BMC Cancer

RESEARCH

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# Effects of BMI on prognosis, disease-free survival and overall survival of breast cancer

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## Abstract

**Background** Obese breast cancer patients have worse prognosis than normal weight patients, but the level at which obesity is prognostically unfavorable is unclear. This study aimed to investigate different effects of Body Mass Index (BMI) on prognosis disease-free survival and overall survivor of breast cancer patients.

**Method** This retrospective cohort study analyzed the medical records of breast cancer patients who sought treatment at Namazi hospital in Shiraz, Iran between 2014 and 2019. Three groups of patients were divided according to BMI. Menopausal status, BMI status, clinicopathological characteristics, treatment, and overall survival (OS), and disease free survival (DFS) were comprehensively evaluated. The World Health Organization (WHO) BMI classification was used to categorize patients into three groups: normal weight (BMI < 25.0 kg/m2), overweight (25.0 ≤ BMI < 30.0 kg/m2), and obese (BMI ≥ 30.0 kg/m2).

**Results** Of the 7134 breast cancer patients, the majority (42.6%) were in 25–30 kg/m$^2$. Menopausal status significantly were associated with obesity ($P < 0.001$). The majority of patients were categorized as grade 2 and stage 2 according to the BMI categories ($P = 0.12$, $P = 0.08$, respectively). BMI categories regardless of menopausal status displayed increased 1, 3, and 5-year DFS and 5- year OS in stage 1 and increased 1, 3, and 5-year OS and 1 and 3-year DFS in stage 2. In stage 3, the risks of relapse and death were significantly decreased in all three groups of BMI patients with post-menopausal period.

**Conclusion** Obesity leads to worse DFS and OS in patients with BC and the effects of obesity on the breast cancer prognosis seem to be clinically related to menopausal status. Once validated, these results should be considered in the development of prevention programs.

**Keywords** Body mass index, Breast cancer, Survival, Prognosis

## Introduction

Breast cancer (BC) stands as the most prevalent malignant tumor and ranks among the primary contributors to cancer-related fatalities in women [1, 2]. Over the last decade, there has been a gradual rise in the global incidence of BC [3]. Thanks to advancements in early detection and the enhancement of treatment modalities, the outlook for breast cancer sufferers has significantly improved [4]. Various factors impacting the prognosis of BC comprise axillary lymph nodes, primary tumor size, the utilization of adjuvant systemic treatments, tumor-infiltrating lymphocytes, estrogen receptor,

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human epidermal growth factor receptor-2 (HER-2), age, menopausal status, ethnicity, alcohol consumption, and smoking habits [5]. Research shows that excess body fat increases the risk for several cancers [6]. Additionally, there is now a widespread consensus on the adverse prognostic implications of obesity or overweight for breast cancer beyond its role as a risk factor [7].

Currently, obesity has reached epidemic proportions, with 69% of adults in the United States and 38% globally falling into the overweight or obese category [8, 9]. Obesity is linked to changes in overall body physiology and hormonal balance that contribute to various health conditions like diabetes and cardiovascular diseases [10]. Moreover, obesity is correlated with an elevated likelihood of developing several types of cancer and with reduced survival rates for individuals diagnosed with those cancers [11]. The National Institute of Health (NIH) categorizes body mass index (BMI) as follows: underweight < 18.5 kg/m$^2$, normal weight 18.5 to < 25 kg/m$^2$, overweight 25.0 to < 30 kg/m$^2$, and obesity ≥ 30.0 kg/m$^2$ [12]. Around 75% of women in the United States and 50% in Europe are overweight or obese at the time of breast cancer diagnosis, and treatments for breast cancer frequently lead to additional weight gain [13]. A high BMI is linked to poorer clinical outcomes in patients with early-stage breast cancer (EBC) [14].

The precise biological mechanisms behind the relationship between adiposity and breast cancer (BC) survival are not fully understood, but they may involve the interplay of hormones, adipocytokines, and inflammatory cytokines, which play roles in cell survival, apoptosis, migration, and proliferation [15]. Numerous studies have explored the connection between obesity and BC outcomes [5, 16, 17]. Li et al. found that a high BMI significantly impacts overall survival (OS) but does not significantly affect disease-free survival (DFS) [18]. Conversely, Fontanella et al. demonstrated that obese patients have significantly shorter average DFS and OS compared to patients with a healthy weight [19]. Most research investigating the correlation between breast cancer and BMI has focused on Western populations. However, the mechanistic understanding of the association between obesity/overweight and the risk of breast cancer recurrence and mortality among Asian women, based on menopausal status, is limited. Given that Asian women typically have lower BMIs than Western women, this study aimed to examine the varying effects of BMI on prognostic factors, OS, and DFS in BC patients with Invasive Ductal Carcinoma subtypes.

## Methods

The study was conducted under the Declaration of Helsinki and with approval from the Ethics Committee of Shiraz Medical Science University.

This retrospective cohort study analyzed the medical records of breast cancer patients who sought treatment at Namazi hospital in Shiraz, Iran between 2014 and 2019. These data were studied in 2024. All cases included in the study displayed tumor characteristics that align with the morphological guidelines specified in the World Health Organization (WHO) histological classification of breast tumors [20]. The selection criteria for patients were centered on the verification of primary breast cancer through histological analysis after curative surgical procedures, as well as the patient being over 18 years of age. Individuals under 18.5 kg/m2, diagnosed with stage IV breast cancer recently, those lacking complete pathological or postoperative treatment data, and patients who were lost to follow-up were excluded from the study.

This study collected weight and height data at the time of initial breast cancer diagnosis. Body Mass Index (BMI) was then calculated by dividing weight in kilograms by the square of height in meters. The World Health Organization (WHO) BMI classification was used to categorize patients into three groups: normal weight (BMI < 25.0 kg/m2), overweight (25.0 ≤ BMI < 30.0 kg/m2), and obese (BMI ≥ 30.0 kg/m2). Subsequently, a stratified analysis was conducted to explore the relationship between BMI and breast cancer prognosis, categorized by the patient's menopausal status at diagnosis. Menopause was defined as either one year of amenorrhea (absence of menstruation) or a history of bilateral oophorectomy (surgical removal of both ovaries). Post-menopause refers to the final stage of menopause, signifying the end of a woman's reproductive period [7].

All participants in the study underwent regular monitoring following surgery, chemotherapy, radiation therapy, and hormonal treatment. This follow-up was conducted every 3–6 months within the first two years after surgery, every 6 months over the subsequent 5 years, and annually thereafter with imaging under guide of National Comprehensive Cancer Network (NCCN) [21]. All occurrences were meticulously documented in the database.

### Pathology analysis

Immunohistochemical (IHC) staining was utilized to evaluate the levels of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2neu) in adherence to a standardized protocol established by the Pathology Department at Shiraz University of Medical Sciences. A confirmed case of HER2neu-amplified breast cancer was used as a positive control for HER2neu. A sample is considered ER negative if < 1% or 0%, tumors demonstrating 1% or more positive nuclear staining for ER or PR were categorized as ER-positive or PR-positive, respectively. In

cases where intermediate (2+) immunohistochemical expression of HER2neu was observed, subsequent testing using fluorescent in situ hybridization (FISH) was conducted to assess HER2neu gene amplification. The breast tumors were stratified into four subtypes based on ER, PR, and HER2neu expression: luminal A (ER-positive and/or PR-positive, HER2neu-negative), luminal B (ER-positive and/or PR-positive, HER2neu-positive), HER2neu+(ER-negative and PR-negative, HER2-positive), and triple-negative (TN) (ER-negative, PR-negative, and HER2neu-negative), following the criteria delineated by Carey [22].

Overall survival (OS) was defined as the period from the initial diagnosis of breast cancer until either death from any cause or the last recorded follow-up visit. Disease-free survival (DFS) was calculated as the duration from the date of surgery to the occurrence of the first metastasis or recurrence [23]. The TNM staging system for breast cancer was assessed according to the guidelines outlined in the seventh edition of the American Joint Committee on Cancer (AJCC).

### Statistical analysis

The normality of the distribution of continuous variables was tested using a one-sample Kolmogorov–Smirnov test. Continuous variables with a normal distribution were presented as mean (SD), while non-normal variables were reported as frequency (percentage). The means of two continuous normally distributed variables were compared using independent samples Student's T-test. When appropriate, frequencies of categorical variables were compared using Pearson Chi-square or Fisher's exact test. Overall survival (OS) and disease-free survival (DFS) were evaluated using the Kaplan–Meier analysis. Analyses were performed using SPSS statistical software (version 25), and a *P*-value of $<0.05$ was considered statistically significant.

## Results

Table 1 displays a comparative analysis of patients based on their body mass index (BMI) status. Among the 7134 breast cancer patients studied, 2026 (28.31%) had a BMI $<25$ kg/m2, 3045 (42.6%) fell within the

**Table 1** Comparative analysis of patient characteristics across body mass index (kg/m$^2$) status of studied patients

| | | BMI group | | | *P*-value |
|---|---|---|---|---|---|
| | | BMI<25 (*n*= 2026) | 25.0≤BMI<30.0 (*n*= 3045) | BMI≥30 (*n*=2063) | |
| Age at diagnosis,(Mean± SD) (year) | | 47.50±12.17 | 48.64±11.05 | 50.13±10.33 | *P* >0.05 |
| Menopausal status | | | | | <0.001 |
| Premenopausal | | 1107 (54.6%) | 1510 (49.5%) | 846 (41.1%) | |
| Postmenopausal | | 919(55.4%) | 1550 (50.5%) | 1217 (58.9%) | |
| Pathology Tumor Grade | 1 | 363 (19.4%) | 498 (17.7%) | 336 (17.6%) | 0.12 |
| | 2 | 1137 (60.8%) | 1739 (61.9%) | 1145 (59.9%) | |
| | 3 | 370 (19.8%) | 571 (20.3%) | 432 (22.6%) | |
| Axillary Type | ALND at first | 916 (45.2%) | 1357 (44.6%) | 924 (44.8%) | 0.82 |
| | SLNB only | 787 (38.8%) | 1230 (40.4%) | 823 (39.9%) | |
| | SLNB then ALND | 323 (15.9%) | 458 (15.0%) | 316 (15.3%) | |
| Stage | 1 | 403 (32.5%) | 582 (29.9%) | 380 (28.2%) | 0.08 |
| | 2 | 730 (58.9%) | 1172 (60.1%) | 820 (60.8%) | |
| | 3 | 107 (8.6%) | 195 (10.0%) | 149 (11.0%) | |
| Preoperative Chemotherapy | No | 1674 (81.1%) | 2574 (83.3%) | 1765 (84.0%) | 0.02 |
| | yes | 391 (18.9%) | 515 (16.7%) | 336 (16.0%) | |
| postoperative Chemotherapy | No | 309 (15.0%) | 416 (13.5%) | 272 (12.9%) | 0.14 |
| | yes | 1756 (85.0%) | 2673 (86.5%) | 1829 (87.1%) | |
| Axillary and Chest Radiotherapy | No | 541 (26.2%) | 700 (22.7%) | 442 (21.0%) | <0.001 |
| | yes | 1524 (73.8%) | 2389 (77.3%) | 1659 (79.0%) | |
| Hormone therapy | No | 495 (24.0%) | 725 (23.5%) | 534 (25.4%) | 0.26 |
| | Yes | 1570 (76.0%) | 2364 (76.5%) | 1567 (74.6%) | |
| Hormone receptor | Luminal A | 1089 (53.8%) | 1726 (56.7%) | 1223 (59.3%) | 0.14 |
| | Luminal B | 435 (21.5%) | 682 (22.4%) | 389 (18.9%) | |
| | Her2 | 210 (10.4%) | 304 (10%) | 223 (10.8%) | |
| | Triple Negative | 292 (14.6%) | 333 (10.9%) | 228 (11%) | |

range of 25.0 ≤ BMI < 30.0 kg/m2, and 2063 (29.1%) had a BMI of 30 kg/m2 or higher. The mean age at diagnosis was similar across the three BMI groups, but there was a tendency for older patients to be more prevalent in the obese group ($P > 0.05$). Median follow up times of studied patients were five years.

