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De Novo bone metastasis in breast cancer: tumor biology and survival outcomes in a retrospective study from Pakistan

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Abstract

Purpose Breast cancer is the leading cause of cancer-related deaths among women, with 20–30% of early-stage patients eventually developing metastases, often in bones. Despite the high incidence, risk factors for de novo bone metastasis are understudied in local populations.

Methods This single-center, retrospective study was conducted at Aga Khan University Hospital, Karachi. Patient demographics, tumor characteristics, and risk factors were assessed. Patients with de novo bone metastasis were compared to non-stage IV cases using binary univariate and multivariate logistic regression, with significance set at $p < 0.05$.

Results Among 2565 patients, 93 (3.6%) presented with bone only metastasis (BOM) and 135 (5.3%) presented with bone and visceral metastasis together. The median age was 51 years, with females predominating. Multivariate analysis revealed that triple-negative breast carcinoma had lower odds (OR 0.36, 95% CI (0.16–0.79) $p < 0.001$). Advanced T and N stages and tumor grade II were linked to higher odds of bone-only metastasis. The 2-year overall survival of participants with BOM was 93% (CI: 83.7–97%).

Conclusion This study identifies key risk factors that provide the basis for early detection and intervention strategies. While it has a few limitations, these findings can guide future research and inform risk assessment models for more diverse populations.

Keywords Breast cancer, Bone metastasis, Stage IV, Overall survival

Introduction

Breast cancer is the most common malignancy worldwide and the leading cause of cancer-related mortality among women [1]. Around 3–6% of patients present with de novo metastatic breast cancer (MBC) in high-income countries, while the percentage is much higher in low-income countries, estimated at 10–30% [2]. In developing countries, the late-stage presentation may be attributed to limited screening, patient-specific delays, and adverse tumor biology [3, 4].

Bone is the most common site of MBC, frequently involving the spine, ribs, pelvis, and long bones, and the

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initial site of distant metastasis in 25–40% of advanced cases [5]. Bone metastases result in substantial morbidity due to increased bone resorption, causing significant symptomatic skeletal-related events (SREs) such as pathological fractures, spinal cord compression, cancer-related pain, and tumor-induced hypercalcemia [6]. SREs are associated with poor morbidity and mortality, with literature stating up to a median survival of only 7 months as compared to asymptomatic bone metastasis [7, 8]. Additionally, these complications significantly impact quality of life by impairing mobility and increasing pain levels, leading to rising rates of hospitalization, which further contribute to the disease burden [9]. As a result, these patients' treatment modalities are shaped to cater to the increased need for palliative interventions, such as bisphosphonates or denosumab, with about 41% requiring radiotherapy for pain control, 10% eventually needing surgical intervention, and almost all patients requiring close monitoring for disease progression [10].

A study by Ali et al. found that among 70 patients with metastatic breast cancer in Pakistan, bone was the most frequently involved site affecting 42 patients [11]. Moreover, a study that analyzed 125 patients with breast cancer in a tertiary care hospital of Pakistan found that 88.8% presented late and 59% had advanced-stage diseases [12]. These findings highlight the crucial need to identify risk factors associated with the development of de novo bone metastases to inform target screening strategies, thereby reducing the disease burden.

Even though there is extensive literature on risk factors related to recurrence and progression to bone, such as age, tumor size, and lymph node involvement, only a few studies have explored factors for de novo metastasis that are not influenced by treatment and may represent tumor biology more accurately [13].

To address this lack of evidence, we conducted a study to determine the clinical features and tumor biology in patients with de novo bone metastasis and compare them with non-stage IV breast cancer patients. Additionally, factors affecting prognosis among patients with bone metastasis are evaluated. To the best of our research, no similar study has been published from our part of the world.

Methods

Study design and setting

This single-center, retrospective study analyzed patient records from the Breast cancer registry at the Aga Khan University Hospital (AKUH), Karachi, Pakistan. It is a hospital-based registry established in 2009 that reports data on breast cancer patients presenting to AKUH, including demographic details, clinical presentation, tumor biology, staging, treatment modalities, and outcomes. It is one of the largest cancer registries in Pakistan and is suitable for the study because it reflects the patterns and outcomes of breast cancer in a diverse patient population.

Sampling and participants

A non-probability consecutive sampling method was employed, utilizing data from a prospectively maintained cancer registry at Aga Khan University Hospital. The study included all patients with biopsy-proven breast carcinoma presenting to the hospital between January 1, 2011, and December 31, 2020, with or without bone metastasis at the time of initial assessment.

Inclusion criteria

- All breast cancer patients aged 18 years and above.
- Both non-stage IV and stage IV patients with de novo metastasis to bone with or without additional visceral metastasis.
- Patients at the initial presentation, without prior treatment.

