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Estimating correlation of body mass index with Nottingham's prognostic index in carcinoma breast

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ABSTRACT

Background: Carcinoma breast, with its rising prevalence, is the cause for high mortality all over the world. Obesity plays a vital part in spread and development of cells of the tumour. It is a modifiable risk factor. Thus, lifestyle modifications including modifications in diet and increased physical activity may aid in weight loss induced alterations associated with proliferation and aggressiveness of tumour cells, their sensitivity to insulin and apoptotic ability. The present study aimed at correlating Quetelet's index (BMI) which is the most widely used indicator for obesity with Nottingham Prognostic Index (NPI). *Objectives:* To analyse BMI in determining proliferative potential and aggressiveness of tumour cells by establishing its correlation with the NPI in Carcinoma Breast. *Methods:* Prospective, observational, analytical and cross-sectional study, conducted over 60 cases of carcinoma breast that underwent modified radical mastectomy for duration of two years in the Department of Pathology in coordination with the Department of General Surgery, AVBRH, Sawangi (M), Wardha. BMI and the NPI were determined in each case and their correlation was studied through a well-tabulated master chart. *Results:* Statistical analysis was conducted using two tailed chi square test and Pearson's correlation coefficient. It was observed that significant association existed between BMI and tumour size, lymph node stage, BR Grade and TNM stage. Statistically significant correlation was established between BMI and NPI. *Conclusion:* This correlation can be used to predict outcome of patients; thus, becoming an adjunct in prognosis of breast carcinoma as well as to scheme out cost-effective strategies to reduce the plight of breast carcinoma.

Keywords: Carcinoma breast, BMI, NPI, Quetelet's index, Obesity.

1. INTRODUCTION

Breast cancer accounts for 25.1% of all malignancies diagnosed in women and is the most frequently occurring malignancy overall (Ghoncheh et al., 2016). In 2018, there were 1, 62, 468 newly diagnosed cases and an estimated 87,090 deaths, accounting for 14% of all female cancers (Figure 1). Breast cancer has a complex aetiology that includes both hereditary and environmental factors.

Women of all ages are more likely to develop breast cancer and overweight cases have a poorer prognosis if they do get the disease. Characteristics include elevated oestrogen signalling, insulin resistance, adipokine imbalance and chronic inflammation. The aberrant growth and survival of breast tissue is what leads to cancer in a pro-tumorigenic setting. Enhanced tumour cell production, invasion and metastasis are thought to result from an increase in local and systemic proinflammatory cytokines, as well as the activation of the most malignant stem cells (Picon-Ruiz et al., 2017).

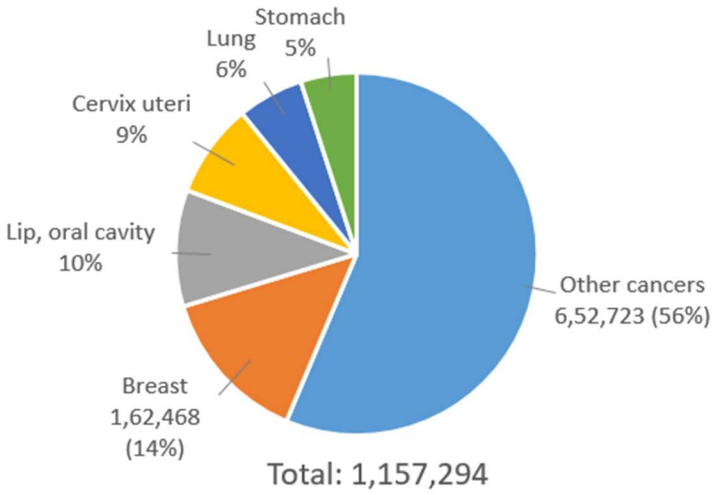


Figure 1 No. of new cases in 2018, both sexes, all ages

Body mass index (Quetelet's Index) is a simple and the most commonly used index used to classify obesity, as it is the same for both genders and for any age of adults. It can be measured by using the formula: Quetelet's Index (kg/m^2) = Weight (kg.) / (Height (m))^2. According to research data, women with a higher Quetelet's Index may have a higher grade, more aggressive tumour, a higher probability of recurrence and an increased death risk (Govind et al., 2018). Several studies imply that enhanced tumour proliferation is the cause of the poorer prognosis of carcinoma breast in obese women (Kamineni et al., 2013). The present research aims at establishing a correlation between Quetelet's index and the Nottingham Prognostic Index to determine the effect of obesity on aggressiveness of the tumour, predicting the survival of patients with breast-carcinoma.

2. MATERIALS AND METHODS

Source of Data

A Total of 60 cases diagnosed as carcinoma breast in Histopathology division of the Department of Pathology, JNMC and operated in the Department of Surgery, AVBRH, Sawangi (M), Wardha from 2020 to 2022 were included in the study.