Premenopausal patients were more likely to have a lower BMI compared to postmenopausal patients, with almost half of the obese patients being in the postmenopausal period (58.9%). Menopausal status was significantly associated with BMI status ($P < 0.001$). The majority of patients were classified as grade 2 and stage 2 across the BMI categories ($P = 0.12$, $P = 0.08$, respectively).

The Luminal A molecular subtype was the most prevalent hormone receptor subtype across all BMI categories, while the Her2 molecular subtype positive was the least common hormone receptor subtype across all BMI categories ($P = 0.14$). The rate of patients undergoing axillary lymph node dissection (ALND) initially was higher compared to other Axillary Types across all BMI categories ($P = 0.82$). Hormone therapy was equally distributed among these three groups ($P = 0.26$). In all three groups, over 80% of patients did not receive preoperative chemotherapy ($P = 0.02$); however, postoperative chemotherapy was administered to over 80% of patients in all three groups ($P = 0.14$).

The highest proportion of patients undergoing axillary and chest radiotherapy had a BMI higher than 25 kg/m$^2$, while this proportion was lower in patients with a BMI below 25 kg/m$^2$ ($P < 0.001$).

Table 2 presents a comparative analysis of patient characteristics and menopausal status based on the BMI (kg/m2) status of the patients under study. Quadrantectomy (BCS) emerged as the most common type of surgery among both pre- and post-menopausal women in all three groups. Mastectomy was more prevalent among postmenopausal patients than premenopausal patients in all three groups ($P < 0.001$ for BMI < 25 and 25.0 ≤ BMI < 30.0 kg/m$^2$, $P = 0.6$ for patients with BMI ≥ 30 kg/m$^2$). Regardless of menopausal status, the majority of patients were classified as grade II based on BMI. Furthermore, stage 3 was more frequently observed in postmenopausal patients across all three groups ($P = 0.16$, $P = 0.17$, $P = 0.51$, respectively).

The incidence of multifocal breast tumors was higher in premenopausal patients compared to postmenopausal patients in all three BMI status groups. A statistically significant association was found between the presence of multifocal breast tumors and menopausal status across the three BMI status groups ($P = 0.004, < 0.001$, and 0.01, respectively).

A statistical examination of tumor grading across three defined categories indicated that the majority of premenopausal patients in all three groups were classified as grade II, regardless of BMI status. Conversely, postmenopausal in all three groups were predominantly classified as grade II. Notably, Grade III Permanent Pathology Tumors were more prevalent in premenopausal women compared to postmenopausal women in all three groups ($P < 0.001$, $P = 0.01$, and $P = 0.01$, respectively).

While the majority of patients did not exhibit tumor invasion across the three BMI categories, premenopausal patients displayed a higher prevalence of non-invasive tumors compared to postmenopausal patients. A statistically significant relationship was observed between the occurrence of various types of invasion and menopausal status in the studied population with a 25.0 ≤ BMI < 30.0 kg/m2 ($P = 0.03$). Vascular invasion was more frequently observed in postmenopausal patients across all three BMI categories. Both Vascular and Preneural invasion, as well as Lymphatic and Vascular invasion, displayed similar distributions based on menopausal status in all three BMI categories. Furthermore, a statistically significant correlation was noted between the occurrence of different invasion types and tumor subtypes ($P < 0.001$).

Axillary lymph node dissection (ALND) was the most common type of axillary surgery performed in postmenopausal patients within the BMI < 25 kg/m2 and 25.0 ≤ BMI < 30.0 kg/m2 groups. For postmenopausal patients with a BMI ≥ 30 kg/m$^2$, ALND then SLNB were the predominant types of axillary surgeries performed ($P = 0.56$). Conversely, a higher proportion of patients in the premenopausal period underwent SLNB alone, regardless of BMI status. A statistically significant correlation was identified between the type of axillary surgery and menopausal status within the studied population with a BMI of 25.0 ≤ BMI < 30.0 kg/m2 ($P = 0.002$).

The Luminal A hormone receptor subtype was prevalent among all breast cancer patients, irrespective of menopausal or BMI status, while Luminal B was more commonly found in premenopausal patients compared to postmenopausal patients across all three BMI groups. A statistically significant variance was noted in the distribution of hormone receptor subtypes based on menopausal status within the three BMI groups ($P < 0.001$ for patients with BMI < 25 kg/m2 and BMI 25.0 ≤ BMI < 30.0 kg/m2, and $P = 0.007$ for patients with BMI ≥ 30 kg/m$^2$, respectively).

Hormone therapy was provided to the majority of patients in all three groups regardless of menopausal status, with postmenopausal women receiving hormone therapy more frequently than premenopausal women across all BMI groups. A statistically significant relationship was found between hormone therapy and

**Table 2** Comparative analysis of patient characteristics and menopausal status according body mass index (kg/m2 ) status of studied patients

| | BMI<25 kg/m$^2$ | | | 25.0≤BMI< 30.0 kg/m2 | | | BMI≥30 kg/m$^2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre menopausal | Post menopausal | *P* value | Pre menopausal | Post menopausal | *P* value | Pre menopausal | Post menopausal | *P*-value |
| Mean age (SD) | 47.57 (8.27) | 66.12 (9.36) | | 49.31 (7.86) | 65.29 (8.855) | | 50.62 (7.56) | 64.67 (8.28) | |
| Surgery Type | | | | | | | | | |
| Quadrantectomy (BCS) | 664 (57.7%) | 436 (49.1%) | <0.001 | 991 (61.4%) | 849 (58.2%) | <0.001* | 585 (61.4%) | 718 (62.7%) | 0.06 |
| Mastectomy | 417 (36.1%) | 417 (46.9%) | | 508 (31.4%) | 553 (37.9%) | | 304 (31.9%) | 374 (32.6%) | |
| Quadrantectomy (BCS) ,then Mastectomy | 69 (6.0%) | 28 (3.1%) | | 111 (6.9%) | 49 (3.4%) | | 111 (6.9%) | 49 (3.4%) | |
| Stage | | | | | | | | | |
| 1 | 242 (33.5%) | 158 (31.7%) | 0.16 | 313 (29.4%) | 267 (30.8%) | 0.17 | 192 (29.4%) | 184 (26.9%) | 0.51 |
| 2 | 427 (59.1%) | 288 (57.8%) | | 655 (61.6%) | 503 (58.1%) | | 392 (60.1%) | 420 (61.4%) | |
| 3 | 53 (7.3%) | 52 (10.4%) | | 95 (8.9%) | 96 (11.1%) | | 68 (10.4%) | 80 (11.7%) | |
| Permanent Pathology Multifocal | | | | | | | | | |
| No | 1049 (91.2%) | 833 (94.6%) | 0.004 | 1479 (91.9%) | 1387 (95.7%) | <0.001 | 867 (91.4%) | 1070 (94.1%) | 0.01 |
| Yes | 101 (8.8%) | 48 (5.4%) | | 867 (8.1%) | 1070 (4.3%) | | 82 (8.6%) | 67 (5.9%) | |
| Permanent Pathology Tumor Grade | | | | | | | | | |
| 1 | 174 (16.7%) | 184 (23.1%) | <0.001 | 232 (15.7%) | 255 (19.5%) | 0.01 | 149 (17.3%) | 185 (17.8%) | 0.01 |
| 2 | 638 (61.3%) | 480 (60.2%) | | 921 (62.5%) | 806 (61.7%) | | 491 (57.0%) | 645 (62.2%) | |
| 3 | 228 (21.9%) | 134 (16.8%) | | 321 (21.8%) | 246 (18.8%) | | 222 (25.8%) | 207 (20.0%) | |
| Invasion | | | | | | | | | |
| Non | 587 (51.0 %) | 414 (47.0 %) | 0.06 | 756 (47%) | 626 (43.2) | 0.03 | 439 (46.3%) | 499 (43.9%) | 0.3 |
| Vascular | 271 (23.6 %) | 217 (24.6 %) | | 392 (24.3%) | 406 (28.0%) | | 239 (25.2%) | 315 (27.7%) | |
| Preneural | 75 (6.5 %) | 76 (8.6 %) | | 120 (7.5%) | 110 (7.6%) | | 68 (7.2%) | 80 (7.0%) | |
| Both of them | 178 (15.5 %) | 155 (17.6 %) | | 290 (18.0%) | 278 (19.2%) | | 170 (17.9%) | 217 (19.1%) | |
| Lymphatic , Vascular | 39 (3.4 %) | 19 (2.2 %) | | 52 (3.2%) | 30 (2.1%) | | 33 (3.5%) | 26 (2.3%) | |
| **Axillary Type** | | | | | | | | | |
| ALND at first | 488 (42.7%) | 403 (47.5%) | 0.07 | 660 (41.3%) | 678 (47.8%) | 0.002 | 381 (40.5%) | 442 (39.9%) | 0.56 |
| SLNB | 458 (40.1%) | 323 (38.0%) | | 682 (42.7%) | 543 (38.3%) | | 151 (16.0%) | 162 (14.6%) | |
| SLNB then ALND | 197 (17.2%) | 123 (14.5%) | | 255 (16.0%) | 198 (14.0%) | | 409 (43.5%) | 503 (45.4%) | |
| **Hormone receptor** | | | | | | | | | |
| Luminal A | 564 (49.0%) | 406 (46.1%) | <0.001 | 772 (48.0%) | 717 (49.4%) | <0.001 | 449 (47.3%) | 579 (50.9%) | 0.007 |
| Luminal B | 211 (18.3%) | 129 (14.6%) | | 288 (17.9%) | 187 (12.9%) | | 142 (15.0%) | 149 (13.1%) | |
| Her2 | 80 (7.0%) | 71 (8.1%) | | 143 (8.9%) | 135 (9.3%) | | 102 (10.7%) | 81 (7.1%) | |
| Triple Negative | 130 (11.3%) | 88 (10.0%) | | 172 (10.7%) | 110 (7.6%) | | 106 (11.2%) | 113 (9.9%) | |
| **Preoperative Chemotherapy** | | | | | | | | | |
| No | 892 (77.6%) | 753 (85.5%) | <0.001 | 1300 (80.7%) | 1248 (86.1%) | <0.001 | 776 (81.8%) | 976 (85.8%) | 0.01 |
| Yes | 258 (22.4%) | 128 (14.5%) | | 310 (19.3%) | 202 (13.9%) | | 173 (18.2%) | 161 (14.2%) | |
| **Postoperative Chemotherapy** | | | | | | | | | |
| No | 154 (13.4%) | 152 (17.3%) | 0.01 | 185 (11.5%) | 228 (15.7%) | <0.001 | 106 (11.2%) | 164 (14.4%) | 0.01 |
| Yes | 996 (86.6%) | 729 (82.7%) | | 1425 (88.5%) | 1222 (84.3%) | | 843 (88.8%) | 973 (85.6%) | |
| Radiotherapy postoperative | | | | | | | | | |
| No | 324 (36.8%) | 204 (17.7%) | <0.001 | 410 (28.3%) | 280 (17.4%) | <0.001 | 272 (23.9%) | 162 (17.1%) | <0.001 |
| Yes | 557 (63.2%) | 946 (82.3%) | | 1040 (71.7%0 | 1330 (82.6%) | | 865 (76.1%) | 787 (82.9%) | |
| Hormone therapy | | | | | | | | | |
| No | 278 (24.2%) | 211(24.0%) | 0.9 | 392 (24.3%) | 328 (22.6%) | 0.26 | 268 (28.2%) | 261 (23.0%) | 0.006 |
| Yes | 872 (75.8%) | 670 (76.0%) | | 1218 (75.7%) | 1122 (77.4%) | | 681 (71.8%) | 876 (77.0%) | |

