Identification Of Risk Factors Of Bone Metastasis Among Iraqi Breast Cancer Women

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Abstract, Background: *The most common site of metastases in people with breast cancer is bone metastasis. Patients with advanced phases of cancer are associated with an increased prevalence of several types of metastases, one of which is bone metastasis.* ***Object:*** *Assessment of the risk factors for bone metastases in patients with breast cancer.* ***Patients and Methods****: This is a retrospective study of 316 patients with breast cancer who either had bone metastases at the time of diagnosis or developed it later on. The study was carried out between January 2013 and April 2018. Three hundred and sixteen patients were assigned into two groups. In the case group, 100 patients with breast cancer had been diagnosed with bone metastasis by CT, MRI, bone scan, and PET scan; in the control group, there were 216 cases in are control group with breast cancer metastasis to sites other than bone. The questionnaire was created to record all factors (with the exception of demographic information), such as age, histopathological reading for invasive lobular carcinoma, invasive ductal carcinoma, or another type of cancer, ER status, PR status, Her2neu status, lymph node status and stage, and menopausal status.* ***Results:*** *The majority were 45 years of age or younger, and 96.5% of them had invasive ductal carcinoma in terms of hormonal status. Positive ER and PR status is found in 67.7% and 67.1% of the cases, respectively; 40.5% of the cases had amplified Her2neu receptors, 78.5% of the cases had positive lymph nodes, and 41.9% of the cases had (N1) stage. The highest proportion of bone metastasis was associated with negative ER and PR receptors (46.2% and 49%, respectively), while no significant statistical association (P= 0.65).* ***Conclusion:*** *negative ER, PR status, and Her2neu receptors not amplified, lymph node involvement, age 45 and less, infiltrating lobular carcinoma (ILC) histological type, and menopausal state are significant risk factors for bone metastasis in breast cancer.*

Keywords*: Breast Neoplasms, Carcinoma, Quality of Life, Bone Neoplasms.*

1. INTRODUCTION

Breast cancer is the most prevalent form of cancer among women. Breast cancer patients now have a favourable prognosis due to advancements in treatment, yet some individuals experience challenges linked to bone metastases and associated conditions. However, about 70% of women with late-phase breast cancer are suffering from it [1]. Furthermore, the predominant cancer types that lead to bone metastases include lung, prostate, and breast cancers. Patients with bone metastases have skeletal-related events (SREs), including pain, pathological fractures, and spinal cord compression, which may adversely affect their quality of life and need prompt medical intervention. [2]. The skeleton is the organ most often affected by breast cancer metastases, and it has a better prognosis than visceral metastases.

Effective treatment is also required for patients with bone-only metastases in order to extend their survival. Patients with PR (progesterone receptors) positive and positive ER (estrogen receptors) should receive endocrine therapy. Bisphosphonates are another treatment for solid tumour-related bone metastases, and they are advised to be used in addition to

conventional cancer treatment [3,4]. A retrospective survey on bone metastatic management carried out in China in 2016 revealed that patients receiving continuous bisphosphonate treatment for more than six months had a significantly lower risk of SREs ($p < 0.05$) [5]. Furthermore, ZOMETA®4 mg, which is taken monthly for a long duration of about one year, can decrease SREs its related symptoms and delay the development of SRE compared to placebo: $p = 0.027$, $p = 0.003$, respectively, according to another study that examined the treatment of bone metastases in 228 Japanese women [6].

2. PATIENTS AND METHODS

Study design

This is retrospective research analyzing data from breast cancer patients treated at the Oncology Teaching Hospital, Medical City, Baghdad, Iraq, from January 2013 to April 2018. Informed permission was acquired from the subjects.

The questionnaire was created to record all variables (risk factors) and demographic information (age, histology findings, lymph node status, lymph node stage, ER, PR, Her2neu status, and menopausal status).

Study population:

A sample of 316 breast cancer patients was identified using histopathological analysis derived from mastectomy, breast-conserving surgery, and Tru-cut biopsy from either the breast mass or metastatic location.