Study Design

Prospective, analytical and cross-sectional

Study Duration

2 years

Ethics committee approval

Study was started after obtaining approval from Institutional Ethics Committee Ref no DMIMS (DU)/IEC/2020-21/9262, dated 17/12/2022. Before commencement of the study, consent was taken from each subject and case proforma was also filled.

Inclusion criteria

All cases diagnosed as Carcinoma Breast on histopathology.
All cases in which, Modified Radical Mastectomy had been done.
All female patients presenting with Carcinoma Breast

Exclusion criteria

Cases other than carcinoma breast and cases with metastatic deposits
Cases where only trucut biopsy, wedge biopsy or lobectomy had been done
Male patients presenting with Carcinoma Breast
Cases with a history of neoadjuvant therapy
Cases having incomplete height and weight data

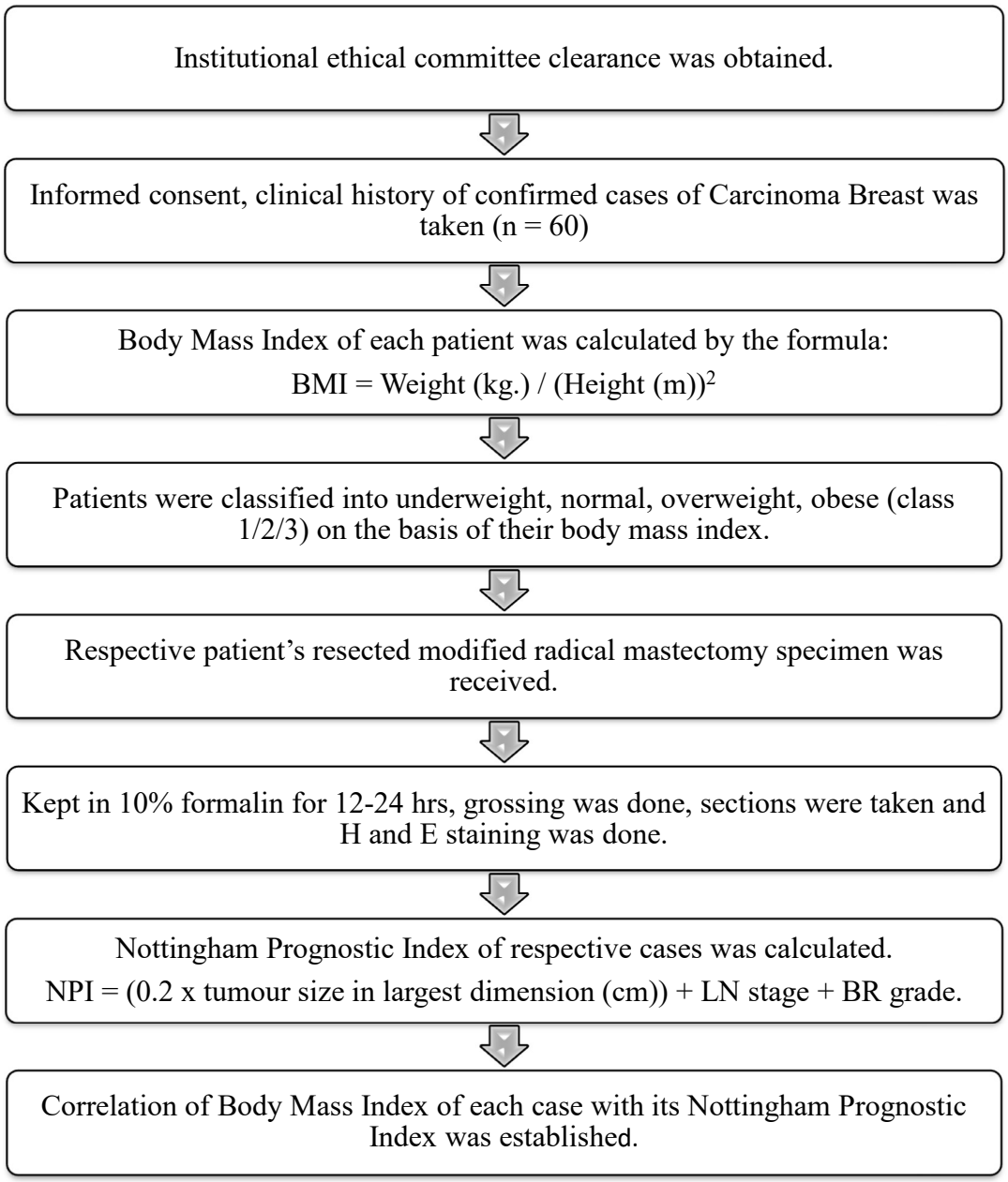
Materials required for the study

60 specimens from confirmed and planned Modified Radical Mastectomy cases of Carcinoma Breast
Formalin fixed, paraffin embedded blocks of tumour masses from resected Modified Radical Mastectomy (MRM) specimens.
10% Formalin
Grossing instruments (grossing tray, knife, scalpel, measuring tape, plain forceps and toothed forceps)
Automated tissue processing assembly.
Haematoxylin & Eosin stain.
Glass slides (Blue Star®). Dimensions: 7.5x 2.5 centimetres.
Binocular research microscope

