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MIB INDEX AS INDEPENDENT PROGNOSTIC FACTOR IN CONTEXT OF CLINICAL FEATURES IN CARCINOMA BREAST PATIENTS.

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ABSTRACT

Introduction: Breast cancer is the commonest malignancy in females and despite recent advancements in treatment it still is the leading cause of death. The importance of various clinical and pathological factors like age, tumor size, hormone receptor status, lymph node status and grade of tumor are already established and play key role in deciding the management of disease. Markers like Mib Index are under evaluation and its role is yet to be established as independent prognostic factor. Our study is an attempt to understand and evaluate its role in the management of breast cancer patients and its relation with other clinical features especially in this era of molecular advancement where tests Oncotype Dx, Mammaprint & likes are not affordable to all. **Materials and Methods:** Mib index and other clinic-pathological markers were retrospectively assessed in 174 breast cancer patients diagnosed and treated between 2018 and 2021. Association and correlation with other established prognostic markers was studied. Statistical analysis was done and p value < 0.05 was taken as significant. **Results:** Mib Index was low in 37.7% and high in 62.3% patients. Next we analyzed the association between MIB index and other prognostic parameters, and we found a statistical significant association with age, grade of the tumor, histology, hormone receptor status, HER 2 neu status and lymph node positivity while there was no significant association with tumor size. **Conclusion:** Mib Index may be considered as a valuable parameters to plan out further treatment strategies in breast cancer patients as "poor woman's Oncotype Dx" in our scenario.

KEYWORDS :

INTRODUCTION

Breast cancer is the commonest female malignancy and a leading cause of death in women worldwide.[1] With its rapid increase in incidence thanks to early screening and diagnosis, new developments in treatment are coming forward. The treatment of breast cancer depends on various pathological and clinical prognostic markers including hormone receptor status, lymph node status and tumor grade which are already known to affect the outcome. The Estrogen receptor (ER), Progesterone receptor (PR) and human epidermal growth factor 2 (Her 2 neu) are universally accepted markers analyzed via immunohistochemistry (IHC) and their impact on cancer treatment and prognosis are well established.[2] All the above mentioned biomarkers are predictive of response to hormonal and chemotherapy and help in deciding the role and advantage of adjuvant treatment in these patients. Numerous novel markers are also arising and their role and relationship with clinicopathological parameters are under study, one of them being the Ki-67 or Mib Index, whose importance has been recently established in CNS and breast malignancy.[3] Mib Index is a nuclear protein linked to cell cycle and is expressed in all actively dividing tumor cells, therefore being a marker of cell proliferation giving information about the rate of replication of cancer cells hence indicating tumor aggressiveness.[4] Even though recently multiple articles have underlined the importance of this important marker in multiple malignancies, still it has not established value to be used in clinical practice. Many molecular tests are available today to decide the role of adjuvant therapy in early breast cancer like Oncotype Dx and Mammaprint but their cost is a very big limiting factor for our patients in a third world country. Hence the understanding of Mib index, its association with other clinical and pathological markers including age, tumor size, grade, lymph node status, hormone receptor status may open new horizons for patient evaluation and guiding treatment strategies even in non affordable patients.[5] The aim of this study is to evaluate the role of Mib index as independent prognostic marker in breast cancer and to correlate this marker with various clinico-pathological parameters which may contribute to further advances in deciding treatment strategies.

MATERIALS AND METHODS

The study was conducted at Ruby Hall Clinic and Galaxy Care Hospital, tertiare care hospitals in Pune. Retrospectively the clinicopathological profile of 174 patients diagnosed with breast cancer between 2019 and 2021 was evaluated and included in this study. Detailed analysis was done and data was collected for each patient including age, sex, tumor size and grade, lymph node status, hormone receptor status and Mib Index were considered and their correlation was analyzed.

