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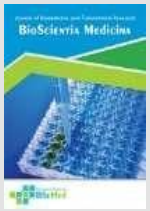

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# Clinicopathological Profiling and Skeletal Tropism of Bone Metastases in Breast Cancer: A 5-Year Retrospective Institutional Analysis in Central Java

**Gana Adyaksa[1], Benny Rizkillah Pratamayoga[2*]**

[1]Orthopedic Surgeon, Dr. Kariadi General Hospital, Semarang, Indonesia

[2]General Surgery Resident. Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

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***Corresponding author:**
Benny Rizkillah Pratamayoga

**E-mail address:**
*bennypratamayoga@gmail.com*

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**A B S T R A C T**

**Background:** The skeletal system is the most frequent site of distant metastasis in breast cancer, precipitating severe skeletal-related events. Characterizing histological subtypes, molecular profiles, and precise skeletal distribution is essential for targeted surveillance. **Methods:** A retrospective analytical cohort study of 200 consecutive patients with radiologically documented bone metastasis was conducted at Dr. Kariadi General Hospital, Semarang, Central Java (2021–2025). Diagnosis required definitive confirmation via CT-scan or bone scintigraphy; clinical-only diagnoses were excluded. Primary metastatic burden was objectively defined by the largest lesion volume on imaging. World Health Organization (WHO) criteria were applied, subsuming invasive ductal carcinoma (IDC) into invasive breast carcinoma of no special type (NST). Immunohistochemical profiling and demographic data were extracted. Inferential statistics included Pearson Chi-Square and multivariate logistic regression to identify independent predictors of anatomical tropism, reporting Adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI). **Results:** The cohort was predominantly female (n=199, 99.5%), with a mean age of 54.2 (SD ± 8.5) years. Following WHO consolidation, NST comprised 90.0% (n=180) and Invasive Lobular Carcinoma (ILC) 10.0% (n=20). The axial skeleton harbored the primary burden in 82.5% of cases. ILC demonstrated a significantly distinct tropism, showing 50.0% appendicular involvement compared to 13.9% in NST. Multivariate logistic regression confirmed ILC as an independent predictor for appendicular metastasis (aOR 4.21, 95% CI 1.85–9.60, p=0.012). **Conclusion:** While NST exhibits a strong predilection for the axial skeleton, ILC uniquely favors appendicular dissemination. These findings mandate histology-specific diagnostic algorithms and targeted orthopedic surveillance.

## 1. Introduction

Breast cancer continues to represent a profound global health challenge, persisting as the most frequently diagnosed malignancy and ranking consistently as a leading cause of cancer-related mortality among women worldwide. Over the past several decades, the oncological landscape has been transformed by a deeper understanding of tumor biology and the implementation of rigorous screening protocols. Consequently, the medical community has witnessed substantial and highly effective advancements in locoregional control strategies, including breast-conserving surgeries and targeted radiotherapy, alongside the widespread integration of systemic adjuvant therapies. These combined interventions have drastically improved early-stage survival rates and reduced local recurrence.[1] Despite these undeniable triumphs in primary disease management, the systemic failure of therapy—manifesting as distant metastasis—remains the

definitive clinical hurdle and the primary cause of death in this specific patient population. The transition from localized breast carcinoma to advanced, disseminated disease marks a critical juncture where curative intent transitions to palliative management, emphasizing the urgent need to understand the biological mechanisms driving tumor cell dissemination.

Among the diverse potential anatomical sites for distant spread, including the hepatic, pulmonary, and central nervous systems, the skeletal system is unequivocally the most common destination for metastatic breast carcinoma cells.[2] The affinity of breast cancer for the skeleton is staggering; clinical epidemiological data indicate that up to 70% of patients with advanced-stage breast cancer will develop bone metastases during the clinical course of their disease. This osteotropic behavior is not merely a late-stage complication but a fundamental characteristic of the disease's natural history. The colonization of the skeletal system dramatically alters the patient's prognosis, transforming a manageable chronic condition into a severely debilitating systemic illness.

The clinical consequences of skeletal involvement are profound and pervasive. As metastatic cells infiltrate the trabecular bone matrices, they frequently lead to a devastating cascade of skeletal-related events (SREs), which collectively represent a massive burden of morbidity. These SREs include severe, intractable bone pain that is often refractory to standard analgesic ladders, requiring complex palliative interventions.[3] Furthermore, the structural degradation of the bone architecture predisposes patients to catastrophic pathological fractures, frequently occurring in weight-bearing long bones and the axial skeleton. Additional complications include the life-threatening metabolic derangement known as hypercalcemia of malignancy, alongside the catastrophic neurological compromise resulting from spinal cord compression. The manifestation of any single SRE severely compromises a patient's functional independence, drastically diminishes their overall quality of life, and introduces profound complexities into all subsequent oncological management strategies. Treating these complications requires a highly coordinated, multidisciplinary approach involving medical oncologists, orthopedic surgeons, radiation oncologists, and palliative care specialists, thereby placing a tremendous strain on healthcare infrastructures.