Immunohistochemistry for the expression of ER, PR, and Her2neu is assessed by either a pathology department laboratory at an oncology teaching hospital or a private pathology clinic laboratory.

Different methods of image modalities or histopathology of the metastatic site have done staging of the disease .

Exclusion criteria

Breast cancer among male patients was excluded from the current study.

Statistical analysis

The data was analyzed using version 25 of the Statistical Package for the Social Sciences (SPSS). Continuous data were presented as ranges, means, and standard deviations. Percentages and frequencies are used to represent categorical data. The correlation between patient characteristics and the incidence of bone metastases was assessed via Pearson's Chi-square test. At this threshold, P-values below 0.05 were considered significant.

3. RESULTS

Three hundred sixteen female patients with breast cancer participated in this research, divided into two groups: the case group and the control group. In the case group, 100 patients with breast cancer were diagnosed with bone metastases by PET or bone scan; in the control group, there were 216 breast cancer cases, regardless of the presence of bone metastasis.

General characteristics

Figures (1 and 2) show the distribution of the study group by certain general characteristics. The patients' ages varied from 29 to 81, with a mean of 50.08 and a standard deviation of ± 11.80 years. Sixty percent of patients diagnosed with bone metastases were 45 years or younger. In the control group, about 65.3% of patients were above 45 years of age.

Regarding menopausal status, 56% of bone metastasis in the case group was in the premenopausal period, while 71.8% of patients in the control group were in the postmenopausal period.
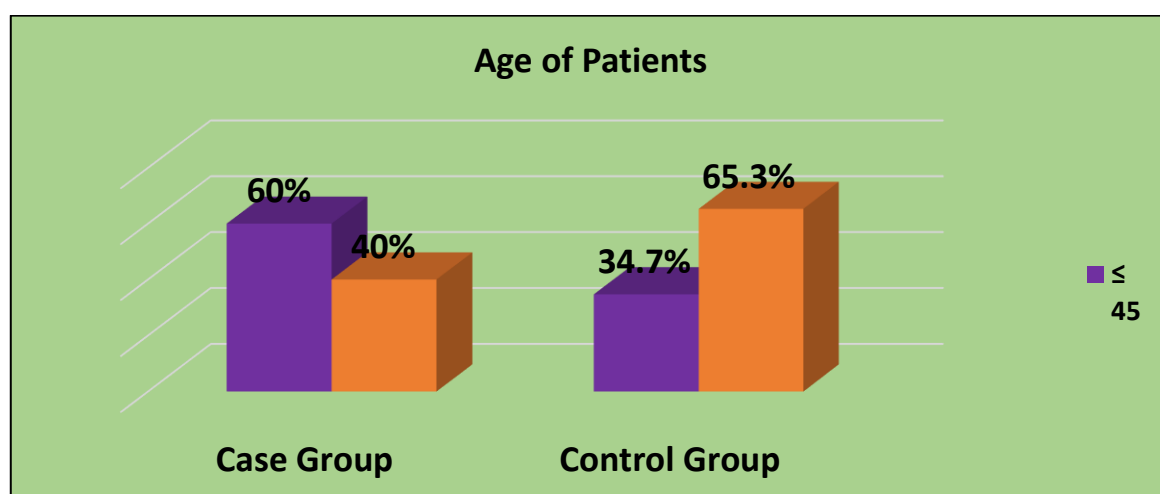

