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Evaluation of sarcopenia-associated survival in breast cancer with computed tomography-based pectoral muscle area measurements

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ABSTRACT

Objective: Breast cancer is the most common and deadly female cancer. In breast cancer cases, survival is closely related to muscle mass, which is one of the components of body composition. Our aim was to investigate the usefulness of computed-tomography (CT)-based pectoral muscle measurements in detecting sarcopenia in patients with non-metastatic breast cancer and the relationship of these measurements with survival.

Patients and Methods: Our study included 62 adult female breast cancer cases diagnosed with breast cancer between January 2012 and January 2018 and without metastasis in positron emission tomography/CT (PET/CT) examination obtained for pre-treatment staging. To evaluate sarcopenia, skeletal muscle index (SMI) and pectoral muscle index (PMI) were calculated by measuring pectoral muscle area and skeletal muscle area at L3 vertebra level on PET/CT images.

Results: Deceased patients were significantly older (Median=73.90, IQR=27.04) than surviving patients (Median=54.60, IQR=13.37, p=0.025) and were diagnosed with cancer later in life (Median=63.92 IQR=30.16' vs. Median=47.51 IQR=15.0, p=0.030). When the threshold of 31 cm2/m2 was selected, there was a statistically significant difference in survival between sarcopenic and non-sarcopenic groups (p=0.031).

Conclusion: In conclusion, the presence of sarcopenia in female breast cancer cases is a parameter that affects survival and can be measured using radiological imaging methods. In addition to the measurements accepted in the literature regarding sarcopenia, pectoral muscle measurements can be chosen as an alternative method in the diagnosis of sarcopenia.

Keywords: Breast cancer, Computed tomography, Sarcopenia, Pectoral muscle

1. INTRODUCTION

Breast cancer is the leading cancer among women worldwide [1]. According to the 2020 Turkey Cancer Statistics, breast cancer has the highest incidence rate, with 23.9%, according to the number of new cases reported in women of all age groups in Turkey [2]. Risk factors for breast cancer include female sex, advanced age, family history of breast cancer, and certain genetic mutations [3]. Although, obesity may be a risk factor in specific groups, its direct association with breast cancer cases remains unclear [4].

Sarcopenia is defined as the loss of skeletal muscle mass [5]. Changes in skeletal muscle proteins with aging cause a loss of muscle mass and strength. Risk factors for sarcopenia include aging, decreased anabolic hormone activity, anorexia, and decreased physical activity [6]. Sarcopenia causes functional loss in healthy individuals and is associated with disability, injury, and death in individuals with non-malignant diseases [7]. In gastrointestinal and genitourinary cancers, overall survival is adversely affected in patients with sarcopenia [8]. Sarcopenia has also been reported to strong and independent predictive factor for poor survival in patients with breast cancer [9].

Sarcopenia is frequently evaluated using total skeletal muscle area measurements at the lumbar level [10,11] on computed

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tomography (CT) examinations, which provide information on muscle mass and density [12]. Pectoral muscle measurements can be a practical and helpful radiological parameter that can be performed simultaneously in cross-sectional imaging of the chest obtained during a cancer diagnosis. However, only a few studies of sarcopenia have used pectoral muscle measurements. [13,14].

The aim of this study was to investigate the usefulness of CT-based pectoral muscle measurements in detecting sarcopenia and the correlation of these measurements with survival in patients with non-metastatic breast cancer.

2. PATIENTS and METHODS

Patients

We included women aged 18 years and older diagnosed with breast cancer at our hospital from 1 January 2012 to 1 January 2018. An important inclusion criterion was a lack of evidence of metastasis on positron emission tomography/CT (PET-CT). We retrospectively evaluated chest and abdomen CT and PET-CT scans, which had been obtained for staging purposes prior to treatment or within six months after the initial diagnosis. We excluded patients with lobular-mixed type breast cancer (n = 4), which is much less common, for tumor type standardization and homogeneity; patients without imaging data before the operation or during chemotherapy/radiotherapy (n = 194); patients whose histopathologic subtype of cancer was not available (n = 3) and patients with metastasis at the time of admission (n = 24). Finally, 62 patients were considered for analysis. The study was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Protocol no: 09.2023.64, Date: 06.01.2023).

