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Asian Journal of Oncology

Original Article

Prognostic significance of body mass index in patients with triple negative breast cancer: A retrospective observational study

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ABSTRACT

Objectives: Triple negative breast cancer (TNBC) lacks expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), making it more aggressive and less responsive to targeted therapies. Our retrospective study aimed to investigate the impact of body mass index (BMI) on the survival of TNBC patients in Eastern India.

Material and Methods:242 TNBC patients were included from January 2016 to December 2020 and were followed up until December 2023. Baseline characteristics were summarized using percentages and frequencies. The Chi-square test was used for clinicopathologic characteristics, and the Kaplan-Meier method evaluated survival functions. Log-rank tests conducted ($p \leq 0.05$).

Results: The median age of the population was 45 years. The majority (92.98%) had no family history. 67.7% were of Grade 2, and 27.69% were Grade 3. The mean BMI was 23.95 [range 14.2 - 37.56 (95% CI 23.49;24.4)]. 62.81% were of a healthy weight, 28.51% were overweight, 4.55% were underweight, and 4.13% were obese. Metastasis-free survival (MFS) rates were 90.91% for underweight, 84.06% for overweight, 76.32% for healthy weight, and 70% for obese patients (p value .376). DFS, considering both local recurrence and metastases as an event, were 94.2% for overweight, 94.08% for healthy weight, 90% for obese, and 54.55% for underweight individuals (p value <0.001). OS was 65.22% for overweight, 61.84% for healthy weight, 60% for obese, and 30.36% for underweight individuals (p value 0.44).

Conclusion: This study's findings highlight significant implications of BMI on survival outcomes. It also reinforces the intricate link between obesity and prognosis, emphasizing the need for weight management strategies in patient care. Further mechanistic research is warranted.

Keywords: Body mass index, Survival outcomes, Triple negative breast cancer

INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide, according to Global Cancer Observatory (GLOBOCAN) 2022. Breast cancer is the most common cancer in India, accounting for 13.8% incidence, with a heterogeneous spectrum of subtypes displaying distinct biological behaviors and clinical outcomes. Triple negative breast cancer (TNBC), characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, represents a particularly aggressive subtype. It constitutes approximately 10-20% of all breast cancer cases.[1,2]

TNBC exhibits a higher propensity for early metastasis, increased rates of recurrence, and poorer overall prognosis compared to other breast cancer subtypes.[3] The absence of therapeutic targets such as hormone receptors and HER2 amplification limits treatment options, restricting patients to conventional chemotherapy regimens, which often yield variable responses and limited survival benefits.[4] Immunotherapy is playing an increasingly important role in the treatment of TNBC, especially in locally advanced & metastatic disease.

Obesity, defined by a higher body mass index (BMI), has emerged as a significant public health concern globally,

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Received: 20 March 2025 **Accepted:** 10 July 2025 **Published:** 04 September 2025 **DOI:** 10.25259/ASJO_17_2025

with escalating prevalence rates observed across diverse demographic profiles.[5] Mounting evidence suggests that obesity not only predisposes individuals to various chronic diseases but also influences cancer development, progression, and treatment outcomes.[6] In breast cancer, obesity has been implicated in promoting tumor initiation, enhancing tumor growth through adipose tissue-derived signaling molecules, fostering inflammation, and modulating hormonal pathways, thereby contributing to tumor aggressiveness and therapy resistance.[7,8]

The association between obesity and breast cancer risk, particularly among postmenopausal women, has been extensively investigated, but its impact on the clinical course and outcomes of TNBC remains less elucidated, especially in regional contexts with distinct epidemiological and socio-cultural profiles, such as Eastern India.

Therefore, this retrospective observational study aims to address this critical knowledge gap by evaluating the prognostic significance of BMI in TNBC patients treated in Eastern India. Specifically, we seek to investigate whether higher BMI is associated with reduced survival outcomes in TNBC patients, providing insights into the impact of obesity on the clinical management and prognostication of this aggressive breast cancer subtype.

MATERIAL AND METHODS

A retrospective observational study was conducted involving 742 patients diagnosed with primary invasive breast cancer at the Institute of Post Graduate Medical Education & Research, Kolkata, India, from January 2016 to December 2020. Data were retrieved from medical records, encompassing socio-demographic variables, clinicopathological characteristics, and pertinent clinical information. Inclusion criteria were all stages except stage IV cancer, ER, PR, or HER2 negative, and left, right, or both-sided breast cancers. Exclusion criteria were male breast cancer, stage IV metastatic disease, ER, PR, or HER2 positive, or inadequate immunohistochemical information.

