RESEARCH ARTICLE

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Risk Factors, Patterns, and Distribution of Bone Metastases and Skeletal-Related Events in High-Risk Breast Cancer Patients

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Abstract

Background: More than a quarter of breast cancer patients are at risk to develop recurrent metastases to the bone. **Objective:** This study was designed to identify risk factors and predilections of bone metastasis and skeletal-related events (SRE) in a population of breast cancer survivors initially diagnosed in advanced stages and with high-risks of relapse. **Methods:** Associated risk factors, distribution, and attainable treatment of bone metastasis and SRE were analyzed in a cohort of 1,329 breast cancer patients. The association with dependent variables was subsequently analyzed using multivariable logistic regression. Sociodemographic and adverse clinical characteristics were included as covariates of progression into bone metastasis and SREs. **Results:** Of 1329 breast cancer patients, 246 patients (18.5%) were diagnosed as metastatic breast cancer in which 232 of them (94.3%) had bone metastases. Spines were the most common sites of bone metastases (25.6%). In multivariable analysis, advanced stage at diagnosis (OR=1.840, 95%CI:1.198-2.826, P=0.005), luminal subtype (OR=1.788, 95%CI:1.206-2.652, P=0.045), lobular histology (OR=1.795, 95%CI:1.012-3/184, P=0.046), positive axillary lymph node (OR=1.771, 95%CI:1.087-2.886, P=0.022), multiple metabolic comorbidities (OR=2.193, 95%CI:1.371-3.508, P=0.001), early menopause (OR=2.136, 95%CI:1.116-4.464, P=0.046) were significantly associated with risk of recurrent bone metastases. SREs occurred in 89 (68.5%) patients. Several risk factors for SREs were early menopausal age (OR=2.342, P=0.024), advanced stages (OR=1.404, P=0.039), lobular histology (OR=2.279, P=0.007), and having multiple metabolic comorbidities (OR=1.728, P=0.039). **Conclusion:** Bone metastases and SREs are relatively high in breast cancer patients diagnosed in advanced stages. Luminal subtypes, having multiple metabolic comorbidities, and lobular histology are associated with higher risks of recurrent bone metastases. Living in rural areas and advanced stage at diagnosis as a risk factors for bone metastases might represent a social gradient of care delivery.

Keywords: Breast cancer- bone metastasis- skeletal-related events- luminal

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Introduction

Breast cancer incidence is continuously increasing over the past decades causing a significant morbidity and economic burden including in countries with traditionally low incidence rates (Sung et al., 2021). More than 90% of cancer-associated mortality is associated with primary distant metastases (Anwar et al., 2021; Harries et al., 2014). At primary diagnosis of breast cancer, around 5% patients presented with bone metastases (Harries et al., 2014). In patients with advanced stages at diagnosis, 75% of them develop bone metastases during period 10 years (Harries et al., 2014). Because of the rapid bone resorption and destruction, patients with bone metastases are often at risk to progress into skeletal related events (SREs) with manifestations of pathological fractures, spinal cord compression, cancer pain, tumor-induced hypercalcemia, and the urgent need of bone surgery or radiotherapy (Gartrell dan Saad, 2014). SREs might significantly deteriorate patient's functioning and quality of life (da Silva et al., 2019; von Moos et al., 2017). Therefore, it is saliently important to identify risk factors of patients at risks of bone metastases and SREs to further improve treatment, prognosis, as well as patient's quality of life and independent functioning.

With the current advancement of cancer treatment, patients with oligometastatic bone manifestation show remarkable prognosis compared patients with visceral metastases (Zhang et al., 2018). Early recognition of recurrent bone metastases is very important to initiate

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intervention and to decrease risks of progression into SREs (von Moos et al., 2017). Morphological imaging and functional examination are currently available to detect early bone metastasis, although the most recent technologies are not usually available in most cancer centers in developing countries (Anwar et al., 2018). The standard care for bone metastasis both using local controls including radiotherapy and systemic treatments has been often associated with immediate symptom relief and disease eradication (Coleman et al., 2020). However, in the progression into pathological bone fractures and spinal cord compression, patients might have further significant decreased quality of life and shorter overall survival (von Moos et al., 2017). The ideal treatment of bone involvement in breast cancer patients, however, depends on clinical manifestations and available resources.

Incidence rates of bone metastases vary according to breast cancer intrinsic subtypes (Buonomo et al., 2017; Zhang et al., 2018). Luminal subtypes have higher frequency of bone metastases than visceral metastases (Buonomo et al., 2017). Although data from current longitudinal studies have significantly improved our knowledge in the incidence and risk factors of recurrent bone metastases and SREs in breast cancer patients (Coleman et al., 2020), gaps according to accurate diagnosis, delivered treatment, and surveillance program remain high. Most studies are from developed nations in which majority patients are diagnosed in early stages and diagnostic imaging as well as multimodal treatments are readily available. There is relatively lack of information about risks of bone metastases among patients with predominantly advanced stages. In addition, attainable treatment of patients with bone metastases in developing countries is also rarely evaluated. Identification of determinants associated with bone metastases among breast cancer survivors will be useful to formulate prevention of SREs. Information about frequency of bone metastases and allocated treatment might also uncover the inadequate care that needs to be addressed through health policy.

Materials and Methods

Research design and construction of the patient cohort

A retrospective cohort study was performed to recruit all breast cancer patients operated at the Division of Surgical Oncology in a tertiary referral center from 2014 to 2018. All breast cancer patients fulfilling the subsequent eligibility criteria: pathologically confirmed diagnosis of breast cancer, obtained standard treatment, and a minimum of 6-month follow-up were recruited.

