IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 7 | Issue: 2 | Mar – Apr 2026 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v7i2.2

The Relationship Between Obesity And 3-Year Overall Survival in Luminal B HER2-Negative Breast Cancer Patients Receiving Neoadjuvant Chemotherapy at Prof. Dr. I.G.N.G Ngoerah Hospital

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ABSTRACT

Background: Luminal B breast cancer is the second most common subtype, with a relatively high mortality rate. The luminal B HER2-negative subtype shows a 26% survival rate over 5 years. One of the factors that can influence survival in breast cancer patients is obesity. Obesity is a public health issue that requires strong preventive intervention strategies, especially among patients diagnosed with breast cancer. ***Methods:*** This study is a survival analysis aiming to find a significant relationship between obesity and 3-year overall survival in Luminal B HER2-negative breast cancer patients receiving neoadjuvant chemotherapy at Prof. Dr. I.G.N.G Ngoerah Hospital. The data were retrospectively reviewed. The target population includes Luminal B HER2-negative breast cancer patients. Data analysis was performed using SPSS, including Chi-Square tests, Independent T-Tests, and Kaplan-Meier survival analysis. ***Results:*** In this study, 57 subjects were divided into 2 groups: the obese group, consisting of 25 subjects, and the non-obese group, consisting of 32 subjects. The results showed that the non-obese group experienced higher mortality rates compared to the obese group (68.8% vs. 32.0%; p=0,006). Obese patients had a significantly lower risk of death, with an odds ratio of 0.465 (95% CI 0.251-0.863; p=0,006), compared to non-obese patients. The Kaplan-Meier analysis indicated that the 3-year overall survival rate was higher in the obese group compared to the non-obese group, with a median survival of 60 months (95% CI 51-70 months) versus 49 months (42-56 months), LRT 4.098, p=0.043. ***Conclusion:*** There is a significant relationship between obesity and 3-year overall survival in Luminal B HER2-negative breast cancer patients receiving neoadjuvant chemotherapy at Prof. Dr. I.G.N.G Ngoerah Hospital.

Keywords: breast cancer HER2-negative; Luminal B; neoadjuvant chemotherapy; survival

INTRODUCTION

Breast cancer is the most prevalent cancer among women globally, with luminal B being the most common subtype. Multiple risk factors contribute to breast cancer, including age, genetic history, BRCA gene mutations, low parity, hormone usage, and obesity. The high morbidity and mortality rates associated with breast cancer underscore the need for effective prevention strategies, especially concerning obesity, which significantly impacts overall survival [1].

According to Globocan 2020, Indonesia reported 68,858 new breast cancer cases (16.6%) out of 396,914 total cancer cases, with over 22,000 breast cancer-related deaths [2]. The World Health Organization (WHO) estimated that in 2020, one in eight women was diagnosed with breast cancer, with 23% having metastasis at the time of diagnosis [3]. The Asia-Pacific region accounts for about 24% of the world's breast cancer cases, approximately 404,000, notably with the highest incidences in China (46%), Japan (14%), and Indonesia (12%)[4].

The global age-standardized incidence rate (ASIR) for breast cancer is 218.6 per 100,000 women, with Asia's ASIR at 223 per 100,000, while ASEAN reports

156 [5]. In Indonesia, the ASIR is 133 per 100,000 women, with Bali reporting 84 per 100,000 [6]. Overall five-year survival rates for breast cancer vary from 40% to 80%, with Indonesian rates being lower than in many other nations, estimated between 80% and 90% for all stages [7].

Luminal B breast cancer is defined by estrogen receptor (ER) positivity, progesterone receptor (PgR) expression, and varied HER2 status [8]. A study found that among 320,124 diagnosed breast cancer cases from 2010 to 2016, 11.2% were luminal B [9]. Further research indicated that this subtype is increasingly prevalent among older non-Hispanic white women and in Asian/Pacific women aged 55 to 69 [9,10].

Research indicates that obesity negatively affects survival rates among breast cancer patients. In Indonesia, obesity prevalence among adults is reported at around 33.5%, which is significant [11]. Obesity has been linked to a higher risk of developing breast cancer and is associated with poorer prognosis and increased recurrence rates [12].

A study revealed that luminal B HER2-positive patients had poorer survival rates, with a five-year mortality risk of 36.73% compared to 12.24% for HER2-negative patients [13]. This suggests that HER2-positive luminal B patients experience worse outcomes than their HER2-negative counterparts [14].