Patients with incomplete information on ER, PR, and HER2 status (n=28) and male breast cancer patients (n=2) within the triple-negative breast cancer subgroup were excluded, resulting in a final cohort of 242 female triple-negative breast cancer patients. Follow-up extended until December 2023, with censoring for individuals alive after the last follow-up date.

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2), categorized according to World Health Organization (WHO) definitions: overweight (BMI 25-29.9 kg/m^2), healthy weight (BMI 18.5-24.9 kg/m^2), obesity (BMI ≥30 kg/m^2), and underweight (BMI <18.5 kg/m^2).[9]

Descriptive statistics summarized baseline characteristics, and the Chi-square test compared clinicopathologic characteristics across BMI groups. Survival endpoints [Overall Survival (OS)- time from diagnosis or treatment start to death from any cause), Disease-Free Survival (DFS)- time after treatment during which the patient remains free of disease), Metastasis-Free Survival (MFS)- time from treatment start to detection of metastasis)] were assessed using the Kaplan-Meier method with log-rank tests for group comparisons.[10] Cox's proportional hazards regression conducted univariate and multivariate analyses to determine hazard ratios (HR) with 95% confidence intervals (CI).[11]

Statistical analyses were performed using the DATA tab platform with a significance level set at $P < 0.05$.

RESULTS

The median age of breast cancer patients is 45 years, range (24 to 83 years).

The onset of menarche was within normal range in 98.76% of cases. Additionally, 54.55% of all were pre-menopausal and 45.45% post-menopausal; 89.67% patients had a history of breastfeeding [Table 1]. Socio-economically, 10.33% reported an addiction to tobacco or alcohol, and 23.97% had comorbidities. Family history (only first-degree relatives included) was positive in 7.02% of patients. The average BMI was 23.95, with a range from 14.2 to 37.56 (95% CI 23.49; 24.4), indicating a normal weight for the majority (62.81%), though overweight and obesity were also present [Figure 1].

Clinically, nearly equal distribution was between the right (52.48%) and left (47.52%) breasts, with major symptoms being lump and pain (97.93%), typically lasting 6-12 months. Most patients underwent Modified Radical Mastectomy, with 67.8% Grade 2 tumors. Lymphovascular invasion (LVI) was present in less than half of the cases, and PNI in 13.2% patients [Table 2].

The study's survival curve over 35 months shows that individuals with underweight have the highest Metastasis Free Survival (MFS) rates (90.91%), with a noticeable decline across all categories at 10 months, and obese individuals have the lowest rate (70%) by the end.

The Chi-Square value of 3.11 and a p-value of 0.376 suggest no statistically significant difference in MFS across BMI categories, failing to reject the null hypothesis [Figure 2].

Conversely, the survival curves for DFS over 25 months indicate a significant difference across BMI categories, with a Chi-Square value of 30.29 and a p-value less than 0.001,

Table 1: Demographic and socio-economic characteristics of the patient population

Demographic characteristics			
Parameters	**Sub parameters**	**Frequency**	**Percentage (%)**
Menarche	Normal onset	239	98.76
	Late onset	3	1.24
Menopause	Pre-Menopause	132	54.55
	Post-Menopause	110	45.45
History of breastfeeding	Present	217	89.67
	Absent	25	10.33
Socio-economic characteristics			
Parameters	**Sub parameters**	**Frequency**	**Percentage (%)**
Addiction history (Tobacco and alcohol)	Absent	217	89.67
	Present	25	10.33
Comorbidity history	Absent	184	76.03
	Present	58	23.97
Family history	Absent	225	92.98
	Present	17	7.02
Body mass index (BMI)	Healthy weight	152	62.81
	Overweight	69	28.51
	Underweight	11	4.55
	Obesity	10	4.13