Data extraction

Patient's demographic and clinical variables were extracted from the electronic and medical chart. Pathological characteristics including histology, grades, types of surgery, peritumoral infiltration, and immunohistochemistry staining of estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67 were recapitulated from the pathological report as previously described (Anwar et al., 2020; Widodo et al., 2017). Staging was determined using American Joint Committee on Cancer (AJCC) (AJCC, 2010), the histological grades and types were classified according to the modified Bloom and Richardson system (mSBR) (Genestie et al., 1998) and the World Health Organization (WHO) guidelines (Sinn dan Kreipe, 2013), respectively. Standard of care (surgery, upfront and adjuvant chemotherapy, radiotherapy, and hormonal therapy) was summarized from the individual patient's chart. Subtypes of breast cancer were classified using surrogate immunohistochemistry staining according to the St. Gallen Consensus 2013 (Goldhirsch et al., 2013; Inwald et al., 2015). Clinical, demographic, and pathological variables were categorized according to the standard criteria as previously described (Anwar et al., 2020).

Clinical follow-up care and monitoring

In this study, the main outcome was bone metastasis and skeletal-related events. Bone metastasis was defined as the presence of cancer spread to the bone shown by clinical manifestations and confirmed with imaging including X-ray, computed tomography (CT)-scan, or magnetic resonance imaging (MRI). Skeletal-related events (SREs) are defined as any event related to progression of bone metastases that are manifested as pathological fractures, spinal compression syndrome, and the necessity of radiotherapy for pain control or surgery to the bone to stabilize the bone fractures (Clemons et al., 2012). Schedule for follow-up visits after core breast cancer care (surgery, chemotherapy, and radiotherapy) was programmed for once a month in the first 6 months and every 6 months afterward. During each visit, a comprehensive clinical examination was performed. Routine blood test, breast and abdominal ultrasonography, chest X-ray, mammography and bone scan were scheduled following the local and national recommendations. Any documented bone metastasis and SRE were recorded until the last date of the follow-up study in February 2021.

Statistical analysis

Continuous and categorical variables were compared between breast cancer patients with and without bone metastasis and SREs using the Mann-Whitney-U tests and $\chi 2$ tests. The association with dependent variables was subsequently analyzed using multivariable logistic regression. In this study, sociodemographic and adverse clinical characteristics were also included as covariates of progression into bone metastasis and SREs. SPSS 17.0 software (SPSS Inc., Chicago) was used to perform statistical analyses. All comparisons were performed in two-sided. P-value less than 0.05 was determined as statistically significant difference. The attributable variables associated with bone metastasis and SREs and statistical analyses were summarized in frequency tables.

Results

Clinical and sociodemographic characteristics of breast cancer patients at diagnosis

During the period of 2014-2018, 1,329 breast cancer patients with median age at diagnosis of 51 years were

recruited. The majority patients were diagnosed in late stages (72.2%, N=960), larger tumor size than 5 cm (68.9, N=916), positive axillary lymph nodes (75.6, N=1005). Tumor extension to the skin or the chest wall was found in 27.9% (N=371) patients. In this study, metastatic breast cancer was diagnosed in 246 patients in which 232 of them (94.3%) had bone metastases. Most patients resided in rural area (75.1%, N=998), from Javanese ethnics (97.7%, N=1298), and did not finish high school (44.8%, N=598). Between metastatic and non-metastatic breast cancers, differences of age at diagnosis, menarche, and menopause, as well as parity, breastfeeding practice, BMI, histological grades, family history of breast cancer were not statistically significant (as shown in the Table 1). Larger tumor size and positive axillary lymph nodes were observed in metastatic disease. The proportion of patients living in rural areas with lower educational levels were significantly observed in metastatic breast cancer patients

Table 1. Baseline Characteristics of Breast Cancer Patients at Diagnosis (N=1329). Distribution of demographic and clinicopathological variables of metastatic and non-metastatic breast cancer patients

