

The Evaluation of Magee Equation 2 in Predicting Response and Outcome in Hormone Receptor-Positive and HER2-Negative Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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Background and Purpose: Magee Equations have been developed as accurate tools for predicting response and clinical outcomes in breast cancer patients treated with adjuvant systemic therapy using basic clinicopathological parameters. This study aims to evaluate the alternative application of Magee Equation 2 score in predicting pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) in hormone receptor (HR)-positive, HER2-negative breast cancer.

Patients and Methods: Patients with HR-positive, HER2-negative breast cancer who received NAC from January 2010 to May 2018 at Siriraj Hospital, Mahidol University, Thailand, were recruited. Pre-treatment status of HR and HER2 was used to calculate the Magee Equation 2 scores. The pCR rates among different clinicopathological parameters were analyzed. Survival analysis was performed by Log-rank test. Kaplan–Meier survival curves were analyzed.

Results: A total of 215 patients were eligible. The pCR rates for low, intermediate, and high scores were 4.8%, 3.6%, and 23.8%, respectively. Patients with high scores had significantly higher size reduction and pCR rates compared to those with intermediate or low scores ($p < 0.001$). Those with high scores had higher rates of locoregional recurrence and death. The patients with high score had significantly lower overall survival ($p = 0.034$).

Conclusion: Among patients with HR-positive and HER2-negative breast cancer treated with NAC, Magee Equation 2 might be used as a tool for predicting the pCR and clinical outcome.

Keywords: breast cancer, Magee Equation, neoadjuvant chemotherapy, pathologic complete response, survival

Introduction

Breast cancer is the most common cancer in women worldwide and it is the leading cause of cancer-related death among females worldwide.¹ Estrogen receptor (ER), progesterone receptor, and HER2 are considered as important biomarkers that can predict not only the response to treatment but also prognosis and disease recurrence.^{2–4}

Ki-67 is known to be present in all proliferating cells and it has been used as a surrogate marker to assess proliferation index.^{5,6}

Approximately 75% of invasive breast cancers are ER-positive and/or PR-positive tumors.⁷ Although approximately 85% of these women may be recurrence free at

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10 years with adjuvant hormonal therapy alone, the addition of chemotherapy leads to relative reduction in the risk of recurrence of approximately 30% on average. This leads to an absolute benefit for an individual patient ranging from 1% to 5%.^{8,9} Many patients with ER-positive breast cancer would, therefore, be over treated with chemotherapy based on clinicopathologic features alone although most of them would have been adequately treated with hormonal therapy alone.^{10,11} On the other hand, neoadjuvant chemotherapy (NAC) before surgery is the standard therapy in the patients with locally advanced breast cancer¹² and also increased the rate of breast conserving surgery in early breast cancer.¹³ The patients with pathological complete response (pCR) after NAC have improved survival.¹⁴

Gene expression profile assessed by the 21-gene assay (Oncotype Dx[®]; Genomic Health, Redwood City, CA) has been developed to precisely identify patients with ER-positive breast cancer who will benefit from chemotherapy using the result expressed as a recurrence score (RS).¹⁵ Furthermore, RS can discriminate pathological complete response (pCR) in the patients who received NAC.¹⁶ However, it has limitations, including a cost of over \$4000 per test and a delay in treatment while waiting for the results. A recent study reported that biomarkers including ER, PR, and HER-2 can be incorporated into a multivariable model (known as Magee Equations; <http://path.upmc.edu/onlineTools/MageeEquations.html>) to predict the RS.^{17,18} The Magee Equations have been studied in both internal and external validation studies.^{19,20} Since the 21-gene assay has been shown to predict the benefit of adjuvant chemotherapy in women with hormone-receptor (HR)-positive, HER2-negative, axillary node-negative breast cancer, we hypothesized that Magee Equation 2 should also predict the response to NAC. This study aims to evaluate the alternative application of Magee Equation 2 score in predicting pCR after NAC in HR-positive, HER2-negative breast cancer.