Demographic data such as sex, age, age at breast cancer diagnosis, height, weight, body mass index (BMI), and menopausal status were obtained from the patients' electronic medical records. In histopathologic analysis, estrogen receptor (ER)/progesterone receptor (PR) percentage, human epidermal growth factor 2 (HER2) presence, and Ki-67 indices were determined, and the patients were divided into three groups according to histopathologic subtypes: luminal A-B, HER2 enriched, and triple-negative breast cancer (TNBC) groups. Tumor grade and stage at diagnosis were determined according to the American Joint Committee on Cancer (AJCC) [1] Tumor-Node-Metastasis (TNM) staging system definitions [1]. The TNM stage, treatment protocols, dates, and methods (adjuvant chemotherapy, adjuvant radiotherapy, and operation history) were also noted. During the follow-up period, the patients' survival status, the relevant dates (date of progression/death), and their progression status were recorded.

Image analysis

Measurements were performed on non-contrast enhanced images. Images were acquired on a 128-slice CT machine with a slice thickness of 5 mm (Discovery ST PET/CT scanner; GE Healthcare, Milwaukee, WI). Images were evaluated by a single radiologist in the axial plane after reconstruction with 1-millimeter thin slices on the local Picture Archiving Communication Systems (PACS) software (Infinitt PACS, invented by Infinitt Co., Seoul, Korea). Thresholding between – 29 and +150 Hounsfield Unit (HU) was performed to isolate skeletal muscle groups from surrounding tissue [15]. The total area and average density of both pectoral muscles were measured at the T4 vertebral level (Figure 1). In the abdominal sections, the total skeletal muscle area (mm^2) and density were measured at the L3 vertebral level. All measurements were performed using the free-hand technique.

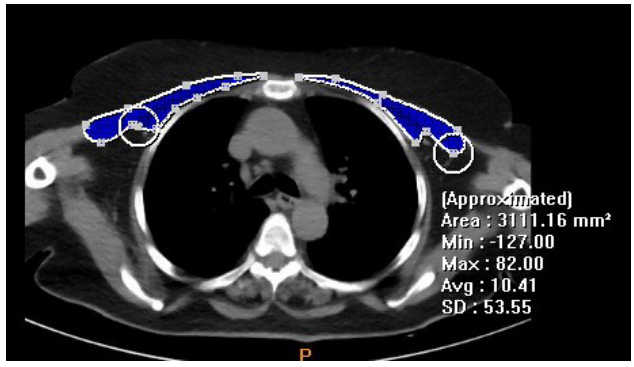

Figure 1. *Bilateral pectoral muscle area and density measurement is shown.*

Data analysis

The participants' BMI was calculated by dividing the body weight (kg) by the square of the height (m^2), and obesity was defined as a BMI of ≥30 kg/m^2 [16]. To calculate the pectoral muscle index (PMI), the total muscle area measured at the T4 vertebral level was converted from square millimeter (mm^2) to square centimeter (cm^2) and divided by the square of the height in meters (cm^2/m^2). To calculate the skeletal muscle index (SMI), the total muscle area obtained at the L3 vertebral level was converted from mm^2 to cm^2 and divided by the square of height in meters (cm^2/m^2). Because the threshold value for the presence of sarcopenia in CT measurements has not been reported for a Turkish population, we used the SMI of <38.5 cm^2/m^2, as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP) for sarcopenia in women [7]. We also considered the value of ≤31 cm^2/m^2 used by Lee et al., for the presence of sarcopenia in Korean participants as an alternative [16].

Statistical Analysis

The normality assumption for numerical variables was examined with a Q-Q plot, skewness-kurtosis, and Kolmogorov-Smirnov tests. The distribution of numerical variables among two independent groups was tested with the Mann-Whitney U test. The numerical variables were presented with median and IQR values. The categorical variables were analyzed with chi-square or Fisher's exact tests. The categorical variables were presented with counts and percentages. The survival analysis was visualized with Kaplan Meier curves, and the survival-time data were analyzed with equality of survivor function test

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and univariate Cox regression analysis. The hazard ratios were presented with 95% confidence intervals. A p-value less than 0.05 was considered significant. All statistical analyses were executed with Stata 15.1 software (StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA).

2. RESULTS

Out of 62 breast cancer patients without metastasis during admission, seven (11.29 %) died during follow-up. Deceased patients were significantly older (Median=73.90, IQR=27.04) than the surviving patients (Median=54.60, IQR=13.37, p=0.025). Similarly, deceased patients were diagnosed with cancer later in their lives (Median=63.92 IQR=30.16 vs. Median=47.51 IQR=15.0, p=0.030). Also, there was no significant difference between the two groups regarding BMI (p=0.079) and tumor size (p=0.902). The median follow-up duration for surviving group was 76.4 (IQR=39.0) and for the mortality group the median value was 38.07 (IQR=24.67), and there was a statistical significance between these two groups for follow-up durations (p<0.001). For all participants, the median follow-up duration was 73.9 (IQR=41.27).