Variables	Category	Overall N (%)	Metastatic breast cancer N (%)	Non metastatic breast cancer N (%)	P value[a]
Age	≤40 years	235 (17.7)	48 (3.6)	187 (14.1)	0.405
	>40 years	1094 (82.3)	198 (14.9)	896 (67.4)	
Ethnicity	Javanese	1297 (97.6)	237 (17.8)	1060 (79.8)	0.161
	Non-Javanese	32 (2.4)	9 (0.6)	23 (1.7)	
Residence	Urban	331 (24.9)	18 (1.3)	313 (23.6)	0.001
	Rural	998 (75.1)	228 (17.2)	770 (57.9)	
Education	Primary school	595 (44.8)	140 (10.5)	455 (34.2)	0.001
	High school and university	734 (55.2)	106 (8.0)	628 (47.3)	
Menarche	≤12 years	229 (17.2)	39 (2.9)	190 (14.3)	0.526
	>12 years	1100 (82.8)	207 (15.6)	893 (67.2)	
Menopause (years)	≤50 years	726 (54.6)	133 (10.0)	593 (44.6)	0.698
	>50 years	373 (28.1)	45 (3.4)	185 (13.9)	
Parity	Nulliparous	140 (10.5)	22 (1.6)	118 (8.9)	0.369
	Multiparous	1183 (58.1%)	224 (16.8)	965 (72.6)	
Breastfeeding	No	261 (19.6)	41 (3.1)	220 (16.6)	0.194
	Yes	1068 (80.4)	205 (15.4)	863 (64.9)	
BMI	≤25	844 (63.5)	172 (12.9)	672 (50.6)	0.021
	>25	485 (36.5)	74 (5.6)	411 (30.9)	
Family history	Yes	237 (7.8)	38 (2.8)	199 (14.9)	0.28
	No	1092 (82.2)	208 (15.6)	884 (66.5)	
Histology grade	I-II	265 (19.9)	49 (3.7)	216 (16.2)	0.993
	III	1064 (80.1)	197 (14.8)	867 (65.2)	
Histology type	Lobular	135 (10.2)	45 (3.4)	90 (6.8)	0.721
	Ductal and others	1194 (89.8)	201 (15.1)	993 (74.7)	
Stage	I-II	369 (37.8)	0 (0)	369 (37.8)	0.862
	III	714 (53.7)	0 (0)	714 (53.7)	
Tumor size	≤ 5 cm	413 (31.1)	55 (4.1)	358 (26.9)	0.001
	> 5 cm	916 (68.9)	191 (14.4)	725 (54.6)	
Tumor status	T1-3	958 (72.1)	104 (7.8)	854 (64.3)	0.001
	T4	371 (27.9)	142 (10.7)	229 (17.2)	
Node status	N0	324 (24.4)	18 (1.4)	306 (35.9)	0.001
	N1-3	1005 (75.6)	228 (17.2)	777 (58.4)	
ER	Negative	580 (43.6)	103 (7.7)	477 (35.9)	0.535
	Positive	749 (56.4)	143 (10.8)	606 (45.6)	
PR	Negative	771 (58.0)	153 (11.5)	618 (46.5)	0.141
	Positive	558 (42.0)	93 (7.0)	465 (35.0)	
HER2	Negative	956 (71.9)	167 (12.6)	789 (59.4)	0.732
	Positive	373 (28.0)	79 (5.9)	294 (22.1)	
Subtype	Luminal	765 (57.6)	144 (10.8)	621 (46.7)	0.732
	Non-Luminal	564 (42.4)	102 (7.7)	462 (34.8)	

[a] Chi-square test between metastatic and nonmetastatic breast cancer at diagnosis

Table 2. The Association of Clinicopathological Variables of Bone Metastatic Cancers and Skeletal-Related Events at Diagnosis. Odds ratios and 95% confidence intervals were calculated using multivariable binary logistic regression

Variables	Category	Reference	Bone metastases (OR, 95%CI)	Skeletal-related events (OR, 95%CI)
Age	≤40 years	>40 years	2.061 (1.001-4.329)	2.500 (1.103-5.649)
Ethnicity	Javanese	Non-Javanese	0.499 (0.172-1.448)	0.540 (0.173-1.686)
Residence	Rural	Urban	4.060 (1.798-9.169)	2.309 (1.094-4.875)
Menarche	≤12 years	>12 years	1.226 (0.703-2.138)	1.493 (0.849-2.628)
Menopause	≤50 years	> 50 years	1.163 (0.603-2.243)	1.171 (0.576-2.375)
Parity	Multiparity	Nulliparity	1.087 (0.416-2.839)	2.079 (0.714-6.058)
Breastfeeding practice	Yes	No	1.030 (0.496-2.139)	0.710 (0.347-1.452)
BMI	>25	≤25	1.072 (0.665-1.727)	1.036 (0.618-1.737)
Family history	Yes	No	1.872 (0.979-3.581)	1.436 (0.749-2.755)
Education	Lower than high school	High school and university	1.335 (0.853-2.087)	1.508 (0.970-2.570)
Tumor size	>5cm	≤ 5 cm	1.116 (0.684-1.821)	1.236 (0.727-2.102)
Axillary node	Positive	Negative	3.679 (1.654-8.182)	2.645 (1.236-5.661)
Estrogen receptor	Positive	Negative	6.802 (1.412-32.769)	5.405 (0.930-31.417)
Progesterone receptor	Positive	Negative	0.962 (0.548-1.688)	0.747 (0.416-1.341)
HER2 expression	Positive	Negative	1.605 (1.013-2.544)	1.400 (0.847-2.313)
Intrinsic subtype	Luminal	Non-Luminal	2.889 (0.634-13.170)	1.857 (0.336-10.267)
Histological type	Lobular	Ductal	2.158 (1.248-3.730)	2.189 (1.222-3.923)
Having multiple metabolic comorbidities	Yes	No	0.855 (0.460-1.588)	1.462 (0.795-2.688)

at diagnosis (Table 1).

The incidence of bone metastasis and SREs at diagnostic and in recurrent metastatic breast cancer patients

Bone metastases were found in 102 patients at diagnosis and in 130 patients as recurrent bone metastatic diseases after median follow up of 4.6 years. We grouped anatomical location of bone metastases into six regions including skull (cranium, maxillae, and mandibulae), upper extremity (humerus, radius, ulnae, carpals, and metacarpals), thoracic cage (clavicle, scapulae, ribs, sternum), spines (cervical, thoracal, lumbar, and sacral vertebrae), pelvic bones (iliac, pubic, and ischia bones), and lower extremity (femur, tibia, fibulae, ankle, and tarsal bones). Among all events of bone metastasis at diagnosis and in recurrent breast cancer, the spines were the most predilection sites of bone metastasis and SREs in breast cancer patients (Table 2). Bones in the lower extremity were the second most affected by distant spread from breast cancer (18.8%, N=69). Of 232 patients with bone metastasis, 101 (43.5%) had multiple metastatic sites. Deep somatic pain that is frequently perceived as dull pain in undetermined location is commonly experienced in bone pain due to metastatic lesion (Coleman et al., 2020). At the time of bone metastasis was diagnosed, 93.5% (N=217) patients had bone pain. However, 1.2% (N=14) patients also complained bone pain when the clinical and radiological imaging did not show any evidence of bone metastasis (Table 3).