Anthropometric instruments

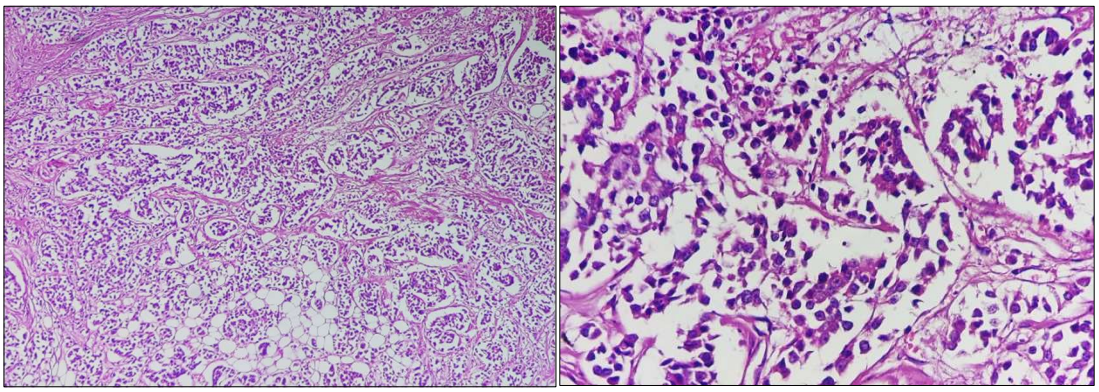
Measuring tape, weighing machine

Methodology



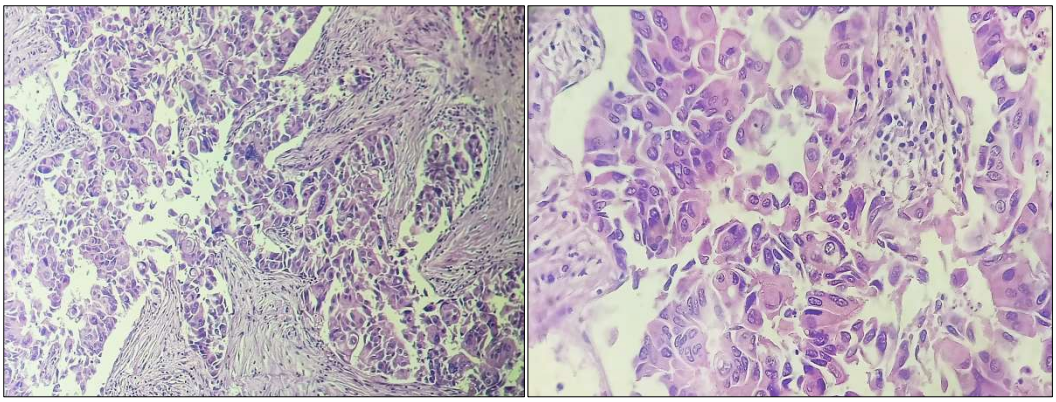
The Nottingham-adapted Bloom-Richardson tumour grading system was used to establish the tumor's histological grade. Tumor grades were assigned using the following system: Grade I = 1, Grade II = 2 and Grade III = 3. Assuming the infiltration to zero nodes was represented by LN stage 1, one with one to three nodes was LN stage 2 and one with more than or equal to four nodes was represented by LN stage 3.

Figure 2 Gross image of cut surface of MRM with greyish white tumour mass with irregular peripheral edges



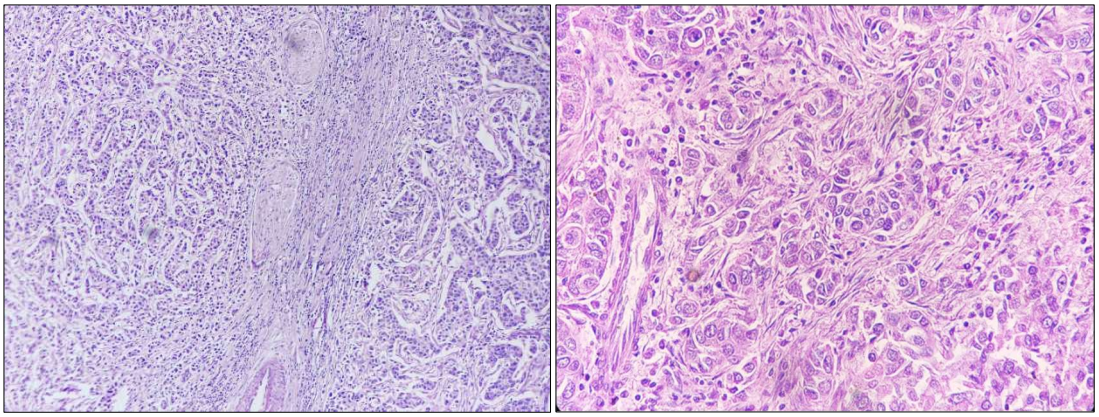
A B

Figure 3 Infiltrating ductal carcinoma of breast (NST), BR Grade I; A: Low power view (10x); B: High power view (40x)