**Table 3** Cox proportional hazard model for overall survival in all patients

| | Single Cox regression | | | Multiple Cox regression | | |
|---|---|---|---|---|---|---|
| **Variables** | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** |
| BMI<25(base) kg/m$^2$ | - | - | - | **-** | **-** | **-** |
| 25<BMI<30 | 0.89 | 0.66 – 1.19 | 0.42 | **2.89** | **1.19- 7.07** | **0.02** |
| BMI>=30 | 1.15 | 0.85-1.55 | 0.36 | **2.97** | **1.19-7.42** | **0.02** |
| Tumor Type (base= Invasive ductal carcinoma) | | | | | | |
| Invasive lobular | 0.35 | 0.5-2.53 | 0.3 | | | |
| Medullary | - | - | 0.96 | | | |
| Mucinous | - | - | 0.97 | | | |
| Papillary | - | - | 0.98 | | | |
| TNM Stage(base= Stage1) | | | | | | |
| Stage2 | 1.63 | 0.8 -3.23 | 0.17 | | | |
| Stage 3 | 2.74 | 1.14 – 6.59 | 0.02 | | | |
| Permanent Pathology Tumor grade (base= Grade1) | | | | | | |
| Grade 2 | 1.81 | 0.81-4.04 | 0.15 | **1.17** | **0.48-2.88** | **0.73** |
| Grade 3 | 3.71 | 1.62-8.47 | 0.002 | **2.26** | **0.88-5.81** | **0.09** |
| Age at diagnosis | 1.02 | 0.99-1.03 | 0.1 | **1.02** | **0.99- 1.04** | **0.09** |
| Menopause status(base=Premenopause) | | | | | | |
| Postmenopausal | 1.27 | 0.6- 2.69 | 0.54 | | | |
| Not identified | 0.74 | 0.47-1.19 | 0.21 | | | |
| Surgery Type (base= Quadrantectomy (BCS)) | | | | | | |
| Mastectomy | 1.59 | 0.98-2.59 | 0.06 | **1.19** | **0.61- 2.32** | **0.62** |
| Quadrantectomy (BCS) , Mastectomy | 6.11 | 3.41-10.93 | <0.001 | **2.87** | **1.43 -5.78** | **0.003** |
| Tumor size (base = Tumor size <2 cm) | | | | | | |
| 2-5 cm | 1.64 | 0.94-2.87 | 0.08 | | | |
| 5 cm< | 1.79 | 0.70-4.59 | 0.22 | | | |
| Invasion (base= none) | | | | | | |
| Vascular | 1.34 | 0.79-2.28 | 0.27 | | | |
| Preneural | 0.36 | 0.09-1.52 | 0.17 | | | |
| Both of them | 1.81 | 1.06-3.09 | 0.03 | | | |
| Lymphatic, Vascular | 0.96 | 0.13-7.02 | 0.96 | | | |
| Margin | 0.76 | 0.19-3.11 | 0.71 | | | |
| Axillary Type (base = AND) | | | | | | |
| SLNB | 0.33 | 0.18 - 0.62 | 0.001 | **0.36** | **0.10-1.23** | **0.10** |
| SLNB then ALND | 1.56 | 0.95 - 12.56 | 0.07 | **1.87** | **1.03- 3.40** | **0.04** |
| Hormone receptor (base= Luminal A) | | | | | | |
| Luminal B | 0.78 | 0.39- 1.55 | 0.48 | | | |
| Her 2 | 2.02 | 1.10- 3.70 | 0.02 | | | |
| Triple Negative | 1.83 | 1.03- 3.25 | 0.04 | | | |
| Estrogen Receptor + | 2.01 | 1.29- 3.14 | 0.002 | | | |
| Proegstrone Receptor + | 2.10 | 1.36 - 3.25 | 0.001 | | | |
| Hormone receptor | 1.06 | 0.66 - 1.71 | 0.80 | | | |
| Preoperative Chemotherapy | 1.95 | 1.20-3.15 | 0.01 | | | |
| Postoperative Chemotherapy | 0.71 | 0.39 - 1.29 | 0.26 | | | |
| Axillary and Chest Radiotherapy | 1.07 | 0.63-1.83 | 0.80 | | | |
| Intraoperative radiation | 0.05 | 0.001- 3.48 | 0.20 | | | |
| Hormone therapy | 0.54 | 0.35-0.85 | 0.01 | | | |

**Table 4** Cox proportional hazard model for disease free survival in all patients

| | Single Cox regression | | | Multiple regression[a] | | |
|---|---|---|---|---|---|---|
| **Variables** | **HR** | **95% CI** | ***P* value** | **HR** | **95% CI** | ***P* value** |
| BMI<25 (base) | - | - | - | | | |
| 25<BMI<30 | 0.94 | 0.77-1.16 | 0.59 | | | |
| BMI>=30 | 1.02 | 0.81-1.27 | 0.87 | | | |
| Tumor type (base= Invasive ductal carcinoma) | | | | | | |
| Invasive lobular | 1.23 | 0.8 -1.91 | 0.35 | | | |
| Medullary | 0.55 | 0.26 – 1.16 | 0.12 | | | |
| Mucinous | 0.16 | 0.02 – 1.54 | 0.07 | | | |
| Papillary | 0.42 | 0.06 – 2.97 | 0.38 | | | |
| TNM Stage(base=stage 1) | | | | | | |
| Stage2 | 1.21 | 0.93 – 1.58 | 0.15 | **0.40** | **0.28-0.58** | **<0.001** |
| Stage 3 | 3.14 | 2.30 – 4.30 | <0.001 | **0.55** | **0.41-0.73** | **<0.001** |
| Permanent Pathology Tumor(Grade 1) | | | | | | |
| Grade 2 | 1.40 | 1.07 – 1.85 | 0.01 | | | |
| Grade 3 | 1.80 | 1.33 – 2.44 | <0.001 | | | |
| Age at diagnosis | 0.99 | 0.982- 0.998 | 0.01 | 0.99 | 0.98 -1.00 | 0.08 |
| Menopausal status (base = Premenopouse) | | | | | | |
| Postmenopausal | 1.62 | 1.19 -2.18 | 0.002 | | | |
| Not identified | 1.2 | 1.00-1.44 | 0.04 | | | |
| Surgery Type (base= Quadrantectomy (BCS)) | | | | | | |
| Mastectomy | 2.17 | 1.8-2.61 | <0.001 | **0.31** | **0.22- 0.45** | **<0.001** |
| Quadrantectomy (BCS) | 4.26 | 3.24 -5.60 | <0.001 | **0.47** | **0.33- 0.68** | **<0.001** |
| Tumor size(base <2 cm ) | | | | | | |
| 2-5 cm | 1.34 | 1.08-1.66 | 0.007 | | | |
| 5 cm < | 1.82 | 1.28-2.60 | 0.001 | | | |
| Permanent Pathology Tumor (base = Grade1) | | | | | | |
| Grade 2 | 1.4 | 1.07-1.85 | 0.01 | | | |
| Grade 3 | 1.8 | 1.33 - 2.44 | <0.001 | | | |
| margin | 1.30 | 0.85-1.99 | 0.23 | | | |
| Axillary Type (base = AND) | | | | | | |
| SLNB | 0.32 | 0.26-0.40 | <0.001 | **1.35** | **1.02-1.78** | **0.03** |
| SLNB then ALND | 0.68 | 0.54-0.87 | **0.002** | **0.49** | **0.32- 0.75** | **0.001** |
| Hormone receptor (base= Luminal A) | | | | | | |
| Luminal B | 1.01 | 0.79-1.28 | 0.94 | **0.86** | **0.63-1.18** | **0.35** |
| Her2 | 1.49 | 1.15-1.93 | 0.003 | **1.37** | **0.97-1.92** | **0.07** |
| Triple Negative | 1.21 | 0.94-1.57 | 0.14 | **1.40** | **0.98-1.99** | **0.06** |
| Estrogen Receptor + | 1.32 | 1.09-1.60 | 0.004 | | | |
| Progesterone Receptor + | 1.26 | 1.05-1.51 | 0.01 | | | |
| Hormone receptor + | 1.13 | 0.94-1.36 | 0.18 | | | |
| Preoperative chemotherapy | 2.4 | 1.98- 2.87 | <0.001 | | | |
| Postoperative Chemotherapy | 0.58 | 0.47-0.72 | <0.001 | **1.74** | **1.24-2.44** | **0.001** |
| Postoperative Radiotherapy | 1.06 | 0.86-1.31 | 0.57 | | | |
| Intraoperative radiation | 0.58 | 0.35-0.95 | 0.03 | | | |
| Hormone therapy | 0.81 | 0.67-0.98 | 0.02 | | | |
| Invasion (base= none) | | | | | | |
| Vascular | 1.40 | 1.13-1.74 | 0.002 | 1.05 | 0.77- 1.42 | 0.76 |
| Preneural | 0.96 | 0.66-1.39 | 0.82 | 1.12 | 0.62- 2.02 | 0.70 |
| Both of them | 1.71 | 1.37-2.14 | <0.001 | **1.40** | **1.04-1.88** | **0.03** |
| Lymphatic Vascular | 2.55 | 1.59 – 4.09 | <0.001 | **2.01** | **1.15-3.52** | **0.01** |

[a] Backward Stepwise (Wald)

