Predictive Importance of Weight during Neoadjuvant Chemotherapy on Pathologic Response and Survival Outcomes in Patients with Breast Cancer

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Abstract

Objectives. The influence of weight change on the response to neoadjuvant chemotherapy (NAC) among adult Filipino patients with breast cancer remains unclear. Currently, there has been increasing evidence that weight gain during NAC is associated with increased recurrence risk and decreased survival. This study aimed to investigate this relationship and identify significant predictors of pathologic complete response (pCR), overall survival (OS) and disease-free survival (DFS)

Methods. This is a retrospective study using data from 52 female patients who received NAC for stage II or III breast cancer and had complete records of weight before and after NAC. Significant predictors of pCR such as host factors and tumor characteristics and associations between weight change and pCR, OS and DFS were examined using univariate and multivariable logistic regression analyses.

Methods. The average weight of all patients before NAC was 57.0 kg while the average weight of all patients after NAC was 59.5 kg. The average BMI of all patients before NAC was 25.8 kg/m^2. In total, 29 patients (55.8%) were classified in the overweight/obese (OW/OB) group, and the rest were classified in the normal weight/underweight (NW/UW) group. The pCR rate was 51.3% in the OW/OB group versus 48.7% in the NW/UW group (p = 0.11). Initial BMI was a significant factor for achieving pCR (hazard ratio, 3.85; 95% confidence interval [CI], 1.72-8.60, p = 0.001), suggesting that a higher initial BMI was associated with an increased likelihood of achieving pCR. Initial BMI was also an independent prognostic factor for OS (p = 0.0006) and DFS (p = 0.0005). On the other hand, no significant correlation was seen between pCR rates as well as OFS and DFS (p = 0.0551) among patients whose weight changed during the course of treatment.

Conclusion. These findings suggest that while initial weight may significantly predict pCR rates and affect DFS and OS, weight change during treatment may not be as influential. Further research is needed to validate these findings in more diverse and larger patient populations.

Keywords. Breast Cancer, Neoadjuvant Chemotherapy, Weight Change, Pathologic Complete Response, Prognostic Factors.

Introduction

The worldwide prevalence of obesity, defined as a body mass index (BMI) of ≥ 30 kg/m^2, has drastically increased.[1] In many Asian countries, the proportion of overweight and obese adults has increased several fold in the last decades.[2] Recent studies have suggested that breast cancer patients with a high BMI upon diagnosis may be a poor prognostic factor. [3-5]

An increasing body of evidence has suggested that weight gain is an important concern for breast cancer recurrence, contralateral breast cancer, second malignancies and overall mortality.[6-10] Recent studies have observed significant weight gain among women with breast cancer during chemotherapy.[11-13] Hormonal factors including higher levels of estrogen, insulin, and insulin-like growth factor have been proposed to play a

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key role in the underlying mechanism of weight gain among these patients.[14-16]

The use of neoadjuvant chemotherapy (NAC) for breast cancer has been the standard of care for inoperable or locally advanced breast tumors. This mode of treatment has allowed for breast conserving surgery and improved survival. [19,20]

In this study, weight change observed during NAC will be evaluated for its influence and predictive value on the pathologic response and overall survival of breast cancer patients in a tertiary hospital in Cebu City. Few studies have investigated the role of BMI as a predictive factor for response to NAC. Moreover, limited data exist on the correlation between overweight and obesity in the overall survival of breast cancer patients in the Philippines.

Methodology

Patients

This retrospective study was performed using data from female patients who received NAC for stage II or III breast cancer in a tertiary hospital in Cebu City from 2019 to 2022. The regimen of NAC in each patient was determined based on the physician's choice. After completion of NAC, the patients underwent curative surgery. Patients who had complete data on weight and BMI before and after NAC were included in this study. The Institutional Review Board of Chong Hua Hospital reviewed and approved this study protocol. Informed consent was not required due to the retrospective format of this study.