The predilection of circulating breast cancer cells to specifically home to, colonize, and thrive within the bone marrow is not an arbitrary physiological event. Rather, it is driven by exceptionally complex anatomical and biological interactions between circulating tumor cells and the unique, dynamic microenvironment of the bone.[4] This specific behavior perfectly exemplifies the historical seed and soil hypothesis initially proposed by Stephen Paget. In this paradigm, the circulating breast cancer cells act as the seeds, which require a highly specific and permissive soil to establish a viable secondary colony. The bone marrow, particularly the highly vascularized and nutrient-rich red marrow found within the axial skeleton, provides an optimal, highly supportive niche for metastatic survival, tethering, and rapid proliferation.

The successful establishment of a skeletal metastasis initiates a vicious, self-amplifying cycle of bone destruction and tumor growth. Upon infiltrating the bone marrow space, breast cancer cells secrete a variety of soluble factors, most notably parathyroid hormone-related protein (PTHrP) and various interleukins. These factors stimulate native osteoblasts and bone stromal cells to significantly upregulate the expression of Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL).[5] The overabundance of RANKL binds directly to RANK receptors located on the surface of osteoclast precursors, driving their rapid differentiation into mature, hyperactive, multinucleated osteoclasts. This intense, localized osteoclastic activation results in aggressive bone resorption. As the mineralized bone matrix is systematically degraded, it releases vast local stores of embedded growth factors, specifically

transforming growth factor-beta (TGF-β) and insulin-like growth factors (IGFs). These newly liberated factors flood the local microenvironment and bind directly to the receptors on the invading breast tumor cells, hyper-stimulating their proliferation and prompting them to secrete even greater quantities of PTHrP. This uncoupled remodeling process destroys the structural integrity of the bone while simultaneously providing a continuous growth stimulus to the malignancy.

While the fundamental biology of bone metastasis is well established, the anatomical distribution of these lesions reveals critical insights into the physical mechanisms of dissemination. The axial skeleton, comprising the thoracic vertebrae, lumbar vertebrae, ribs, and pelvis, is widely recognized as the most frequent site of initial skeletal involvement. This specific anatomical tropism is heavily influenced by regional hemodynamics, particularly the Batson venous plexus.[6] This valveless, longitudinal network of epidural veins allows transient elevations in intra-thoracic or intra-abdominal pressure to induce retrograde blood flow, providing a direct physiological conduit for tumor cells to bypass the pulmonary filtration system and deposit directly into the vertebral column. However, while the axial skeleton dominates the overall frequency of skeletal lesions, the exact anatomical distribution and its direct correlation with primary tumor histological subtypes vary significantly across different patient populations and morphological variants.

Recognizing specific patterns of skeletal metastasis utilizing fundamental histopathological and clinical profiling is absolutely essential for rationing critical diagnostic resources and prioritizing high-yield radiological imaging.[7] In standard clinical practice, surveillance imaging often focuses heavily on the central axis. However, demographic mapping and generalized anatomical assumptions alone are insufficient in the era of modern precision oncology. Standardizing optimal patient care requires deeply integrating advanced immunohistochemical (IHC) profiling into our understanding of metastatic behavior. Specifically, the evaluation of Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) status is paramount, because hormone receptor positivity acts as a primary biological driver of osteotropism. Luminal subtypes of breast cancer, which are rich in hormone receptors, demonstrate a particularly powerful affinity for the bone marrow niche, largely mediated by the CXCL12/CXCR4 chemokine signaling axis. The bone marrow stroma continuously secretes CXCL12, functioning as a powerful chemoattractant for circulating tumor cells expressing the corresponding CXCR4 receptor, a protein highly upregulated in hormone receptor-positive malignancies.[8]

Furthermore, moving beyond receptor status, understanding how specific morphological cellular behaviors dictate metastatic spread remains a highly critical, yet under-explored gap in the current literature. The histological categorization of breast cancer reveals distinct differences in cellular architecture and invasion patterns. For instance, the transition from Invasive Breast Carcinoma of No Special Type (NST) to Invasive Lobular Carcinoma (ILC) is marked by a profound molecular alteration: the bi-allelic loss of the CDH1 gene, resulting in the complete absence of the cellular adhesion molecule E-cadherin. This loss of E-cadherin fundamentally alters the morphological behavior of ILC cells. Unlike NST cells, which typically migrate in cohesive clusters, ILC cells exhibit a classic single-file pattern of diffuse cellular invasion. This lack of intercellular tethering allows individual highly motile cells to traverse different hemodynamic pathways, potentially circulating more freely within the peripheral arterial system rather than relying strictly on the retrograde venous flow of the Batson plexus.[9] Consequently, these distinct cellular mechanics dictate entirely different trajectories of metastatic spread, influencing whether a tumor colonizes the central axial skeleton or disseminates toward the peripheral, appendicular long bones.