**Table 5** Overall survival and disease survival rate for BMI categories across menopausal status in TNM stage

| **Overall Survival times (%)** | | | | | | **Disease Survival times (%)** | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Stage 1** | | | | | | | | | |
| | | **1** | **3** | **5** | ***P* value*** | **1** | **3** | **5** | ***P* value*** |
| Pre-menopausal | BMI<25 | 99 | 99 | 91 | 0.83 | 97 | 96 | 92 | 0.31 |
| | 25.0≤BMI< 30.0 | 100 | 99 | 95 | | 96 | 93 | 89 | |
| | BMI ≥30 | 100 | 99 | 90 | | 97 | 96 | 94 | |
| Post-menopausal | BMI<25 | 100 | 100 | 85 | 0.91 | 99 | 97 | 94 | 0.25 |
| | 25.0≤BMI< 30.0 | 100 | 100 | 91 | | 98 | 97 | 94 | |
| | BMI ≥30 | 99 | 98 | 96 | | 96 | 95 | 90 | |
| **Stage 2** | | | | | | | | | |
| Pre-menopausal | BMI<25 | 100 | 98 | 88 | 0.43 | 96 | 92 | 88 | 0.35 |
| | 25.0≤BMI< 30.0 | 100 | 99 | 93 | | 98 | 93 | 91 | |
| | BMI ≥30 | 99 | 99 | 81 | | 96 | 91 | 88 | |
| Post-menopausal | BMI<25 | 100 | 100 | 85 | 0.81 | 94 | 91 | 87 | 0.09 |
| | 25.0≤BMI< 30.0 | 100 | 98 | 91 | | 96 | 94 | 92 | |
| | BMI ≥30 | 100 | 99 | 90 | | 96 | 95 | 92 | |
| **Stage 3** | | | | | | | | | |
| Pre-menopausal | BMI<25 | 100 | 100 | 100 | 0.05 | 92 | 82 | 70 | 0.82 |
| | 25.0≤BMI< 30.0 | 98 | 97 | 70 | | 88 | 82 | 78 | |
| | BMI ≥30 | 100 | 97 | 78 | | 91 | 85 | 81 | |
| Post-menopausal | BMI<25 | 100 | 98 | 63 | 0.42 | 90 | 86 | 82 | 0.67 |
| | 25.0≤BMI< 30.0 | 99 | 98 | 80 | | 88 | 81 | 80 | |
| | BMI ≥30 | 100 | 97 | 79 | | 92 | 87 | 85 | |

* Wilcoxon (Gehan) test

menopausal status in patients with a higher BMI of ≥ 30 kg/m$^2$ ($P=0.006$).

Radiotherapy was administered to a significant percentage of patients in all three BMI groups, with a higher prevalence among postmenopausal patients in all three groups ($P<0.001$ in all groups). Postoperative chemotherapy was utilized in a considerable number of patients across all three groups, but it was more common among premenopausal patients in all three BMI groups ($P=0.01$, $P<0.001$, $P=0.01$ in the three groups, respectively). Preoperative chemotherapy was not a common treatment regardless of the patients' BMI status. Preoperative chemotherapy was more frequently administered to premenopausal patients in all three BMI groups ($P<0.001$ in patients with BMI < 25 kg/m2 and BMI 25.0 ≤ BMI < 30.0 kg/m2, and $P=0.01$ in patients with BMI ≥ 30 kg/m$^2$, respectively).

According to Table 3, when BMI was considered as a quantitative variable, a significant inverse correlation was observed between higher BMI and shorter overall survival rates among patients (HR = 3.54, 95% CI = 1.69–7.41; $P=0.001$). However, the association between BMI and shorter disease-free survival rates was not statistically significant (HR = 1.01, 95% CI = 0.90–1.13; $P=0.86$).

In the univariate Cox regression model, normal BMI was associated with higher survival rates, although this association was not statistically significant (HR = 0.89, 95% CI = 0.66–1.19; $P=0.42$). Conversely, a BMI of 30 or higher was associated with lower survival rates, but this association was also not statistically significant (HR = 1.15, 95% CI = 0.85–1.55; $P=0.36$).

Higher age (HR = 1.02, 95% CI = 0.99–1.03; $P=0.10$), mastectomy and quadrantectomy compared to quadrantectomy alone (HR = 1.59, 95% CI = 0.98–2.59; $P=0.06$ and HR = 6.11, 95% CI = 3.41–10.93; $P<0.001$, respectively), permanent pathology tumor grades 2 and 3 (HR = 1.81, 95% CI = 0.81–4.04; $P=0.15$ and HR = 3.71, 95% CI = 1.62–8.47; $P=0.002$, respectively), sentinel lymph node biopsy followed by axillary lymph node dissection (HR = 1.56, 95% CI = 0.95–12.56; $P=0.07$), and stages 2 and 3 (HR stage 2 = 1.63, 95% CI = 0.80–3.23; $P=0.17$ and HR stage 3 = 2.74, 95% CI = 1.14–6.59; $P=0.02$) were associated with lower survival rates. However, sentinel lymph node biopsy alone (HR = 0.33, 95% CI = 0.18–0.62; $P=0.001$) was associated with higher survival rates. Additionally, increasing tumor size was associated with lower survival rates (HR2-5 = 1.64, 95% CI = 0.94–2.87; $P=0.08$ and HR < 5 = 1.79, 95% CI = 0.70–4.59; $P=0.22$).

Her2 and Triple Negative molecular subtypes were significantly associated with lower survival rates among patients (HR Her2 = 2.02, 95% CI = 1.10–3.70; $P = 0.02$, HR Triple Negative = 1.83, 95% CI = 1.03–3.25; $P = 0.04$). In contrast, the Luminal B subtype did not exhibit a significant effect on the survival of the studied patients.

The presence of vascular invasion (HR = 1.34, 95% CI = 0.79–2.28; $P = 0.27$) and both vascular and perineural invasion (HR = 1.81, 95% CI = 1.06–3.09; $P = 0.03$) were significantly associated with lower survival rates. However, the presence of perineural invasion alone was associated with higher survival rates (HR = 0.36, 95% CI = 0.09–1.52; $P = 0.17$). Neither vascular invasion nor lymphatic or vascular margin invasion had a significant impact on survival rates.

Positive estrogen receptor (HR = 2.01, 95% CI = 1.29–3.14; $P = 0.002$) and positive progesterone receptor (HR = 2.10, 95% CI = 1.36–3.25; $P = 0.001$) were significantly associated with lower survival rates. However, positive hormone receptors did not significantly affect overall survival (HR = 1.06, 95% CI = 0.66–1.71; $P = 0.80$).

Preoperative chemotherapy was significantly associated with lower survival rates among patients (HR = 1.95, 95% CI = 1.20–3.15; $P = 0.01$). However, postoperative chemotherapy (HR = 0.71, 95% CI = 0.39–1.29; $P = 0.26$), axillary and chest radiotherapy (HR = 1.07, 95% CI = 0.63–1.83; $P = 0.80$), and intraoperative radiation (HR = 0.05, 95% CI = 0.001–3.48; $P = 0.20$) were not significantly correlated with overall survival rates. Conversely, hormone therapy was significantly associated with higher survival rates (HR = 0.54, 95% CI = 0.35–0.85; $P = 0.01$).

In the final multivariate Cox proportional hazards regression analysis using a backward selection method, BMI status, permanent pathology tumor grade, surgery type, and axillary type were retained as significant predictors. The effects of these predictors on overall survival rates were similar to those observed in the univariate Cox regression analysis (Table 3).

As shown in Table 4, in the univariate Cox regression model, BMI status did not significantly impact disease-free survival rates among patients. Medullary (HR = 0.55, 95% CI = 0.26–1.16; $P = 0.12$) and mucinous (HR = 0.16, 95% CI = 0.02–1.54; $P = 0.07$) tumor types

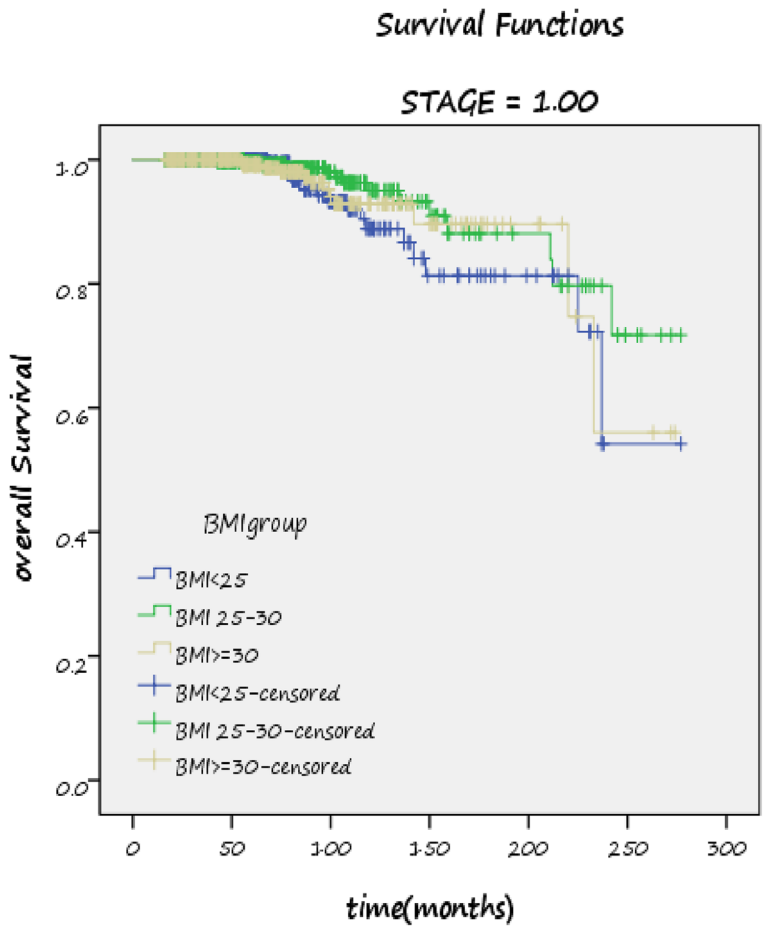


**Fig. 1** OS times-based patient's BMI status among patients in premenopausal period in Stage 1

were associated with higher disease-free survival rates. Invasive lobular and papillary tumor types did not significantly affect disease-free survival.

Tumor stages 2 and 3 (HR stage 2 = 1.21, 95% CI = 0.93–1.58; $P = 0.15$ and HR stage 3 = 3.14, 95% CI = 2.30–4.30; $P < 0.001$) were associated with lower disease-free survival rates. Permanent pathology tumor grades 2 and 3 (HR = 1.40, 95% CI = 1.07–1.85; $P = 0.01$ and HR = 1.80, 95% CI = 1.33–2.44; $P < 0.001$, respectively) were also associated with lower disease-free survival rates. Conversely, higher patient age was associated with higher disease-free survival rates (HR = 0.99, 95% CI = 0.982–0.998; $P = 0.01$).

Sentinel lymph node biopsy followed by axillary lymph node dissection (HR = 0.68, 95% CI = 0.54–0.87; $P = 0.002$) and sentinel lymph node biopsy alone (HR = 0.32, 95% CI = 0.26–0.40; $P < 0.001$) were associated with higher disease-free survival rates. Increasing tumor size (HR2-5 = 1.34, 95% CI = 1.08–1.66; $P = 0.007$ and HR < 5 = 1.82, 95% CI = 1.28–2.60; $P = 0.001$) was associated with lower disease-free survival rates. Mastectomy and both quadrantectomy and mastectomy compared to quadrantectomy alone were associated with lower disease-free survival rates (HR = 2.17, 95% CI = 1.80–2.61; $P < 0.001$ and HR = 4.26, 95% CI = 3.24–5.60; $P < 0.001$, respectively).