In both deceased and surviving groups, most patients had grade II tumors (100.0% and 60.0%, respectively) with luminal subtypes (85.71% and 83.33%, respectively) at the time of diagnosis and the distributions showed no significant difference (p=1.00 and p=1.00, respectively). While most of the patients in the deceased group were either in the T1 or T2 category (42.86% and 42.86%) at the time of diagnosis, most of the patients in surviving group were in the T2 category (66.04%). However, no statistically significant difference was found. On the other hand, deceased patients were nearly twice as likely to have advanced disease (T3 or T4) (14.29% vs 7.55%, p=0.544) than surviving patients. Although, deceased patients tended to be in the N0 (42.86%) or N3 (42.86%) category at the time of diagnosis, most of the surviving patients were in the N1 category at the time of diagnosis (50.94%) (p=0.001). Nevertheless, the surviving patients had a higher percentage of lymph node positivity (n=46, 86.79%) compared to the deceased group (n=4, 57.14%) (p=0.083). The percentage of patients undergoing surgery and receiving adjuvant radiotherapy was higher in the surviving patient group (n=53, 96.36% and n=51 92.73%, respectively) compared to the deceased group (n=6, 85.71% and n=6, 85.71%). However, the difference was statistically non-significant (p=0.462). The percentage of patients receiving adjuvant chemotherapy was higher in the deceased group compared to surviving group, without statistical significance (p=0.696).

There was no statistically significant difference between right, left or total pectoral muscle areas between the deceased and surviving patient groups (p=0.345, p=0.991, and p=0.41 respectively). Similarly, no significant differences were found regarding right, left, and total pectoral muscle average densities (p=0.345, p=0.714, and p=0.312, respectively). In addition, there was no statistically significant difference regarding total muscle area, density, and SMI at the L3 vertebral level (p=0.588, p=0.863, and p=0.844, respectively).The median PMI for surviving group was 945.12 (IQR=297.71) and greater than mortality group (Median=798.72, IQR=439.45), however there was no significant difference among the groups (p=0.648) (Table I).

Table I. *Sociodemographic and clinical characteristics of patients*

Characteristics		Statistics	Survival (n=55, 88.71%)	Mortality (n=7, 11.29%)	P value
Age (year)		Median (IQR)	54.6 (14.37)	73.901 (27.04)	**0.025***
Age at diagnosis (year)		Median (IQR)	47.51 (15.0)	63.92 (30.16)	**0.030***
BMI		Median (IQR)	27.05 (4.804)	24.671 (3.186)	0.079
Tumor size		Median (IQR)	2.25 (1.5)	2.05 (1.3)	0.902
Follow-up duration (month)		Median (IQR)	76.4 (39.0)	38.07 (24.67)	**<0.001***
Tumor grade	1	Count (%)	3 (6.38%)	0 (0%)	1.00
	2	Count (%)	22 (46.81%)	3 (60.0%)	
	3	Count (%)	22 (46.81%)	2 (40.0%)	
Molecular Subtype	Luminal	Count (%)	45 (83.33%)	6 (85.71%)	1.00
	Her2+	Count (%)	2 (3.70%)	0 (0.0%)	
	TNBC	Count (%)	7 (12.96%)	1 (14.29%)	
T Stage	1	Count (%)	14 (26.42%)	3 (42.86%)	0.104
	2	Count (%)	35 (66.04%)	4 (42.86%)	
	3	Count (%)	4 (7.55%)	0 (0.0%)	
	4	Count (%)	0 (0.0%)	1 (14.29%)	
N stage	0	Count (%)	7 (13.21%)	3 (42.86%)	**0.001***
	1	Count (%)	27 (50.94%)	0 (0.0%)	
	2	Count (%)	16 (30.19%)	1 (14.29%9	
	3	Count (%)	3 (5.66%)	3 (42.86%)	
Operation		Count (%)	53 (96.36%)	6 (85.71%)	0.306
Adjuvant radiotherapy		Count (%)	51 (92.73%)	6 (85.71%)	0.462
Adjuvant chemotherapy		Count (%)	25(45.45%)	4(57.14%)	0.696
Right pectoralis muscle area		Median (IQR)	1167.3 (365.25)	1107.21 (459.68)	0.345
Left pectoralis muscle area		Median (IQR)	1146.31 (415.81)	1009.94 (597.85)	0.991
Total pectoralis muscle area		Median (IQR)	2357.48 (669.47)	2096.17 (940.32)	0.411
Right pectoralis muscle density		Median (IQR)	16.86 (20)	4.62 (44.6)	0.345
Left pectoralis muscle density		Median (IQR)	-1.1 (6.37)	-1.8 (8.52)	0.714
Total pectoralis muscle density		Median (IQR)	16.47 (15.96)	8.78 (29.84)	0.312
L3 total muscle area		Median (IQR)	10437.48 (2443.31)	9913.43 (3285.17)	0.588
L3 density		Median (IQR)	17.555 (19.77)	15.32 (20.22)	0.863
Skeletal muscle index (SMI)		Median (IQR)	41.95 (10.65)	42.91 (16.97)	0.844
Pectoral muscle index (PMI)		Median (IQR)	945.12 (297.71)	798.72 (439.45)	0.648