The baseline clinicopathological characteristics of the patients including age, menopausal status, past medical history, weight, BMI, pathological tumor characteristics at diagnosis and surgery, and neoadjuvant treatment information were obtained by reviewing medical records of Chong Hua Hospital. Patients received treatment as per their physicians' choice. Survival status was obtained through outpatient medical history and/or phone calls

Weight and weight change were collected by reviewing medical records of Chong Hua Hospital. Weight gain or loss of >2kg following NAC was considered to be significant whereas weight changes ranging between −2 and 2 kg were considered to indicate a stable weight. BMI was calculated by dividing the weight in kilograms by the square of height in meters. BMI of < 25 kg/m^2 was categorized using the normal weight/underweight (NW/UW); 25.0 to 29.9 kg/m^2 as overweight (OW); and ≥ 30 kg/m^2 as obese (OB). BMI change was defined as the difference in BMI between day 1 of the first cycle of NAC and the day prior to definitive surgery. The day of surgery varies depending on the NAC regimen utilized according to the physician's choice of NAC treatment.

Pathologic Assessment

All of the patients had undergone core needle biopsy and were pathologically diagnosed with breast cancer before NAC administration. Histopathological information including breast cancer pathological type, histological grade, tumor size, lymph node status, and immunohistochemical (IHC) results of hormone receptor (HR) status specifically estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER2) status, were obtained from patients' pathological reports and review of medical records. Tumors were classified into four breast cancer subtypes in this study: HR+/HER2–, HR–/HER2+, HR+/HER2+, and HR−/HER2−. The latter subtype is designated as triple negative breast cancer (TNBC). The pCR was defined as the absence of residual invasive carcinoma in the breast during surgery (ypT0/is).

Statistical Analysis

For the purpose of comparison, patients were divided either into NW/UW group, OW, or OB group according to initial BMI before NAC. Patients were also categorized into BMI-gain, BMI-stable, or BMI-loss group according to the BMI change during NAC. DFS was defined as the time interval from the date of curative breast cancer surgery to the date of breast cancer recurrence at local or regional sites, metastasis to distant sites, newly diagnosed breast cancer in the contralateral breast, other malignancies, or death from any cause. OS was defined as the time interval from the date of breast cancer surgery to the date of death from any cause.

Univariate models were used to evaluate the predictive effect of categorical variables on initial weight and weight change as well as BMI and BMI change. Univariate and multivariable logistic regression analyses were used to calculate the odds ratio (OR) and 95% confidence intervals (CIs) of different clinicopathological variables for pCR.

Survival curves were plotted using the Kaplan-Meier method and compared between groups using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to calculate hazard ratios and 95% CI for clinicopathological variables and survival. A value of $p < 0.05$ was considered statistically significant.

Results

In total, 52 patients who received NAC were included in the final analysis. The average weight of all patients before NAC was 57.0 kg, 29 patients (55.8%) were OW or OB. The average weight of all patients after NAC was 59.5 kg. The average BMI of all patients before NAC was 25.8 kg/m^2. The average BMI after NAC was 21.8 kg/m^2. The average change value was 1.7 kg/m^2.

The clinicopathological characteristics according to initial BMI categories along with p-values indicating whether there was a statistically significant association between each characteristic and initial BMI group are listed in Table 1. It appears that the presence of diabetes mellitus (DM) is the only characteristic that shows a statistically significant association with the initial BMI group in this analysis ($p = .033$).

Table 1: Baseline patient characteristics stratified by initial BMI and BMI-change.