Exclusion criteria

- Patients with tumor histology other than carcinoma.
- Isolated visceral metastases such as liver, lung, and brain at presentation without bone involvement.
- Bilateral breast cancer.
- Patients presenting with recurrence or prior treatment.
- Records with unknown stage, grade, and tumor subtype.

For the survival analysis, patients with less than 1 month of follow-up were also excluded. Detailed eligibility criteria are shown in Fig. 1.

Data collection

Patient demographic factors comprised age, gender, date of presentation, diagnosis, and date of death or last follow-up. Tumor characteristics included histopathological features based on the International Classification of Diseases for Oncology, Third Edition, tumor subtypes, and clinical stages according to the American Joint Committee on Cancer (AJCC) staging 8th edition. Tumor grading was based on the Nottingham Criteria [14–16].

According to the hospital's standard of care, bone metastasis was primarily diagnosed through Bone Scintigraphy scans. When these were not available, other modalities such as X-rays, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) were used.

Statistical analysis

Subjects were grouped into three categories:

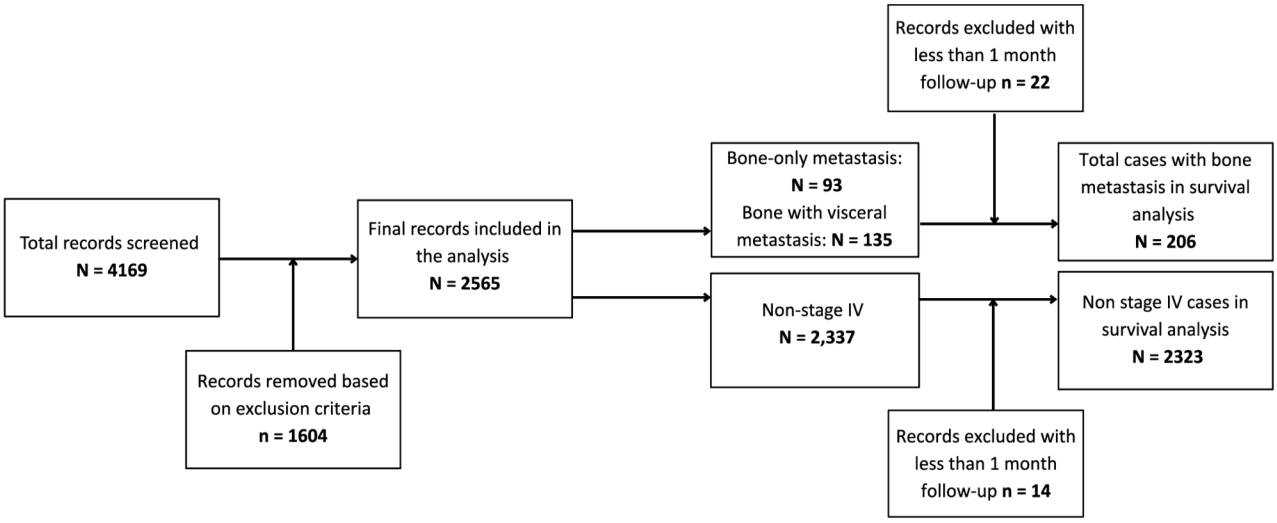

Fig. 1 Flow diagram of patient selection

1) De novo bone-only metastasis (BOM) without concurrent visceral involvement.
2) De novo bone metastasis with concurrent visceral involvement.
3) Non-stage IV participants.

Continuous variables were reported as mean ± standard deviation or median with interquartile range (IQR) depending on the normality of the data. Categorical variables were reported as frequencies and percentages and compared using chi-square and Fisher's exact tests. Independent variables included patient and tumor