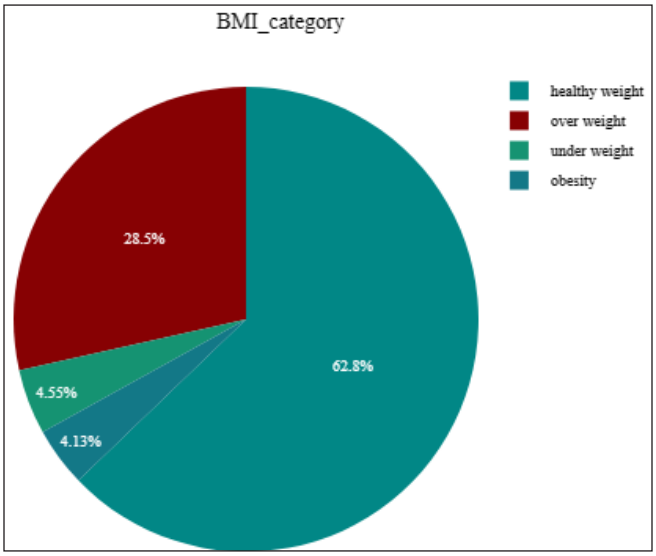

Figure 1: Distribution of body mass index (BMI) categories. 62.8% constitutes a healthy weight, 28.5% overweight, 4.55% underweight, and 4.13% obesity.

leading to the rejection of the null hypothesis and suggesting BMI's influence on DFS [Figure 3].

Table 2: Clinico-pathological characteristics of the patient population

Clinico-pathological characteristics			
Parameters	**Sub parameters**	**Frequency**	**Percentage (%)**
Sites of breast cancer	Right breast	127	52.48
	Left breast	115	47.52
Symptoms	Lump and pain	237	97.93%
	Lump and ulcer	4	1.65%
	Only pain	1	0.42%
Duration of symptoms	6-12 months	123	50.83%
	<6 months	78	32.23%
	>12 months	41	16.94%
Surgery type	MRM	205	84.71%
	No surgery	30	12.4%
	Toilet mastectomy	5	2.06%
	BCS	2	0.83%
Tumor grade	Grade 2	164	67.77%
	Grade 3	67	27.69%
	Grade 1	11	4.54%
Lymphovascular invasion (LVI)	Absent	135	55.79%
	Present	107	44.21%
Perineural invasion (PNI)	Absent	210	86.78%
	Present	32	13.22%

MRM: Modified radical mastectomy, BCS: Breast-conserving surgery

Lastly, the OS rates curve for 40 months shows no significant difference across BMI categories [Figure 4], with a Chi-Square value corresponding to a non-significant p-value of 0.444, indicating that BMI may not significantly affect OS rates [Table 3].

DISCUSSION

The retrospective observational study conducted in Eastern India provides a nuanced view of the prognostic significance of BMI in patients with triple-negative breast cancer (TNBC). The findings suggest a complex relationship between BMI and survival outcomes in TNBC patients.

The demographic profile of the study indicates a median age of 45 years for breast cancer patients, which is consistent with global epidemiological data showing a higher incidence of breast cancer in middle-aged women.[12] The high rate of breastfeeding history (89.67%) among the participants aligns with previous research.[13]

The clinical distribution of breast cancer between the right and left breasts does not show a significant preference, which

Table 3: Association between BMI categories and survival outcomes

BMI category	Total no of patients	No of events			No of censored		
		MFS	DFS	OS	MFS	DFS	OS
Healthy weight	152	36	9	58	116	143	94
Over weight	69	11	4	24	58	65	45
Obesity	10	3	1	4	7	9	6
Under weight	11	1	5	7	10	6	4
LOG RANK test		Chi-square	df		p-value		
Metastasis free survival (MFS)		3.11	1		.376		
Disease-free survival (DFS)		30.29	1		<.001		
Overall survival (OS)		2.68	1		.444		

p-value significance level is <0.05. BMI: Body mass index, MFS: Metastasis-free survival, DFS: Disease-free survival, OS: Overall survival, df: Degrees of freedom

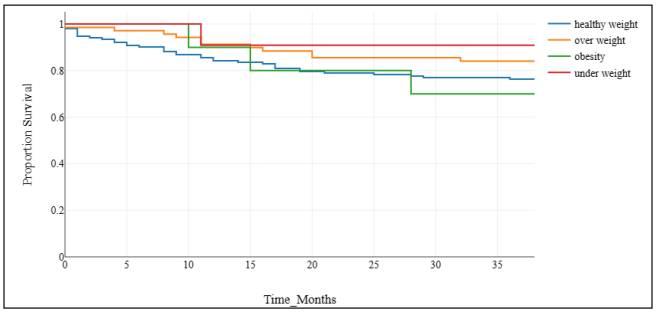

Figure 2: Kaplan-Meier curve analysis of metastasis-free survival (MFS) across BMI categories: p value 0.376.