Characteristics	No. (%)	Initial BMI			BMI change		
		NW/UW	OW/OB	p-value	BMI-stable / loss	BMI-gain	p-value
Age (yr)				0.310			1.000
40 and below	4 (7.7)	3 (75.0)	1 (25.0)		4 (100)	0	
above 40	48 (92.3)	20 (41.7)	28 (5)8.3		45 (93.8)	3 (6.3)	
Menopausal status				0.090			1.000
Pre/Peri-menopausal	20 (38.5)	12 (60.0)	8 (40.0)		19 (95)	1 (5)	
Post-menopausal	32 (61.5)	11 (34.4)	21 (65.6)		30 (93.8)	2 (6.3)	
Initial BMI							0.577
NW/UW	23 (44.2)				21 (91.3)	2 (8.7)	
OW/OB	29 (55.8)				28 (96.6)	1 (3.4)	
BMI - change				0.577			
Stable/Loss	49 (94.2)	21 (42.9)	28 (57.1)				
Gain	3 (5.8)	2 (66.7)	1 (33.3)				
DM				0.033			1.000
No	37 (71.2)	20 (54.1)	17 (45.9)		35 (94.6)	2 (5.4)	
Yes	15 (28.8)	3 (20.0)	12 (80.0)		14 (93.3)	1 (6.7)	
HTN				1.000			0.110
No	41 (78.8)	18 (43.9)	23 (56.1)		40 (97.6)	1 (2.4)	
Yes	11 (21.2)	5 (45.5)	6 (54.5)		9 (81.8)	2 (18.2)	
Pathologic Type			1.000				0.217
IDC	48 (92.3)	21 (43.8)	27 (56.3)		46 (95.8)	2 (4.2)	
Other	4 (7.7)	2 (50)	2 (50)		3 (75.0)	1 (25.0)	
Clinical Tumor stage			0.722				0.167
T0–1	4(7.7)	1(25)	3 (75)		3 (75)	1 (25)	
T2	37 (71.2)	17 (45.9)	20 (54.1)		36 (97.3)	1 (2.7)	
T3–4	11 (21.2)	5(45.5)	6 (54.5)		10 (90.9)	1 (9.1)	
Node Status			0.734				0.481
Negative	10 (19.2)	5(50)	5 (50)		9 (90)	1 (10)	
Positive	42 (80.8)	18 (42.9)	24 (57.1)		40 (95.2)	2 (4.8)	
AJCC stage			1.000				1.000
II	21 (40.4)	9(42.9)	12 (57.1)		20 (95.2)	1 (4.8)	
III	31 (59.6)	14 (45.2)	17 (54.8)		29 (93.5)	2 (6.5)	
ER				0.269			0.577
Negative	23 (44.2)	8(34.8)	15 (65.2)		21 (91.3)	2 (8.7)	
Positive	29 (55.8)	15 (51.7)	14 (48.3)		28 (96.6)	1 (3.4)	
PR				0.588			0.104
Negative	25 (48.1)	10 (40)	15 (60)		22 (88)	3 (12)	
Positive	27 (51.9)	13 (48.1)	14 (51.9)		27 (100)	0	
HER2				1.000			0.173
Negative	38 (73.1)	17 (44.7)	21 (55.3)		37 (97.4)	1 (2.6)	
Positive	14 (26.9)	6 (42.9)	8 (57.1)		12 (85.7)	2 (14.3)	
Subtypes				0.761			0.288
HR+/HER2-	23						
HR+/HER2+	(44.2)	11					
HR-/HER2+	(47.8)	12 (52.2)		23 (100)	0		
TNBC	5 (9.6)	3 (60.0)	2 (40)		4 (80)	1 (20)	
pCR							
No	13 (25)	3 (23.1)	10 (76.9)		11 (84.6)	2 (15.4)	
Yes	39 (75)	20					

Table 2 presents the pCR rate and the results of univariate analysis, including odds ratios (OR) with 95% confidence intervals (CI) and p-values, for various patient characteristics. These results indicate that several patient characteristics, including ER and PR status and subtype, are associated with pCR rates, while others such as age, menopausal status, and various clinical and pathologic factors do not show significant associations with pCR rates. This univariate analysis suggests that ER and PR status, as well as subtype TNBC, are significantly associated with pCR rates in breast cancer patients. Other patient characteristics, including age, menopausal status, BMI, comorbidities (DM and HTN), pathologic type, clinical tumor stage, node status, and AJCC stage, did not show significant associations with pCR rates in this study.

Table 2. Univariate and multivariate logistic regression analyses of clinicopathologic factors and OR of pCR.