Breast cancer, particularly the luminal B subtype, presents considerable challenges, significantly influenced by various factors, including obesity. The concerning link between obesity and breast cancer progression emphasizes the critical need for targeted prevention and treatment strategies to enhance patient outcomes. Further research focusing on the luminal B HER2-negative population is crucial in understanding and improving management approaches for breast cancer patients, especially as obesity rates continue to rise globally. Addressing obesity as a modifiable risk factor could play a pivotal role in improving survival and quality of life for breast cancer patients.

METHOD

This study is an observational cross-sectional design aimed at investigating the relationship between obesity and survival in patients with Luminal B HER2-negative breast cancer undergoing neoadjuvant chemotherapy.

Survival analysis was conducted retrospectively using the Kaplan-Meier method to evaluate the 3-year overall survival probability. The research was conducted at RSUP Prof. Dr. I.G.N.G Ngoerah, Denpasar, with data collection from August 1 to November 31, 2023.

Inclusion criteria comprised patients aged 20 to 70 years with Luminal B HER2-negative breast cancer who received at least three cycles of neoadjuvant chemotherapy at RSUP Prof. Dr. I.G.N.G Ngoerah and had complete data on age, menstrual status, and hormonal contraceptive use. Exclusion criteria included male breast cancer patients, those with bleeding disorders, infections, diabetes mellitus, kidney or liver diseases, immunocompromised conditions, and mortality due to causes other than breast cancer.

Data analysis involved descriptive statistics to summarize sample characteristics. The Shapiro-Wilk test assessed normality for numerical data. Comparative analyses for categorical variables used Chi-Square tests with odds ratios, while numerical data comparisons employed independent T-tests or Mann-Whitney tests, depending on data distribution. Kaplan-Meier survival analysis was applied to estimate survival probabilities over the 3-year follow-up period.

RESULT

In this study, a total of 57 subjects met the inclusion and exclusion criteria. The subjects were divided into two groups: 25 subjects in the obese group and 32 subjects in the non-obese group. The data characteristics are presented in Table 5.1.

The majority of subjects were under 50 years old. The mean age was 47.88 ± 8.62 years in the obese group and 48.41 ± 9.77 years in the non-obese group. The median BMI in the obese group was 27.7 (25.39-35.56) kg/m^2, while the non-obese group had a median BMI within the normal range at 21.90 (14.15-24.98) kg/m^2. Statistical analysis showed a significant difference with $p < 0.001$.

Menstrual status was predominantly premenopausal in both groups. Contraceptive use was reported in 4 subjects in the obese group and 1 subject in the non-obese group, with no significant difference between groups ($p = 0.094$). The number of deaths was higher in the non-obese group compared to the obese group. Deaths in the non-obese group numbered 22 (68.8%) versus 8 (32.0%) in the obese group, with a statistically significant difference ($p = 0.006$).

TABLE 1: Research Data Characteristics.

Variable	Group		p-value
	Obese (n=25)	Non-Obese (n=32)	
Age (years) [mean±SD]	***47.88 ± 8.62***	***48.41 ± 9.77***	***0.781[a]***
≥ 50 years	10 (40%)	14 (43.8%)	0.776[b]
< 50 years	15 (60%)	18 (56.3%)	
BMI (kg/m^2) [median (min-max)]	27.7 (25.39-35.56)	21.90 (14.15-24.98)	<0.001[c*]

Variable	Group		p-value
	Obese (n=25)	Non-Obese (n=32)	
Menstrual Status			
Postmenopause	11 (44.0%)	14 (43.8%)	0.392[b]
Premenopause	14 (56.0%)	18 (56.3%)	
Contraceptive Use			
Yes	4 (14.3%)	1 (3.6%)	0.094[b]
No	9 (32.1%)	14 (50.0%)	
Survival Status			
Die	8 (32.0%)	22 (68.8%)	0.006[b]
Alive	17 (68.0%)	10 (31.3%)	

a Independent t-test; b Chi-Square; c Mann-Whitney *Significant if p < 0.05 SD: standard deviation

Bivariate analysis using the Chi-Square test was performed to examine the relationship between obesity and survival in Luminal B HER2-negative breast cancer patients receiving neoadjuvant chemotherapy, along with the odds ratio (OR). Survival analysis was further conducted using the Kaplan-Meier method to estimate survival probability.