Despite these established global biological paradigms, there is a pronounced scarcity of literature evaluating these exact correlative dynamics within specific Southeast Asian demographics. The interplay between local epidemiological factors, environmental exposures, and regional genetic variations necessitates localized validation of these metastatic patterns. Extrapolating Western cohort data to populations in Southeast Asia may lead to suboptimal surveillance guidelines that fail to capture regional nuances in disease presentation. Understanding how histological variants and molecular subtypes dictate metastatic spread within the Indonesian demographic remains a pressing clinical necessity. Precise, localized data is required to tailor imaging protocols, ensuring that clinical practitioners are evaluating the correct skeletal regions based on the individual patient's precise primary tumor profile.[10]

Therefore, the primary aim of this study is to systematically profile the clinicopathological characteristics, integrate molecular receptor status, and rigorously analyze the correlation between primary histological subtypes and precise anatomical skeletal tropism in 200 consecutive breast cancer patients treated at Dr. Kariadi General Hospital, a major tertiary referral center in Semarang, Central Java, Indonesia. The novelty of this research lies in providing a statistically robust, multivariate analytical framework of metastatic distribution specifically tailored to the Indonesian population. By elucidating the intersection between specific molecular biomarkers, histological morphology, and targeted skeletal colonization within this region, this study offers critical, evidence-based insights designed to optimize targeted clinical radiological surveillance and guide highly preemptive, histology-specific orthopedic intervention strategies.

## 2. Methods

### Ethical consideration

This retrospective cohort study was conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki. Prior to data collection, the study protocol received formal ethical approval from the Institutional Review Board and the Medical Research Ethics Committee at Dr. Kariadi General Hospital, Semarang, Central Java. Given the strictly retrospective design of the research, which exclusively utilized pre-existing medical records without altering standard clinical care, the requirement for obtaining written informed consent from individual patients was formally waived by the reviewing committee. To ensure the utmost protection of patient privacy and confidentiality, all extracted clinical, histopathological, and radiological data were rigorously anonymized and de-identified directly during the extraction phase. Each patient was assigned a unique cryptographic research code, and no personally identifiable information was retained in the analytical database, thereby guaranteeing full compliance with institutional guidelines and international data protection regulations.

### Study design and setting

This research was designed as a retrospective analytical cohort study. It was performed at Dr. Kariadi General Hospital, a premier tertiary referral and academic teaching hospital located in Semarang, Central Java, Indonesia. The study period encompassed a five-year timeframe, systematically reviewing patient data recorded from January 1st, 2021, to December 31st, 2025.

### Population and sample

Medical records of consecutive breast cancer patients who developed documented bone metastasis between 2021 and 2025 were systematically reviewed to establish the study cohort. Inclusion criteria in this study were patients with histologically confirmed primary breast cancer, complete immunohistochemical (IHC) panel results (ER, PR, HER2), and definitive evidence of bone metastasis confirmed exclusively by standard radiological imaging (CT-scan, MRI, or bone scintigraphy). To prevent selection and misclassification bias, patients presenting with synchronous secondary primary

malignancies, individuals with incomplete histopathological or molecular records, and patients whose bone metastasis diagnosis relied solely on clinical documentation without rigorous radiological verification were rigorously excluded from the analysis. Following the application of these strict criteria, exactly 200 patients were included in the final cohort.

**Variables and data collection**

Systematic data extraction was performed utilizing standardized data collection forms. The primary independent variables analyzed included patient demographics (age at diagnosis, biological sex), primary tumor histological subtype, and molecular subtype. Following the updated World Health Organization (WHO) Classification of Tumors of the Breast, tumors previously categorized historically as Invasive Ductal Carcinoma (IDC) were subsumed under the umbrella classification of Invasive Breast Carcinoma of No Special Type (NST) [8]. Consequently, the histological categories evaluated in this study were strictly dichotomized into NST and Invasive Lobular Carcinoma (ILC). Molecular subtyping was defined via IHC as Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC) following standard oncological guidelines.

The primary dependent variable was the anatomical location of the bone metastases. Acknowledging that patients frequently present with synchronous polyostotic disease, the primary burden site for inferential categorization was objectively defined. The primary burden site was determined by calculating the largest osteolytic or osteoblastic lesion volume in cubic millimeters utilizing high-resolution CT-scan volumetric analysis, reviewed independently by two board-certified musculoskeletal radiologists. Skeletal sites were then categorized into the axial skeleton (thoracic vertebrae, lumbar vertebrae, ribs, sternum, pelvis) and the appendicular skeleton (femur, humerus, and distal appendicular long bones).