Characteristics	pCR rate		Univariate analysis		Multivariate analysis	
	Non-pCR	pCR	OR (95%)	p-value	OR (95%)	p-value
Age (yr)				0.816		
40 and below	0	4 (100)				
above 40	13 (27.1)	35 (72.9)	1.0 (.95-1.07)			
Menopausal status				1		
Pre/Peri-menopausal	5 (25)	15 (75)				
Post-menopausal	8 (25)	24 (75)	1 (.28-3.63)			
Initial BMI				0.086		
NW/UW	3 (13)	20 (87)				
OW/OB	10 (34.5)	19 (65.5)	.285 (.07-1.196)			
BMI - change				0.129		
Stable/Loss	11 (22.4)	38 (77.6)				
Gain	2 (66.7)	1 (33.3)	.144 (.01-1.750)			
DM				0.229		
No	11 (29.7)	26 (70.3)				
Yes	2 (13.3)	13 (86.7)	2.75 (.529-14.28)			
HTN				0.333		
No	9 (22)	32 (78)				
Yes	4 (36.4)	7 (63.6)	.49 (.12-2.06)			
Pathologic Type				0.251		
IDC	11 (22.9)	37 (77.1)				
Other	2 (50)	2 (50)	.29 (.037-2.36)			
Clinical Tumor stage						
T0–1	1 (25)	3 (75)				
T2	7 (18.9)	30 (81.1)	1.4 (.13-15.87)	0.772		
T3–4	5 (45.5)	6 (54.5)	0.4 (.031-5.15)	0.482		
Node Status				0.685		
Negative	3 (30)	7 (70)				
Positive	10 (23.8)	32 (76.2)	1.37 (.29-6.32)			
AJCC stage				0.417		
II	4 (19)	17 (81)				
III	9 (29)	22 (71)	.57 (.151-2.19)			
ER				0.043	.63 (.03-12.75)	0.763
Negative	9 (39.1)	14 (60.9)				
Positive	4 (13.8)	25 (86.2)	4.0 (1.04-15.46)			
PR				0.023	7.49 (.15-371.26)	0.312
Negative	10 (40)	15 (60)				
Positive	3 (11.1)	24 (88.9)	5.3 (1.26-22.57)			
HER2				0.719		
Negative	10 (26.3)	28 (73.7)				
Positive	3 (21.4)	11 (78.6)	1.31 (.302-5.68)			
Subtypes						
HR+/HER2-	3 (13)	20 (87)			.96 (.25-3.68)	0.958
HR+/HER2+	1 (20)	4 (80)	.6 (.049-7.35)	0.689		
HR-/HER2+	2 (22.2)	7 (77.8)	.525 (.072-3.82)	0.525		
TNBC	7 (46.7)	8 (53.3)	.17 (.035-.833)	0.029		

The hazard ratio for initial BMI is 9.32. Individuals with a one-unit increase in initial BMI are estimated to have a 9.32 times higher hazard or risk of experiencing the event (e.g., a medical event or failure) compared to individuals with a one-unit decrease in initial BMI. The hazard ratio is statistically significant (p = 0.046), indicating that there is evidence that initial BMI is associated with the outcome. Therefore, initial BMI appears to be a statistically significant predictor in this survival analysis.