** A p-value of 0.05 or lower is considered statistically significant.*

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According to the Cox regression analysis, age was a significant risk factor for mortality; each additional year increasing mortality with an HR of 1.087 (95% CI 1.017-1.162, p=0.015). Similar to patient age, the age at the time of diagnosis significantly affected mortality (HR=1.084, 95% CI 1.016-1.157 and p=0.014). However, BMI (HR=0.853 with 95% CI 0.691-1.052 and p=0.138) and tumour size (HR=1.0113, 95% CI=0.425-2.404 and p=0.980) did not affect mortality risk. Right pectoral muscle area (HR=0.999, 95% CI=0.996-1.002 and p=0.389), left pectoral muscle area (HR= 0.9995, 95%CI 0.997-1.002 and p= 0.736) and total pectoral muscle area (HR=0.9995, 95% CI =0.998-1.001 and p= 0.483) did not significantly affect mortality. Similarly, the average right pectoral muscle density (HR=0.984, 95% CI = 0.946-1.023 and p=0.413), left average pectoral muscle density (HR=1.049, 95% CI=0.907-1.212 and p=0.522) and average total pectoral muscle density (HR=0.986, 95%CI=0.946-1.028 and p=0.506) did not affect mortality. In addition, L3 total muscle area (HR=0.9997, 95% CI= 0.9991-1.0002 and p=0.221), L3 total muscle density (HR=0.994, 95% CI = 0.946-1.044 and p=0.812) and SMI (HR=0.993, 95%CI 0.906-1.089 and p=0.881) did not have a significant effect on mortality. Having a history of surgery (HR=4.807 95% CI= 0.569-40.592 and p=0.149), adjuvant radiotherapy (HR=1.887, 95% CI = 0.227-15.687 and p=0.557) or chemotherapy (HR=0.659, 95%CI= 0.148-2.946 and p= 0.585) had a non-significant effect on mortality.

We stratified patients according to the presence of sarcopenia regarding previous literature by using the thresholds of 38.5 cm^2/m^2 and 31 cm^2/m^2 [7,8,17]. According to the threshold of 38.5 cm^2/m^2, there was no statistically significant difference between the sarcopenic and non-sarcopenic groups in terms of survival functions equality (p=0.909). The Cox regression model using this stratification was not significant (HR=1.101, 95% CI =0.214 – 5.675 and p=0.909). However, there was a statistically significant survival difference between the sarcopenic and non-sarcopenic groups if the 31 cm^2/m^2 threshold was selected (p=0.031) (Figure 2, 3). Nevertheless, the higher risk of mortality of the sarcopenic group compared to the non-sarcopenic group as revealed by the Cox regression model was statistically not significant (HR= 7.389, 95% CI= 0.879-62.124 and p=0.066) (Table II).