Her2 and Triple Negative molecular subtypes were significantly associated with lower disease-free survival rates among patients (HR Her2 = 1.49, 95% CI = 1.15–1.93; $P = 0.003$, HR Triple Negative = 1.21, 95% CI = 0.94–1.57; $P = 0.14$). However, the Luminal B molecular subtype did not exhibit a significant correlation with disease-free survival rates.

Positive estrogen receptor (HR = 1.32, 95% CI = 1.09–1.60; $P = 0.004$), positive progesterone receptor (HR = 1.26, 95% CI = 1.05–1.51; $P = 0.01$), and hormone receptors (HR = 1.13, 95% CI = 0.94–1.36; $P = 0.18$) were significantly associated with lower disease-free survival rates. Conversely, postoperative chemotherapy (HR = 0.58, 95% CI = 0.47–0.72; $P < 0.001$), hormone therapy (HR = 0.81, 95% CI = 0.67–0.98; $P = 0.02$), and intraoperative radiation (HR = 0.58, 95% CI = 0.35–0.95;

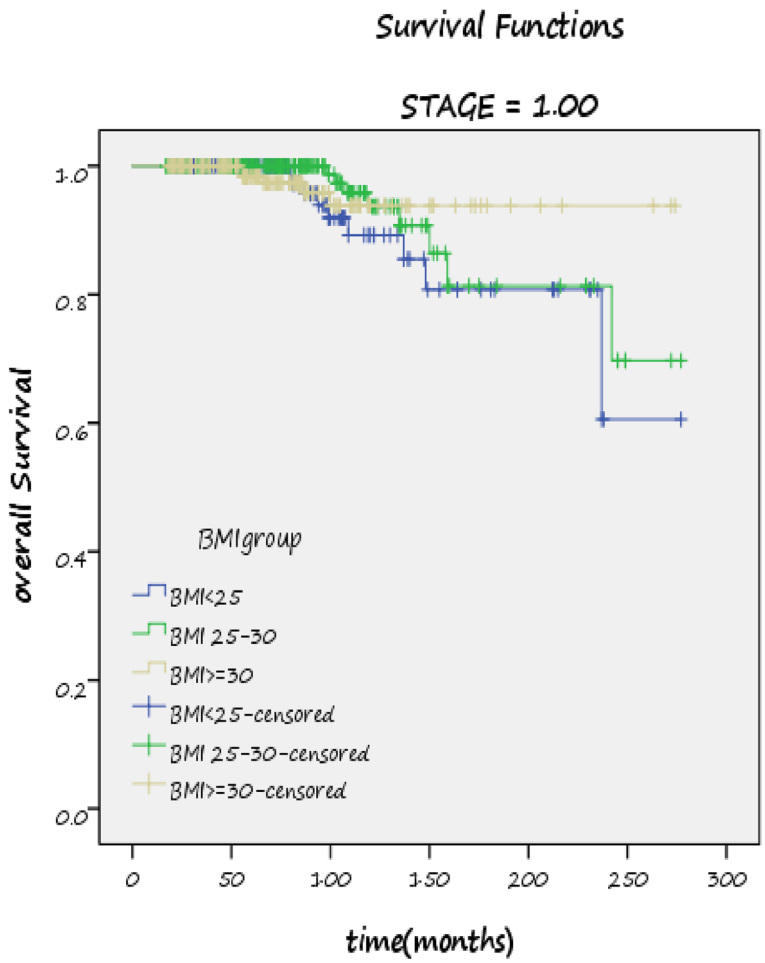


**Fig. 2** OS times-based patient's BMI status among patients in post-menopausal period in Stage 1

$P=0.03$) were significantly associated with higher disease-free survival rates. However, preoperative chemotherapy was significantly associated with lower disease-free survival rates (HR = 2.4, 95% CI = 1.98–2.87; $P<0.001$), while postoperative radiotherapy did not exhibit a significant correlation with disease-free survival.

In the final multivariate Cox proportional hazards regression analysis using a backward selection method, TNM tumor stage, age at diagnosis, surgery type, axillary type, postoperative chemotherapy, and hormone receptors were retained as significant predictors. TNM stages 2 and 3 (HR stage 2 = 0.4, 95% CI = 0.28–0.58; $P<0.001$, HR stage 3 = 0.55, 95% CI = 0.41–0.73; $P<0.001$), mastectomy (HR = 0.31, 95% CI = 0.22–0.45; $P<0.001$), and quadrantectomy (HR = 0.47, 95% CI = 0.33–0.68; $P<0.001$) were significantly associated with higher disease-free survival rates. Conversely, postoperative chemotherapy (HR = 1.74, 95% CI = 1.24–2.44; $P=0.001$) was significantly associated with lower disease-free survival rates.

Sentinel lymph node biopsy axillary type (HR = 1.35, 95% CI = 1.02–1.78; $P=0.03$) was significantly associated with lower disease-free survival rates, while sentinel lymph node biopsy followed by axillary lymph node dissection (HR = 0.49, 95% CI = 0.32–0.75; $P=0.001$) was significantly associated with higher disease-free survival rates. The Luminal B, Her2, and Triple Negative hormone receptor subtypes did not significantly affect disease-free survival rates (Table 4).

Table 5 provides a summary of the 1-, 3-, and 5-year OS and DFS outcomes for various BMI categories based on menopausal status in different TNM stages.

In stage 1, all three BMI groups showed OS rates above 99% at 1 and 3 years in premenopausal patients (Fig. 1). For post-menopausal patients, those with BMI < 25 kg/m$^2$ and BMI 25.0 ≤ BMI < 30.0 kg/m$^2$ categories displayed exceptional 100% OS rates at 1 and 3 years. Additionally, post-menopausal patients with BMI ≥ 30 kg/m$^2$ exhibited OS rates of 99% and 98% at 1 and 3 years, respectively (Fig. 2). Irrespective of menopausal status, all patients across all BMI categories demonstrated OS rates of ≥ 85% at 5 years in TNM stage 1. The OS outcomes for BMI categories based on menopausal status in stage 1 did not show any statistically significant differences ($P=0.83$ in premenopausal and $P=0.91$ in postmenopausal women).

Moving to stage 2, patients in all BMI categories, regardless of menopausal status, exhibited OS rates above 98%

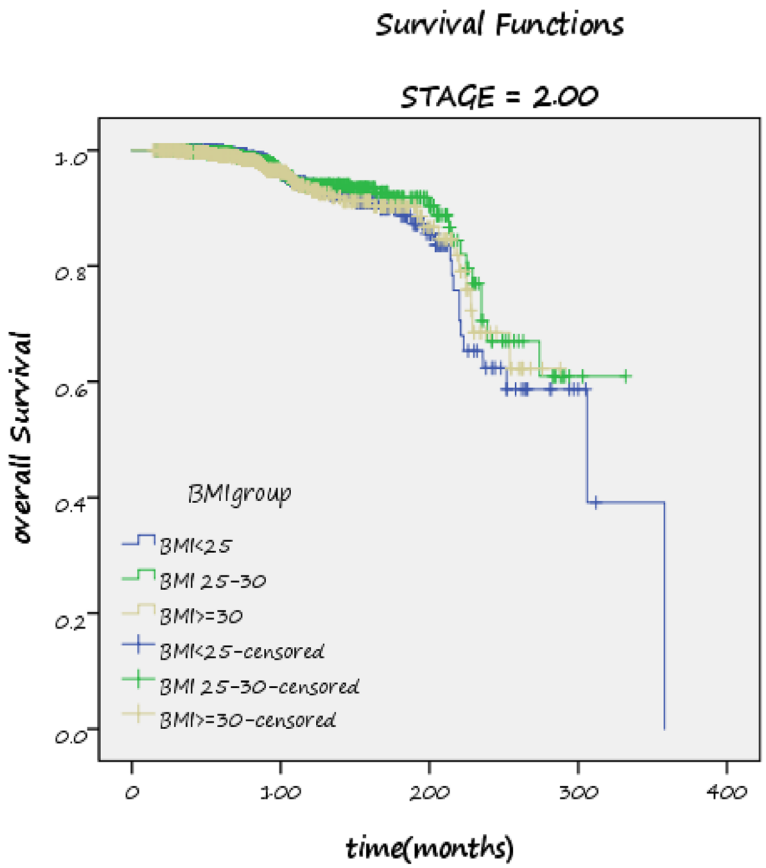


**Fig. 3** OS times-based patient's BMI status among patients in premenopausal period in stage 2

for 1, 3, and 5 years. Notably, postmenopausal patients with BMI less than 25 kg/m$^2$ exhibited OS rates of 85% at 5 years (Figs. 3 and 4). The OS outcomes for BMI categories based on menopausal status in stage 2 did not reveal any statistically significant variations ($P=0.43$ in premenopausal women and $P=0.81$ in postmenopausal women).

In TNM stage 3, premenopausal patients categorized as BMI < 25 displayed exceptional 100% OS rates over 1, 3, and 5 years. Patients in the other two BMI categories in the premenopausal group showed OS rates exceeding 97% at 1 and 3 years of follow-up. Moreover, premenopausal patients in the remaining two BMI categories demonstrated OS rates of 70% and 78% at the 5-year mark in stage 3 (Fig. 5). During this stage, all three BMI groups exhibited OS rates surpassing 97% at 1 and 3 years in post-menopausal patients. Post-menopausal patients in the BMI < 25 category showed a 63% OS rate at the 5-year mark. Additionally, post-menopausal patients in the other two BMI categories displayed OS rates of 80% and 79% at 5 years in stage 3, respectively (Fig. 6). The OS outcomes for BMI categories based on menopausal status in stage 2 did not yield statistically significant differences ($P=0.05$ in premenopausal and $P=0.42$ in postmenopausal women).

In stage 1, all three BMI groups exhibited DFS rates of 89% or higher for 1, 3, and 5 years, irrespective of menopausal status (Figs. 7 and 8). The DFS outcomes for BMI categories across menopausal status in TNM stage 1 did not show statistically significant differences ($P=0.31$ in premenopausal women and $P=0.25$ in postmenopausal women).

Moving to stage 2, all three BMI groups demonstrated DFS rates exceeding 90% for 1 and 3 years, regardless of menopausal status (Figs. 9 and 10). Premenopausal patients with a BMI between 25.0 ≤ BMI < 30.0 kg/m2 exhibited a 91% DFS rate over 5 years. Patients in the other two BMI categories achieved an 88% DFS rate over 5 years (Fig. 9). Postmenopausal patients with BMI between 25.0 ≤ BMI < 30.0 and BMI ≥ 30 categories showed 92% DFS rates over 5 years, while patients with a BMI > 25 kg/m$^2$ had an 87% DFS rate over the same period (Fig. 10). Similar to stage 1, DFS outcomes for BMI categories across menopausal status in TNM stage 2 were not statistically significant ($P=0.35$ in premenopausal women and $P=0.25$ in postmenopausal women).