RESULT

On data analysis (Table 1) it was found that 25% patients were in the age group of 41-50 years, 26 % were of age 51-60 years and 20% patients were of 61-70 years. All 174 patients (100%) were female, 69.5% (121) patients had tumor size 2-5 cm, 91.4% (159) had unifocal tumor, 45.4% (79) had grade II disease while majority i.e 51.7% (90) had grade III disease. The most common histology was NOS (IDC) seen in 90.2% (157) patients. ER receptor positivity was seen in 77% (134), PR positivity in 67% (117) and HER 2 was positive in 28% (40) patients. 47.7% (83) patients had at least one lymph node positive, MIB Index was < 15% in 37.7% (63) and >15% in 62.3% (104) patients.

Next we analyzed the association between MIB index and above mentioned parameters (Table 2), and we found a statistical significant association with age, grade of the tumor, histology, hormone receptor status, HER 2 neu status and lymph node positivity.

The mean of age in MIB Index <15% was 58.6 years and 53.3 years in MIB Index >15%, there was a significant difference between the 2 groups in terms of age (years) with the mean age being highest in the MIB Index <15% group. The participants in the group MIB Index > 15% had the larger proportion of Age: 21-30 years while in group with < 15% had

larger proportion of age 31-40 years, hence indicating the fact that younger patients have more aggressive disease.

Association between MIB Index and size of tumor was not significant although group with Mib Index >15% had more patients with tumor size >5cm as compared to group I (13.5 % vs 4.8%), maybe due to less sample size.

It was seen that patients having MIB Index <15% had larger proportion of grade I and II disease (98.4%) while MIB index >15% had majority of grade III (82.7%) disease hence confirming that high MIB index is associated with higher tumor grade.

Association between MIB index and ER, PR status: patients having MIB Index <15% had larger proportion of ER positive patients (96%), while 36.5% patients having ER negative had MIB index > 15%. Similar trend was seen with PR negative patients, statistically significant finding, indicating that hormone receptor negative patients have a higher MIB index therefore need more aggressive treatment.

Patients having high Mib index >15% had larger proportion of HER 2 Neu positive patients (37.4% vs 10.9%) thus confirming the relation between high Mib index and aggressive Her 2 neu tumors.

There was a significant association between high Mib Index and lymph nodes positivity. 54.8% patients having any lymph node positive had Mib Index >15% vs 36% in Mib index <15%, median number of positive nodes was 1.14 in Mib index <15% and 3.21 in >15% again indicating the positive correlation between high Index and aggressive tumors.

TABLE 1:

All Parameters	Mean ± SD || Median (IQR) || Min-Max OR N (%)
Age (Years)	55.31 ± 13.29 || 55.00 (46.00-65.00) || 25.00 - 98.00
Age	
21-30 Years	4 (2.3%)
31-40 Years	21 (12.1%)
41-50 Years	44 (25.3%)
51-60 Years	46 (26.4%)
61-70 Years	35 (20.1%)
71-80 Years	21 (12.1%)
81-90 Years	1 (0.6%)
>90 Years	2 (1.1%)
Gender (Female)	174 (100.0%)
Size (mm)	32.39 ± 17.76 || 30.00 (22.00-39.75) || 0.50 - 140.00
Size	
<2cm	33 (19.0%)
2-5 cm	121 (69.5%)
>5 cm	20 (11.5%)
Focality	
Unifocal	159 (91.4%)
Multifocal	15 (8.6%)
Grade	
Grade I	5 (2.9%)
Grade II	79 (45.4%)
Grade III	90 (51.7%)
Histology	
NOS	157 (90.2%)
Mucinous	8 (4.6%)
ILC	5 (2.9%)
Cribriform	1 (0.6%)
ILC+IDC	1 (0.6%)
Metaplastic	1 (0.6%)
Papillary	1 (0.6%)
ER (Positive)	134 (77.0%)
PR (Positive)	117 (67.2%)
HER2Neu (Positive)	40 (28.0%)
Any Nodes Positive (Yes)	83 (47.7%)
MIB Index	
<15 %	63 (37.7%)
≥15 %	104 (62.3%)