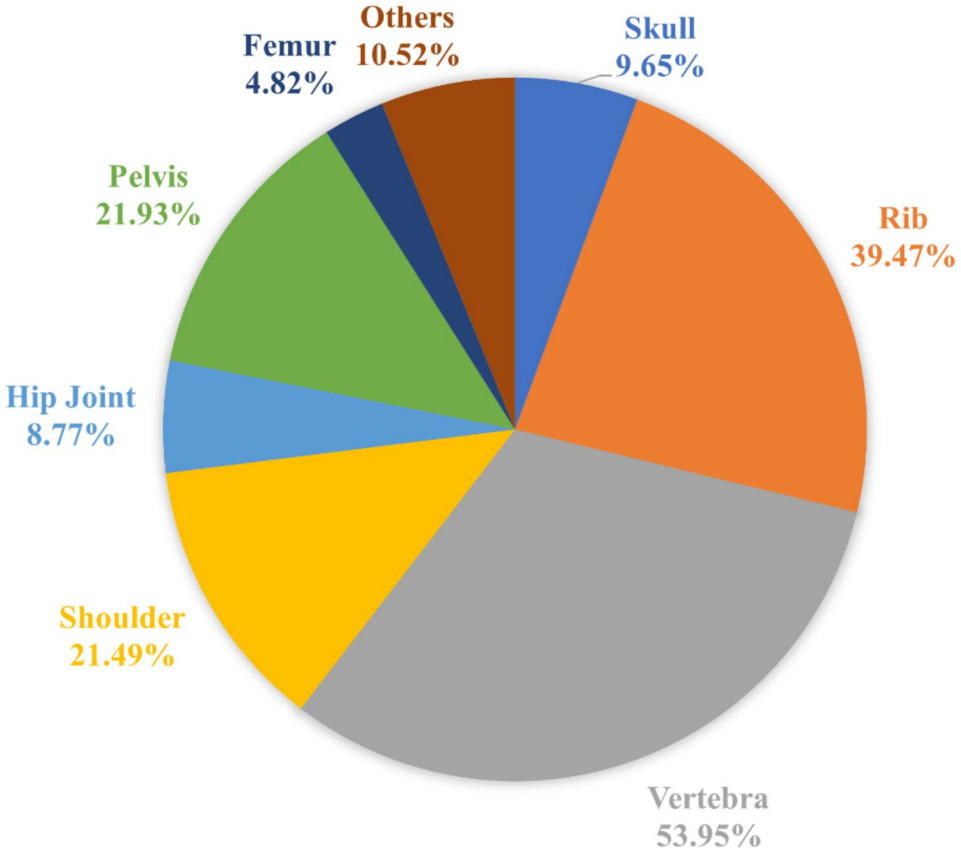

Fig. 2 Distribution of Metastatic Bone Sites Among Patients with Bone Metastasis

Table 1 Baseline characteristics and disease characteristics

Baseline Characteristics	Bone-only metastasis	Bone with visceral metastasis	Non-stage IV	*P*-value
	n (%)	n (%)	n (%)	
N	93(3.6)	135 (5.3)	2,337 (91.1)	
Age				0.974
> 51	47 (50.5)	65 (48.2)	1,130 (48.4)	
≥ 51	46 (49.5)	70 (51.9)	1,207 (51.7)	
Gender				0.021[†]
Female	91 (97.9)	131 (97.0)	2,320 (99.3)	
Male	2 (2.2)	4 (3.0)	17 (0.7)	
Site primary				< 0.001
Breast UOQ[a]	29 (31.2)	30 (22.2)	784 (33.6)	
Breast Overlapping Lesion	19 (20.4)	21 (15.6)	496 (21.2)	
Breast NOS[b]	10 (10.8)	40 (29.6)	242 (10.4)	
Others	35 (37.6)	44 (32.6)	815 (34.9)	
Histology				0.045
In situ carcinoma (DCIS[c], Intraductal)	0 (0.0)	0 (0.0)	41 (1.8)	
Invasive breast carcinoma- No special type	81 (87.1)	119 (88.2)	1,905 (81.5)	
Invasive lobular carcinoma	8 (8.6)	8 (5.9)	134 (5.7)	
Others	4 (4.3)	8 (5.9)	257 (11.0)	
Molecular Subgroup				0.014
Luminal A	60 (64.5)	78 (57.8)	1,327 (56.8)	
Luminal B	16 (17.2)	33 (24.4)	420 (18.0)	
TNBC[d]	7 (7.5)	13 (9.6)	420 (18.0)	
HER-type	10 (10.8)	11 (8.2)	170 (7.3)	
Clinical T stage				< 0.001
T0/Tis	0 (0.0)	0 (0.0)	76 (3.3)	
T1/T2	44 (47.3)	49 (36.3)	1,584 (67.8)	
T3/T4	49 (52.7)	86 (63.7)	677 (29.0)	
Clinical N stage				< 0.001
N0	20 (21.5)	24 (17.8)	1,162 (49.7)	
N1	58 (62.4)	81 (60.0)	967 (41.4)	
N2	11 (11.8)	20 (14.8)	171 (7.3)	
N3	4 (4.3)	10 (7.4)	37 (1.6)	
Grade				0.013
I	1 (1.1)	4 (3.0)	137 (5.9)	
II	65 (70.0)	74 (54.8)	1,259 (53.9)	
III	27 (29.0)	57 (42.2)	941 (40.3)	

[†]Fischer Exact test

All other p-values were calculated by chi-square test

([a]Upper Outer Quadrant

[b]Not Otherwise Specified

[c]Ductal Carcinoma in Situ

[d]Triple-negative breast cancer)

characteristics. Binary univariate logistic regression was employed to assess the association of all independent variables and the occurrence of de novo bone metastasis (with and without visceral involvement). Variables with significant univariate tests and those of known clinical importance were selected for multivariate logistic regression, which included four variables. The significance level for chi-squared, Fisher's exact tests, T-tests, and multivariate logistic regression was set at $p < 0.05$, indicating statistical significance.