The results of the bivariate and Kaplan-Meier analyses are presented in Table 5.3, showing that death occurred more frequently in the non-obese group compared to the obese group (68.8% vs. 32.0%; p = 0.006). Obese patients had a significantly lower risk of death, with an OR of 0.465 (95% CI 0.251-0.863; p = 0.006). Kaplan-Meier analysis showed that the mean 3-year overall survival was higher in the obese group compared to the non-obese group: 60 months (95% CI 51-70 months) versus 49 months (42-56 months), with a log-rank test (LRT) of 4.098 and p = 0.043. The Kaplan-Meier survival curve for Luminal B HER2-negative breast cancer patients receiving neoadjuvant chemotherapy with obesity is shown in Figure 1.

TABLE 2: Association Between Obesity and 3-Year Overall Survival in Luminal B HER2-Negative Breast Cancer Patients Receiving Neoadjuvant Chemotherapy.

Variable Obesity	3-Year Overall Survival		OR	95% CI	p-value	Log Rank	Mean survival		p-value
	Die (n=30)	Alive (n=27)					Month	95% CI	
BMI > 25	8 (32.0%)	17 (68.0%)	0.465	0.251 - 0.863	0.006 [a]*	4.098	60	51-70	0,043[b]*
BMI ≤ 25	22 (68.8%)	10 (31.3%)					49	42-56	

a Chi-Square test; b Kaplan-Meier test *Significant if p < 0.05

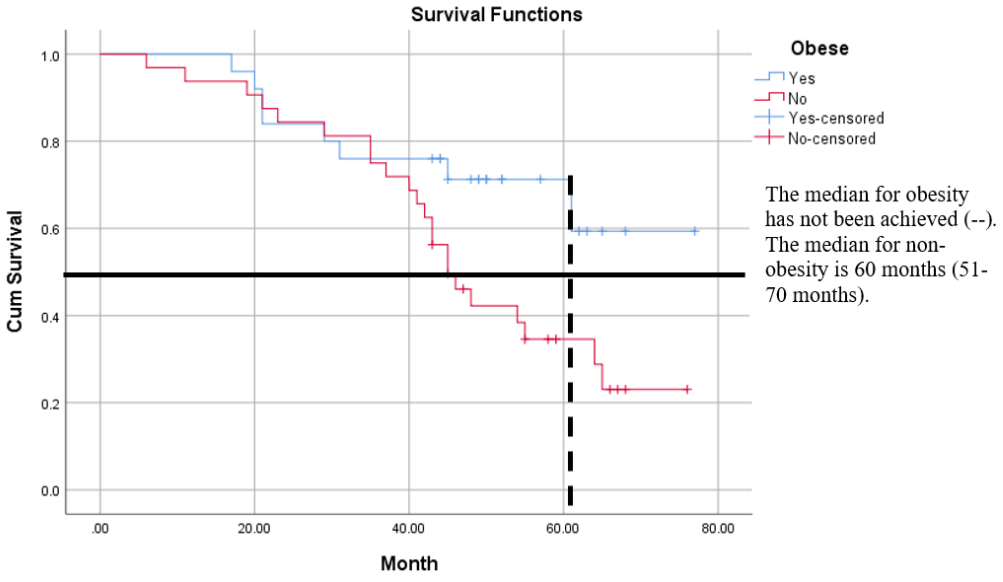

FIGURE 1: Kaplan-Meier overall survival curve of Luminal B HER2-negative breast cancer patients receiving neoadjuvant chemotherapy with obesity.

In the Kaplan-Meier curve, the median survival for the obese group was not reached, while the median survival for the non-obese group was reached at 49 months (95% CI: 42-56 months).

DISCUSSION

In this study, 25 patients with obesity had a mean age of 47.88 ± 8.62 years, while 32 non-obese patients had a mean age of 48.41 ± 9.77 years. The focus was on patients diagnosed with HER2-negative Luminal B subtype breast cancer undergoing neoadjuvant chemotherapy with contraceptives. These findings are comparably close to Tong's 2022 study, which involved 2,875 Luminal B breast cancer patients with an average age of 56.41 ± 12.71 years. Notably, 32.2% of these patients were under 50. The study suggests that obesity did not significantly impact recurrence-free survival (RFS) and overall survival (OS) in Luminal B patients but showed worse outcomes in other subtypes, like Luminal A. The differing results may be attributed to lifestyle, genetic, and environmental factors.

Further research by Meniksiwela et al. in 2022 indicated that Luminal B breast cancer patients had higher Body Mass Index (BMI) and identified increased risks among Black patients compared to their White and Hispanic counterparts [15]. The average age of patients with Luminal B breast cancer was 51.1 years, highlighting that this subtype is more frequently found in younger patients than Luminal A, which had an average age of 54.6 years.