TABLE 2 Summary Table for Association between MIB Index and Parameters

Parameters	MIB Index		p value
	<15 % (n = 63)	≥15 % (n = 104)	
Age (Years)***	58.60 ± 14.76	53.31 ± 11.94	0.0181
Age***			0.0142
21-30 Years	0 (0.0%)	4 (3.8%)	
31-40 Years	10 (15.9%)	9 (8.7%)	
41-50 Years	11 (17.5%)	33 (31.7%)	
51-60 Years	13 (20.6%)	31 (29.8%)	
61-70 Years	15 (23.8%)	18 (17.3%)	
71-80 Years	11 (17.5%)	9 (8.7%)	
81-90 Years	1 (1.6%)	0 (0.0%)	
>90 Years	2 (3.2%)	0 (0.0%)	
Gender (Female)	63 (100.0%)	104 (100.0%)	1.0003
Size (mm)	29.05 ± 12.11	32.75 ± 16.23	0.2204
Size			0.1753
<2cm	12 (19.0%)	21 (20.2%)	
2-5 cm	48 (76.2%)	69 (66.3%)	
>5 cm	3 (4.8%)	14 (13.5%)	
Focality			0.4543
Unifocal	56 (88.9%)	96 (92.3%)	
Multifocal	7 (11.1%)	8 (7.7%)	
Grade***			<0.0012
Grade I	5 (7.9%)	0 (0.0%)	
Grade II	57 (90.5%)	18 (17.3%)	
Grade III	1 (1.6%)	86 (82.7%)	
Histology***			0.0012
NOS	51 (81.0%)	100 (96.2%)	
Mucinous	7 (11.1%)	1 (1.0%)	
ILC	3 (4.8%)	1 (1.0%)	
Cribriform	1 (1.6%)	0 (0.0%)	
ILC+IDC	0 (0.0%)	1 (1.0%)	
Metaplastic	0 (0.0%)	1 (1.0%)	
Papillary	1 (1.6%)	0 (0.0%)	
ER (Positive)***	61 (96.8%)	66 (63.5%)	<0.0013
PR (Positive)***	58 (92.1%)	53 (51.0%)	<0.0013
HER2Neu (Positive)***	5 (10.9%)	34 (37.4%)	0.0013
Any Nodes Positive (Yes)***	23 (36.5%)	57 (54.8%)	0.0223
Nodes Positive***	1.14 ± 2.54	3.21 ± 5.43	0.0044

***Significant at p<0.05, 1: t-test, 2: Fisher's Exact Test, 3: Chi-Squared Test, 4: Wilcoxon-Mann-Whitney U Test

DISCUSSION

The present study was carried out in a tertiary care hospital, Pune, retrospectively analyzing the clinical record of breast cancer patients diagnosed and treated between 2019 and 2021. Data of total 174 patients was retrieved and studied including their histopathological reports. In our study 62% patients had higher Mib Index indicating highly proliferative tumors while 38% patients had low proliferative index which is similar to findings reported by Gogoi et al.[6], Madani SH[7] et al and Hassan I et al[8]. the cut off for Mib Index varies from 5-30% according to various literature and since there is no fixed standard because of the use of different antibodies leading to different results, we took the cut off as 15% in our institute. We found a statistical significant correlation between Mib index and lymph node status, higher proliferation index was found

with higher number of positive lymph nodes i.e 3.21, similar to Nishimura et al who found that higher Ki-67 was seen in tumors having more than 4 positive lymph nodes. A statistically significant correlation was found between Mib index and histological grade, the proliferation index being higher in grade III tumours. This is similar to the studies of Kilickap et al[9] , Sharath et al[10] and Hassan et al.[8]

Among the hormonal markers studied, a statistically significant negative correlation was found between Mib index and ER/PR status and a positive correlation was found with Her2/neu. This is similar to the findings of Madani et al[7], Nishimura et al[11], and Haroon S et al[3].Higher Ki-67 was seen in tumours which were negative for ER and PR. Also, it was seen that higher proliferation index was seen in tumours showing higher expression of Her2/neu. A positive correlation with younger age was seen in our study as confirmed by Madani et al[7] that younger carcinoma breast patients have higher Ki-67 values indicating aggressive tumors needing equally aggressive treatment. No statistical significant correlation was seen with tumor size and Mib Index although larger proportion of patients having high proliferation index had larger tumors, similar findings were noted by Haroon S et al[3].