In stage 3, patients across all BMI categories, irrespective of menopausal status, exhibited DFS rates higher than 90% for 1 year. Notably, patients with a BMI of

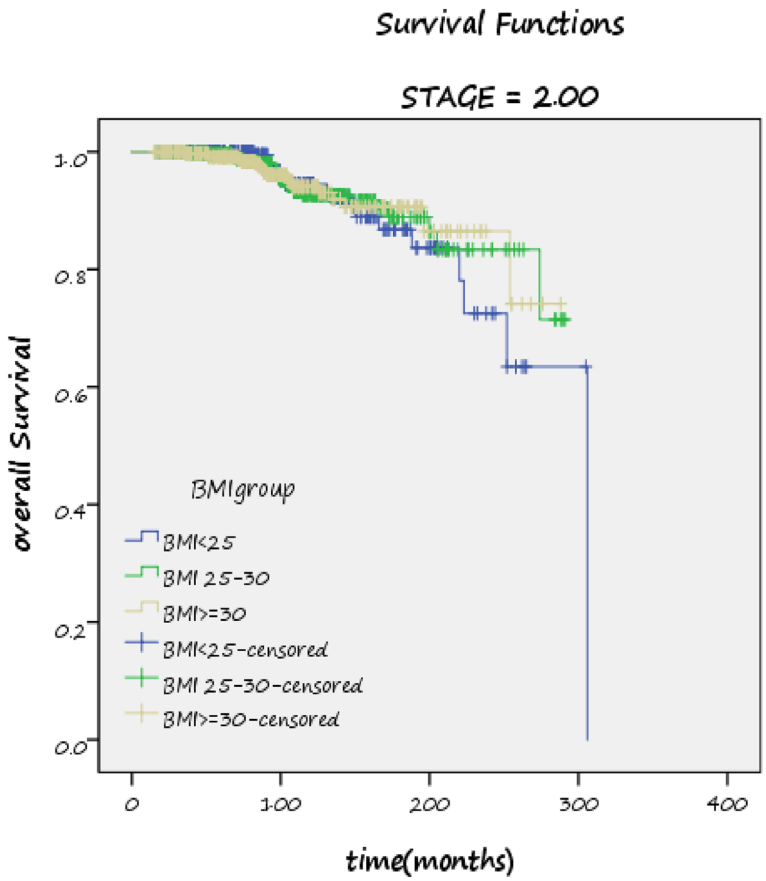


**Fig. 4** OS times-based patient's BMI status among patients in post-menopausal period in stage 2

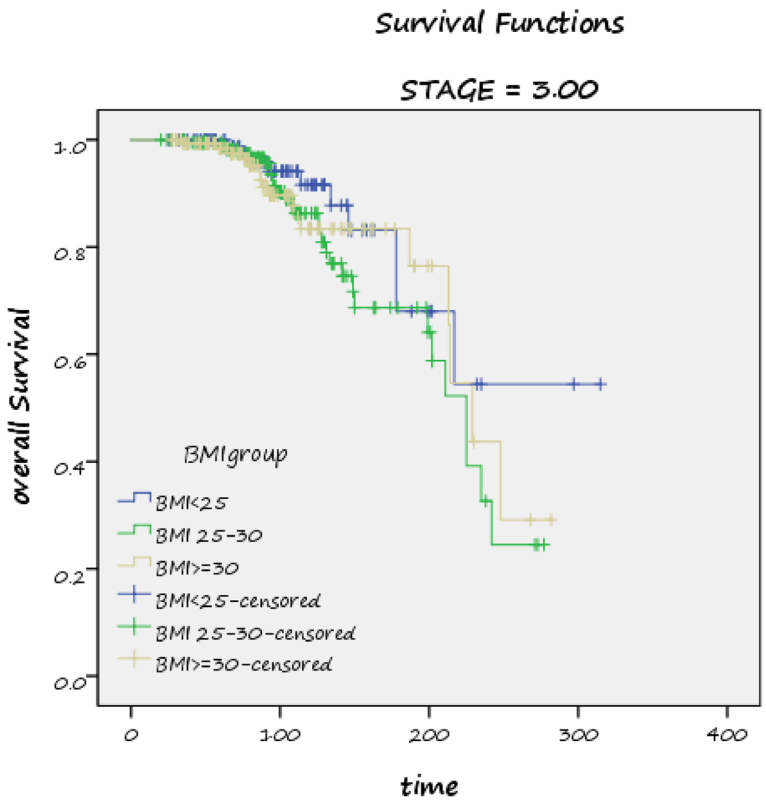


**Fig. 5** OS times-based patient's BMI status among patients in premenopausal period in stage 3

$25.0 \leq \text{BMI} < 30.0$ kg/m$^2$ showed an 88% DFS rate in the first year, regardless of menopausal status. Furthermore, all three BMI categories displayed DFS rates exceeding 80% for 3 years, independent of menopausal status (Figs. 11 and 12). Specifically, premenopausal patients in the BMI $\geq 30$ kg/m$^2$ category showed an 81% DFS rate over 5 years. Patients in the other two BMI categories demonstrated DFS rates of 70% and 78% over 5 years in TNM stage 3 (Fig. 11). As in the previous stages, DFS outcomes for BMI categories across menopausal status in TNM stage 3 did not yield statistically significant differences ($P=0.82$ in premenopausal women and $P=0.67$ in postmenopausal women).

## Discussion

Obesity is a significant factor in the development of several prevalent diseases such as cardiovascular diseases, diabetes, and cancers [24]. Evidence is accumulating regarding the association between obesity and the early onset, recurrence, and elevated risk of cancer-related mortality, whether in terms of susceptibility or prevention. The influence of obesity on the prognosis of breast cancer has been extensively documented in Western nations, although conflicting perspectives exist [25, 26]. To bridge this knowledge gap, we undertook a retrospective study to investigate the correlation between obesity and the prognosis of breast cancer.

In our investigation, we observed a correlation between the elevated incidence of breast cancer and a high BMI, possibly attributable to metabolic and endocrine alterations [27]. Obesity could accentuate estrogen production, instigate chronic subclinical inflammation, and elevate the presence of proinflammatory proteins in the bloodstream, thereby promoting cancer development [28]. Furthermore, our analysis of patients across various clinicopathological groups revealed a significant association between BMI and age. Typically, patients were of advanced age with a higher representation of postmenopausal individuals. Numerous studies indicate that obese women are prone to developing aggressive forms of breast cancer when compared to women of normal weight [29, 6]. Additionally, patients with a BMI greater than or equal to 25 kg/m$^2$ tended to be older, with a prevalence of postmenopausal patients in the higher BMI group (BMI $\geq 25.8$ kg/m$^2$) [30]. Research suggests that women tend to gain weight primarily as they age [31]. Following menopause, there is an escalation in the free androgen index and a decline in sex hormone-binding

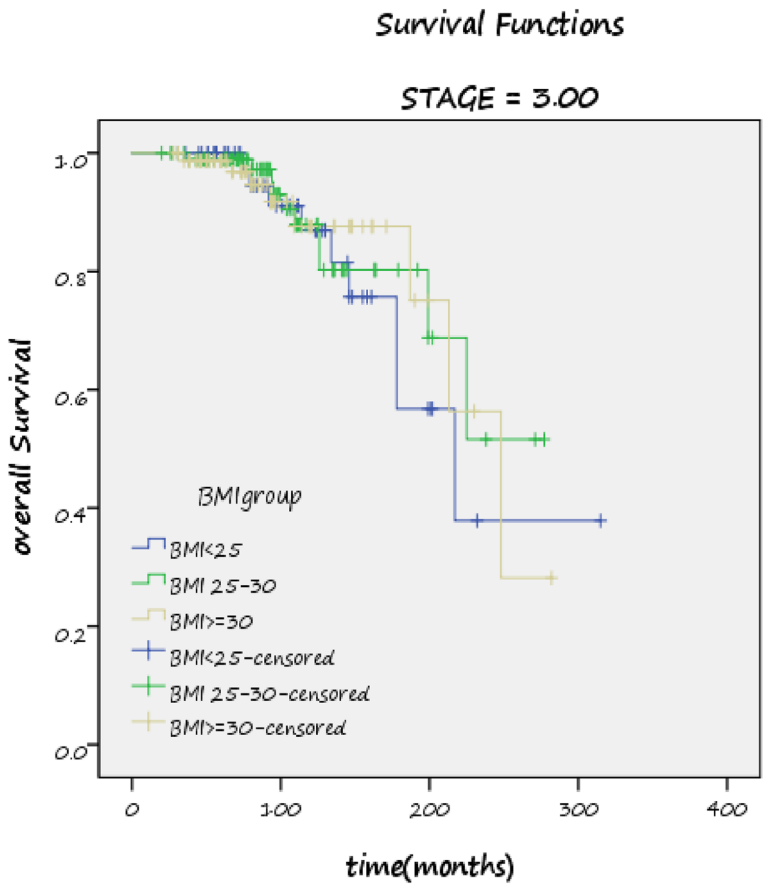


**Fig. 6** OS times-based patient's BMI status among patients in post-menopausal period in stage 3

globulin levels, likely contributing to a gradual increase in patient BMI [32]. This explanation aligns with the findings derived from our study.

In congruence with a study [33] Luminal A and B subtypes are indicative of hormone receptor-positive breast cancer patients. This investigation revealed that Luminal A molecular subtype predominated as the most prevalent hormone receptor subtype across all BMI categories, while the HER2 molecular subtype exhibited the lowest incidence of hormone receptor positivity across all BMI categories. Correspondingly, Elidrissi et al. discovered that the luminal A subtype was the most frequent subtype at 65%, whereas the HER2 subtype was the least common at 6% [34]. These results contrast with the findings of Sahin et al., who noted a lower prevalence of the luminal-like subtype among patients with a BMI ≥ 30 kg/m$^2$ [35]. Moreover, Verdial et al., in their investigation at the University of Washington, found that women with luminal B tumors were more inclined to have a BMI < 25 kg/m$^2$ [36].