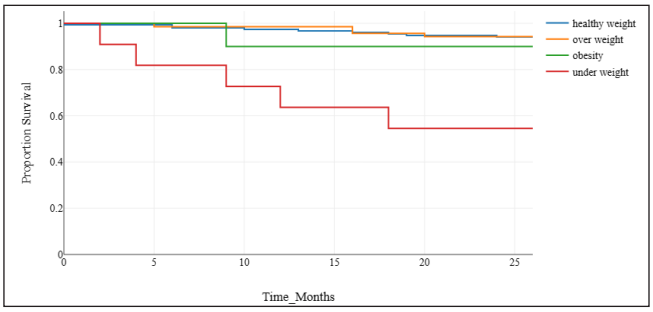

Figure 3: Kaplan-Meier Curve Analysis of Disease-Free Survival (DFS) Across BMI Categories: p value <0.001.

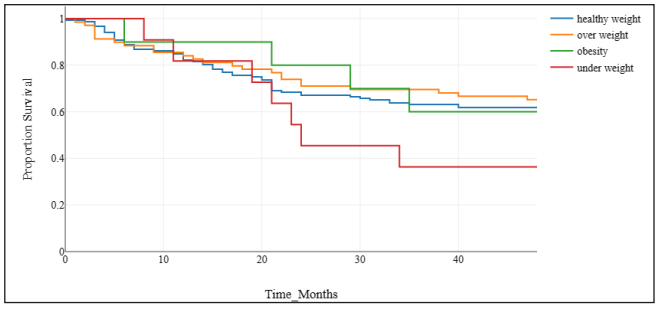

Figure 4: Kaplan-Meier Curve Analysis of Overall Survival (OS) Across BMI Categories: p value 0.444.

is in accordance with the literature, breast cancer can occur in either breast without predilection.[12] The predominance of symptoms such as lumps and pain, and the commonality of Modified Radical Mastectomy, reflect standard clinical presentations and treatment approaches for TNBC.[12]

The study's survival analysis over 35 months reveals that individuals with a healthy BMI have high MFS rates. This observation is intriguing, as it suggests that a normal BMI may confer a survival advantage in TNBC. However, the lack of statistical significance in MFS across BMI categories (Chi-Square = 3.11, p-value = .376) indicates that BMI alone may not be a strong independent prognostic factor for MFS in this population.

In contrast, the significant difference in DFS across BMI categories (Chi-Square = 30.29, p-value < .001) suggests that BMI may influence DFS in TNBC patients. This is supported by a systematic review and meta-analysis, which found that overweight was associated with shorter DFS in TNBC patients.[14] The current study's findings add to this body of evidence, indicating that higher BMI may be associated with reduced DFS.

Lastly, the OS rates over 40 months showed no significant difference across BMI categories (Chi-Square value corresponding to a non-significant p-value of 0.444). This aligns with other studies that have reported mixed results regarding the impact of BMI on OS in breast cancer patients.[15,16] It suggests that while BMI may influence DFS, its impact on OS is less clear and may be confounded by other factors such as treatment response, comorbidities, and socioeconomic status.

Limitation of the study

The study's limitations include a small, region-specific sample, retrospective biases, single-center scope, short follow-up duration, and unaccounted confounding factors.

CONCLUSION

The study conducted in Eastern India on the prognostic significance of BMI in TNBC patients reveals that higher BMI is associated with reduced DFS, but it does not significantly affect MFS or OS. The lack of statistical significance in MFS and OS suggests that factors other than BMI may play a more critical role in the long-term prognosis of TNBC. The significant impact of BMI on DFS underscores the need for a nuanced understanding of how obesity influences cancer progression and patient outcomes. This study contributes to the body of evidence that supports the inclusion of BMI in the clinical management and prognostication of TNBC. Further research is warranted to explore the complex interplay between BMI and TNBC outcomes, considering various confounding factors.

Author contribution: SM :Manuscript preparation, Data analysis; SD: Concept, design, manuscript editing and design; RD:Concepts, design, literature search, clinical studies, experimental studies, data analysis, data acquisition, statistical analysis, manuscript preparation, manuscript editing and review, concepts; SHA: Concepts, design, definition of intellectual content, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and review, clinical studies; SMD: Concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, manuscript preparation, manuscript editing and review; AM: Concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, manuscript preparation, manuscript editing and review.

Ethical approval: Institutional Review Board approval is not required because it is retrospective study. The research/study complies with the Helsinki Declaration of 1964.

Declaration of patient consent: Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Das R, Ali SH, Das SM, Mahalanabish A, Mondal S, Das S. Prognostic significance of body mass index in patients with triple negative breast cancer: A retrospective observational study. Asian J Oncol. 2025;11:13. doi: 10.25259/ASJO_17_2025