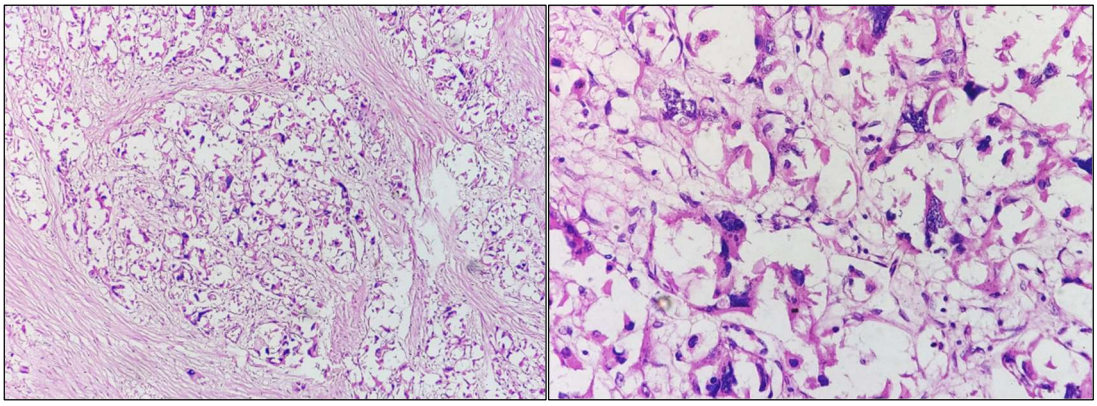
A B

Figure 4 Infiltrating ductal carcinoma of breast (NST), BR Grade II; A: Low power view (10x); B: High power view (40x)



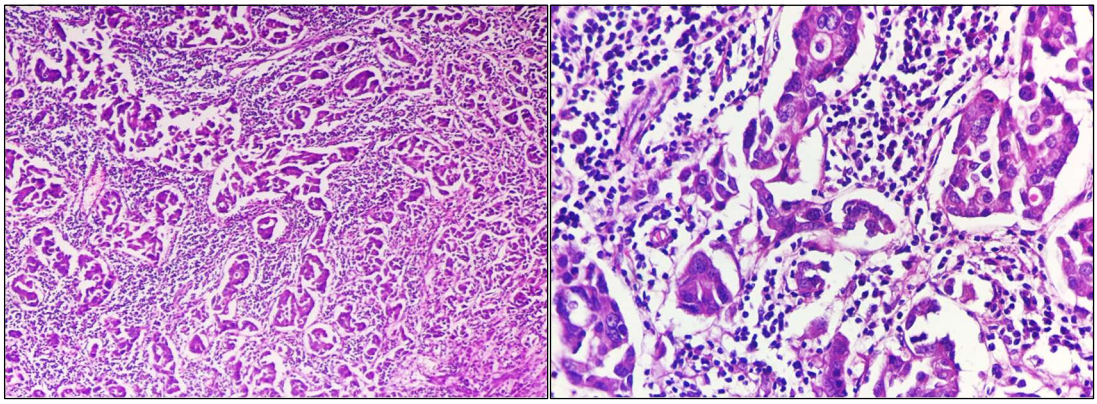
A B

Figure 5 Infiltrating ductal carcinoma of breast (NST), Grade III; A: Low power view (10x); B: High power view (40x)



A B

Figure 6 Infiltrating ductal carcinoma of breast (NST) BR Grade III showing high grade of pleomorphism and mitoses; A: Low power view (10x); B: High power view (40x)



A B

Figure 7 Section from lymph node showing deposits of infiltrating ductal carcinoma of breast; A: Low power view (10x); B: High power view (40x)

Statistical analysis

Statistical analysis was done by descriptive and analytical statistics using Chi-square test and Pearson's correlation coefficient. Software used for analysis was SPSS software version 23 and $p<0.05$ was considered as level of significance.