For survival analysis, the Kaplan-Meier method was used to calculate Overall Survival (OS), and differences between groups were compared using the log-rank test. Cox proportional hazards models were used to assess the factors independently associated with OS. All statistical analyses were performed using STATA version 29.

Table 2 Univariate and multivariate regression of participants with bone only metastasis at initial presentation

Factors	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age				
< 51 (ref)	-	-	-	-
≥ 51	0.93 (0.62, 1.41)	0.737	-	-
Gender				
Male (Ref)	-	-	-	-
Female	0.28 (0.06, 1.27)	0.099	-	-
Site				
Breast UOQ[a] (ref)	-	-	-	-
Breast Overlapping Lesion	1.04 (0.58, 1.87)	0.902	-	-
Breast NOS[b]	1.15 (0.55, 2.39)	0.713	-	-
Others	1.17 (0.71, 1.93)	0.540	-	-
Histology				
Invasive breast carcinoma- No special type (ref)	-	-	-	-
Lobular	1.40 (0.67, 2.96)	0.373	-	-
Others	0.43 (0.16, 1.18)	0.102	-	-
Molecular Subtype				
Luminal A (ref)	-	-	-	-
Luminal B	0.80 (0.46, 1.41)	0.442	0.71 (0.40, 1.26)	0.243
TNBC[d]	0.36 (0.16, 0.79)	0.011	0.36 (0.16, 0.82)	0.014
HER-type	1.24 (0.62, 2.46)	0.547	0.99 (0.49, 2.00)	0.97
Clinical T stage				
T1/T2 (Ref)	-	-	-	-
T3/T4	2.60 (1.71, 3.95)	< 0.001	2.05 (1.31, 3.21)	0.002
Clinical N stage				
N0 (ref)	-	-	-	-
N1	3.26 (1.95, 5.46)	< 0.001	2.70 (1.59, 4.62)	< 0.001
N2	3.49 (1.64, 7.41)	0.001	2.69 (1.22, 5.95)	0.014
N3	6.75 (1.91, 18.0)	0.002	4.74 (1.47, 15.31)	0.009
Grade				
I	0.27(0.04, 2.00)	0.2	0.30 (0.04, 2.27)	0.040
II	1.84 (1.17, 2.91)	0.009	1.81 (1.12, 2.90)	< 0.001
III (Ref)	-	-	-	-

([a]Upper Outer Quadrant

[b]Not Otherwise Specified

[d]Triple-negative breast cancer)

Results

The study included 2565 patients, of whom 93 (3.6%) had BOM, 135 (5.3%) had bone metastasis with other visceral metastasis, and 2337 (91.1%) were non-stage IV at diagnosis. Figure 2 illustrates the distribution of various metastatic sites within the bone. The vertebra (53.95%) and ribs (39.47%) were the most common sites, followed by the pelvis (21.93%).

Baseline and disease characteristics

The median age of all participants was 51 years (IQR: 19 years). The baseline characteristics distribution among the three groups has been presented in Table 1. The differences between the groups were evaluated using the Fisher Exact and Chi-square tests, and relevant *p*-values were calculated.

Univariate and multivariate analysis of factors affecting the development of bone metastasis

The univariate binary logistic regression analysis identified several factors significantly associated with the development of BOM. For the multivariate analysis, variables were selected based on their statistical and clinical significance. These included molecular subtype, clinical T stage, clinical N stage, and tumor grade. Gender, although statistically significant, was not considered due to small number of male participants.

The multivariate analysis confirmed several independent predictors of BOM. Patients with the TNBC molecular subtype showed reduced odds of metastasis (OR: 0.36, 95% CI: 0.16–0.82, $p = 0.014$) relative to the Luminal A group. Advanced T stages (T3/T4) (OR: 2.05, 95% CI: 1.31–3.21, $p = 0.002$) and N3 clinical stage (OR: 4.74, 95% CI: 1.47–15.31, $p = 0.009$) were also significant predictors.

Table 3 Univariate and multivariate regression of patients with bone and visceral metastasis at initial presentation