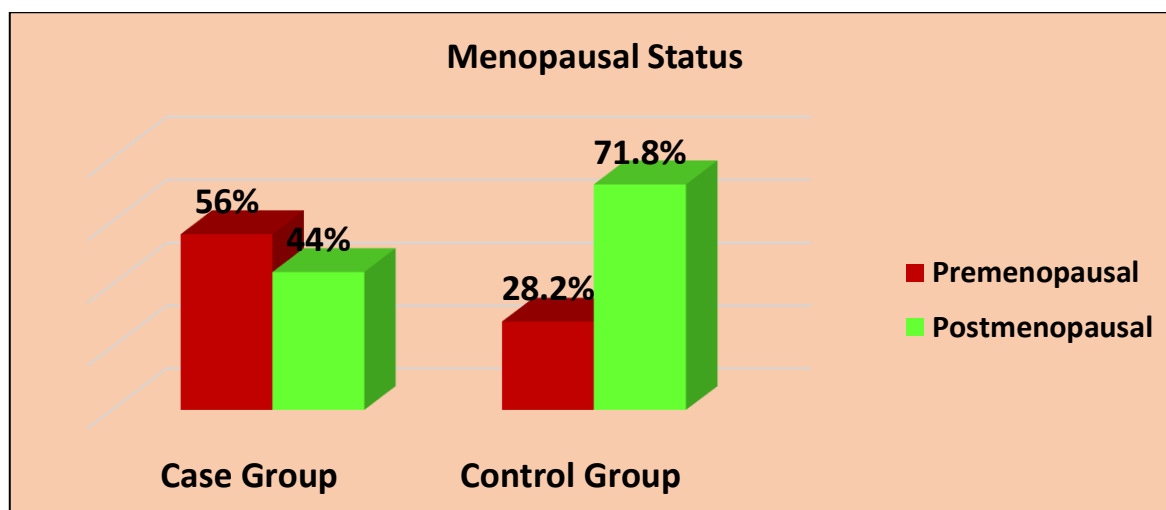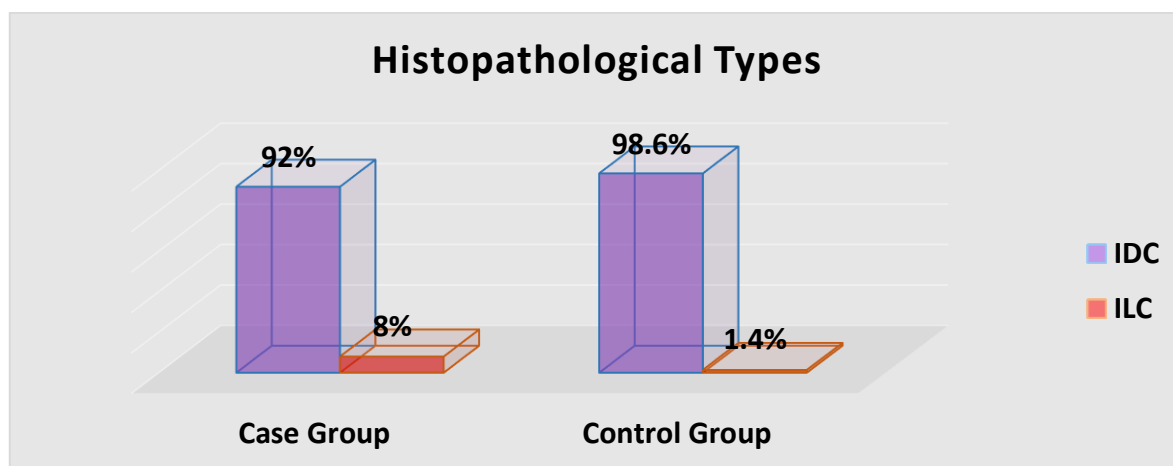**Figure 1: Distribution of study groups by age**

Figure 2: Distribution of patients by menopausal status

Histopathological Types

Histological data indicate that the predominant type of cancer among women in both the case and control groups was invasive ductal carcinoma, accounting for 92% and 98.2%, respectively. Figure (3.3) shows the distribution of patients by histological results.

Figure (3): Distribution of study groups by histological findings

ER, PR and Her2neu Receptors

Table 1 shows the distribution of patients according to ER, PR, and Her2neu receptor status. The majority of women in both groups exhibited positive estrogen receptor (ER) and progesterone receptor (PR) status. Positive ER status was observed in 52% of the case group and 74.1% of the control group. Conversely, PR status was present in 51% of the case group and 75.5% of the control group. Her2neu receptors were non-amplified in 52% of bone metastasis cases and 63% of patients in the control group.