Patients and Methods

Patients

This study was approved by Siriraj Institutional Review Board. The patient consent to review their medical records was not required due to this study involved the collection of existing data recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subject. This study was conducted in accordance with the Declaration of Helsinki. Patients with HR-positive, HER2-negative breast cancer who received NAC from January 2010 to May 2018 at Siriraj Hospital,

Mahidol University, Thailand were retrospectively reviewed. pCR was defined as the absence of invasive tumor in the surgical specimen (pCR in both breast and axillary nodes). Residual carcinoma in situ without invasive carcinoma was allowed for pCR.²¹ Estimated tumor size reduction in the breast was calculated using the following equation: Estimated percent tumor size reduction = ((pre-therapy clinical size-pathology size)/pre-therapy clinical size) x 100.

The pathology size is the largest dimension of the gross tumor bed by the invasive tumor cellularity. Pre-treatment status of ER, PR, HER2, and Ki-67 was available from core biopsy pathology reports and were used to calculate Magee Equation 2 scores using the equation:

$$\begin{aligned} \text{Magee Equation 2 score} = & 18.8042 + \text{Nottingham score} \times 2.34123 \\ & + \text{ERH} - \text{score} \times (-0.03749) + \text{PRH} - \text{score} \times (-0.03065) \\ & + (0 \text{ for HER2} - \text{negative}, 1.82921 \text{ for equivocal}, 11.51378 \text{ for} \\ & \text{HER2} - \text{positive}) + \text{tumor size} \times 0.04267 \end{aligned}$$

The H-score was calculated by summation of the results of multiplication of the percentage of cells (0–100%) with staining intensity (0 for negative, 1 for weak, 2 for moderate, and 3 for strong intensity). The results can be ranged from 0 to 300.²² Magee Equation 2 scores were divided into 3 categories according to the RS obtained from Oncotype Dx: 0–<18=low; 18–<31=intermediate; and ≥31=high.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0[®] (SPSS Inc., Chicago, USA). Continuous parameters were compared by independent *t*-test or Wilcoxon rank sum test. Categorical parameters were analyzed by chi-square statistics and the *p*-values were obtained from a two-sided Fisher exact test. Patients with missing or unknown information were excluded from the test. Confidence intervals were obtained using Wald normal approximation. Multivariable analysis for prediction of pCR was performed after including variables that were significant on univariable analysis. Survival analyses were performed using the Log-rank (univariate analysis) and Cox regression (multivariate analysis) methods. Two-sided tests were used in all analyses. The significance level was set at *P*<0.05.

Results

Breast cancer cohort was searched for the term NAC and resulted in 757 patients. Of the 757 patients, 215 patients with ER-positive, HER2-negative or equivocal were eligible for participation (excluding 75 patients without NAC; 293 patients with HR-negative or HER2-positive; 127 patients

with de novo metastatic breast cancer; and 47 patients with incomplete data or incomplete treatment). The demographic and tumor characteristics data with respect to pCR for the 215 ER-positive, HER2-negative/equivocal patients are shown in Table 1.

NAC regimens were chosen at the discretion of the medical oncologists and resulting in different NAC regimens. However, the majority (96.3%) received an anthracycline (AC) and a sequential anthracycline and taxane (AC-T) regimens. Five patients (2.3%) had received neoadjuvant endocrine therapy for 6 months before surgery. After neoadjuvant treatment, 49 patients underwent breast conserving surgery, while 166 patients underwent total mastectomy. Axillary lymph node dissection was performed in 181 patients and sentinel lymph node biopsy was performed in 34 patients. All pathological reports of both breast conserving surgery and mastectomy specimens showed free surgical margin.

Overall, 17 patients (7.9%) had pCR. The patients with pCR had significantly lower ER H-score and PR H-score ($p=0.003$ and $p=0.027$, respectively). Of the 215 patients, the distribution of Magee Equation 2 scores was low in 62 (28.8%), intermediate in 111 (51.6%), and high in 42 (19.5%) patients. The pCR rates for low, intermediate, and high Magee Equation 2 scores were 4.8%, 3.6%, and 23.8%, respectively (Table 2). Patients with high Magee Equation 2 scores were more likely to have pCR compare to those with intermediate or low scores (OR= 7.41, 95% CI 2.63–20.91, $p<0.001$). Subgroup analysis of those who received AC-based regimen showed that the patients with high scores were more likely to have pCR (OR=14.17, 95% CI 2.58–77.87, $p=0.002$). The rate of pCR was significantly higher in those who received AC-T chemotherapy than those who received AC-based chemotherapy (13.3% vs 4.8%, $p=0.031$, respectively). The estimated tumor size reduction was also significantly higher in the patients with high Magee Equation 2 score when compare to those with low and intermediate scores. Multivariate analysis by binary logistic regression showed that Magee Equation 2 score was the only independent predictor for pCR (Table 3). The factors that were utilized to calculate Magee 2 score (tumor size, Nottingham score, ER H-score, PR H-score, and HER2 status) were not included in this multivariate analysis.