Factors	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age				
< 51 (ref)	-	-	-	-
≥ 51	1.02 (0.72, 1.45)	0.89	-	-
Gender				
Male (ref)	-	-	-	-
Female	0.20 (0.07, 0.63)	0.006	-	-
Site				
Breast UOQ[a] (ref)				
Breast Overlapping Lesion	1.11 (0.63, 1.96)	0.722	-	-
Breast NOS[b]	4.44 (2.70, 7.28)	< 0.001	-	-
Others	1.42 (0.88, 2.29)	0.146	-	-
Histology				
Invasive breast carcinoma- No special type (ref)	-	-		
Lobular	0.96 (0.46, 2.00)	0.904	-	-
Others	0.58 (0.28, 1.21)	0.149	-	-
Molecular Subtype				
Luminal A (ref)	-	-	-	-
Luminal B	1.27 (0.83, 1.94)	0.263	1.11 (0.72, 1.71)	0.637
TNBC[d]	0.51 (0.28, 0.93)	0.029	0.43 (0.23, 0.78)	0.006
HER-type	1.05 (0.54, 2.00)	0.894	0.80 (0.41, 1.55)	0.506
Clinical T stage				
T1/T2 (ref)	-	-	-	-
T3/T4	4.10 (2.85, 5.89)	< 0.001	2.97 (2.02, 4.37)	< 0.001
Clinical N stage				
N0 (ref)	-	-	-	-
N1	3.79 (2.39, 6.03)	< 0.001	2.83 (1.75, 4.57)	< 0.001
N2	5.29 (2.86, 9.78)	< 0.001	3.20 (1.67, 6.13)	< 0.001
N3	12.2 (5.45, 27.39)	< 0.001	7.21 (3.08, 16.85)	< 0.001
Grade				
I	1.95 (0.70, 5.41)	0.202	-	-
II	1.96 (0.70, 5.49)	0.201	-	-
III (ref)	-	-	-	-

([a]Upper Outer Quadrant

[b]Not Otherwise Specified

[d]Triple-negative breast cancer)

Additionally, intermediate-grade tumors (Grade II) showed a higher likelihood of metastasis (OR: 1.81, 95% CI: 1.12–2.90, $p < 0.001$) (Table 2).

A univariate/multivariate binary logistic analysis was also done to assess the factors associated with the development of bone with visceral metastasis. The multivariate analysis confirmed several independent predictors of bone with visceral metastasis. Patients with the TNBC molecular subtype showed reduced odds of metastasis (OR: 0.43, 95% CI: 0.23–0.78, $p = 0.006$) relative to the Luminal A group. Advanced T stages (T3/T4) (OR: 2.97, 95% CI:2.02–4.37, $p < 0.001$) and N1, N2, and N3 clinical stages were also significant predictors (Table 3).

Survival analysis

The median follow-up period for all participants was 71 months. The 1-year, 2-year, and 5-year OS of all participants with bone metastasis, with and without other visceral metastasis, included in survival analysis ($n = 206$) was 91.1% (95% CI: 86.0-94.4%), 80.1% (95% CI: 73.1- 85.4%), and 56.4% (95% CI: 45.5-66.0%) respectively, evaluated using the Kaplan Meier method.

The 2-year OS of participants with BOM was 93.0% (95% CI: 83.7-97.0%) at a median follow-up of 101 months, which compared favourably to those who had concurrent visceral metastasis (liver, lung, brain, and other organs) and had a 2-year OS of 69.5% (95% CI: 58.9-77.9%) at a median follow-up of 47 months ($p < 0.001$). For non-stage IV patients, the 2-year OS was 96.7% (95% CI: 95.8-97.5%) with a median follow-up of 62 months, which significantly differed from the BOM group ($p = 0.005$). These differences are illustrated in Fig. 3.