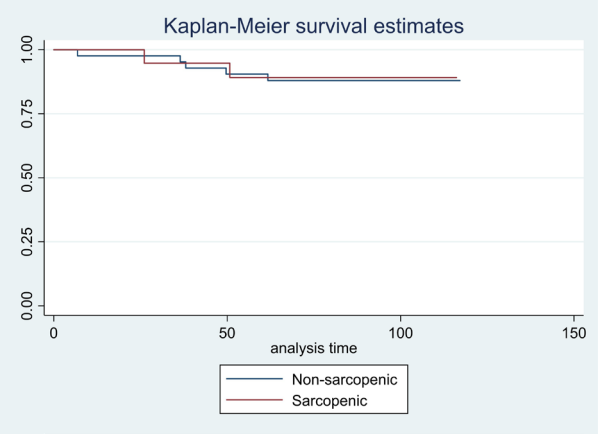

Figure 2. *Kaplan-Meier survival curves for sarcopenic and non-sarcopenic patients according to the threshold of 38.5 cm2/m2*

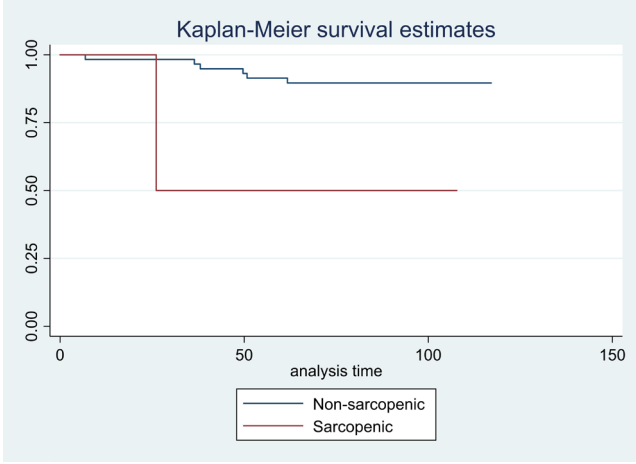

Figure 3. *Kaplan-Meier survival curves for sarcopenic and non-sarcopenic patients according to the threshold of 31 cm2/m2*

Table II. *Univariate Cox regression models for prediction of mortality*

Characteristics	Hazard Ratio with 95% Confidence Interval	P Value
Age	1.087 (1.017-1.162)	**0.015***
Age at diagnosis	1.084 (1.016-1.157)	**0.014***
BMI	0.853 (0.691-1.052	0.138
Tumor size	1.011 (0.425-2.404)	0.980
Right pectoralis muscle area	0.999 (0.996-1.002)	0.389
Left pectoralis muscle area	0.9995 (0.997-1.002)	0.736
Total pectoralis muscle area	0.9995 (0.998-1.001)	0.483
Right pectoral muscle density	0.984 (0.946-1.023)	0.413
Left pectoral muscle density	1.049 (0.907-1.212)	0.522
Total pectoral muscle density	0.986 (0.946-1.028)	0.506
L3 vertebral level total muscle area	0.9997 (0.9991-1.0002)	0.221
L3 vertebral level total muscle density	0.994 (0.946-1.044)	0.812
Skeletal muscle index (SMI)	0.993 (0.906-1.089)	0.881
Pectoral muscle index (PMI)	0.9991 (0.9956-1.0026)	0.604
History of surgery	4.807 (0.569-40.592)	0.149
Adjuvant radiotherapy	1.887 (0.227-15.687)	0.557
Adjuvant chemotherapy	0.659 (0.148-2.946)	0.585
Presence of sarcopenia (Threshold= 38.5 cm^2/m^2)	1.101 (0.214 – 5.675)	0.909
Presence of sarcopenia (Threshold= 31.0 cm^2/m^2)	7.389 (0.879-62.124)	0.066

** A p-value of 0.05 or lower is considered statistically significant.*

3. DISCUSSION

In the present study, we investigated the effect of sarcopenia assessed using pectoral muscle measurements on the survival of patients with non-metastatic breast cancer. Our data indicated that patient age and age at cancer diagnosis were the two prominent risk factors for mortality. Regarding the sarcopenia–survival relationship, no significant difference was found when the SMI threshold of <38.5 cm^2/m^2 was used, but the sarcopenic

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group had a significantly increased mortality risk when the SMI threshold of ≤31 cm^2/m^2 was selected (p = 0.031).

Pectoral muscle measurements have been used to assess sarcopenia and found to be more practical and straightforward compared to the standard way of measuring sarcopenia from the whole muscle area at the abdominal level [9,13]. Go et al., compared pectoral muscle and total skeletal muscle areas at the L3 vertebral level in lymphoma patients and reported that pectoral muscle measurements could also be used to define sarcopenia [17]. They also report that combining pectoral muscle area measurements with L3 vertebral level total muscle area may provide more information to predict a patient's prognosis [17]. Kinsey et al., emphasized the relationship between poor overall survival and low pectoral muscle area in a study involving pectoral muscle measurements on chest CT examinations in patients with small-cell lung cancer. This enabled sarcopenia assessments without the need for additional imaging [18]. In our study, no statistically significant correlation was found between pectoral muscle measurements and survival, which may be due to the small sample size and the younger mean age of the patients compared to the literature [17, 18]. The prediction of sarcopenia based on pectoral muscle measurements in female breast cancer patients and its effect on survival need to be clarified in studies conducted in larger patient groups and among different age groups.