3. RESULTS AND OBSERVATIONS

The clinical details of patients and various parameters were recorded in a well tabulated master chart. The collected data was analysed and the observations and results were depicted in tables and graphs as follows:

Table 1 Baseline characteristics among the study subjects

Variables	Minimum	Maximum	Mean	SD
Age (in years)	19	85	49.75	13.341
Height (cm)	145	168	156.58	4.774
Weight (kg)	45	90	67.03	8.920
BMI (kg/m^2)	18	36	27.40	3.665

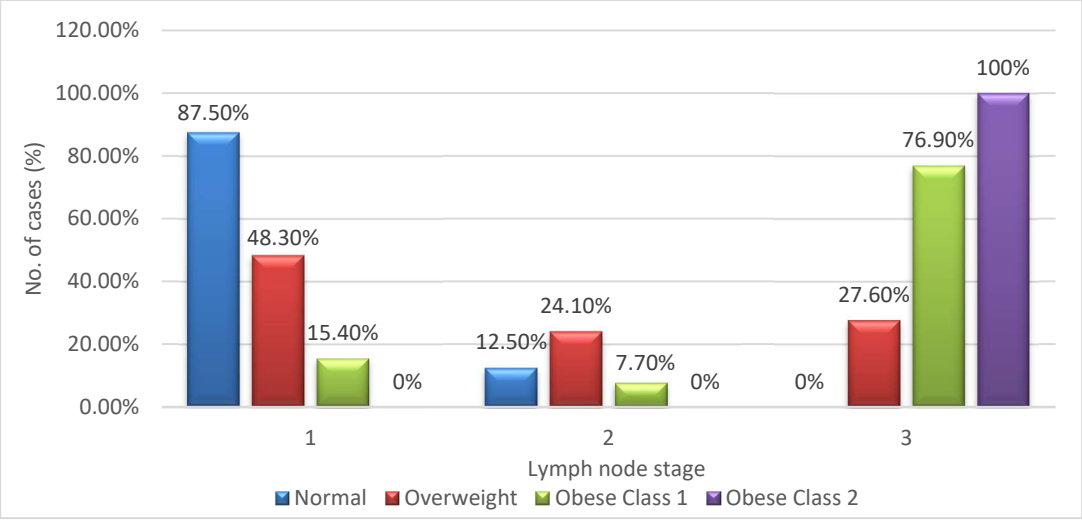
The minimum age noted among the study subjects was 19 years whereas the maximum age noted was 85 yrs. Mean age (in years) among the study subjects was found to be 49.75±13.341 yrs. Minimum height noted among the cases was 145 cm and maximum was 168 cm with a mean of 156.58±4.774 cms. The mean weight (kgs) found in study subjects was 67.03±8.920 with minimum weight noted as 45 kgs and a maximum weight of 90 kgs. Mean body mass index was found to be 27.40±3.665 kg/m^2 with a minimum of 18 kg/m^2 and maximum of 36 kg/m^2 (Table 1).

Table 2 Correlation of BMI with tumour size

Tumour Size (cm.)		BMI Category				Total
		Normal	Overweight	Obese Class 1	Obese Class 2	
2 to 5	N	15	18	4	1	38
	%	39.5%	47.4%	10.5%	2.6%	100.0%
>5	N	1	11	9	1	22
	%	4.5%	50.0%	41%	4.5%	100.0%
Total	N	16	29	13	2	60
	%	26.7%	48.3%	21.7%	3.3%	100.0%
Chi Square		12.48				
p value		0.006*				n = 60

* Statistically significant (where p value <0.05 was considered as statistically significant)

When tumour size was compared according to BMI categories, statistically significant results were found with a p value of <0.006 (Table 2). Hence, in the present study, it was observed that patients in the overweight and obese categories had higher chance of having larger tumour size than those who belonged to normal category of BMI.



Graph 1 Correlation between BMI category and lymph node stage

In our study, all of the reported obese class 2 category cases had lymph node stage 3. Among the obese class 1 cases, most of the cases had lymph node stage 3. Among the overweight as well as normal category patients, maximum patients had lymph node stage 1. None of the cases in normal category was belonged to lymph node stage 3 (Graph 1). When lymph node staging was compared with BMI categories, statistical significance existed between the two variables as p value was noted to be <0.01. Hence, in

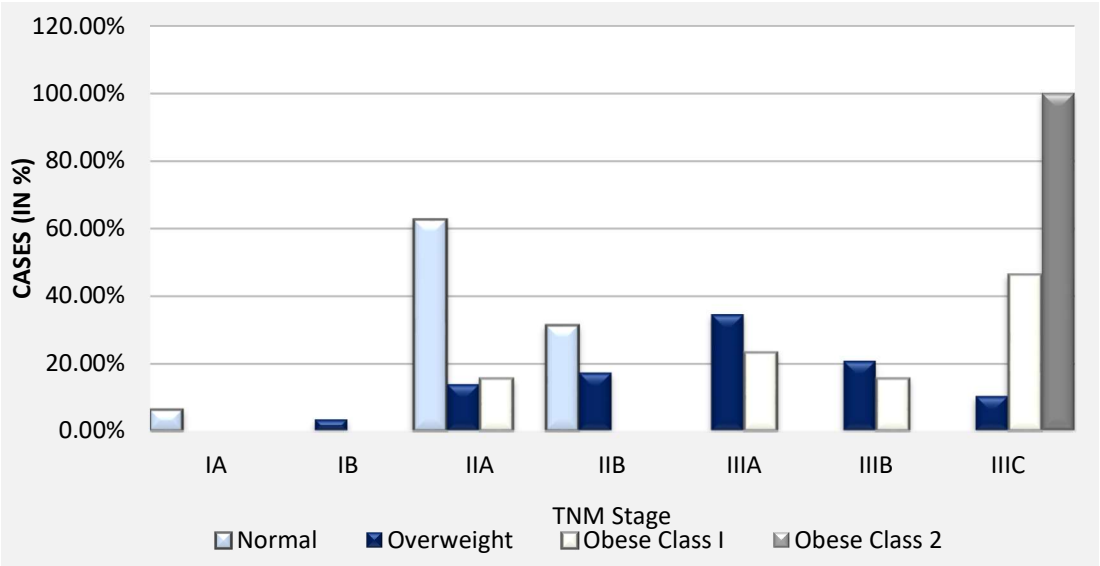
the present study, it was observed that with increasing BMI, higher lymph node stage that is more number of positive lymph nodes was noted among the study subjects.