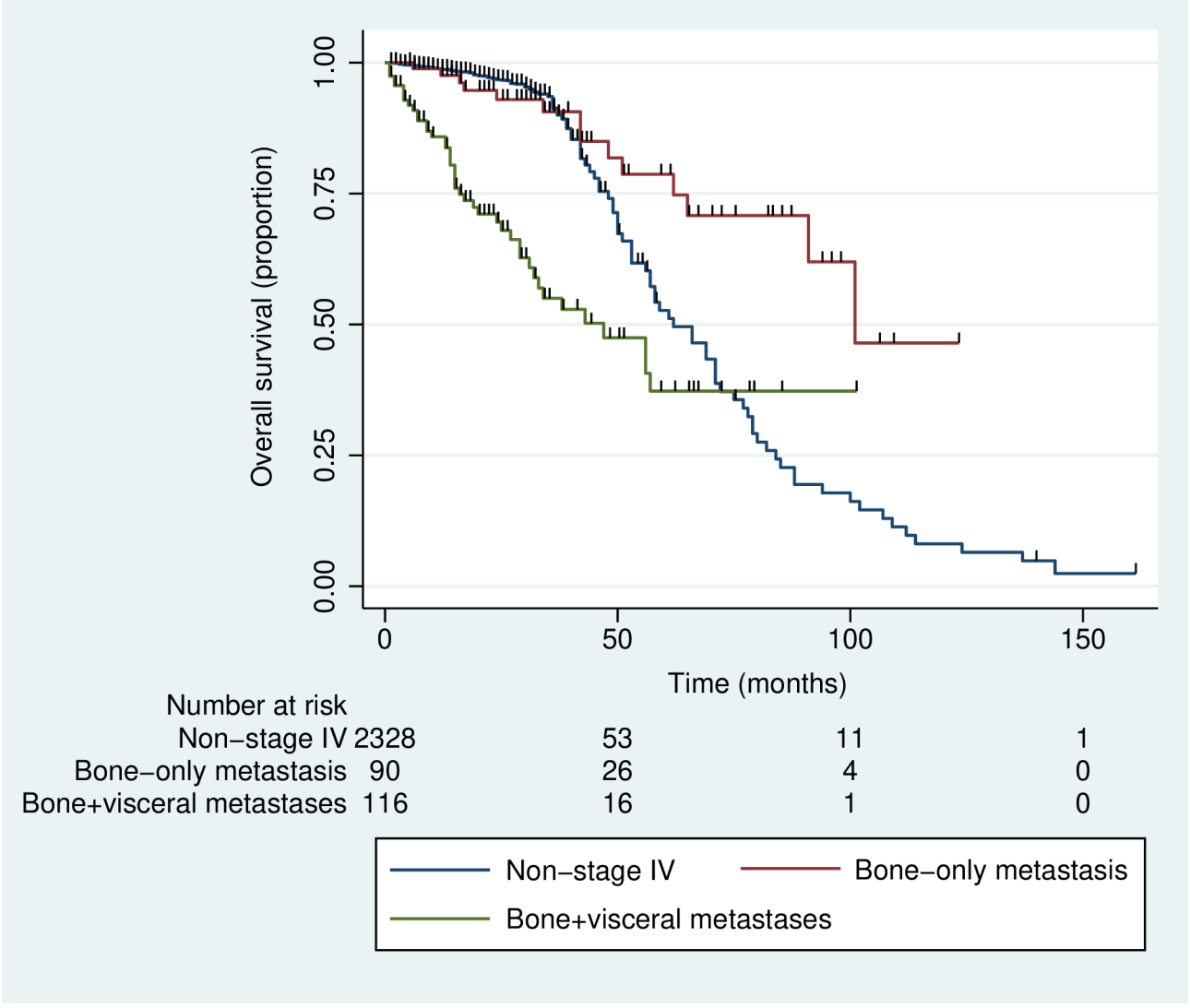

Fig. 3 Kaplan-Meier plot of overall survival probabilities according to bone with or without additional metastasis

The survival analysis of participants with bone metastasis, with and without other visceral metastasis, by molecular subtypes showed that molecular subtypes significantly impact outcomes ($p = 0.037$). TNBC had the worst prognosis, with a 1-year OS of 64.1% (95% CI: 32.9-83.7%). This is shown in Fig. 4.

Cox regression analysis for factors affecting overall survival

In the Cox regression analysis of factors affecting OS among participants with bone metastasis, with and without other visceral metastasis, only the molecular subtype emerged as a significant factor influencing the hazard ratio (HR). The HR for TNBC 2.93 (95% CI: 1.28–6.69, $p < 0.001$), indicating that patients with TNBC subtype have a significantly worse prognosis compared to Luminal A (Table 4). Multivariate Cox regression was not performed due to the non-significance of other predictors.

Discussion

Data on the clinical features associated with de novo bone metastasis in breast cancer are limited. This study is the first detailed analysis from Pakistan to investigate the clinicopathological factors linked to de novo bone metastasis in breast cancer patients. It provides a comprehensive evaluation of these factors and assesses their prognostic significance, specifically within a lower income setting where there are general trends towards lower incidence rates than in high-income countries, but higher mortality rates due to inadequate health services and other factors [1, 17].

The pattern of bone involvement in our study was like other studies, indicating vertebrae as the most frequent site, followed by ribs [18, 19]. This is due to the dissemination of breast cancer cells to neighboring structures such as vertebrae via the Batson venous plexus, a network