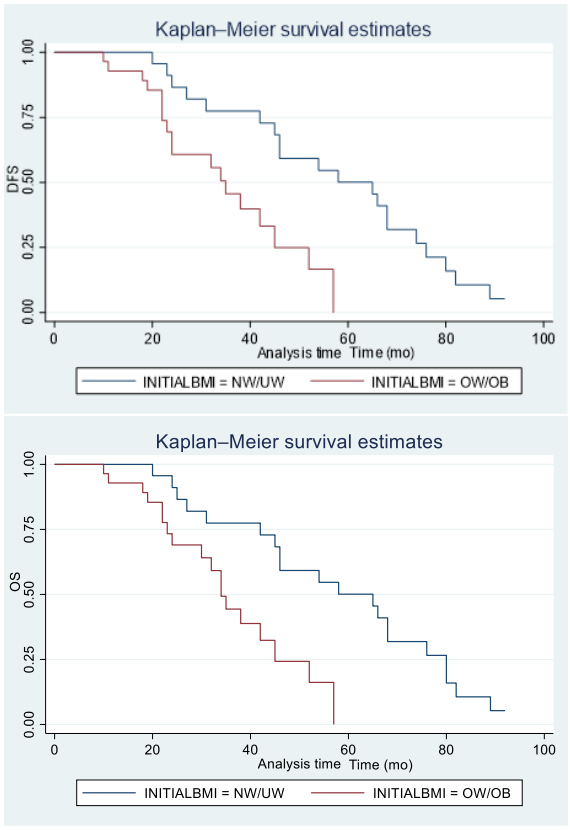

Figure 1. Kaplan-Meier plot of DFS (A) and OS (B) by initial body mass index.

The figure above (Figure 1) shows strong evidence of a difference in survival with respect to achieving pCR between the NW/UW and OW/OB groups. This suggests that initial BMI is a significant predictor of achieving pCR. There is also a statistically significant difference in survival between the NW/UW and OW/OB groups based on their initial BMI. This suggests that initial BMI is a significant predictor of survival.

The second figure (Figure 2) indicates that there is some evidence of a difference in survival with respect to achieving pCR between the BMI stable/loss and BMI gain groups, but this difference is not statistically significant at the 0.05 alpha level. While it suggests some difference in survival between the groups based on BMI change, it is not statistically significant at the conventional alpha level of 0.05. This means that the evidence for a difference in survival between these two groups is weaker compared to the initial BMI test.

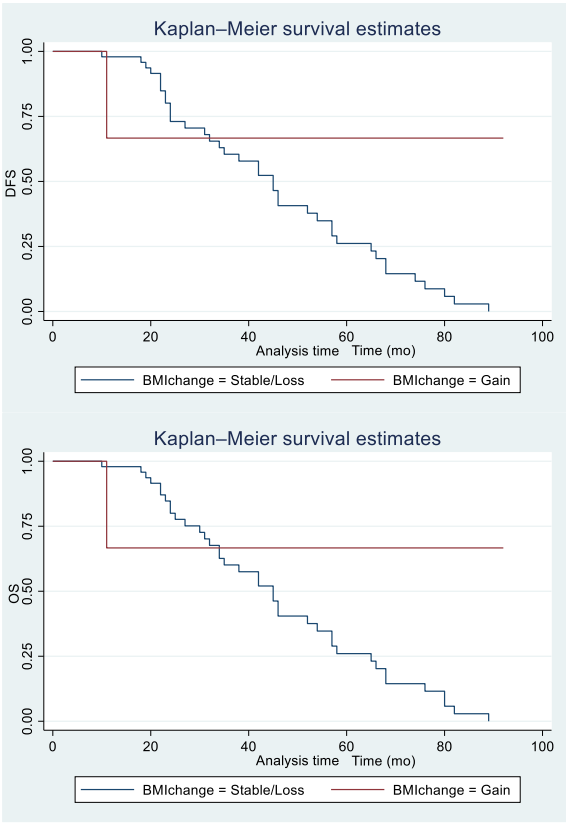

Figure 2. Kaplan-Meier plot of DFS (A) and OS (B) by BMI change.

There is some evidence of a difference in survival with respect to achieving pCR between the stable/loss and gain groups, but the difference is not statistically significant at the 0.05 alpha level. For initial BMI, there is strong evidence of a difference in survival with respect to achieving pCR between the NW/UW and OW/OB groups, indicating that initial BMI is a significant predictor of achieving pCR. In addition, the Log-rank test for initial BMI indicates a statistically significant difference in survival between the NW/UW and OW/OB groups, suggesting that initial BMI is a significant predictor of survival. On the other hand, the Log-rank test for BMI change shows some difference in survival between the stable/loss and gain groups, but this difference is not statistically significant at the 0.05 alpha level.