Table 3 Correlation between BMI category and BR grade

BMI Category		BR Grade			Total
		I	II	III	
Normal	N	0	10	6	16
	%	0%	62.6%	37.4%	100.0%
Overweight	N	6	10	13	29
	%	20.7%	34.4%	44.9%	100.0%
Obese Class 1	N	1	11	1	13
	%	7.7%	84.6%	7.7%	100.0%
Obese Class 2	N	0	1	1	2
	%	0.0%	50%	50%	100.0%
Chi Square		11.73			
p value	0.034*	n = 60			
* Statistically significant (where p value < 0.05 was considered as statistically significant)					

In the present study, it was noted that BR grade II and III were reported with maximum number of cases belonging to obese class 1 and 2 categories of BMI, respectively. When BR grade was compared according to BMI, statistically significant correlation was found as p value was <0.01 (Table 3). Hence, in the present study, it was observed that higher BMI correlated with higher BR Grade in the study subjects.

In our study, it was noted that TNM Stage IIIC was found maximum in subjects with obese class 2 and class 1 category while Stage IIIB was found to be associated maximum with overweight category patients (Graph 2). When TNM stage was compared according to BMI, statistically significant correlation was found between them as p value was <0.01. Hence, in the present study, it was observed that cases with higher BMI were reported to have higher TNM stage.



Graph 2 Correlation between BMI category & TNM stage among the study subjects

When NPI category was correlated with BMI, statistically significant correlation was found between BMI and NPI of the patients with a p value of <0.01 (Table 4). In our study, it was noted that all of the obese class 2 category patients belonged to NPI category C. Among the obese class 1 patients, majority belonged to NPI category C followed by NPI category B. None of the subjects in normal category belonged to NPI category C.

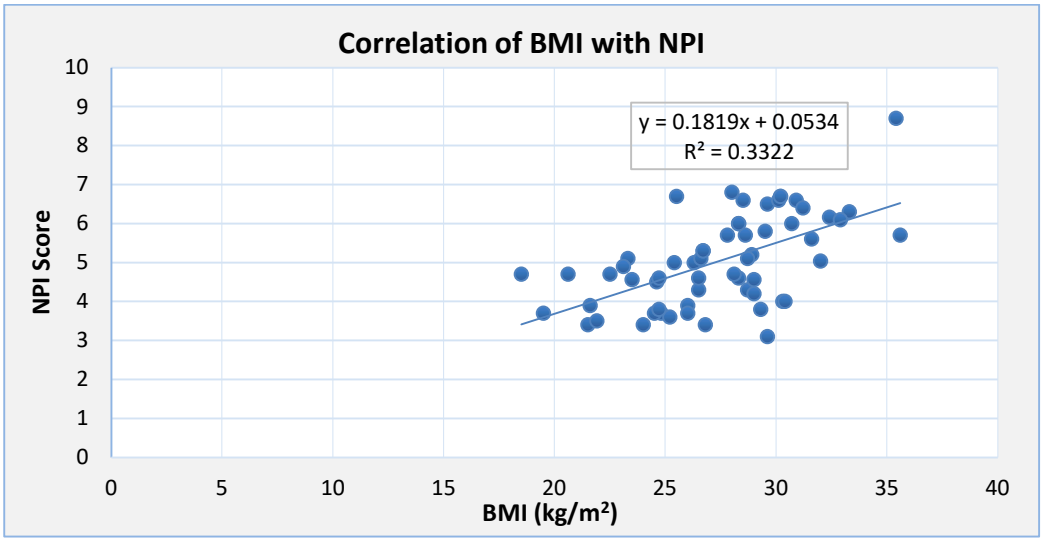
Table 4 Correlation between BMI category and NPI category

Category		NPI Category			Total
		A	B	C	
Normal	N	0	16	0	16
	%	0.0%	100.0%	0.0%	100.0%
Overweight	N	1	19	9	29
	%	3.4%	65.6%	31.0%	100.0%
Obese Class 1	N	0	3	10	13
	%	0.0%	23.1%	76.9%	100.0%
Obese Class 2	N	0	0	2	2
	%	0.0%	0.0%	100.0%	100.0%
Chi Square		23.75			
p value	0.001*	n = 60			
* Statistically significant (where p value <0.05 was considered as statistically significant)					