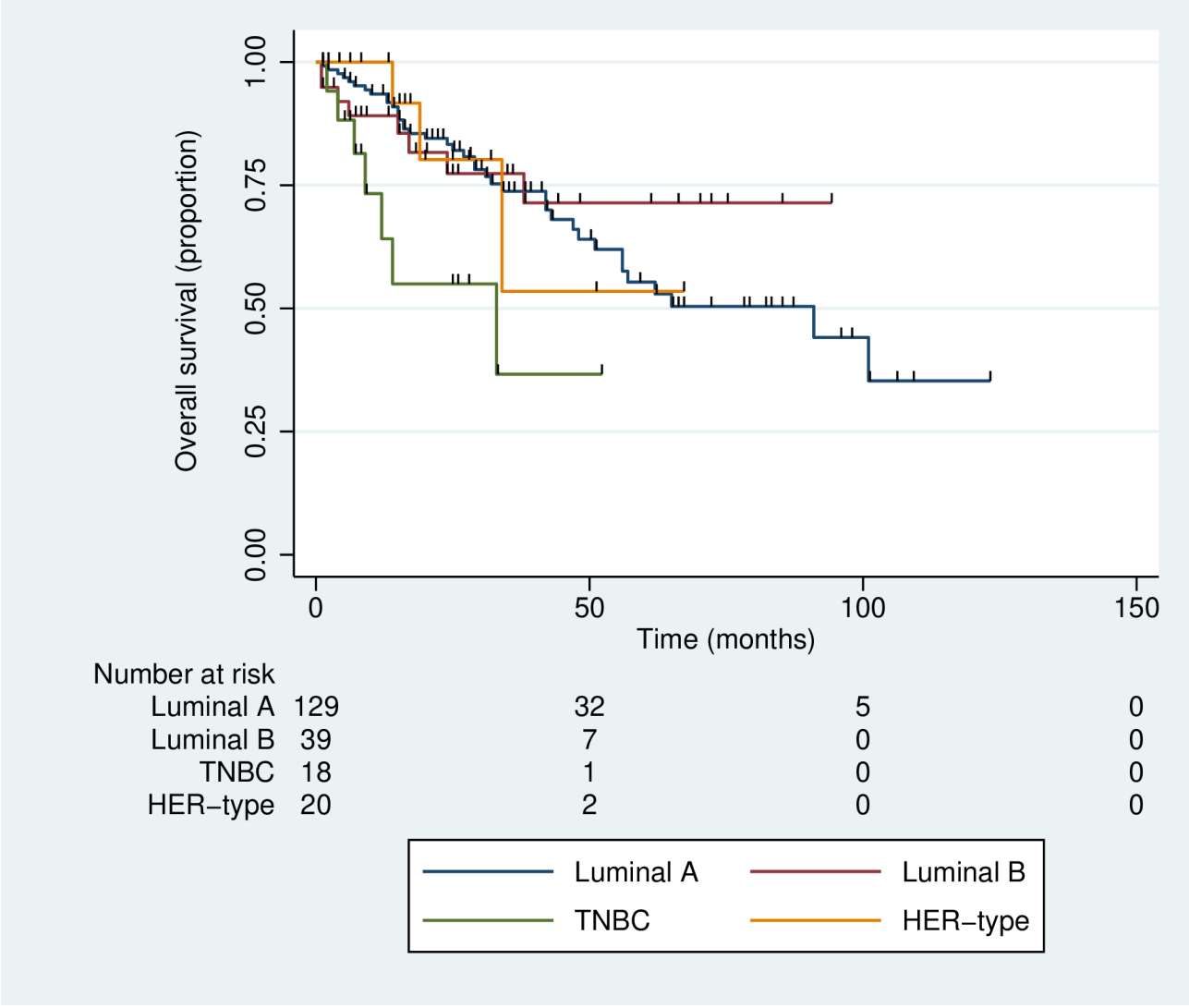

Fig. 4 Kaplan-Meier plot of overall survival probabilities according to molecular subtype

of valveless paravertebral veins connecting internal thoracic and intercostal veins to the veins draining the vertebrae [20].

The degree of tumor differentiation has been identified as a predictor of bone metastasis [21]. In our study, among patients with known histological grades, grade II tumors were associated with higher odds of metastasis. The findings align with a study conducted using the Surveillance, Epidemiology, and End Results (2010–2018) (SEER) cohort, which identified histological grades II and III as independent predictors of metastasis [22]. Although the grade is primarily a prognostic factor, it is correlated with receptor status and hence may influence the initial spread to bone [23].

Larger tumor size and lymph node involvement are documented to increase the risk of bone metastasis across multiple studies, as demonstrated in our results; T3/T4 stage and N1-N3 stages were linked to higher odds of bone metastasis [19, 24, 25]. In malignant tumors, T and N stages reflect tumor volume and progressive involvement of adjacent structures and lymph nodes, indicating the invasive potential of the disease [16].

Moreover, the molecular subtype is a well-established factor influencing metastasis, with hormone-receptor-positive tumors preferentially metastasizing to bone [26]. Our study showed a similar trend, as TNBC was independently associated with reduced odds of bone metastasis as compared to the Luminal A subtype. Gong et al. (2018) supported these findings, reporting lower odds of bone metastasis in triple-negative tumors [OR: 0.470 (95% CI: 0.426-0.519), $p < 0.001$] as compared to the hormone-receptor-positive category [23]. In mouse models, estrogen receptor activation has been shown to induce tumor secretion of osteolytic factors like parathyroid