Clinical and pathological risk factors of bone metastasis and SREs in metastatic breast cancer at diagnosis

Association of clinical and pathological determinants with bone metastasis and SREs in metastatic breast cancer was analyzed using multivariable regression analysis and was summarized in Supplementary Table 4. Patients living in rural areas (OR 4.060, 95%CI: 1.798-9.169, P=0.001), younger age at diagnosis (OR 2.061, 95%CI: 1.001-4.329, P=0.05), axillary lymph node positive (OR 3.679, 95%CI: 1.654-8.182, P=0.001), estrogen receptor positive (OR 6.802, 95%CI: 1.412-32.769, P=0.017), Her-2 receptor positive (OR 1.605, 95%CI: 1.013-2.544, P=0.044), and histology subtype of lobular carcinoma (OR 2.158, 95%CI: 1.248-3.730, P=0.006) were significantly associated with bone metastasis at diagnosis. Younger age than 40 years (OR 2.500, 95%CI: 1.103-5.649, P=0.028), living in rural area (OR 2.309, 95%CI: 1.094-4.875, P=0.028), and lobular carcinoma (OR 2.189, 95%CI: 1.222-3.923, P=0.008) were significantly associated with SREs in metastatic breast cancer at diagnosis.

Associations of clinicopathological and social variables with recurrent bone metastases after median follow-up of 4.6 years

In our study, breast cancer patients who were living in rural areas were significantly associated with recurrent bone metastasis (OR 1.749, 95% CI: 1.071-2.856, P=0.025). Post-menopausal women who were diagnosed breast cancer under 50 years were also significantly associated with the development of bone metastasis (OR 2.136, 95% CI: 1.116-4.464, P=0.046). The rates of metastatic bone disease were significantly higher in breast cancer who were initially diagnosed with axillary lymph node positive (OR 1.771, 95% CI:1.087-2.886, P=0.022) and in advance stages (OR 1.840, 95% CI: 1.198-2.826, P=0.005). Primary tumors with estrogen

Table 3. The Association of Clinicopathological Variables with the Risks of Recurrent Bone Metastases and Skeletal-Related Events in Breast Cancer Patients after Median Follow up of 4.6 Years. Odds ratios and 95% confidence intervals were calculated using multivariable binary logistic regression

Variables	Category	Reference	Bone metastases (OR, 95%CI)	Skeletal-related events (OR, 95%CI)
Age	≤40 years	>40 years	1.460 (0.730-2.195)	1.364 (0.627-2.924)
Ethnicity	Javanese	Non-Javanese	0.713 (0.227-2.240)	0.505 (0.159-1.608)
Residence	Rural	Urban	1.749 (1.071-2.856)	1.994 (1.140-3.490)
Menarche	≤12 years	>12 years	1.456 (0.908-2.334)	1.236 (0.724-2.110)
Menopause	≤50 years	> 50 years	2.136 (1.116-4.464)	2.342 (1.120-4.902)
Parity	Multiparity	Nulliparity	1.142 (0.451-2.892)	1.289 (0.446-3.720)
Breastfeeding practice	Yes	No	1.355 (0.676-2.715)	1.402 (0.650-3.023)
BMI	>25	≤25	0.919 (0.598-1.413)	1.024 (0.641-1.637)
Family history	Yes	No	0.967 (0.590-1.587)	0.992 (0.573-1.718)
Education	Lower than high school	High school and university	0.772 (0.511-1.165)	0.769 (0.485-1.782)
Stage	III (Advance)	I-II (Early)	1.840 (1.198-2.826)	2.327 (1.404-3.855)
Tumor size	>5cm	≤ 5 cm	0.893 (0.591-1.348)	0.883 (0.561-1.392)
Axillary node	Positive	Negative	1.771 (1.087-2.886)	1.795 (1.035-3.112)
Estrogen receptor	Positive	Negative	1.760 (1.192-2.596)	1.786 (1.160-2.749)
Progesterone receptor	Positive	Negative	0.741 (0.443-1.241)	0.642 (0.369-1.116)
HER2 expression	Positive	Negative	1.054 (0.676-1.644)	0.992 (0.604-1.631)
Intrinsic subtype	Luminal	Non-Luminal	1.788 (1.206-2.652)	1.548 (0.322-7.436)
Histological type	Lobular	Ductal	1.795 (1.012-3.184)	2.279 (1.258-4.129)
Having multiple metabolic comorbidities	Yes	No	2.193 (1.371-3.508)	1.728 (1.027-2.907)

receptor positive (OR = 1.760, 95% CI: 1.192-2.596, P=0.040), histology type of lobular (OR 1.795, 95% CI: 1.012-3.184, P=0.046), and intrinsic subtype of luminal (OR 1.788, 95%CI: 1.206-2.652, P=0.045) were significantly associated with recurrent metastatic disease to the bone. In addition, having multiple metabolic comorbidities were significantly associated with risks of recurrent bone metastasis (OR 2.193, 95% CI: 1.371-3.508, P=0.001) (Supplementary Table 5).