Median follow-up time was 33 months (1–106 months). There were 30 locoregional recurrences, 59 distant metastasis, and 36 deaths occurred. Those with high Magee Equation 2 scores had higher rates of locoregional recurrence and death when compared to those with low/intermediate score

(OR=2.47, 95% CI 1.05–5.78, $p=0.033$, and OR=2.57, 95% CI 1.16–5.71, $p=0.018$, respectively) (Table 2). Five-year disease-free survival (DFS) rates for low, intermediate, and high Magee Equation 2 scores were 69.7%, 50.8%, and 54.9%, respectively. The survival analysis by Log-rank test showed worse DFS for high Magee Equation 2 category but the level of statistically significant was not reached ($p=0.101$). Five-year overall survival (OS) rates for low, intermediate, and high Magee Equation 2 scores were 80.2%, 81.0%, and 61.8%, respectively. Univariate analysis by Log-rank test showed that the patients with high Magee Equation 2 scores had significantly lower OS ($p=0.034$). The survival curves estimated by Kaplan–Meier method are shown in Figures 1 and 2. Multivariate analysis by Cox regression revealed that N stage and Magee Equation 2 score were the independent predictors for both DFS and OS. The factors that were utilized to calculate Magee 2 score (tumor size, Nottingham score, ER H-score, PR H-score, and HER2 status) were not included in this multivariate analysis (Tables 4 and 5).

Discussion

Achievement of pCR following NAC was associated with better DFS and OS, especially in the patients with triple-negative or HER2-positive breast cancer.²³ Several clinicopathological parameters were reported to be the predictors for response to NAC.^{24,25} Luminal breast cancer subtype had lower response to NAC when compare to other subtypes.^{26,27}

Although there were higher proportion of T4 breast cancer recruited in this current study, the rate of pCR in the current study was similar to the recent report of clinically node-positive breast cancer receiving NAC.²⁵ However, approximately 70% of the patients received neoadjuvant AC regimen which resulted in lower response when compare to the addition of taxane-based regimen.²⁸

Gene expression profiles assessed by Oncotype DX in the patients with locally advanced breast cancer who received neoadjuvant paclitaxel and doxorubicin revealed that high *RS* were strongly associated with pCR.¹⁶ In a study by Yardley et al, 108 patients with HER2-negative breast cancer who received neoadjuvant ixabepilone and cyclophosphamide were assessed for pCR rate. The patients with a high-risk score had a pCR rate of 26% compared to 0% in patients with low or intermediate risk scores.²⁹ These patients were most likely to receive the greatest clinical benefit from NAC. However, the Oncotype DX carries a high cost and may not be widely available in Thailand. Utilization of conventional clinicopathological parameters derived from pretreatment