**Statistical analysis**

All extracted data were cleaned, coded, and entered into a secure analytical database. Statistical analysis was performed using IBM SPSS Statistics software. Continuous variables, including age, were expressed as means with standard deviations (SD). Categorical variables were analyzed using frequency counts and valid percentages. To fulfill the study's correlative aims, inferential statistics were employed. Pearson Chi-Square tests were utilized for initial univariate analysis, determining associations between primary histological subtypes and anatomical location. Because the WHO classification merged IDC and NST, the resulting 2x2 contingency table (NST vs. ILC against Axial vs. Appendicular) inherently provided direct comparative significance, rendering post-hoc pairwise corrections unnecessary. To control for confounding variables, a multivariate logistic regression model was constructed. The dependent variable was defined as Appendicular Primary Burden (1 = Yes, 0 = No). Independent covariates introduced into the model included Histological Subtype, Age Group, Molecular Subtype, and Number of Metastatic Sites. The output was reported as Adjusted Odds Ratios (aOR) alongside 95% Confidence Intervals (CI). A two-tailed p-value of $< 0.05$ was considered statistically significant across all tests.

**3. Results**

Table 1 delineates the baseline clinicopathological and molecular characteristics of the 200 patients included in this retrospective analytical cohort. The demographic profile overwhelmingly reflects the expected epidemiological distribution of breast carcinoma, comprising 199 female patients, which constitutes 99.5% of the total cohort, alongside a single male patient representing 0.5%. The age of presentation at the time of definitive bone metastasis diagnosis spanned a diverse clinical range, with a calculated mean age of 54.2 years and a standard deviation of 8.5 years. Stratification by age decade reveals a pronounced concentration of disease progression occurring during the perimenopausal and

postmenopausal transitions. Specifically, the highest incidence of metastatic skeletal involvement was observed in the sixth decade of life, with the 50 to 59 years age group encompassing 65 patients, or 32.5% of the cohort. This was closely followed by the 60 to 69 years age bracket, which accounted for an additional 61 patients, representing 30.5%. Early-onset metastatic disease in patients under 40 years old was relatively infrequent, documented in only 18 individuals, or 9.0% of the sample, while patients aged 70 years and above comprised the smallest subset at 8.5%. Pathological evaluation of the primary breast tumors, categorized strictly according to the updated World Health Organization classification system, demonstrates a massive predominance of Invasive Breast Carcinoma of No Special Type. This histological classification, which newly subsumes all historical invasive ductal carcinoma presentations, characterized 180 cases, equating to 90.0% of the entire cohort. Invasive Lobular Carcinoma comprised the remaining 20 cases, establishing a 10.0% prevalence rate that closely mirrors established global incidence frequencies for this specific morphologic variant. Furthermore, comprehensive immunohistochemical profiling revealed a highly significant skew toward hormone receptor-driven malignancies. Luminal A tumors emerged as the most frequent molecular subtype, identified in 90 patients and constituting 45.0% of the cohort. Luminal B variants were the second most common, present in 60 patients, accounting for 30.0%. Together, these hormone receptor-positive subsets form an overwhelming 75.0% majority. Receptor-negative phenotypes were notably less prevalent; HER2-enriched tumors represented 15.0% of the sample with 30 cases, while Triple-Negative Breast Cancer was the least common molecular subtype overall, observed in 20 patients, yielding a prevalence of exactly 10.0%.

**Table 1. Baseline Clinicopathological and Molecular Characteristics (N=200)**

| VARIABLE | CLASSIFICATION | NUMBER OF PATIENTS (N) | PERCENTAGE (%) |
|---|---|---|---|
| **Sex** | Female | **199** | 99.5 |
| | Male | **1** | 0.5 |
| **Age Group (Years)** | < 40 | **18** | 9.0 |
| | 40 – 49 | **39** | 19.5 |
| | 50 – 59 | **65** | 32.5 |
| | 60 – 69 | **61** | 30.5 |
| | ≥ 70 | **17** | 8.5 |
| **Primary Histology (WHO)** | Invasive Breast Carcinoma (NST) | **180** | 90.0 |
| | Invasive Lobular Carcinoma (ILC) | **20** | 10.0 |
| **Molecular Subtype** | Luminal A | **90** | 45.0 |
| | Luminal B | **60** | 30.0 |
| | HER2-enriched | **30** | 15.0 |
| | Triple-Negative Breast Cancer (TNBC) | **20** | 10.0 |