Several factors that predisposed patients to develop SREs as the complications of bone metastases were also identified. Using multivariable regression analysis, we found that breast cancer patients living in rural areas were significantly associated with higher risks of SREs (OR 1.994, 95% CI: 1.140-3.490, P=0.016). Post-menopausal women at younger age than 50 years were also associated with greater risks of SREs (OR 2.342, 95%CI: 1.120-4.902, P=0.024). Positive axillary lymph node and advanced stages at diagnosis were also significantly with higher risks of SREs (OR 1.795, 95%CI: 1.035-3.112, P=0.037 and OR 2.327, 95% CI: 1.404-3.855, P=0.039; respectively). Primary tumors with positive expression of estrogen receptor and histology type of lobular also had greater risks to develop SREs (OR 1.786, 95% CI: 1.160-2.749, P=0.046 and OR 2.279, 95% CI: 1.258-4.129, P=0.007; respectively). Breast cancer patients with multiple metabolic comorbidities at diagnosis were also significantly associated with risks to develop SREs (OR 1.728, 95% CI: 1.027-2.907, P=0.039), Supplementary Table 5.

Specific treatments for bone metastases and skeletal-related events (SREs)

In patients with bone metastases, 45.5% (N=106) received chemotherapy and 67.2% (N=156) received endocrine therapy. In association with specific bone pain and bone metastases, 86 patients (37.1%) were treated with non-opioid analgesic, 196 (84.5%) received opioid analgesic, 193 (83.2%) received radiotherapy. Only selected patients were treated with spine surgery (N=8, 3.4%) and bone stabilization (N=28, 12.1%) with bone stabilization and fixation.

Discussion

In our series of 1329 breast cancers, 232 patients were diagnosed with bone metastasis in which 102 were found at the time of diagnosis and 130 were detected after median follow-up of 4.6 years. The total incidence of bone metastasis was 17.4%, which was much higher than previously reported (12-13%) (Body et al., 2017; Buonomo et al., 2017; Liede et al., 2016). The spines were the most frequently affected from distant metastasis with higher proportion of SREs (Table 2). Other studies have also reported that the spines are the most predilection sites for bone metastasis in breast (Adler et al., 2019; Chen et al., 2017). Migration of breast cancer cells to the spines is facilitated through reverse spread via Batson plexus (Carpenter et al., 2021). Spine involvement to some extent indicates significant frailty because 10% of them have potential disease progression into pathological fractures, neurological deficits, and debilitating pain (Adler et al.,

2019).

In metastatic breast cancer at diagnosis, involvement of axillary node, estrogen receptor and Her-2 positivity were significantly associated with risks of bone metastases (Supplementary Table 4). Living in rural areas and lobular histology were associated with both bone metastasis and SREs at diagnosis (Supplementary Table 4). Additional variables including luminal subtype, advanced stages, and early menopause were found as risk factors of de novo bone metastases and SREs after median follow up of 4.6 years (Supplementary Table 5). Chen et al., (2017) identified positive lymph nodes as major risk factors for bone metastases among breast cancer patients. Lymph node infiltration is a risk factors for distant metastasis in breast cancer (Anwar et al., 2020). Positive axillary lymph node is also reported as an independent risk for bone metastases (Wei et al., 2008; Yamashiro et al., 2014) although another study failed to provide the evidence (Diessner et al., 2016). Bigger tumor size has been associated with an elevated risk of bone metastases although multivariate analysis does not consistently reveal the association (Wei et al., 2008; Yamashiro et al., 2015). Rather than tumor size, pathological stage tends to be risk factors for the development of bone metastasis (Yamashiro et al., 2014). We also confirmed previous study showing association between young age at diagnosis with bone metastases and risks of SREs (Diessner et al., 2016). Although effect of age at diagnosis with bone metastasis development is still controversial, Purushotham et al., (2014) reported the inverse correlation. Histological grade has been conversely associated with risk of bone metastases although our study did not find association between histological grades with risks of bone metastases and SREs (Supplementary Tables 4-5). Using combination of multivariate models with algorithms of chi-square and regression tree, Diessner et al., (2016) found that primary tumor characteristics including histological type, tumor size, axillary lymph node status, and histological grades played only trivial roles in the risk of recurrent bone metastases.

Bone remodeling is regulated by several mechanisms including estrogen levels by providing microenvironment to induce bone metastasis (Guise et al., 2004). Status of menopause has also been associated with elevated risks of bone metastases than visceral metastases (Coleman et al., 1998) although several studies were not able to show significant association (Body et al., 2017; Zhang et al., 2018). Our study found that menopause at younger age was associated with a higher risk of recurrent bone metastases and SREs (Supplementary Table 5). Lobular histology of breast cancer is also reported as a risk factors for bone metastases (Purushotham et al., 2014). Although our study also supported the relation of lobular type with risks of bone metastasis, further multivariate analysis showed lack of evidence with the premise that lobular histology represents as surrogate marker of intrinsic luminal subtype (Diessner et al., 2016). Subtypes of breast cancer with high expression of estrogen as luminal types have strong association with higher risks of bone metastasis (Anwar et al., 2020; Guo et al., 2020). Using multivariable analyses, we also found the association of luminal subtype with bone metastases and SREs (Supplementary Table 4-5). Although there is no solid evidence of the relation between metabolic syndrome and risks of bone spread, we found significant association between multiple metabolic comorbidities with recurrent bone metastases and SREs (Supplementary Table 5). Metabolic syndrome particularly obesity has been linked with distant metastases although not specifically to the bone (Annett et al., 2020; Anwar et al., 2021). Further research is required because clustering of metabolic comorbidities in our study is predominantly found in luminal subtypes that has been largely associated with elevated risk of bone metastasis among breast cancer patients.