Table I Patient and Tumor Characteristics

	Total n=215	No pCR n=198; 92.1%	pCR n=17; 7.9%	p value
Continuous Variables: Mean (Std. Dev)				
Age	50.6 (10.8)	50.4 (10.58)	52.71 (13.09)	0.398
Pre-therapy tumor size	44.7 (28.1)	44.42 (26.35)	48.52 (45.30)	0.623
ER H-score	193.9 (100.2)	201.24 (94.6)	109.29 (125.51)	0.003
PR H-score	125.5 (102.1)	130.22 (120.2)	71.35 (84.65)	0.027
Ki-67 labeling index in %	42 (21.0)	41.98 (21.29)	42.10 (20.02)	0.987
Categorical Variables: N (%)				
Menopausal Status				
Premenopausal	119 (55.3)	111 (56.1)	8 (47.1)	0.474
Postmenopausal	96 (44.7)	87 (43.9)	9 (52.9)	
Pre-Therapy T Stage				
T1	13 (6)	9 (4.5)	4 (23.5)	0.969
T2	82 (38.1)	78 (39.4)	4 (23.5)	
T3	26 (12.1)	25 (12.6)	1 (5.9)	
T4a	1 (0.5)	1 (0.5)	0	
T4b	69 (32.1)	64 (32.3)	5 (29.4)	
T4c	4 (1.9)	4 (2.0)	0	
T4d	20 (9.3)	17 (8.6)	3 (17.6)	
Pre-Therapy N Stage				
N0	55 (25.6)	52 (26.3)	3 (17.6)	0.550
N1	100 (46.5)	91 (46)	9 (52.9)	
N2	41 (19.1)	38 (19.2)	3 (17.6)	
N3	19 (8.8)	17 (8.6)	2 (11.8)	
Pre-Therapy Staging				
I	4 (1.9)	3 (1.5)	1 (5.9)	0.360
II	82 (38.1)	77 (38.9)	5 (29.4)	
III	129 (60.0)	118 (59.6)	11 (64.7)	
Pre-Therapy Nuclear Grade				
Grade 1	16 (7.4)	14 (7.1)	2 (11.8)	0.985
Grade 2	127 (59.1)	118 (59.6)	9 (52.9)	
Grade 3	70 (32.6)	6 (32.3)	6 (35.3)	
Unknown	2 (0.9)	2 (1)	2 (0.9)	
Histology				
Ductal	207 (96.3)	190 (96)	17 (100)	0.420
Lobular	3 (1.4)	3 (1.5)	0	
Others	5 (2.3)	5 (2.5)	0	
HER2 Status				
Negative	171 (79.5)	157 (79.3)	14 (82.4)	0.697
Equivocal ^a	44 (20.5)	41 (20.7)	3 (17.6)	
Neoadjuvant Chemotherapy Regimen				
AC-based regimen	147 (68.4)	140 (70.7)	7 (41.2)	0.044
AC-T regimen	60 (27.9)	52 (26.3)	8 (47.1)	
Other NAC regimens	3 (1.4)	2 (1.0)	1 (5.9)	
Neoadjuvant hormonal therapy	5 (2.3)	4 (2.0)	1 (5.9)	

(Continued)

Table 1 (Continued).

	Total n=215	No pCR n=198; 92.1%	pCR n=17; 7.9%	p value
Breast Surgery				
Total mastectomy	166 (77.2)	153 (77.3)	13 (76.5)	0.940
Breast conserving surgery	49 (22.8)	45 (22.7)	4 (23.5)	
Axillary Surgery				
Sentinel node biopsy	34 (15.8)	30 (15.2)	4 (23.5)	0.319
Axillary dissection	181 (84.2)	168 (84.8)	13 (76.5)	
Radiotherapy				
No	19 (8.9)	14 (7.1)	5 (29.4)	0.01
Yes	195 (91.1)	183 (92.9)	12 (70.6)	
Hormonal Therapy				
Tamoxifen	131 (60.9)	122 (61.6)	9 (52.9)	0.078
Aromatase inhibitors	72 (33.5)	67 (33.8)	5 (29.4)	
Others	12 (5.6)	9 (4.5)	3 (17.6)	

Notes: For categorical variables, the p value is obtained from a two-sided Fisher exact test. For continuous variables, the p value is obtained from a two-sided Wilcoxon rank sum test. ^aHER2 in situ hybridization was not performed in 44 patients and the patients were categorized into HER2 equivocal group.

Table 2 Magee Equation 2 Score Categories and Outcomes

Outcomes	Magee Equation 2 Score Categories			Odds Ratio (95% CI) (Magee Equation 2 ≥ 31 vs <31)	p-value
	<18	18 to <31	≥ 31		
	n=62	n=111	n=42		
pCR (overall)	3 (4.8)	4 (3.6)	10 (23.8)	7.41 (2.63–20.91)	<0.001
pCR (after AC)	1 (2.3)	1 (1.3)	5 (19.2)	14.17 (2.58–77.87)	0.002
Size Reduction (Overall)					
Mean \pm SD	3.3 \pm 89.0	9.4 \pm 81.6	27.7 \pm 115.8	Mean rank 100.4 vs 139.5	$<0.001^a$
Median (min-max)	23.7 (–438.5–100.0)	20.0 (–525.0–100.0)	56.9 (–490.9–100.0)		
Size Reduction (After AC)					
Mean \pm SD	2.0 \pm 91.8	0.8 \pm 86.5	30.4 \pm 120.9	Mean rank 68.0 vs 101.9	$<0.001^a$
Median (min-max)	11.1 (–438.5–100.0)	16.7 (–525.0–100.0)	56.9 (–490.9–100.0)		
Locoregional recurrences	7 (11.3%)	13 (11.7%)	10 (24.4%)	2.47 (1.05–5.78)	0.033
Distant recurrences	15 (24.2%)	31 (27.9%)	13 (31.7%)	1.28 (0.61–2.68)	0.510
Death	6 (9.7%)	18 (16.2%)	12 (29.3%)	2.57 (1.16–5.71)	0.018