Table 1: Distribution of patients by ER, PR, and Her2neu receptors status

Variable	Groups		Total (%) n= 316
	Proportion of case group n= 100	Proportion of Control group n = 216	
ER Receptors			
Positive	52 (52.0)	160 (74.1)	212 (67.1)
Negative	48 (48.0)	56 (25.9)	104 (32.9)
PR Status			
Positive	51 (51.0)	163 (75.5)	214 (67.7)

Negative	49 (49.0)	53 (24.5)	102 (32.3)
Her2n Status			
Amplified	48 (48.0)	80 (37.0)	128 (40.5)
Non Amplified	52 (52.0)	136 (63.0)	188 (59.5)

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Lymph Nodes Status and Staging

In regard to lymph node status and staging, positive lymph nodes were observed in 88% of cases with bone metastasis, while 48% exhibited the (N1) stage. In the control group, 74.1% of patients exhibited positive lymph node involvement, with 33.3% classified as N2 lymph node staging. Figures (4) and (3.5) show the study group distribution by lymph node status and staging.
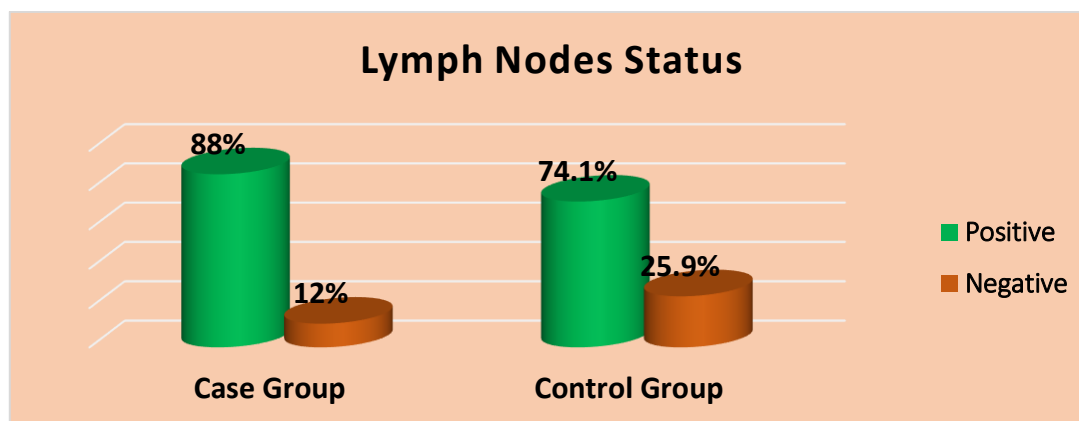

Figure 4: Distribution of study patients by lymph node status
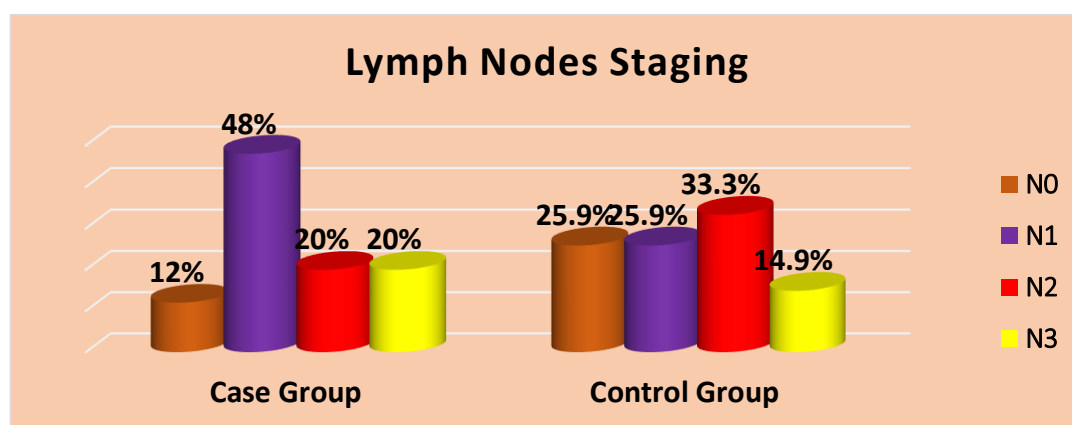

Figure 5: Distribution of study patients by lymph node staging

The association between bone metastasis of breast cancer and specific general characteristics of study groups is shown in Table 2. Sixty percent of patients diagnosed with bone metastasis were aged 45 years or younger, indicating a significant statistical correlation (P=0.001) between patient age and bone metastasis in breast cancer.