In this study, diagnosis of bone metastases was determined using morphologic imaging of bone survey and computed tomography (CT)-scan due to lack of functional imaging availability in our center. Although our study used morphologic imaging only, the frequency of bone metastases is higher than other reports (Body et al., 2017; Buonomo et al., 2017; Liede et al., 2016). Lytic, sclerotic, or mixed features of a bone metastatic lesion can be detected using plain radiograph of bone survey only if the lesions affect more 50% loss of density in at least 1 cm of the bones (Coleman et al., 2020; Isaac et al., 2020). However, CT-scan provides additional information of potential infiltration of metastatic bone lesions into the adjacent soft tissue. Magnetic resonance imaging (MRI) provides better precision to display the integrity of spinal cord and the surrounding tissues in patients with spinal bone metastases (Isaac et al., 2020). In addition, bone metastatic lesions can be detected with functional imaging through uptake of radiolabeled dyes (Isaac et al., 2020). Bone scintigraphy detects bone turnover particularly for lytic lesions that usually needs second examination in borderline results. PET detects metastatic bone lesions through uptake of radiolabeled glucose with high sensitivity and relatively low specificity (Ulmert et al., 2015). Biopsy is required if imaging is not sufficient to differentiate with other pathology, relapse cases to assess nature of the disease and to determine systemic therapy (Isaac et al., 2020). Because this study particularly used morphologic imaging for detection, smaller or subtle bone metastatic lesions might not be detected.

Treatment of metastatic bone lesions consists of locoregional and systemic therapy involving multidisciplinary team members. We summarized treatment received by patients with bone metastases **(Table 6?).** Radiotherapy has been considered as safe and effective treatment of metastatic bone lesions. In general, single fraction radiotherapy up to 8-10 Gy for should be considered for uncomplicated bone metastatic lesions (Coleman et al., 2020). Multiple fractions of radiotherapy up to 10 x 3 Gy should be considered to achieve re-calcification of bone lesions and to provide local control of spinal metastases with spinal cord compression syndrome with compromised long-term prognosis (Lutz et al., 2017). Radiotherapy interrupts osteolysis, decreases tumor burden, alters neuromodulatory pain mechanisms through reduction of inflammatory mediators and cells including bradykinin, serotonin, adenosine triphosphate, lipids, and ion channels

(D'Oronzo et al., 2019; Erdogan dan Cicin, 2014). Radiotherapy also stimulates re-ossification around 80% of lytic lesions after period of 6 months (D'Oronzo et al., 2019). However, dose and volumes of radiotherapy are decided according to the ultimate aims of the cancer treatment (Coleman et al., 2020; Lutz et al., 2017). In palliative setting, the aim is to control symptoms and local disease growth by using combination treatment with orthopedic intervention and pain control (Coleman et al., 2020). In our study, 83.2% patients with bone metastases received radiotherapy both to achieve disease control and palliative intent. Further study is required to improve the outreach, cost-effectiveness, and the clinical outcome of radiotherapy in patients with various extension of bone metastases (DeGrendele dan O'Shaughnessy, 2003).

Although regional treatment with radiotherapy was commonly delivered, spine and bone stabilization surgery for SREs and pathological fractures were performed only 3.4% and 12.1%, respectively. Surgery is considered as both curative and palliative intents (Soeharno et al., 2018). Excisional surgery procedures can be performed as wide bone excision with curettage, cementing, and prosthesis and are usually performed in oligometastatic lesion with limited soft tissue involvement (Soeharno et al., 2018). To plan for a bone surgery, consideration of prognostic outcome is required because surgery procedures need time to heal and require cessation of other systemic therapies (Soeharno et al., 2018; Wegener et al., 2012). Bone metastasis in breast cancer patients is generally considered as favorable long-term survival particularly in oligometastatic lesion without involvement of visceral metastases. Several studies have argued that wide bone excisions are generally not required to preserve survival and pain control (Wegener et al., 2012). Palliative surgery includes internal and external fixation and are usually performed in lesions with fractures or high risk of pathological fractures, and with neurological vertebral symptoms to improve quality of life (Soeharno et al., 2018; Wegener et al., 2012).

Chemotherapy was administrated in 45.7% patients with bone metastasis (Table 6). Chemotherapy was commonly administrated to patients with metastatic breast cancer at diagnosis or to patients with accompanied visceral metastasis. Systematic treatment remains the primary strategy in the treatment of breast cancer patients with bone metastases in which preferred regiments depend on the intrinsic subtypes, previous administrated treatment, and extent of disease spread (Coleman et al., 2020). In hormonal resistant and triple negative breast cancers (TNBCs), primary chemotherapy using anthracycline- or taxane-based regimens are usually selected. Alternative options are recently available including monotherapy or combination of capecitabine, vinorelbine, gemcitabine, eribulin, or carboplatin. However, bone lesions usually have lower response rates to chemotherapy 7,39. To avoid high grade bone marrow suppression, concomitant radiotherapy and cytotoxic therapy are not usually delivered. Sequential treatment should be considered to determine the urgent need of pain relief or systemic disease control. In hormonal positive breast cancers, anti-estrogen therapy becomes the primary option in the absence of visceral crisis or rapidly progressive breast cancer with combination of CDK4/6 inhibitors, mTOR inhibitors, or PI3KCA inhibitors (Coleman et al., 2020; Shibata et al., 2016). Different from cytotoxic systemic therapy, antihormonal and targeted therapies can be concomitantly administrated with radiotherapy. However, options of systemic treatment for patients with recurrent bone metastases depend on the individual circumstances, performance, and disease dissemination (Coleman et al., 2020; Shibata et al., 2016). Bisphosphonate has been used to reduce risk of bone metastasis and SREs, and the benefit is higher particularly for postmenopausal women (Mei et al., 2020; Schmidt, 1995). In our study, 79.3% patients with metastatic bone lesions received bisphosphonate treatment. However, further study is also recommended to expand the use as well as to evaluate the tradeoffs the benefits and cost of chemotherapy and bone-modifying agents for each individual patient (Lipton, 2007; Mei et al., 2020).