Notes: The p value is obtained from a two-sided Fisher exact test. The confidence interval is obtained from a Wald normal approximation. ^aObtained from Mann–Whitney test.

core biopsy might be suitable in this situation. Magee Equation score can accurately estimate the RS and might be used as an alternative predictor for response to chemotherapy.¹⁸ Magee Equation 3 score was previously reported to be accurately predict the response to NAC in HR-positive, HER2-negative breast cancer.³⁰ Due to Ki67 was not available in a significant proportion of the patients in our cohort, Magee Equation 2 that does not require Ki67 results was utilized in the current study. High Magee Equation 2 score was the independent predictor for pCR in HR-positive,

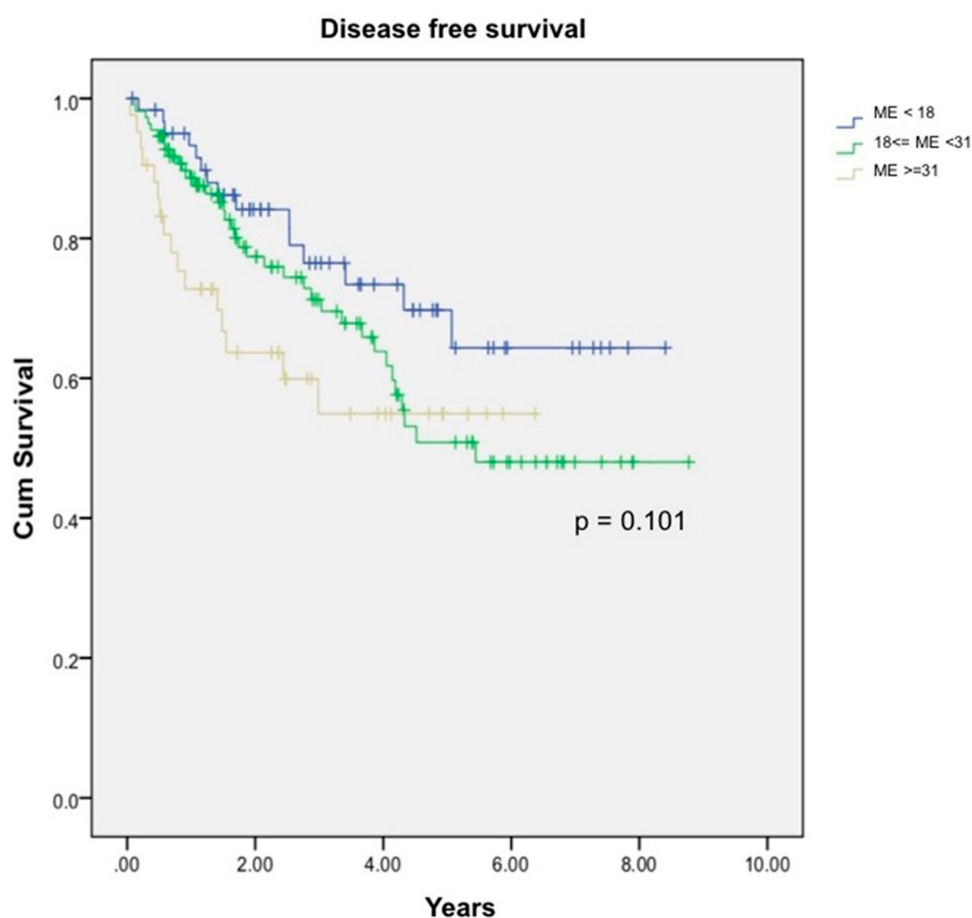
HER2-negative breast cancer. In contrast, high Magee Equation 2 score was also the independent predictor of lower DFS and OS. The patients with high score had unfavorable clinicopathological parameters and aggressive tumor biology. However, the rate of pCR is also higher in the tumor that had more aggressive biology when compared to the tumor that had favorable biology (eg Luminal breast cancer). Subgroup analysis of the patients with high score showed that among 37 patients with high score, approximately one-fourth of the patients (24.3%) had pCR.