A significant statistical association was identified between women's menopausal status and breast cancer bone metastasis, with 56% of cases occurring during the premenopausal period and a P value of approximately 0.001.

Table 2: Association between bone metastasis of CA breast and certain general characteristics of study groups

Variable	Groups		P- value
	Proportion of case group n= 100	Proportion of Control group n = 216	
≤ 45	60 (60.0)	75 (34.7)	0.001
> 45	40 (40.0)	141 (65.3)	
Premenopausal	56 (56.0)	61 (28.2)	0.001
Postmenopausal	44 (44.0)	155 (71.8)	

Regarding the association between bone metastasis and histological findings, we found that 8% of metastatic cases were with infiltrating lobular carcinoma (ILC), with a significant statistical association (P=0.001) between histological findings and bone metastasis. About 92% of patients were associated with invasive ductal carcinoma, P value = 0.003. This association is shown in Table 3.

Table 3: Association between bone metastasis of CA breast and histological findings

Variable	Groups		P-value
	Proportion of case group n= 100	Proportion of Control group n = 216	
IDC	92 (92.0)	213 (98.6)	**0.003**
ILC	8 (8.0)	3 (1.4)	0.001

IDC: Invasive Ductal Carcinoma   **ILC:** infiltrating lobular carcinoma

Table 4 shows the association between bone metastasis of CA breast and ER, PR, and Her2neu receptors. We noticed that ER and PR receptors were significantly associated with bone metastasis of breast tumors (P= 0.001). The highest proportion of bone metastasis was associated with negative ER and PR receptors (46.2% and 49%, respectively), while no significant statistical association (P= 0.65) was seen between bone metastasis and Her2neu receptors.

Table 4: Association between bone metastasis of breast tumor and ER, PR, and Her2neu receptors

				P-value
ER	Positive	52 (52.0)	160 (74.1)	**0.001**
	Negative	48 (48.0)	56 (25.9)	
PR	Positive	51 (51.0)	163 (75.5)	**0.001**
	Negative	49 (49.0)	53 (24.5)	
HER2neu	Amplified	48 (48.0)	80 (37.0)	**0.65**
	Non-Amplified	52 (52.0)	136 (63.0)	

Concerning the association with lymph node involvement and staging, we found that the highest proportion of metastatic cases (88.0%) were with positive lymph node involvement, and this correlation between lymph node status and bone metastases in breast cancer was statistically significant (P= 0.005). A significant correlation (P= 0.001) was seen between lymph node staging and bone metastases in breast cancer, with 48% of metastatic patients exhibiting N1 stage lymph nodes. This association is shown in table (3.5).

Table 3.5: Association between bone metastasis of breast tumor and lymph node status and staging

Variable	Groups		*P- value*
	Proportion of case group n= 100	**Proportion of Control group n = 216**	
Positive	88 (88.0)	160 (74.1)	**0.005**
Negative	12 (12.0)	56 (25.9)	

N1	48 (48.0)	56 (25.9)	
N2	20 (20.0)	72 (33.3)	**0.001**
N3	20 (20.0)	32 (14.9)	

4. DISCUSSION

The most prevalent cancer and a leading contributor to morbidity and death in women is breast cancer. Twenty to thirty per cent of patients experience a recurrence in distant areas [7]. The most frequent location of metastases is the bone. Between 60% and 75% of metastases in British Columbia are initially diagnosed as bone metastases or bony metastases [8]. Severe complications and a significant reduction in 5-year survival are caused by bone metastasis [9]

A multitude of foundational studies has been conducted to ascertain the demographic, clinical, pathological, and genetic aspects affecting osseous metastases in breast cancer patients. The International Breast Cancer Study Group investigated a cohort of 6,000 individuals about osseous metastases. Large tumor size, several malignant axillary lymph nodes, and estrogen receptors were identified as risk factors for bone metastasis. Others who look into clinical risk factors linked to bone metastasis have found that the most important factor influencing bone metastasis is age [10].