Table 5 Correlation of Quetelet's Index (BMI) with Nottingham Prognostic Index

Correlation	Mean	Std. Deviation	N	Pearson's Correlation Coefficient (r)	P-Value
BMI (kg/m^2)	27.382	3.6915	60	0.576	0.001*
NPI	5.0337	1.16486			
* Statistically significant (where p value <0.05 was considered as statistically significant)					

When body mass index was correlated with Nottingham Prognostic Index, a positive correlation was found between BMI and NPI of the patients with Pearson's correlation coefficient of 0.576 and a p value of <0.001 which was statistically significant (Table 5).



Graph 3 Correlation of body mass index with Nottingham prognostic index

Hence, in the present study, it was observed that in breast carcinoma patients, with increasing BMI a higher NPI score was noted, thus, indicating a poor prognosis (Graph 3).

4. DISCUSSION

Among women, breast cancer has the highest incidence rate and is a primary cause of cancer-related death (WHO, 2016). Postmenopausal women with a higher BMI have an increased chance of developing breast cancer. Higher BMI has been linked in a small number of studies to increased proliferation index, histological grade and tumour size and axillary node metastatic rates when diagnosis was rendered (Petrelli et al., 2002). Hence, the present study was undertaken to analyse correlation of the Quetelet's index with the Nottingham's Prognostic Index for determining the effect of obesity on aggressiveness of the tumour, predicting the survival of patients with breast-carcinoma.

Distribution of tumour size among the study subjects with its correlation with Body Mass Index in the present study and its comparison with other studies

In the present study, it was observed that patients in the overweight and obese categories had higher chance of having larger tumour size than those who belonged to normal category of BMI. We compared the results of our study with the other similar studies in literature as follows: The studies conducted by Daling et al., (2001), Loi et al., (2005) and Abrahamson et al., (2006) indicate that the obese patients have a delayed clinical identification of the tumour, resulting in a larger size of the tumour at the time when they are diagnosed.

Higher body mass index was found to be significantly associated with larger size of the tumor upon presentation in another large study by Biglia et al., (2013) forty five percent of postmenopausal women with BMI of more than 25 kg/m^2 had a tumour measuring more than 2 cm, compared to thirty three percent in normal and twenty one percent in underweight women in this study. In the study conducted by Govind et al., (2018), mean tumour size for women with body mass index less than 25 kg/m^2 was 3.99 cm; for body mass index 25–29.9 kg/m^2 was 4.13 cm and for body mass index ≥30 kg/m^2 was 4.30 cm. The findings of our study were in accordance with the above-mentioned studies in the literature.

Hence, we can conclude that patients who belong to the overweight and obese categories of body mass index present with a larger tumour size as compared to the patients in the normal category of body mass index. It may be because of delayed clinical presentation of tumour in the obese patients, resulting in poorer prognosis.

Correlation of Lymph Node status with Body Mass Index in the present study and its comparison with other studies

In the present study it was observed that with increasing BMI, higher lymph node stage was noted among the study subjects. We compared the results of our study with the other similar studies in literature as follows: In a study by Wang et al., (2020), positive linear dose response relationships between BMI and lymph node metastasis risk were observed among Asian, European, American, premenopausal, postmenopausal, study period less than 5 years and more than 5 years groups. For every 1 kg/m^2 increment of BMI, the risk of lymph node metastasis increased by 0.99, 0.85, 0.61, 1.44, 1.45, 2.22 and 0.61%, respectively. Keskin et al., (2013) in their study showed that number of the dissection of lymph nodes was significantly higher in obese patients.

Obesity and weight gain are not only potential causes for breast cancer, but they also contribute to the diagnosing process. A study from Switzerland's Geneva Cancer Registry examined the diagnostic characteristics of obese and non-obese breast cancer patients. Obese patients were shown to have much more advanced stage disease, more surgical delays and a longer hospital stay after surgery, according to the data. The authors speculated that the advanced stage at diagnosis could be attributable to obese women's larger breast size containing more fatty tissue, making palpation of the primary tumour and the axillary lymph nodes tougher. Furthermore, women who are obese might be more hesitant to undertake physical examinations due to their weight embarrassment. They advise that women and clinicians should be educated about the fact that obese women's self-examination and clinical examination may be less reliable and measures to prevent severe disease at diagnosis should be devised for this rising group of patients (Montazeri et al., 2008). When we compared the results of our studies they were in accordance with the above-mentioned studies in the literature.

Correlation of BR Grade and BMI in the present study and its comparison with other studies

In the present study, it was observed that higher BMI correlated with higher BR Grade in the present study. We compared the results of our study with the other similar studies in literature as follows: Ayoub et al., (2019) and Daling et al., (2001) in their study mentioned significant associations between obesity and grade, which is in accordance to our study.