Zhang et al. in 2021 found that younger breast cancer patients (under 40 years) often exhibit more aggressive tumor characteristics [16]. Young patients with Luminal B tumors had a death risk 2.5 times higher than older patients. This pattern aligns with Schettini et al. in 2020, who reported that younger patients with HER2-negative Luminal B breast cancer showed higher Ki67 levels, correlating with poorer prognoses [13]. Younger patients also typically presented at a later tumor stage with greater lymphovascular invasion than their older counterparts.

Poor dietary habits and lack of physical activity are significant contributors to obesity in younger populations. High-calorie, sugary, and fatty food consumption, coupled with inadequate physical exercise, significantly raises weight and obesity levels from a young age. Genetic predisposition to obesity plays a crucial role too; individuals with a family history of obesity are more likely to struggle with it themselves. Additionally, obesity can increase estrogen hormone production, which is linked to breast cancer development. This excess estrogen produced by fat tissue can ignite cancer cell growth at a younger age. Social factors, such as socioeconomic status and access to healthy food and exercise opportunities, critically impact youth obesity rates. Children and teens from lower socioeconomic backgrounds often have limited access to nutritious food and exercise facilities, enhancing obesity risks. Early puberty, especially in girls, correlates with a higher chance of breast due to increased exposure to estrogen [12,17,18].

The study findings showed that non-obese patients had a higher mortality rate compared to their obese counterparts, with respective death rates of 68.8% versus 32.0% (p=0.006). Obese patients exhibited a significantly lower risk of death—0.465 times lower—compared to non-obese individuals (CI 95% 0.251-0.863; p=0.006). Kaplan-Meier analysis revealed that the average three-year overall survival in the obese group was higher: 60 months (CI 95% 51-70 months) compared to 49 months (42-56 months) in the non-obese group, with a Log-Rank Test (LRT) value of 4.098 and p=0.043. These findings resonate with Rahman et al. (2022), who indicated that obesity might have a protective effect on Luminal B breast cancer patients, as evidenced by a lower death risk rate, although it did not reach statistical significance.

Biologically, tumors in obese patients may exhibit different gene expression profiles than those in non-obese patients. Generally, this might lead to an increase in genes associated with proliferation and metabolic stress responses, enhancing tumor cell survival during treatment. Moreover, obese patients may have larger nutritional reserves, enabling them to better endure severe chemotherapy side effects. Certain studies indicate that obesity may also affect the immune response, potentially lowering mortality rates in specific cases [19]. Chemotherapy pharmacokinetics can change in obese patients, potentially optimizing drug distribution [15].

Obesity is also linked to metabolic changes, such as insulin resistance, oxidative stress, and increased inflammatory cytokine production. Excess fatty tissue augments estrogen production through androgen aromatization, influencing tumor growth and hormonal therapy response [20]. However, it is vital to acknowledge that endocrine resistance is a crucial aspect of Luminal B breast cancer, especially in obese patients. This condition can lead to diminished hormonal therapy efficacy due to elevated peripheral estrogen and disruptions in insulin signaling that stimulate cancer cell proliferation pathways resistant to therapies like tamoxifen [21].

This study has several substantial strengths, notably a strong design and comprehensive statistical analysis that provide a solid foundation for interpreting results. It uniquely contributes by presenting findings that diverge from the predominant theories that obesity can have a protective effect on breast cancer mortality. This shifts the understanding of obesity in relation to breast cancer, traditionally viewed only as a risk factor.

However, there are limitations, primarily the reliance on retrospective data, which may introduce bias and limit the ability to draw broader conclusions. Future research with prospective designs and extended follow-up periods is needed to enhance the validity

and generalization of the findings. Additionally, the Kaplan-Meier analysis indicates that median survival has not yet been reached, suggesting that follow-up data may be insufficient for providing a clearer picture of mortality within the study group.

In conclusion, while the findings of this study present a unique perspective on the relationship between obesity and breast cancer mortality, further investigation is essential to clarify these associations. Understanding the complexity of obesity's role in breast cancer can lead to improved treatment strategies and outcomes for patients.

CONCLUSION

The study highlights a significant relationship between obesity and survival outcomes in breast cancer patients. It was found that obese patients have a lower risk of mortality compared to their non-obese counterparts. Additionally, survival analysis showed that obese patients enjoy a higher average overall survival compared to those who are not obese. However, since the median survival for the obese group has not yet been reached, it is recommended that future analyses extend the observation period to achieve a more comprehensive understanding of long-term survival trends in this patient population.

Acknowledgments
All support in the paper

Declarations
Funding: No funding sources
Conflict of interest: None declared

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