The study comprised three hundred sixteen women diagnosed with breast cancer. Two groups were established from them. A total of 100 breast cancer patients with osseous metastases, diagnosed using Magnetic Resonance Imaging (MRI), Computed Tomography (CT), bone scans, and/or Positron Emission Tomography (PET) scans constituted the case group, whereas 216 breast cancer cases without osseous metastases formed the control group.

Histopathological Types

In this study, the majority of women in the case and control groups were with invasive ductal carcinoma (IDC) (92% and 98.6%, respectively). In comparison to the study by Purushotham et al. in 2016, a different result was found, as the majority of the patients with metastatic BC included in their study had the ductal type of BC (75.5%) [11,12].

ER, PR, and Her2neu Receptors

The present study explores. The majority of women in both groups exhibited positive estrogen receptor (ER) and progesterone receptor (PR) status, with ER status at 52% in cases and 74.1% in controls and PR status at 51% in cases and 75.5% in controls. Her2neu receptors were non-amplified in 52% of bony metastasis cases and 63% of patients in the

control group. Different results were noticed in kreutzfeldt et al. study in 2020, which observed that among BC patients with BM, eighty-five percent had either ER+ or PR+ breast cancer; the remaining 8.2% had HER2+ breast cancer, and 6.8% had triple-negative breast cancer [13,14]

Xiong et al. (2021) reported that 70.5% of patients with bony metastases were hormone receptor-positive, with 57.6% classified as HR+/HER2− and 12.9% as HR+/HER2+. In contrast, triple-negative breast cancer constituted only 8% of the cases. [15].

Gong and colleagues (2018) identified that patients with hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative status exhibited the highest incidence proportions among those with metastatic disease, at 73.9%. [16].

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Our study demonstrated that 88% of bony metastasis cases had positive lymph nodes, and 48% of them showed (N1) stage. In the control group, 74.1% of patients had positive lymph node involvement, and 33.3% showed (N2) lymph node staging.

Similarly, Chen and colleagues found in their study in 2017 that the (N1) stage was the predominant one among patients with metastatic BC involved in their study, constituting 35.4%, while the lowest observed in the (N2) stage, when observed in 9.8% of the participants [17]. Early detection of BC by mammography, surgery, and more advanced treatment were among the factors that led to changes in the stage of the disease in the studies [18,19].

The present study found a statistically significant inverse association between bony metastasis of breast cancer and patient age. The majority of patients (60.0%) diagnosed with bony metastasis were aged 45 years or younger (P=0.001).

In the multivariate analysis conducted in the 2014 study by Harries et al., women diagnosed with breast cancer (BC) under 40 years exhibited the highest hazard ratio (HR) for developing bone metastases. In contrast, those diagnosed with BC over 70 years had the lowest HR (0.54, 95% confidence interval [CI] 0.45–0.64). [20]. The univariate analysis conducted in the study by Diessner et al. (2016) indicated a significant difference in the behaviour of bone metastases between women under 65 years old (20.1%) and those over 65 years old (33.1%, p < 0.001). [21].

Gong and colleagues (2018) observed that patients with bony metastasis from HR-positive/HER2-negative breast cancer were significantly older, with those aged ≥ 65 years comprising 40.1% of the study population (P < 0.001). In contrast, patients with HR-negative/HER2-positive breast cancer were significantly younger, with individuals aged 50-64 years representing 45.2% of the study cohort (P < 0.001). [16].

In this study, there was a statistically significant association between menopausal status and bony metastasis of CA breast; 56.0% of bony metastasis cases were in the premenopausal period (P=0.001). In comparison to the Diessner et al. study in 2016, different results were observed, as it was noticed that BC with bone-only metastases was significantly more prevalent in postmenopausal women (28.0%, P=0.026) [21].