Table 3 Multivariate Analysis of Predictive Factors for pCR

Parameters	B	SE	Wald	Df	p-value	Exp (B)	95% CI
Age	0.008	0.028	0.074	1	0.786	1.008	0.954–1.064
N0 (ref)			0.330	3	0.954		
N1	−0.088	0.763	0.013	1	0.908	0.915	0.205–4.084
N2	−0.319	0.933	0.117	1	0.733	0.727	0.117–9.608
N3	0.267	1.018	0.069	1	0.793	1.305	0.177–9.608
AC-based regimen (ref)			4.704	2	0.095		
AC-T regimen	1.085	0.586	3.436	1	0.064	2.960	0.940–9.327
Neoadjuvant hormonal therapy	2.030	1.419	2.046	1	0.153	7.611	0.472–122.779
Low Magee score (ref)			12.530	2	0.002		
Intermediate Magee score	−0.107	0.836	0.016	1	0.898	0.898	0.175–4.621
High Magee score	1.987	0.785	6.402	1	0.011	7.291	1.565–33.973

Lower percentage of death was occurred in the patients with pCR when compared with the patients without pCR (11.8% vs 17.2%, respectively). pCR was not a significant predictor for DFS and OS. This finding might be due to a small number

of patients with pCR. Furthermore, pooled analysis of more than 11,000 patients among 12 studies suggested that achievement of pCR was associated with better OS in non-luminal (HER2-positive or triple-negative), and grade

**Figure 1** DFS by Magee Equation 2 score category. ME: Magee Equation 2 score.

Abbreviation: ME, Magee Equation 2 score.