In the present study, higher Mib Index was seen in tumours with positive lymph node involvement, higher histological grade, negative ER and PR status, positive HER2/neu expression and younger age all of which are poor prognostic factors in breast cancer.

CONCLUSION

Although the prognostic and predictive value of this proliferation index is more useful in combination with other prognostic markers, especially hormone receptor status and Her 2 neu expression, we can conclude the study by saying that MIB index has a high prediction value of nature of the disease as seen in our results. A positive correlation between high MIB Index of >15% has been found with young age patients having IDC Histology, ER PR negative status, Her 2 neu receptor positive, grade III disease having larger number of positive lymph nodes. Hence the value of this marker should not be ignored, and it can be useful for the clinician to predict the nature and biology of disease therefore outline the course of management accordingly. As the prohibitive cost and availability issues of ONCOTYPE DX/ MAMMAPRINT make it less accessible, maybe we could use MIB Index as a prognostic marker for poor females patients and in the near future we may be able to name it as the poor man's ONCOTYPE DX. Of course, this was a small institutional study and further studies with larger number of patients also comparing the treatment outcome and overall survival/ disease free survival are needed.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward EFD. Global cancer statistics. Cancer J Clin. 2011;61:69–90.
2. Skh K, Shilpa K, Geeta S. Study of KI-67 expression in carcinoma breast. Int J Appl Res. 2017;3:98–100.
3. Haroon S, Hashmi AA, Khurshid A, Kanpurwala MA, Mujtuba S, Malik B. Ki-67 index in breast cancer: Correlation with other prognostic markers and potential in pakistani patients. Asian Pac J Cancer Prev. 2013;14:4353–8.
4. Park D, Kåresen R, Noren T, Sauer T. Ki-67 expression in primary breast carcinomas and their axillary lymph node metastases: Clinical implications. Virchows Arch. 2007;451:11–8.
5. Sun J, Chen C, Wei W, Zheng H, Yuan J, Tu YI. Associations and indications of Ki-67 expression with clinicopathological parameters and molecular subtypes in invasive breast cancer : A population-based study. Oncol Lett. 2015;10:1741–8.
6. Gogoi S, Das B, Borgohain M, Gogoi G, Das J, Ki67 and P53 expression in breast cancer and their correlation with clinicopathological parameters. Indian J Pathol Oncol 2021;8(4):478-484.
7. Madani SH, Payandeh M, Sadeghi M, Motamed H, Sadeghi E. The correlation between Ki-67 with other prognostic factors in breast cancer: A study in Iranian patients. Indian J Med Paediatr Oncol. 2016;37:95–9.
8. Hassan I,Tarcisia T,Agnestina A,Cornain S,Nasar IM.Ki-67marker useful for classification of malignant invasive ductal breast cancer. Univ Med. 2015;32:179–86.
9. Kilickap S, Kaya Y, Yucel B, Tuncer E, Akgul N, Elagoz S. Higher Ki-67 Expression is Associates With Unfavorable Prognostic Factors and Shorter Survival in Breast Cancer. Asian Pac J Cancer Prev. 2014;15:1381–5.
10. Skh K, Shilpa K, Geeta S. Study of KI-67 expression in carcinoma breast. Int J Appl Res. 2017;3:98–100.
11. Nishimura R, Osako T, Okumura Y, Hayashi M, Totoyozumi Y, Arima N. Ki-67 as a prognostic marker according to breast cancer subtype and a predictor of recurrence time in primary breast cancer. Exp Ther Med. 2010;1:747–54.