The nodal status of the axilla (ALN) undoubtedly plays a crucial role in surgical decision-making and the formulation of treatment plans, exerting a significant impact on overall prognosis [37]. Surgical axillary staging remains the standard method for assessing ALN status in breast cancer patients, utilizing either axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) [38]. Currently, SLNB has replaced ALND for the evaluation of ALN in patients presenting with clinically negative nodes [39]. In our investigation, the majority of patients initially underwent ALND compared to other types of axillary procedures, which is similar to study by Zangouri et al. [33] For postmenopausal patients with a BMI ≥ 30 kg/m2, ALND and SLNB were the predominant types of axillary surgeries performed ($P = 0.56$). Conversely, a higher proportion of patients in the premenopausal period underwent sentinel lymph node biopsy (SLNB) alone, regardless of BMI status. Furthermore, a higher proportion of patients receiving axillary and chest radiotherapy had a BMI exceeding 25 kg/m2. Recent research has shown that lymphedema rates are elevated among patients subjected to ALND, particularly those with more advanced disease stages and higher BMIs [40]. Moreover, not only are obese women at greater

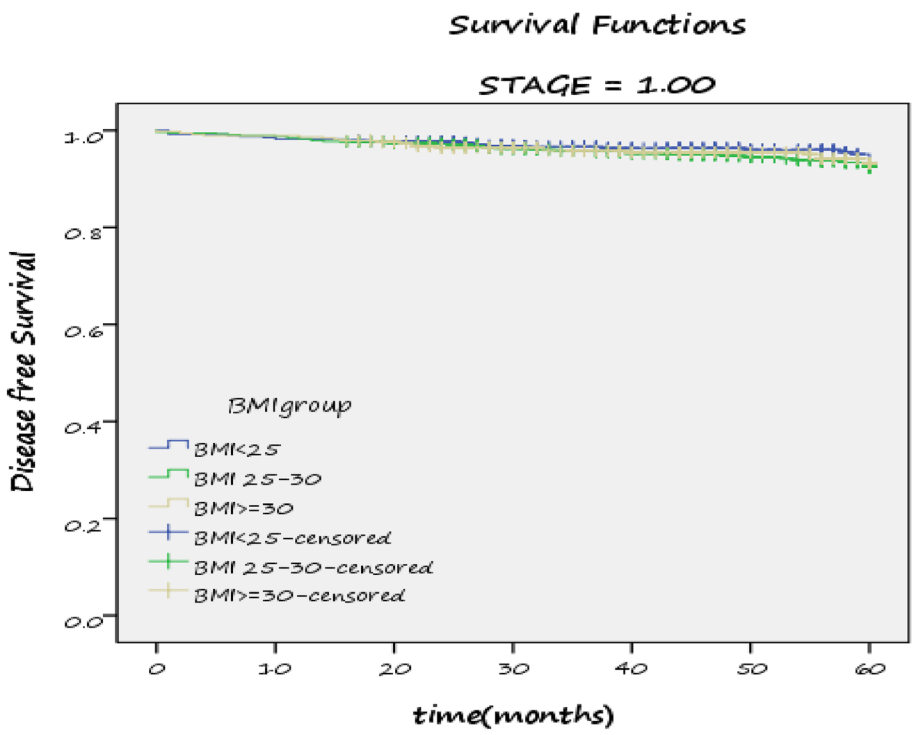


**Fig. 7** DFS times-based patient's BMI status among patients in premenopausal period in Stage 1

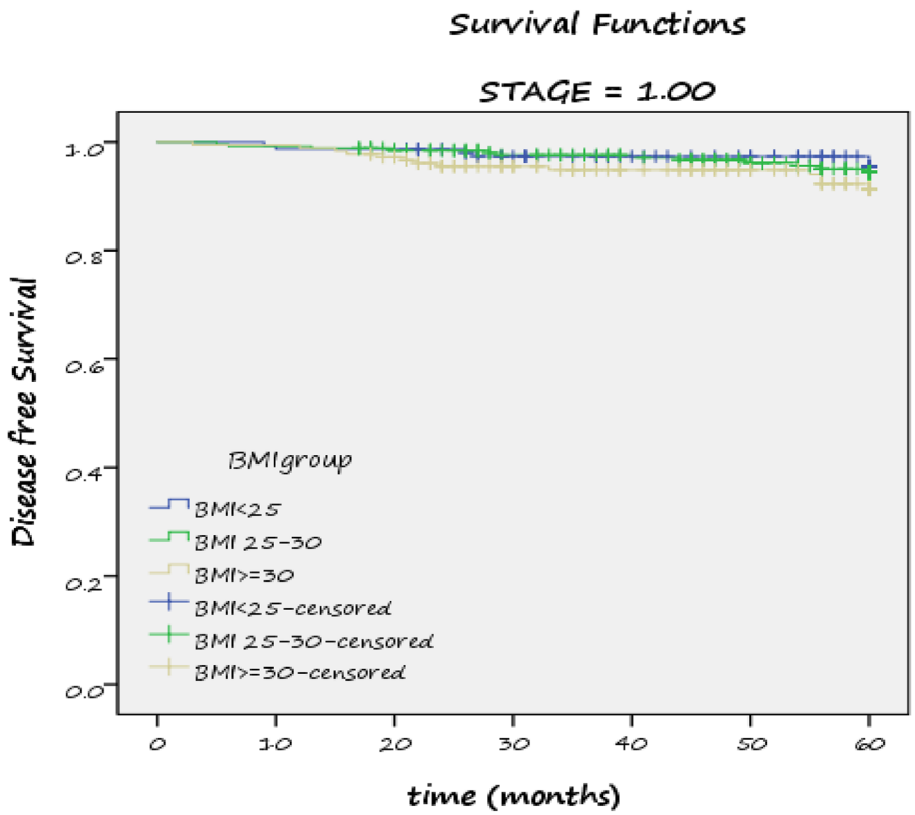


**Fig. 8** DFS times-based patient's BMI status among patients in post-menopausal period in Stage 1

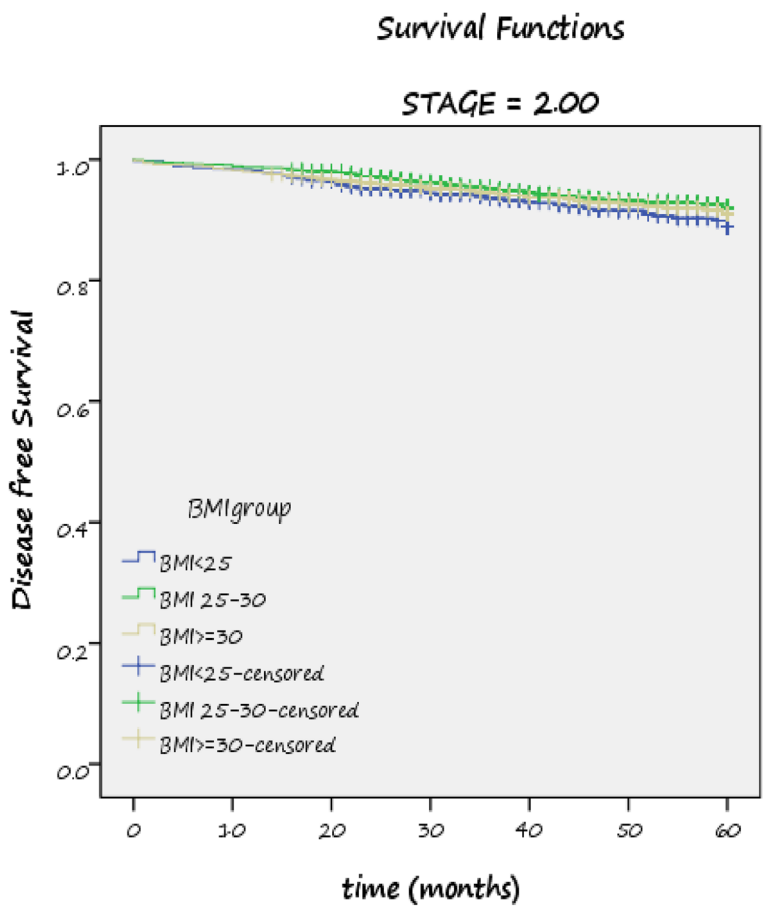


**Fig. 9** DFS times-based patient's BMI status among patients in premenopausal period in stage 2

risk of developing post-operative lymphedema, but they also face an increased likelihood of pre-operative lymphedema [41].

Numerous studies concentrate on the diagnosis and management of primary malignancies, aiming to enhance survival rates, particularly in the context of breast cancer treatment [42]. For early-stage breast cancer, surgical interventions such as mastectomy or quadrantectomy are commonly recommended for local control and the prevention of disease progression. The lack of early breast cancer detection emphasizes the importance of surgical interventions in treatment strategies [42] that in the study by Zangouri et al. [43] mastectomy was performed in most of the breast cancer patients. In our recent investigation, quadrantectomy emerged as the predominant surgical approach among both pre- and post-menopausal women in three distinct groups, while mastectomy was more prevalent among postmenopausal individuals compared to their premenopausal counterparts across the three BMI categories. Noteworthy, we did not observe significant variations in the choice of surgical procedures, chemotherapy regimens, or hormone therapy across different BMI groups. This observation suggests that treatment decisions are typically guided by the Chinese Society of Clinical Oncology (CSCO) guidelines [44] and NCCN guidelines [21] for breast cancer management, regardless of the patient's BMI. Patients with varying BMIs exhibit comparable prognoses following the implementation of standardized treatment regimens. Thus, the treatment protocols outlined in the guidelines are deemed suitable for all patients irrespective of their BMI, with no significant differences in patient outcomes based on BMI following the administration of identical treatment modalities.

In this investigation, it was observed that the majority of BC patients were classified as grade II, regardless of their menopausal status. This result is in the opposite line with a study reported lower proportions of grade II tumors and a higher prevalence of grade III histology [34]. Tumor grade emerged as a significant factor influencing OS and DFS, corroborating findings from prior

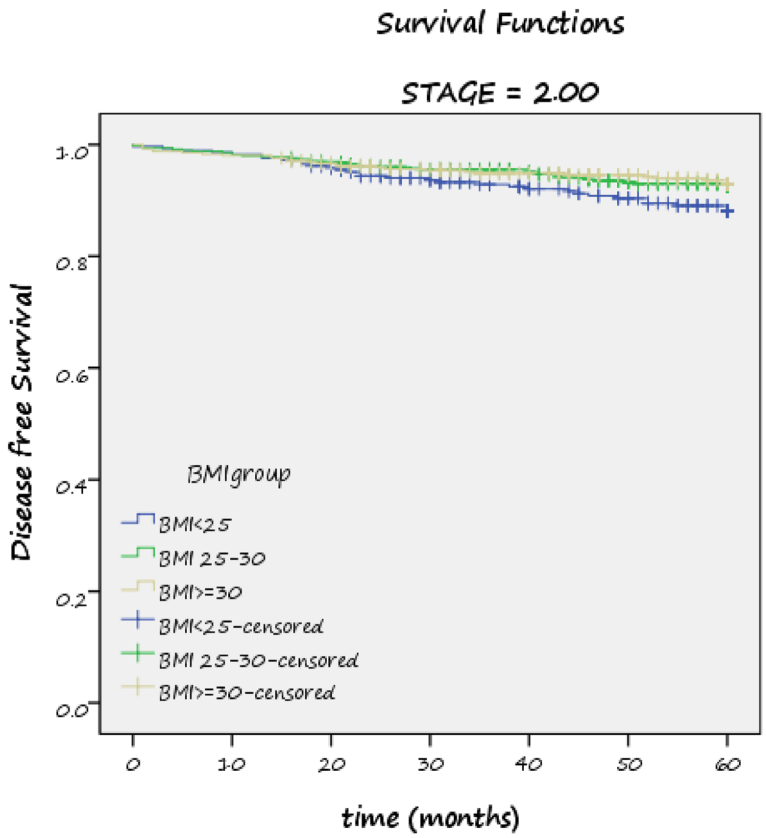


**Fig. 10** DFS times-based patient's BMI status among patients in post-menopausal period in stage 2

research [45]. Histological grading plays a pivotal role as a robust prognostic indicator and is an essential component of various clinical decision-making tools like the Nottingham Prognostic Index and Adjuvant online [46].