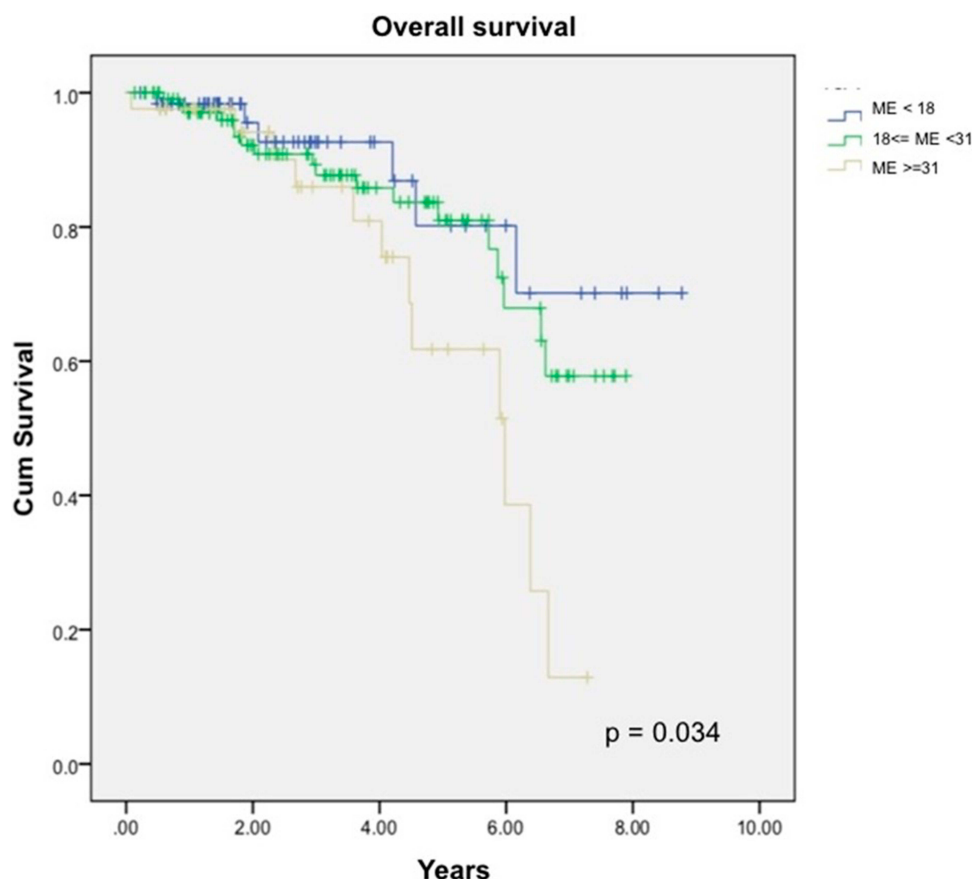


Figure 2 OS by Magee Equation 2 score category.

Abbreviation: ME, Magee Equation 2 score.

3 luminal, HER2-negative breast cancer. In contrast, pCR failed to demonstrate this association in grade 1/2 HR-positive, HER2-negative breast cancer¹⁴ which accounted for the major proportion of the patients in this current study.

High Magee Equation 2 score was associated with tumor size reduction after NAC. This finding might suggest the application of Magee Equation for prediction of NAC in HR-positive, HER2-negative breast cancer patients who will

Table 4 Multivariate Analysis of Independent Prognostic Factors for DFS

Parameters	B	SE	Wald	Df	p-value	Exp (B)	95% CI
Age	-0.000	0.014	0.001	1	0.975	1.000	0.973–1.027
N0 (ref)			12.637	3	0.005		
N1	0.317	0.362	0.766	1	0.382	1.373	0.675–2.792
N2	0.880	0.398	4.892	1	0.027	2.410	1.105–5.254
N3	1.515	0.485	9.760	1	0.002	4.548	1.758–11.762
AC-based regimen (ref)			0.604	2	0.740		
AC-T regimen	0.016	0.810	0.000	1	0.984	1.016	0.208–4.968
Neoadjuvant hormonal therapy	0.247	0.828	0.089	1	0.766	1.280	0.253–6.483
Low Magee score (ref)			6.427	2	0.040		
Intermediate Magee score	0.299	0.322	0.863	1	0.353	1.349	0.717–2.537
High Magee score	0.970	0.395	6.043	1	0.014	2.639	1.217–5.721
pCR	-0.870	0.640	1.848	1	0.174	0.419	0.119–1.469

Table 5 Multivariate Analysis of Independent Prognostic Factors for OS

Parameters	B	SE	Wald	df	p-value	Exp (B)	95% CI
Age	−0.003	0.019	0.019	1	0.891	0.997	0.962–1.035
N0 (ref)			14.086	3	0.003		
N1	0.371	0.531	0.490	1	0.484	1.450	0.513–4.101
N2	0.950	0.578	2.702	1	0.100	2.587	0.833–8.033
N3	2.036	0.616	10.911	1	0.001	7.657	2.288–25.625
AC-based regimen (ref)			1.244	2	0.537		
AC-T regimen	0.089	1.145	0.006	1	0.938	1.093	0.116–10.319
Neoadjuvant hormonal therapy	−0.441	1.198	0.136	1	0.713	0.643	0.062–6.729
Low Magee score (ref)			8.783	2	0.012		
Intermediate Magee score	0.450	0.505	0.794	1	0.373	1.568	0.583–4.216
High Magee score	1.475	0.553	7.108	1	0.008	4.371	1.478–12.925
pCR	−0.794	0.798	0.990	1	0.320	0.452	0.095–2.159

receive NAC with the aim of downsizing for conversion from total mastectomy to breast conserving surgery. However, this was not the objective of this study and further study is required to address this issue.

Our study had some limitations as follows. Due to a retrospective study, selection bias might be occurred. Majority of the patients had locally advanced breast cancer and might result in lower pCR rate. The follow up time was relatively short as the HR-positive breast cancers tend to recur later.

Conclusion

Our findings demonstrate an association between high Magee Equation 2 scores and pCR after NAC. The Magee Equation 2 might be used for predicting pCR and clinical outcomes in the patients who will receive NAC especially in countries with limited resource for high-cost gene expression assays.

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Disclosure

The authors report no conflicts of interest in this work.

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