Regarding histological type in the current study, 92.0 % of metastatic cases were with IDC, with a statistically significant association between histological findings and bone metastasis (P=0.001). Similar findings were reported by Diessner et al. A 2016 study found a notable difference in the occurrence of bony metastasis between invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). Thirty-five percent of patients with lobular or other subtypes of breast cancer and twenty-three percent with invasive ductal carcinoma exhibited bone-only metastases (p = 0.002). [21]. In a 2018 study, Gong et al. discovered that almost two-thirds of metastatic breast cancer to bone was frequent in invasive ductal carcinoma, revealing a very significant correlation between histological type and bone metastasis. [16].

In the current study, the highest proportion of bony metastasis was significantly associated with positive ER and PR receptors (52.0 % and 51.0%, respectively, P= 0.001), while no statistically significant association with Her2neu receptors (P= 0.65).

A 2016 study by Diessner et al. found a similar outcome: bony metastasis was significantly more common in BC with +ve receptor status (29.9%, P <0.001) and significantly more common in those with -ve HER2/neu (27%, P = 0.047) (17). Conversely, the 2014 multivariate study performed by Harries et al. revealed no significant correlation between ER and PR and the probability of bone metastases [21].

Conversely, other univariate analyses revealed a substantial impact of both estrogen receptors (ER) and progesterone receptors (PR) on the heightened likelihood of bone being the primary location of metastases. [22]. There is no known mechanism for the +ve hormone receptor BC's propensity to metastasize to the bone, although studies have suggested that BC cells diffuse [23,24].

Regarding the differences observed among the results mentioned above, various factors play an important role, such as the sample size included in each study, the length of the patient's follow-up, the duration of the disease diagnosis, whether it was recent or late, and the effect of

individual adjuvant treatments on incidence [24]. Furthermore, a number of causes were proposed to be responsible for bony metastasis [25,26].

A number of causes were proposed to be in charge of bony metastasis. The factors that elevate the incidence of bone cancer include the blood supply. The bone marrow gets blood from the breast via the vertebral-venous plexus, which is likely a principal factor in the metastasis of breast cancer to the bone since haematogenous dissemination considerably facilitates distant metastasis in breast cancer. [27].

Fundamental attributes:

The mean age of the patients in this study was 50.08 years, with a standard deviation of 11.8 years, and ages ranged from 29 to 81 years. Patients aged 45 years or younger constituted the largest proportion of the cohort, accounting for 60% of the total. In regard to menopausal status, 56% of cases with bony metastasis occurred during the premenopausal period, whereas 78.1% of patients in the control group were in the postmenopausal period.

In comparison to other studies, Billena and colleagues found in their 2021 study that the median age of the patients included in their study was 47 years (ranging between 18 and 76 years) [28]. Another study conducted by Diessner and colleagues in 2016 noticed that the mean and SD of age at primary diagnosis of the 226 patients in their study with bone-only metastases was 65 ±14.3 years, which ranged between 30 and 93 years [17].

Ultimately, Başdelioğlu and associates discovered an alternative outcome in their research. The mean age of the participants was 55.9 years, with a range spanning from 22 to 94 years. [29]. The sample size in each study, together with ethno-geography and data sources, may account for the discrepancies shown in the conclusions above.

5. CONCLUSION

Many identified variables heighten the probability of breast cancer spread. The greatest prevalence of bone metastases was linked to negative estrogen and progesterone receptors (46.2% and 49%, respectively). At the same time, no significant statistical association (P= 0.65) was seen between bone metastasis and Her2neu receptors. Bone-only metastases are typically linked to positive ER and PR hormonal status. IDC histological type is more commonly linked to bone-only metastasis than ILC; bone-only metastasis is primarily associated with positive lymph node involvement, particularly N1 status; and premenopausal women, 45 years of age and younger, are often associated with bone-only metastasis

Recommendation:

Further extensive investigation is necessary to validate the findings and extrapolate the results. Formulate a treatment strategy and implement preventive strategies to mitigate any issues that may adversely affect quality of life.

Ethical consideration

The scientific and ethical committee of the Iraqi Board of Medical Specialties provided the idea for the study with a thorough discussion and ultimately gave their approval. Prior to starting data collecting, the oncology hospital's health authority's approval was obtained.

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