The histological type of the tumor was identified as an independent predictor of survival outcomes in BC patients. Multifocality, defined as the presence of two or more clearly separated tumor foci within the same breast [47, 48], exhibited a higher prevalence among premenopausal patients compared to postmenopausal patients across three distinct BMI groups in this study. This trend aligns with existing literature indicating multifocality incidences ranging from 30 to 60% in women under 35 years of age and highlighting that multifocal breast carcinomas are associated with a heightened occurrence of positive lymph nodes and unfavorable patient prognoses when compared to unifocal tumors [46, 49]. A study reported the occurrence of multifocal breast tumors was more common in BC patients with invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) subtypes [34].

There is a scarcity of literature that directly compares the clinical and progressive characteristics of in situ breast cancer based on menopausal status. Sheikh et al. [50] conducted an analysis of breast cancer in a patient cohort divided by age, specifically comparing those aged above and below 50 years. They observed a similar prevalence of the in situ component in both groups, ranging from 9 to 14%. Conversely, Reinier et al. [51] identified nulliparity and advanced maternal age as risk factors for ductal carcinoma in situ (DCIS) that were more prevalent among premenopausal patients. In our research, we observed that premenopausal patients in our study exhibited in situ components across three BMI groups in varying proportions (58.9%, 58%, and 60%, respectively).

While there exists debate regarding the link between obesity/overweight and the prognosis of breast cancer patients, it has been suggested that the impact of BMI on breast cancer prognosis could be influenced by menopausal status [52]. In our present investigation, we did not observe a statistically significant association between BMI and DFS or OS among both premenopausal and postmenopausal breast cancer patients. Notably, in stage 3, the 3-year OS was 97% and the 5-year OS was 71% in the $25.0 \leq \text{BMI} < 30.0$ group, indicating a potentially negative impact on survival in stage 3. Conversely, in stages 1 and 2, the OS was lower in the group with $\text{BMI} < 25$ (87%) compared to other groups, suggesting a predictive value

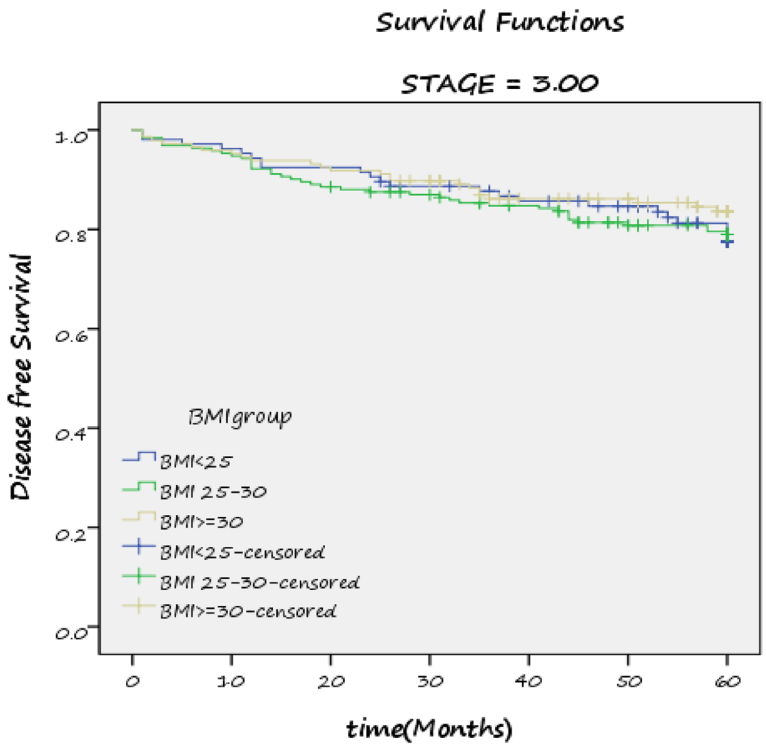


**Fig. 11** DFS times-based patient's BMI status among patients in premenopausal period in stage 3

for breast cancer mortality. The general adverse effect of obesity on outcomes in breast cancer patients has been widely recognized and has recently been reinforced by two extensive meta-analyses [53, 54]. In the past years, an increasing body of literature has highlighted an inverse relationship between obesity and survival rates among individuals diagnosed with breast cancer [55]. Adequate evidence supports the notion that elevated BMI (25.0 kg/$m^2$) is correlated with a poorer prognosis in patients with breast cancer [6, 7, 15].

Patients exhibiting a BMI of less than 25 kg/$m^2$ displayed a DFS rate of 74% in stage 3, which was lower than that of the other groups. This suggests that BMI below 25 may be indicative of a poorer prognosis for disease relapse in stage 3 of breast cancer. A recent meta-analysis investigating the relationship between obesity and survival outcomes revealed that individuals with breast cancer and obesity experienced higher overall mortality (HR: 1.26, 95% CI: 1.20–1.33, $P<0.001$) and inferior DFS (HR: 1.14, 95% CI: 1.10–1.19, $P<0.001$) compared to those without obesity [11]. Additionally, findings from a study conducted by Ladoire et al. indicated a moderate association between obesity and decreased DFS (HR: 1.18, 95% CI: 1.01–1.39, $P=0.04$), predominantly affecting OS (HR: 1.38, 95% CI: 1.13–1.69, $P=0.002$) based on their univariate analysis results [56]. These outcomes contrast with the findings of our study.

According to certain authors, postmenopausal women with a higher BMI may experience an elevated synthesis of peripheral estrogen in adipose tissue and a reduction in sex hormone binding globulin, potentially contributing to an unfavorable prognosis in breast cancer. The heightened aromatase activity resulting from these factors could promote the proliferation of abnormal mammary cells, leading to poorer outcomes [57, 58]. Furthermore, it has been suggested that postmenopausal women with higher BMI might not fully benefit from aromatase inhibitors [59]. In stage 2, postmenopausal women with a BMI less than 25 kg/$m^2$ demonstrated a DFS rate of 87%, which was lower compared to other groups. Consequently, a BMI below 25 kg/$m^2$ was linked to a non-significantly higher risk of breast cancer recurrence in postmenopausal women [60]. Similarly, in stage 3, postmenopausal women with a BMI ranging between $25.0 \leq BMI < 30.0$ kg/$m^2$ exhibited a 70% OS rate, which was lower than that of other groups. Therefore, a $25.0 \leq BMI < 30.0$ kg/$m^2$ was associated with a non-significantly higher risk of breast cancer-related mortality in postmenopausal women. In stage 3, premenopausal women with a BMI less than 25 kg/$m^2$ displayed a DFS rate of 70%, which was lower than other groups. As a result, a BMI below 25 kg/$m^2$ was associated with a non-significantly higher risk of breast cancer recurrence in premenopausal women.

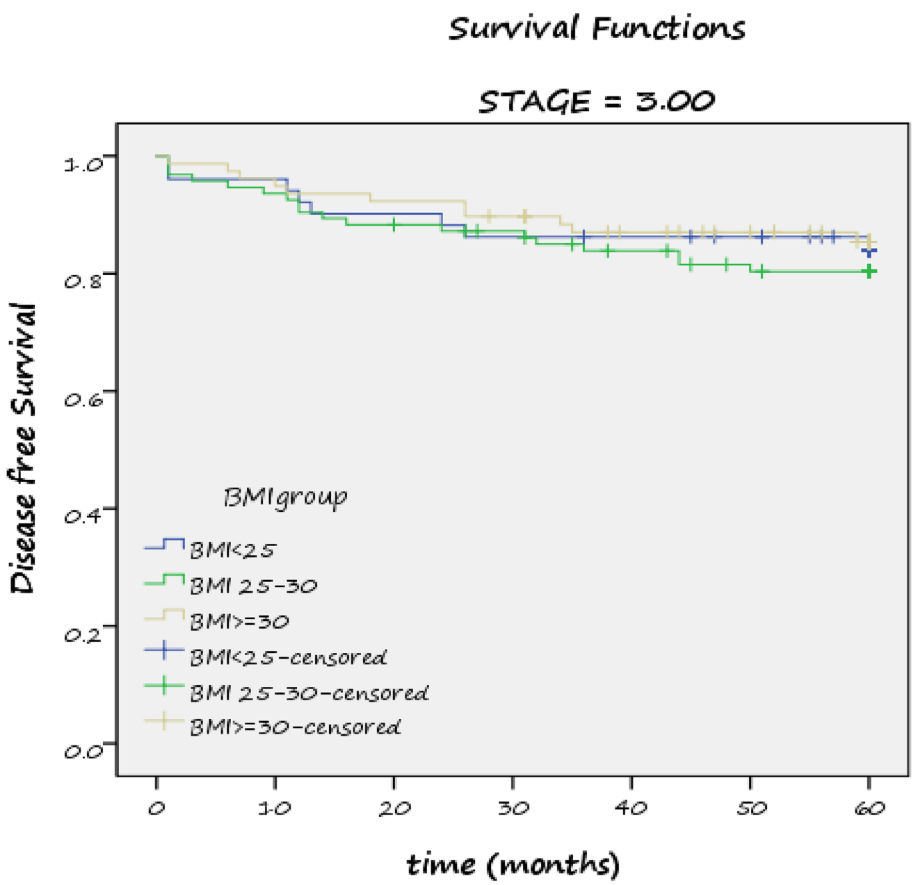


**Fig. 12** DFS times-based patient's BMI status among patients in post-menopausal period in stage 3

### Limitations of study

The study assessed BMI only in invasive ductal carcinoma and at a singular time point; however, alterations in weight and body composition over time and assessing BMI in different subtypes could exert the most significant impact on cancer outcomes.

## Conclusion

Key gained findings of this study was that an amount of BMI could be prognostic factor of breast cancer patients OS but not correlated with patients DFS. In considering other prognostic factors (similar menopause status, TNM stage of disease), no association was remarkable between BMI and OS.

Among our studied population, it was observed that the majority of BC patients were classified as grade 2, regardless of their menopausal status. Furthermore, the majority of patients initially underwent ALND compared to other types of axillary procedures. Moreover, for postmenopausal patients with a BMI $\geq 30$ kg/m$^2$, SLNB then ALND were the predominant types of axillary surgeries performed. Conversely, a higher proportion of patients in the premenopausal period underwent SLNB alone, regardless of BMI status. The incidence of multifocal breast tumors was higher in premenopausal patients compared to postmenopausal patients in all three BMI status groups.

### Acknowledgements

The authors would like to express their gratitude to the clinical research development unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, for English editing.

### Authors' contributions

M. A., V. Z., S. S. B., and A. A. H. contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by R. G., E. K., S. B., S. A. M., M. A..The first draft of the manuscript was written by M. A. All authors read and approved the final manuscript.

### Funding

This project is financially supported by the vice chancellor of research, Shiraz University of Medical Sciences.

### Data availability

Data is provided within the manuscript or supplementary information files.

## Declarations

### Ethics approval and consent to participate

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Shiraz University of Medical Sciences. The study was carried out with the informed consent of all participants. All participants were fully informed of the aim and confidentiality of the study and were assured that the information provided by them would be kept confidential.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

Received: 6 May 2024 Accepted: 4 February 2025
Published online: 13 February 2025

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## Publisher's Note