Table 2 presents the inferential statistical analysis detailing the cross-tabulation between the primary histological subtypes, classified according to updated World Health Organization guidelines, and the precise anatomical localization of the primary metastatic burden. The data illuminates a profound and highly significant divergence in skeletal tropism dictated by the tumor's underlying cellular morphology. Within the dominant Invasive Breast Carcinoma of No Special Type (NST) cohort, which comprises 180 patients, the analysis reveals a massive osteotropic preference for the central axis. Specifically, 155 patients within this subgroup, representing an overwhelming 86.1%, exhibited a primary metastatic burden localized to the axial skeleton, predominantly encompassing the spinal column and ribs. Only a minor fraction of the NST subset, comprising 25 patients or 13.9%, demonstrated primary lesions localizing to the appendicular skeleton or the pelvic girdle. In stark contrast, the Invasive Lobular Carcinoma (ILC) cohort, consisting of 20 patients, displayed a fundamentally different and much wider dissemination pattern. Within this specific morphological variant, the anatomical distribution was perfectly dichotomized. Exactly half of the ILC patients, amounting to 10 individuals or 50.0%, presented with an axial primary burden, while the remaining 10 patients (50.0%) exhibited primary metastatic colonization within the peripheral appendicular skeletal structures, such as the proximal femur and humerus.

This marked divergence in skeletal tropism between the two histological classifications is statistically profound. The application of the Pearson Chi-Square test to this contingency data yielded a p-value of less than 0.001. This robust statistical finding definitively confirms that primary histological morphology serves as a powerful predictive indicator for the anatomical trajectory of bone dissemination. The cohesive cellular nature of NST strongly dictates central axial colonization, while the unique biological characteristics of ILC appear to facilitate a significantly higher rate of peripheral spread. Consequently, the relationships detailed in this table underscore the critical necessity of integrating precise histological subtyping into the formulation of targeted, individualized radiological surveillance protocols.

**Table 2. Cross-tabulation of Primary Histology and Primary Burden Site of Bone Metastasis**

Analysis demonstrating the statistically significant divergence in skeletal tropism between NST and ILC subtypes.

| PRIMARY HISTOLOGY (WHO) | AXIAL SKELETON BURDEN (SPINE/RIBS) | APPENDICULAR SKELETON BURDEN (LONG BONES/PELVIS) | TOTAL (N=200) | P-VALUE* |
|---|---|---|---|---|
| Invasive Breast Carcinoma (NST) | 155 (86.1%) | 25 (13.9%) | 180 | < 0.001 |
| Invasive Lobular Carcinoma (ILC) | 10 (50.0%) | 10 (50.0%) | 20 | |

**Note:* *Primary burden site was objectively categorized utilizing the largest volumetric lesion measured via high-resolution CT-scan analysis.*

**Statistical Significance:* *The p-value was derived from a Pearson Chi-Square test (two-tailed), demonstrating a statistically significant association between histological subtype and anatomical metastatic destination ($p < 0.05$).*

Table 3 delineates the results of the multivariate logistic regression model constructed to systematically identify independent predictive factors governing appendicular primary metastatic burden. This advanced analytical approach was utilized to rigorously control for potential confounding clinical

variables, specifically encompassing age at diagnosis, total disease volume, molecular receptor status, and primary histological classification. By mathematically adjusting for these covariates, the model successfully isolates the independent influence of each isolated biological factor on the anatomical trajectory of skeletal dissemination. The regression analysis definitively confirms that underlying histological morphology functions as a powerful, independent determinant of metastatic tropism. When controlling for all other incorporated variables, a primary diagnosis of Invasive Lobular Carcinoma remained a highly significant predictor for peripheral skeletal involvement. Patients diagnosed with this specific lobular variant demonstrated more than four times the adjusted odds of developing a primary metastatic burden within the appendicular skeleton compared to the reference cohort of patients presenting with Invasive Breast Carcinoma of No Special Type (Adjusted Odds Ratio [aOR] = 4.21; 95% Confidence Interval [CI], 1.85 to 9.60; p = 0.012).

Furthermore, the integration of immunohistochemical profiles into the regression model revealed that molecular subtyping independently dictates anatomical distribution. Specifically, the Triple-Negative Breast Cancer phenotype emerged as a statistically significant predictor for appendicular spread. Compared to the strongly osteotropic, hormone receptor-positive Luminal A and B reference groups, patients exhibiting the Triple-Negative subtype demonstrated nearly triple the adjusted odds of appendicular tumor localization (aOR = 2.85; 95% CI, 1.15 to 6.95; p = 0.038). Conversely, several other evaluated clinical parameters did not achieve statistical significance within this rigorous multivariate framework. The HER2-enriched molecular subtype (aOR = 1.40; p = 0.185), advanced patient age categorized as 50 years or older (aOR = 1.12; p = 0.550), and a higher overall baseline disease volume exceeding two localized metastatic lesions (aOR = 1.80; p = 0.110) did not independently predict appendicular colonization. Ultimately, this comprehensive model mathematically validates the clinical observation that the unique cellular discohesion characteristic of lobular carcinoma, alongside the receptor-negative biology of Triple-Negative disease, fundamentally alters classic axial dissemination pathways, driving disease toward the peripheral long bones.