This study identified predisposing factors for bone metastases among high-risk breast cancer patients that are potentially useful for SRE prevention and future planning to improve assessment and clinical management. The other strengths were the identification of disparity among breast cancer patients from different social-economic backgrounds and medical comorbidities. Attributable factors of clinical, pathological, and social determinants have been evaluated in multivariable analysis to minimize the competing selection biases. The particular limitations of this study lied in the natural weakness of retrospective study. In addition, specific variables of treatment including residual disease after surgery, completion of chemotherapy and hormonal therapy adherence were not specifically addressed in this study. Detection of bone lesions in this study used anatomical imaging that might detect larger size of metastatic lesions. To extend our findings, larger multicenter studies with prospective design are required to build further evidence of risk factors, prognosis, and to evaluate and improve the treatment of recurrent bone metastatic diseases that are frequently experienced by high-risk breast cancer patients.

In conclusion, frequency of bone metastases and SREs are relatively higher among high-risk breast patients. We identified axillary node infiltration, Luminal-A subtype, and lobular histology as risks factors of bone metastases and SREs in metastatic disease at diagnosis as well as in recurrent bone metastatic breast cancers. In this study, living in rural areas and advanced stages at diagnosis have been significantly associated with bone metastases indicating disparity in the healthcare delivery that need further intervention. Advancement in the diagnosis, clinical management, and prevention of progression into SREs are required to improve overall survival and quality of life.

Abbreviations

AJCC: American Joint Committee on Cancer
CDK: Cyclin-dependent Kinase
CT-scan: Computed Tomography -scan
EC: Ethical Clearance
ER: Estrogen Receptor

Her2: Human epidermal growth factor receptor 2
MRI: Magnetic Resonance Imaging
mSBR: modified Bloom and Richardson System
mTOR: mammalian Target of Rapamycin
OR: Odds Ratio
PET-scan: Positron Emission Tomography -scan
PI3KCA: Phosphatidylinositol 3-kinase
PR: Progesterone Receptor
SD: Standard Deviation
SRE: Skeletal-related event
TNBC: Triple Negative Breast Cancer
WHO: World Health Organization

Author Contribution Statement

SLA conceptualized the study. SLA, WSA, and EKD collected the data used for the analysis. SLA drafted the manuscript. All authors reviewed and approved the final draft of the manuscript.

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Ethics approval and consent

The study protocol has been approved by the Ethics Committee, Medical Research Council of the Universitas Gadjah Mada (Nr. 1049/EC/2018). The study has been performed in accordance with the Declaration of Helsinki. Informed consent was provided from all study participants.

Availability of data and materials

The dataset is available upon request to the corresponding author.

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Competing interest

All authors have declared for no existing conflict of interests.

References

Adler D, Pepke W, Akbar M (2019). Operative treatment of metastatic breast cancer in the spine with regard to molecular phenotypes. *J Cancer Metastasis Treat*, **2019**.

AJCC (2010). Breast Cancer Staging 7th Edition. *Am Jt Comm Cancer*, pp 1–2.

Annett S, Moore G, Robson T (2020). Obesity and cancer metastasis: Molecular and translational perspectives. *Cancers (Basel)*, **12**.

Anwar SL, Adistyawan G, Wulaningsih W, Gutenbrunner C, Nugraha B (2018). Rehabilitation for cancer survivors: How we can reduce the healthcare service inequality in low- and middle income countries. *Am J Phys Med Rehabil*, **1**.

Anwar SL, Avanti WS, Nugroho AC, Choridah L, Dwianingsih EK (2020). Risk factors of distant metastasis after surgery among different breast cancer subtypes: a hospital-based study in Indonesia. *Observational Study*, **18**, 117–33.

Anwar SL, Cahyono R, Prabowo D, Avanti WS, Choridah L (2021). Metabolic comorbidities and the association with risks of recurrent metastatic disease in breast cancer survivors. *BMC Cancer*, **21**, 1–13.

Body JJ, Quinn G, Talbot S, et al (2017). Systematic review and meta-analysis on the proportion of patients with breast cancer who develop bone metastases. *Crit Rev Oncol Hematol*, **115**.

Buonomo OC, Caredda E, Portarena I, et al (2017). New insights into the metastatic behavior after breast cancer surgery, according to well-established clinicopathological variables and molecular subtypes. *PLoS One*, **2017**.

Carpenter K, Decater T, Iwanaga J, et al (2021). Revisiting the vertebral venous plexus–a comprehensive review of the literature. *World Neurosurg*, **145**.

Chen WZ, Shen JF, Zhou Y, et al (2017). Clinical characteristics and risk factors for developing bone metastases in patients with breast cancer. *Sci Rep*, **7**.

Clemons M, Gelmon KA, Pritchard KI, Paterson AHG (2012). Bone-targeted agents and skeletal-related events in breast cancer patients with bone metastases: The state of the art. *Curr Oncol*, **19**.

Coleman R, Hadji P, Body JJ, et al (2020). Bone health in cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*, **31**.

Coleman RE, Smith P, Rubens RD (1998). Clinical course and prognostic factors following bone recurrence from breast cancer. *Br J Cancer*, **77**.

D'Oronzo S, Coleman R, Brown J, Silvestris F (2019). Metastatic bone disease: Pathogenesis and therapeutic options: Up-date on bone metastasis management. *J Bone Oncol*, **15**.

da Silva GT, Bergmann A, Thuler LCS (2019). Incidence and risk factors for bone metastasis in Non-Small Cell Lung Cancer. *Asian Pac J Cancer Prev*, **20**.

