A. Rakha et al. [21]	D. B. R. Hungundet al. [8]
Grade 1	1 (0.8 %)	10 (6.7 %)	28 (10 %)	143 (13.3 %)	21 (15.4 %)
Grade 2	79 (63.2 %)	83 (55.3 %)	156 (58 %)	323 (30.1 %)	80 (58.8 %)
Grade 3	45 (36 %)	57 (38 %)	82 (30.8 %)	530 (49.3 %)	35 (25.7 %)

Molecular Markers	Our study	V. Dutta et al. [22]	H. H. Wu et al. [23]	M. Briffod et al. [24]
ER+	66 %	24 %	62 %	62 %
PR+	55 %	30 %	37 %	37 %
HER2NEU+	22 %	10 %	18 %	18 %

ER	Our study	G. Angela et al. [25]	A. Shabaik et al. [26]
SENSITIVITY	56 %	92.7 %	85.7 %
SPECIFICITY	50 %	85.7 %	100 %
PPV	43 %	92.7 %	100 %
NPV	62.7 %	85.7 %	85.7 %

PR	Our study	G. Angela et al. [25]	A. Shabaik et al. [26]
SENSITIVITY	47 %	92.7 %	80 %
SPECIFICITY	58 %	94.7 %	100 %
PPV	43 %	97.7 %	100 %
NPV	61.4 %	87 %	88.8 %

HER-2/NEU	Our study	G. Angela et al. [25]	A. Shabaik et al. [26]
SENSITIVITY	13.7 %	70 %	Not observed
SPECIFICITY	79.7 %	100 %	Not observed
PPV	31.8 %	100 %	Not observed
NPV	57.2 %	94.5 %	Not observed

were triple negative, 5 (4 %) cases were triple positive. ER+ were 66 %, PR+ were 55 % and HER-2/neu+ were 22 % of cases which were comparable to following studies. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor (HER-2/neu) sensitivity, specificity, positive predictive value (PPV) and negative predictive value was compared with Nottingham prognostic index. Excellent and good prognostic group couldn't be calculated because of less number of patients in there groups.

In the present study, out of 125 patients, the NPI of the majority of cases – 65 (52 %) were under the moderated prognosis, 51(41 %) cases under poor prognosis, and 8 (6 %) cases under good prognosis and 1 (1 %) case under excellent prognosis. Similar pattern was observed in studies of E.A. Rakha et al. [21] (2008), Y. Fong et al. [7] (2015) and D. B. R. Hungund et al. [8] (2015). The NPI considered as surrogate marker for prognosis of breast carcinoma. In our study, out of 125 patients, the majority of ER and PR cases comes under moderate prognostic group 1 of the NPI. There was no significant difference between the ER positive and negative groups in terms of distribution of the NPI category (χ^2=2.091, p=0.588). There was no significant difference between PR positive and negative groups in terms of distribution of NPI category (χ^2=2.513, p=0.491). In the study conducted by F. Kurshumliu et al. [27] (2014), the rate of ER and PR expression decreased with increasing NPI. Whereas in the present study, the majority of ER and PR positive cancers comes under moderate prognostic group of the NPI. It was observed that majority of cases with HER-2/neu expression were in moderate and poor prognostic groups, whereas excellent and good prognostic group comprises less cases. Even though, there was no significant correlation with NPI categories (χ^2=1.580, p=0.641). Out of 125 cases, 22 (17.6 %) were showing positive HER-2/neu expression, which was significantly comparative to the studies conducted by R. D. Köseoğlu et al. [28] 12 (20.3 %), H. J. Huang et al. [29] 241 (17.7 %), F. Kurshumliu et al. [27] 25 (20.8 %), P. Mehta et al. [9] 3 (20 %).

In overall study sample, mean NPI was found to be 4.99±1.23 SD. No significant difference was observed between Nottingham prognostic index (NPI) and molecular markers cases. Our study results showed that the MM are not efficient predictor for prognosis in comparison with the NPI in breast cancer patients. In the presents study, we did not measure survival in these patients, as the study was time bound. None the less, we suggest continuation of the study for long term follow in order to determine the prognostic implications of the NPI measured in the present study. Rakha et al. [30] in their study applied a wide range of biomarker panel related to breast cancer to a large and well-characterized series of breast cancer and combined several variables to estimate known as the «Nottingham Pronostic Index Plus (NPI±)» and applied it to predict outcome in different molecular classes. They reported that the 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.

Conclusion. On comparison of molecular markers with Nottingham prognostic index, no statistically significant result was found, which could determine the prognosis. The Nottingham prognostic index is a better tool for prognosis determination and provides improved individualized clinical decision making for breast carcinoma then the molecular markers in diagnosed cases of carcinoma breast. The findings were 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

The authors declare no conflict of interest.

Compliance with ethical principles

The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

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