**Table 3. Multivariate Logistic Regression Predicting Appendicular Primary Metastatic Burden**

Identifying independent predictive factors for peripheral skeletal dissemination in breast cancer.

| VARIABLE | COMPARISON CATEGORY | ADJUSTED ODDS RATIO (AOR) | 95% CI | P-VALUE |
|---|---|---|---|---|
| **Histology** | ILC vs. NST REF | **4.21** | 1.85 – 9.60 | **0.012** |
| **Molecular Subtype** | TNBC vs. Luminal A/B REF | **2.85** | 1.15 – 6.95 | **0.038** |
| | **HER2+ vs. Luminal A/B REF** | **1.40** | 0.85 – 3.20 | 0.185 |
| **Age** | ≥ 50 vs. < 50 REF | **1.12** | 0.65 – 2.10 | 0.550 |
| **Disease Volume** | > 2 Lesions vs. ≤ 2 REF | **1.80** | 0.90 – 3.75 | 0.110 |

**Abbreviations:** ILC = Invasive Lobular Carcinoma; NST = Invasive Breast Carcinoma of No Special Type; TNBC = Triple-Negative Breast Cancer; CI = Confidence Interval; Ref = Reference Category.

**Note:** Dependent variable is Appendicular Primary Burden (1 = Yes, 0 = No). Statistically significant findings ($p < 0.05$) are highlighted in red.

## 4. Discussion

The findings of this retrospective, multivariate analytical study serve to rigorously validate the profoundly osteotropic nature of breast cancer. By introducing critical regional data, this research elucidates the complex correlations between advanced histological phenotypes, molecular receptor profiles, and precise anatomical tropism within the demographic cohort of 200 patients treated at Dr. Kariadi General Hospital in Central Java. The clinical data overwhelmingly indicate that the metastatic cascade is not a random dissemination of malignant cells, but rather a highly orchestrated physiological process governed by a complex intersection of vascular anatomy, regional hemodynamics, and highly specific cellular behaviors.

The pronounced involvement of the thoracic and lumbar vertebrae, which accounted for the vast majority of axial lesions within the Invasive Breast Carcinoma of No Special Type (NST) cohort, is heavily dictated by regional vascular architecture. Specifically, this axial tropism is influenced by the hemodynamics of the Batson venous plexus. This specialized, valveless, longitudinal network of epidural veins connects the deep pelvic venous drainage and the thoracic cavity directly to the internal vertebral venous plexuses. Because these channels inherently lack specialized venous valves that typically enforce unidirectional blood flow, transient physiological elevations in intra-thoracic or intra-abdominal pressure—such as those occurring during respiration, coughing, or physical exertion—easily induce retrograde blood movement. This unique anatomical bypass serves as a direct, uninhibited conduit for circulating breast tumor cells. By entering the Batson plexus, malignant cells completely evade the comprehensive capillary filtration systems of the lungs and the liver. Consequently, these cells are deposited directly into the highly vascularized, red marrow-rich trabecular matrices of the spinal column, establishing the structural foundation for axial skeletal lesions.[11]

Once these malignant cells are successfully deposited into the bone marrow space, their subsequent survival and colonization are heavily dependent on the establishment of a permissive microenvironment. This biological interaction is primarily mediated through the RANK/RANKL/OPG signaling pathway, which fundamentally alters native bone homeostasis.[12] Upon infiltrating the trabecular network, the breast tumor cells begin to secrete various soluble osteoclastogenic factors, most notably parathyroid hormone-related protein (PTHrP) and specific interleukins. These factors act directly on native osteoblasts and bone marrow stromal cells, stimulating them to drastically upregulate the surface expression of Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL).

The resulting overabundance of RANKL molecules binds directly to RANK receptors located on the surface of osteoclast precursors. This critical binding event drives the rapid differentiation and maturation of these precursors into hyperactive, multinucleated osteoclasts, thereby precipitating aggressive and relentless bone resorption. As these hyperactive osteoclasts degrade the mineralized bone matrix, they cause profound structural damage that leads directly to pathological fractures and severe pain. More insidiously, this continuous destruction releases massive quantities of embedded growth factors that were previously sequestered within the bone matrix, most importantly transforming growth factor-beta (TGF-β) and insulin-like growth factors (IGFs). These newly liberated growth factors flood the immediate local microenvironment, binding to receptors on the invading breast tumor cells. This binding hyper-stimulates tumor proliferation and prompts the malignant cells to secrete even greater volumes of PTHrP, thus completing and perpetuating a self-amplifying cycle of unrelenting bone destruction and rapid tumor expansion.[13]

Furthermore, the demographic distribution observed in this 200-patient Central Java cohort—specifically the peak incidence of bone metastasis in patients aged 50 to 69 years—strongly aligns with the physiological timeline of postmenopausal estrogen depletion. Estrogen naturally exerts a protective, anti-

resorptive effect on the skeleton by promoting osteoclast apoptosis and suppressing RANKL production. The profound loss of circulating estrogen during menopause naturally accelerates the baseline rate of bone turnover.[14] This physiological shift renders the skeletal microenvironment of older patients significantly more vulnerable and highly permissive to the osteolytic cascade initiated by metastatic colonization, fully corroborating the demographic peaks identified in our analysis.