The literature has reported that sarcopenia increases the risk of death in lung, stomach, and colorectal cancer cases [19]. In addition, sarcopenia in cancer patients has been associated with increased chemotherapy toxicity and postoperative complications during treatment [20]. Different results have been reported in the literature regarding the relationship between sarcopenia and breast cancer. Unrelated results may be attributed to the different cancer types and stages of the cases and the different thresholds accepted for sarcopenia during imaging [21]. In a meta-analysis investigating sarcopenia and the causes of mortality in female breast cancer patients, it was recommended that all breast cancer cases be screened for sarcopenia, an important prognostic marker [22].

Among the contrasting results reported in the literature, Del Fabbro et al., investigated sarcopenia, BMI, and survival processes in breast cancer cases and found longer survival rates in sarcopenic cases. They attributed this unexpected result to the fact that chemotherapy toxicity was well tolerated and that the study specifically focused on cases of earlier-stage breast cancer [23]. Our study examined the association between sarcopenia and survival in non-metastatic breast cancer cases by measuring the pectoral muscles. However, we found no significant relationship between sarcopenia and survival based on SMI values calculated from measurements at the L3 vertebral level. This lack of significance at specific threshold values may also be attributed to the inclusion of early-stage cancer cases and a relatively younger female population compared to previous studies in the literature. Additionally, thresholds for sarcopenia differ between populations [16].

The pectoral muscle has also been studied in non-oncological scenarios and can be used to predict prolonged hospitalization and death [24,25]. Recently, during the COVID-19 pandemic, a relationship between pectoral muscle density and disease severity and mortality was reported [26]. In another study, a decrease in pectoral muscle area and density was associated with 30-day mortality in cases of acute pulmonary embolism [27]. Pectoral muscle measurements can also be performed simultaneously in breast MR images obtained in breast cancer cases and have been reported to correlate with CT measurements [9].

Our study identified the patient's current age and their age at breast cancer diagnosis as independent risk factors contributing to an increased mortality risk. The large-scale Health, Eating, Activity, and Lifestyle (HEAL) study conducted by Villasenor et al., also supported the notion that age at diagnosis is a significant risk factor for poor prognosis [28]. Another study revealed that an early age at breast cancer diagnosis, specifically cases diagnosed younger than 35 years, was linked to a poorer prognosis, potentially attributable to cancer type and aggressiveness. Conversely, cases diagnosed older than 65 years, had higher mortality rates, likely due to increased comorbidity and treatment noncompliance [29]. It is important to note that the age at breast cancer diagnosis can vary based on racial, genetic, and environmental risk factors, which may introduce heterogeneity to the results [3].

Studies examining the impact of body mass index (BMI) on survival in cancer cases have yielded varying results, which can be attributed to the specific type of cancer under investigation [30]. Increased BMI is generally considered a risk factor in liver, colon, gallbladder, kidney, endometrium, and ovarian cancers [31]. However, in the case of female breast cancer, the relationship is more complex and influenced by menopausal status [32]. While, obesity during the premenopausal period may exhibit a protective effect in female breast cancer cases, a paradoxical association arises in the postmenopausal period when accompanied by sarcopenia, which poses a mortality risk factor [33,34]. In our study, there was no difference in BMI between the groups, and BMI was not a risk factor for mortality. In evaluating survival in obese oncology patients, the possibility of discordant and unexpected results should be considered by bearing in mind the increased cardiovascular risk, comorbidities, and chemoradiotherapy toxicities seen with an increased BMI [32].

The limitations of our study include its retrospective nature and the small number of patients involved. Another area for improvement was the absence of nationally standardized cut-off values based on radiologic measurements for diagnosing sarcopenia. Large prospective studies involving different age groups in female breast cancer cases are needed to understand the relationship between sarcopenia and breast cancer.

In conclusion, sarcopenia is a prognostically important parameter in female breast cancer cases and can be determined using radiologic imaging methods. In addition to the measurements accepted in the literature, measurements of the pectoral muscle can be used as an alternative method for diagnosing sarcopenia.

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Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Protocol no: 09.2023.64, Date: 06.01.2023).

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