Discussion

Several studies reported significant weight gain during chemotherapy in women with breast cancer [6–10], with growing evidence linking such weight gain to increased recurrence risk and reduced survival [3,17–18]. Hormonal factors, particularly elevated estrogen, insulin, and insulin-like growth factor, have been proposed as key mechanisms underlying this weight gain [14–16].

Several studies reported significant weight gain during chemotherapy in women with breast cancer [6–10], with growing evidence linking such weight gain to increased recurrence risk and reduced survival [3,17–18]. Hormonal factors, particularly elevated estrogen, insulin, and insulin-like growth factor, have been proposed as key mechanisms underlying this weight gain [14–16].
In the present study, baseline characteristics were analyzed in relation to initial BMI. DM is only variable significantly associated with initial BMI, a finding consistent with existing literature. However, DM did not significantly correlate with pCR, underscoring the complexity of its role and indicating a need for more investigation.

Key variables associated with pCR included ER and PR status, as well as breast cancer subtype (specifically triple-negative breast cancer, TNBC). This aligns with prior studies linking HR status and subtype to NAC response. However, initial BMI and changes in BMI were not significantly associated with pCR, suggesting that weight status and fluctuations may not directly impact treatment response. Likewise, other factors such as hypertension, age, and menopausal status did not significantly correlate with pCR, indicating these may have limited influence on pathologic response.

When ER, PR status, and subtype were assessed together in a multivariate model, their combined effect was not significantly predictive of pCR. This may indicate potential interaction effects that diminish their individual predictive value when analyzed collectively.

Survival analysis revealed that higher initial BMI and PR status were significant predictors of outcomes, with both associated with higher hazards. The hazard ratio for ER status was minimal, though its significance remains uncertain without additional statistical details. These findings suggest that some baseline characteristics may impact survival, though additional investigation is warranted to clarify these associations.

Interestingly, while initial BMI was associated with both pCR and survival outcomes, weight change during treatment was not significantly linked to pCR, OS, or DFS. This finding contradicts earlier studies suggesting weight gain may adversely affect prognosis. It suggests that baseline weight, rather than weight fluctuations during treatment, may be more relevant to predicting outcomes.

Overall, these results reinforce the importance of considering HR status and baseline BMI in evaluating response to NAC, while indicating that weight change during treatment may have less prognostic value. Continued research is needed to explore the biological mechanisms underlying these relationships and their implications for clinical decision-making.

Conclusion

The study provides valuable insights into the factors affecting the pCR and survival outcomes in adult Filipino patients diagnosed with breast cancer. The results underscore the significant roles of initial weight in impacting these outcomes. It is notable that the initial weight was a significant predictor of pCR and the event of interest in the survival analysis. Conversely, the findings suggest that weight change during treatment may not play a significant role in determining these outcomes in this specific population. Furthermore, no significant associations were determined between pCR rates and factors such as age, menopausal status, comorbidities, and various clinical and pathologic factors. This research contributes to a growing body of literature that seeks to understand how diverse factors can influence breast cancer outcomes, particularly in populations that may have unique genetic, lifestyle, or healthcare-related characteristics.

Although weight change during treatment did not show a significant association with pCR or survival outcomes in this study, monitoring weight changes could still be important in the overall care of breast cancer patients, given its potential influence on patients' general health and quality of life. Further research is needed to confirm these findings in larger and more diverse populations; in addition, prospective data collection may also minimize bias. Furthermore, more studies are needed: 1) to understand the underlying biological mechanisms that explain the observed associations, particularly the role of weight in influencing treatment responses and 2) explore the potential effects of other patient characteristics, including genetic factors, lifestyle factors, and other comorbidities, on breast cancer outcomes. This may contribute to improved understanding and management of breast cancer. It would be beneficial to conduct studies that look into the impact of weight management and lifestyle interventions on breast cancer outcomes. This could contribute to the creation of a comprehensive, holistic treatment plan for patients with breast cancer

Conflict of Interest

The author has no conflict of interest to declare

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