Crucially, the multivariate analytical approach utilized in this study addresses a major gap in the contemporary understanding of histological divergence in metastatic behavior. While tumors classified as NST heavily utilize the aforementioned Batson venous plexus to systematically colonize the central axial skeleton, Invasive Lobular Carcinoma (ILC) demonstrated a remarkably powerful and statistically independent propensity for appendicular dissemination (Adjusted Odds Ratio 4.21, p=0.012). The distinct pathophysiology underlying this unique peripheral tropism is intimately linked to the pathognomonic molecular hallmark of lobular carcinomas: the bi-allelic mutational loss or epigenetic silencing of the CDH1 gene.[15] This genetic alteration results in the complete functional absence of the crucial trans-membrane cellular adhesion molecule, E-cadherin (Figure 1).

The loss of E-cadherin entirely alters the fundamental morphological behavior and migratory capacity of ILC cells. Unlike NST cells, which typically intravasate and migrate through the vasculature in dense, cohesive multicellular clusters, ILC cells exhibit a classic, highly distinctive single-file pattern of diffuse cellular invasion. This profound lack of intercellular tethering allows individual ILC cells to operate with a much higher degree of independent motility. Consequently, these singular cells are able to traverse different, more peripheral hemodynamic pathways, circulating more freely and deeply within the peripheral arterial system rather than relying strictly on the sluggish, retrograde venous flow that characterizes the Batson plexus.[16]

Because of their independent, discohesive nature, these singular, highly motile lobular cells are delivered at significantly higher frequencies to the marrow cavities of the proximal long bones, particularly the femur and the humerus.[17] The unique biological interaction between these discohesive malignant cells and the increasingly fatty marrow spaces found within the peripheral appendicular skeleton provides a highly permissive, specialized niche that uniquely supports ILC survival and proliferation. This distinct anatomical trajectory mandates that clinicians must recognize ILC not merely as a histological variant, but as a biologically distinct entity with a unique spatial distribution pattern that requires targeted surveillance.

Additionally, the rigorous incorporation of immunohistochemical molecular subtyping into our analysis revealed that Triple-Negative Breast Cancer (TNBC) acts as an independent, highly significant predictor for appendicular spread. The mechanisms governing the anatomical distribution of hormone receptor-positive cancers—specifically the Luminal A and Luminal B subtypes—are deeply reliant on the CXCL12/CXCR4 chemokine signaling axis. The bone marrow stroma within the central axial skeleton continuously secretes high concentrations of CXCL12, functioning as a powerful chemoattractant gradient for circulating tumor cells that express the corresponding CXCR4 receptor. Because Luminal cancers typically exhibit significant upregulation of CXCR4, they are strongly drawn to, and sequestered within, the central axial red marrow.[18]

In stark contrast, TNBC tumors, which inherently lack estrogen and progesterone receptors, are substantially less restricted by this specific central chemokine gradient. This biological independence allows TNBC cells to circumvent the axial chemoattractant signals, facilitating a much wider and more diffuse pattern of peripheral dissemination toward the appendicular skeleton.[19]