In a study conducted by Mardiah et al., (2021), the distribution of body mass index when correlated with grading of carcinoma breast, revealed that majority of the patients within overweight category of BMI were reported with grade II carcinoma breast. It was revealed that there was a significant correlation between BMI with breast cancer grading. The results of the study established that the likelihood of developing carcinoma breast was 3.57 times higher with grade II and 3.27 times higher with grade III in the patients who belonged to overweight to obese category of body mass index than those who belonged to the normal category of BMI. Thus, it was concluded that there was a significant correlation of body mass index with breast cancer grading. A higher BMI correlated with higher BR Grade in the present study which was in concordance with the above similar studies mentioned in the literature.

Correlation of TNM Staging and BMI in the present study and its comparison with other studies

In the present study, it was observed that cases with higher BMI were reported to have higher TNM stage. We compared the results of our study with the similar studies conducted as follows: Ayoub et al., (2019) in their study mentioned significant associations between obesity and each of tumor stage, which is in accordance to this study.

Studies by Biglia et al., (2013), Eichholzer et al., (2013), Chen et al., (2010), Rosenberg et al., (2009) and Sahin et al., (2017) showed a positive correlation of BMI with tumour stage. Porter et al., (2006) in their study stated that T1 tumors were common in the normal and overweight groups, whereas T2-4 tumors were seen more frequently in the obese group. Hence, it can be concluded that cases with higher BMI were associated with higher TNM stage and thus worse prognosis as depicted by the present study which was in concordance with the above-mentioned studies.

Correlation NPI with BMI in the present study and its comparison with other studies

In the present study, when NPI category was correlated with BMI, it was observed that patients with higher BMI presented with higher NPI score and thus a poor prognosis. Lubian-Lopez et al., (2021) in their study reported that the obese patients with carcinoma breast showed larger tumour sized with a significantly unfavourable NPI indicating poor prognosis of patients. When we compared the results of our study, they were in concordance with the study conducted by Lubian-Lopez et al., (2021).

Obesity has been linked to chronically minimal grade inflammation that has been identified as one of the stimuli for tumour formation (Hillers et al., 2018). Adipose tissue expansion along with increased BMI and obesity may produce persistent inflammation under settings that further lead to resistance to insulin, resulting in increased circulating proinflammatory cytokines, leptin and insulin as factors that contribute to the onset of carcinoma breast (Hillers et al., 2018). Postmenopausal obese patients have estrogenic production from adipocytes, where IGF-1 and insulin are possible growth factors (Prawirohardjo et al., 2018). The combined effects of both will reduce normal apoptosis while continuously stimulating cell division, perhaps leading to breast cancer.

Obesity is related with poorer results; however, data on the influence of weight decrease on outcomes following diagnosis is ambiguous. However, to maintain a healthy weight, all breast cancer patients should get weight loss, lifestyle adjustment, physical activity and nutrition counselling. The motive to maintain a healthy bodyweight is for overall health benefit, as there is high-level evidence of improved outcomes with weight control in circumstances of patients who are devoid of diagnosis.

5. CONCLUSION

Hence, we can conclude from our study that patients with higher BMI tend to have a larger tumour size, increased risk of nodal metastasis, higher BR grade, advanced TNM stage as well as higher NPI score suggestive of poor prognosis in breast carcinoma patients. In the literature, this association is most probably attributable to hormonal (menopausal status, estrogen burden, insulin, insulin-like growth factors, leptin) and non-hormonal (dietary factors, later diagnosis in obese patients, cytokines) factors. Obesity is a modifiable risk factor. Thus, behavioural changes (dietary and exercise) may help to achieve alterations in cell proliferation, insulin sensitivity, circulating oestrogen and apoptosis in response to weight loss.

Obesity reduction techniques may prove to be cost effective strategies for reducing breast cancer risk and improving breast cancer outcomes. Body mass index, being the most widely used indicator for obesity, when correlated with Nottingham Prognostic Index (NPI), which is a commonly used indicator for prognosis in breast cancer patients, can predict the outcome of patients; thus, becoming an adjunct in prognosis as well as aiding to scheme out the cost-effective strategies to reduce the plight of breast carcinoma.

Author Contribution

Dr Ketki Wajpeyi collected the data related to this study, conducted the study and prepared the manuscript under the guidance of Dr Mrs Sunita Vagha, who gave the necessary inputs towards the designing of the study and contributed to the final manuscript.

Acknowledgement

I am very thankful to my patients for contributing to this study as well as my institute where this study was conducted, for giving me the opportunity and environment to conduct the research.

Ethics committee approval

Study was started after obtaining approval from Institutional Ethics Committee Ref no DMIMS (DU)/IEC/2020-21/9262, dated 17/12/2022.

Informed consent

Oral and written informed consent was taken from all the participants of the study.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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