DeGrendele H, O'Shaughnessy JA (2003). Update on the use of radiopharmaceuticals for the treatment of painful bone metastases. *Clin Breast Cancer*, **4**.

Diessner J, Wischnewsky M, Stüber T, et al (2016). Evaluation of clinical parameters influencing the development of bone metastasis in breast cancer. *BMC Cancer*, **16**.

Erdogan B, Cicin I (2014). Medical treatment of breast cancer bone metastasis: From bisphosphonates to targeted drugs. *Asian Pac J Cancer Prev*, **2014**.

Gartrell BA, Saad F (2014). Managing bone metastases and reducing skeletal related events in prostate cancer. *Nat Rev Clin Oncol*, **2014**.

Genestie C, Zafrani B, Asselain B, et al (1998). Comparison of the prognostic value of Scarff-Bloom-Richardson and Nottingham histological grades in a series of 825 cases of breast cancer: Major importance of the mitotic count as a component of both grading systems. *Anticancer Res*, **18**, 571–76.

Goldhirsch A, Winer EP, Coates AS, et al (2013). Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol*, **24**, 2206–23.

Guise TA, Kozlow WM, Heras-Herzig A, et al (2004). Molecular mechanisms of breast cancer metastases to bone. *Clin Breast Cancer*, **5**.

Guo Y, Arciero CA, Jiang R, et al (2020). Different breast cancer subtypes show different metastatic patterns: A Study from A Large Public Database. *Asian Pac J Cancer Prev*, **21**.

Harries M, Taylor A, Holmberg L, et al (2014). Incidence of bone metastases and survival after a diagnosis of bone metastases in breast cancer patients. *Cancer Epidemiol*, **38**, 427–34.

Inwald EC, Koller M, Klinkhammer-Schalke M, et al (2015).

4-IHC classification of breast cancer subtypes in a large cohort of a clinical cancer registry: use in clinical routine for therapeutic decisions and its effect on survival. *Breast Cancer Res Treat*, **2015**.

Isaac A, Dalili D, Dalili D, Weber MA (2020). State-of-the-art imaging for diagnosis of metastatic bone disease. *Radiologe*, **60**.

Liede A, Jerzak KJ, Hernandez RK, et al (2016). The incidence of bone metastasis after early-stage breast cancer in Canada. *Breast Cancer Res Treat*, **156**.

Lipton A (2007). Efficacy and safety of intravenous bisphosphonates in patients with bone metastases caused by metastatic breast cancer. *Clin Breast Cancer*, **7**.

Lutz S, Balboni T, Jones J, et al (2017). Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol*, **7**.

Mei M, Xiang Z, Yang J, Xiang R (2020). Efficacy of zoledronic acid for prevention of bone loss in early-stage breast cancer patients receiving adjuvant therapy: A meta-analysis of 13 randomized controlled trials. *Curr Probl Cancer*, **44**.

Purushotham A, Shamil E, Cariati M, et al (2014). Age at diagnosis and distant metastasis in breast cancer - A surprising inverse relationship. *Eur J Cancer*, **2014**.

Schmidt RG (1995). Management of extremity metastatic bone cancer. *Curr Probl Cancer*, **19**.

Shibata H, Kato S, Sekine I, et al (2016). Diagnosis and treatment of bone metastasis: Comprehensive guideline of the Japanese Society of Medical Oncology, Japanese Orthopedic Association, Japanese Urological Association, and Japanese Society for Radiation Oncology. ESMO Open.

Sinn HP, Kreipe H (2013). A brief overview of the WHO classification of breast tumors, 4th edition, focusing on issues and updates from the 3rd edition. *Breast Care*, **2013**.

Soeharno H, Povegliano L, Choong PF (2018). Multimodal treatment of bone metastasis - A surgical perspective. Front *Endocrinol (Lausanne)*, **2018**.

Sung H, Ferlay J, Siegel RL, et al (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*, **71**.

Ulmert D, Solnes L, Thorek DL (2015). Contemporary approaches for imaging skeletal metastasis. *Bone Res*, **3**.

Moos RV, Costa L, Ripamonti CI, Niepel D, Santini D (2017). Improving quality of life in patients with advanced cancer: Targeting metastatic bone pain. *Eur J Cancer*, **2017**.

Wegener B, Schlemmer M, Stemmler J, et al (2012). Analysis of orthopedic surgery of bone metastases in breast cancer patients. *BMC Musculoskelet Disord*, **13**.

Wei B, Wang J, Bourne P, et al (2008). Bone metastasis is strongly associated with estrogen receptor-positive/ progesterone receptor-negative breast carcinomas. *Hum Pathol*, **39**.

Widodo I, Dwianingsih EK, Anwar SL, et al (2017). Prognostic value of clinicopathological factors for Indonesian breast carcinomas of different molecular subtypes. *Asian Pac J Cancer Prev*, **18**, 1251–6.

Yamashiro H, Takada M, Nakatani E, et al (2014). Prevalence and risk factors of bone metastasis and skeletal related events in patients with primary breast cancer in Japan. *Int J Clin Oncol*, **19**.

Yamashiro K, Tanaka R, Hoshino Y, et al (2015). The prevalence and risk factors of cerebral microbleeds in patients with Parkinson's disease. *Park Relat Disord*, **21**.

Zhang H, Zhu W, Biskup E, et al (2018). Incidence, risk factors and prognostic characteristics of bone metastases and skeletal-related events (SREs) in breast cancer patients: A systematic review of the real world data. *J Bone Oncol*, **2018**.