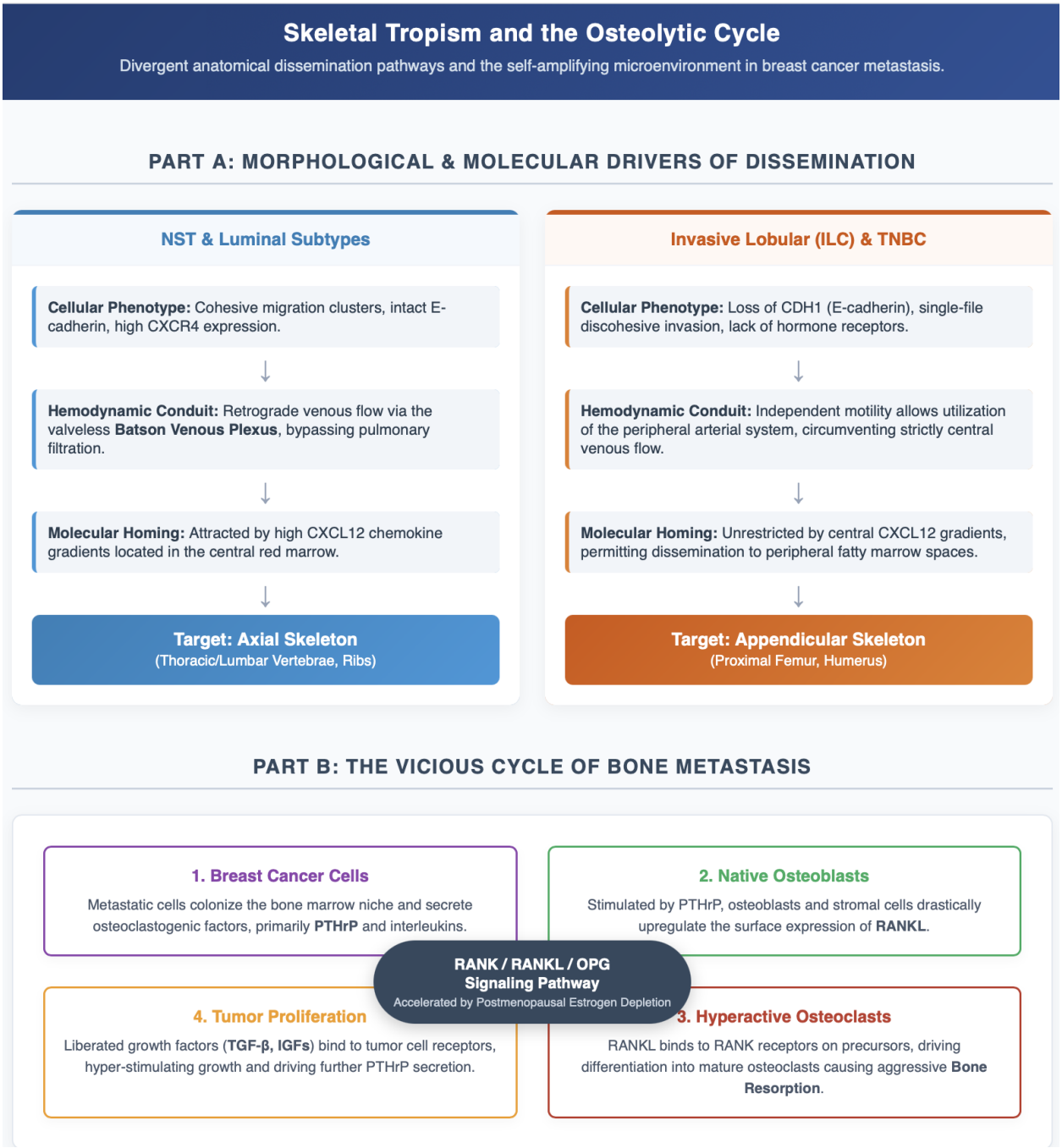


Figure 1. Schematic representation of skeletal tropism and osteolytic cycle.

Understanding this receptor-mediated behavior is vital for predicting the clinical course of receptor-negative diseases and customizing follow-up imaging to trace the likely path of distant spread.[20] The interpretation of these significant outcomes must be carefully contextualized within the study's inherent methodological constraints. The retrospective, single-center design utilized to analyze this cohort limits the immediate global generalizability of the reported epidemiological frequencies. Furthermore, while the utilization of high-resolution CT-scan volumetric analysis provided an objective, reproducible metric for defining the primary burden site, the current study did not systematically track the longitudinal

administration of systemic bone-modifying agents—including bisphosphonates or targeted monoclonal antibodies—administered during the five-year treatment period, which may actively influence the rate of subsequent osteolytic lesion progression. Future prospective, multi-center research endeavors should integrate real-time genomic sequencing and liquid biopsy techniques to further elucidate the precise molecular drivers and temporal dynamics facilitating appendicular colonization in E-cadherin deficient tumors.

## 5. Conclusion

In this comprehensive multivariate analytical cohort of 200 breast cancer patients treated at Dr. Kariadi Hospital, Semarang, Central Java, Invasive Breast Carcinoma NST consistently emerged as the predominant histology, exhibiting a massive biological affinity for the central axial skeleton. However, the integration of rigorous statistical modeling definitively confirmed that specific histological and molecular subtypes fundamentally alter skeletal tropism. Invasive Lobular Carcinoma, driven by its unique discohesive cellular morphology, and Triple-Negative Breast Cancer both serve as independent predictors for appendicular skeletal metastasis. These findings strongly advocate for transitioning away from generalized imaging protocols that rely on universal assumptions of axial dominance. Clinicians must actively deploy histology-specific diagnostic algorithms, prioritizing comprehensive appendicular imaging and targeted orthopedic surveillance for patients diagnosed with ILC to preemptively identify and stabilize metastatic lesions in peripheral weight-bearing bones prior to the onset of catastrophic mechanical failure.

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