Table 4 Cox regression analysis of patients with bone metastasis

Factors	Unadjusted HR (95% CI)	*P*-value
Age		
< 51 (ref)	-	-
≥ 51	1.34 (0.79, 2.27)	0.272
Gender		
Male (ref)	-	-
Female	0.44 (0.11, 1.85)	0.264
Site		
Breast UOQ[a] (ref)	-	-
Breast Overlapping Lesion	0.83 (0.38, 1.83)	0.649
Breast NOS[b]	1.56 (0.73, 3.35)	0.25
Others	0.75 (0.37, 1.53)	0.43
Histology/Behavior		
Invasive breast carcinoma-No special type (ref)	-	-
Lobular	0.51 (0.12, 2.09)	0.348
Others	N/A[†]	N/A[†]
Molecular Subtype		
Luminal A (Ref)	-	-
Luminal B	0.83 (0.39, 1.77)	0.625
TNBC [d]	2.93 (1.28, 6.69)	0.011
HER-type	0.86 (0.26, 2.79)	0.798
Clinical T stage		
T1/T2 (ref)	-	-
T3/T4	1.23 (0.72, 2.10)	0.443
Clinical N stage		
N0 (ref)	-	-
N1	1.02 (0.47, 2.21)	0.953
N2	1.52 (0.60, 3.86)	0.378
N3	1.08 (0.29, 4.10)	0.378
Grade		
I	1.77 (0.39, 7.95)	0.456
II	1.35 (0.74, 2.44)	0.326
III (ref)	-	-

([a]Upper Outer Quadrant

[b]Not Otherwise Specified

[d]Triple-negative breast cancer)

[†]No deaths recorded in the category cohort

hormone-related peptide, which may explain the osteolytic lesions in hormone-receptor-positive tumors compared to receptor-negative subtypes [27]. Molecular profiling may be used routinely to aid clinicians in predicting metastatic patterns, allowing for more tailored surveillance.

Upon evaluating survival among patients with metastatic bone involvement, the molecular subtype of the tumor was a significant predictor. TNBC had the lowest OS amongst all subtypes, consistent with results from other studies [28]. This may be due to the limited treatment options for TNBC, along with a more aggressive disease course [29]. Due to the relatively low incidence of initial bone-only metastasis in the TNBC subtype, estimated at 9.7% by Piedra-Delgado et al., tumor features and treatment options could be underexplored in this unique group but warrant further research due to adverse outcomes [30].

BOM generally has a more favorable prognosis as compared to metastasis to other organs. In Pan et al.'s cohort, the 3-year OS of the BOM was 49.8% as compared to 35.0% for bone with visceral metastasis [31]. This corresponds with our findings, highlighting how the presence of concurrent visceral involvement contributes to increased mortality. It underscores the importance of early identification and prompt management for BOM to prevent subsequent spread and improve patient outcomes.

A major limitation of the study is the single-center design, in which cases of de novo bone metastasis are limited to a tertiary hospital in a densely populated urban setting. Population-based registries are more appropriate to evaluate a wider number and variety of de novo cases thoroughly, including those attributed to healthcare disparities and delayed presentation [2].

Conclusion

By identifying higher T and N stages and intermediate grades as predictors for the development of BOM, the findings can contribute to growing evidence on risk stratification and targeted surveillance strategies. Timely intervention is critical since SREs can significantly affect the quality of life and increase morbidity rates. Understanding that patients with bone-only metastasis have better survival than those with visceral involvement can influence decisions regarding the aggressiveness of therapy. Unlike previous studies from high-income settings, this paper provides region-specific insight tailored to the local context, reflecting challenges associated with late-stage presentation, healthcare disparities, and weak screening protocols. By highlighting high-risk patients, resource-limited countries like Pakistan can prioritize diagnostic imaging and systemic therapy resources more effectively to improve outcomes.

Abbreviations

AJCC	American Joint Committee on Cancer
OR	Odds Ratio
CIs	Confidence intervals
UOQ	Upper Outer Quadrant
NOS	Not Otherwise Specified
DCIS	Ductal Carcinoma In Situ
TNBC	Triple-negative breast cancer
HER2	Human epidermal growth factor receptor 2-neu
ICD-O-3	International Classification of Diseases for Oncology-Third edition
OS	Overall survival
BOM	Bone-only metastasis
Ref	Reference category
HR	Hazard Ratio
SEER	Surveillance, Epidemiology, and End Result

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Author contributions
EA, AA, and MMA drafted the initial version of the manuscript, while EA and AA also performed data analysis. MMA, AJZ, and SZ contributed to the conception, design, and editing of the manuscript for the study. All authors have reviewed and approved the final manuscript. The corresponding author, SZ confirms that all listed authors meet the criteria for authorship and that no eligible contributors have been excluded.

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Data availability
The datasets used during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol complied with the Declaration of Helsinki and received approval from the Ethics Review Committee (ERC) of Aga Khan University (ERC ID: 2023-9402-27165). The ERC waived the need for consent from participants due to the retrospective nature of the study. To ensure confidentiality, all patient data was anonymized, and unique identifiers were assigned.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Disclaimers
The views expressed in the submitted article are our own and not the official position of the institution.

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