Preoperative platelet distribution width predicts bone metastasis in patients with breast cancer

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Abstract

Purpose Bone metastases occur in 50-70% of patients with breast cancer (BC) and result in high mortality. Platelet distribution width (PDW), a commonly used parameter of activated platelets, has been associated with a poor prognosis in BC. We aim to investigate the prognostic role of PDW for bone metastasis in BC patients.

Methods 515 patients who received BC surgery in the Harbin Medical University Cancer Hospital from July 1, 2016, to December 31, 2017, were reviewed. Patients' characteristics and platelet indices upon enrollment in this study were collected. The Kaplan-Meier method was used to estimate the 5-year bone metastasis incidence. The univariate and multivariate Cox regression analyses were utilized to identify risk factors associated with bone metastasis.

Results The patients with bone metastases exhibited lower PDW levels than the patients without bone metastases. Moreover, decreased PDW was significantly correlated with histologic type, multifocal disease, and lymph node status. In addition, the patients with reduced PDW levels were more likely to develop bone metastasis. Multivariate analysis showed that PDW was an independent predictor for bone metastasis.

Conclusion PDW is an independent predictor of bone metastasis in BC. Further research is warranted.

Keywords Breast cancer, Bone metastasis, Platelet distribution width

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Introduction

The most prevalent form of female malignant tumor is breast cancer (BC) [1, 2]. Despite the advancement of treatment options, BC still accounts for the majority of cancer-related deaths in females. Distant metastases are the primary cause of BC fatalities [3]. In between 50% and 70% of BC patients, metastasis has been observed to most frequently occur in the bone [4]. Patients with bone metastasis are accompanied by excessive, osteoclast-mediated bone destruction and have an overall 5-year survival rate of 22.8% [5, 6]. Therefore, the identification of predictive markers for bone metastasis is urgently needed.

Numerous studies have shown how important platelet activation and interactions with cancer cells are for

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metastasis. A worse prognosis is associated with thrombocytosis in several malignancies, including ovarian, pancreatic, colorectal, and endometrial cancer [7–11]. A normal platelet count, however, may mask the existence of highly hypercoagulative and pro-inflammatory cancer phenotypes due to the availability of effective compensatory mechanisms [12].

Commonly used parameters of platelet activation include mean platelet volume (MPV) and platelet distribution width (PDW) in clinical practice. MPV reflects platelet size, and PDW indicates variation in platelet size. There have been reports of altered MPV levels in breast, lung, stomach, colon, and ovarian cancer [13–16]. Moreover, higher PDW levels are associated with poor prognosis in a number of tumor types, such as melanoma, laryngeal cancer, BC, non-small cell lung cancer, gastric cancer, and hepatocellular carcinoma [13–17]. Previous research from our group has established associations between platelet indices and overall survival in BC patients [18, 19]. Moreover, a recent study revealed that cancer cells are reprogrammed to a metastatic state through the acquisition of platelet mitochondria [20]. Blockade of platelet cysteinyl leukotriene receptor 1 counteracts platelet protumoral action and inhibits metastasis of cancer cells to the bone in BC [21]. Nevertheless, applying PDW to predict bone metastasis has not been investigated. In this study, we aim to examine the predictive role of PDW for bone metastasis in BC patients.

Methods

Study population

515 consecutive female patients with BC at Harbin Medical University Cancer Hospital from January 1, 2016, to December 31, 2017, were reviewed in this study. The eligibility criteria were as follows: (1) age at diagnosis > 18 years old; (2) all patients had a post-operative pathological diagnosis of BC; (3) no distant metastasis before surgery; and (4) complete clinical and follow-up information. The exclusion criteria were: (1) a history of antitumor treatments; (2) a history of malignancy; (3) insufficient chest computed tomography (CT) images; and (4) failure to follow up. Bone metastases are first defined by emission-computed tomography scans and then confirmed by CT scans. Bone metastasis-free survival was defined as the time interval from surgery to bone metastasis or to the last follow-up visit. The last follow-up time was December 31, 2022.

We collected the following information from the hospital information system: age, menstrual status, tumor size, lymph node metastasis, histopathological type, proliferation index expression, lymphovascular invasion, molecular classification, clinical stage, and postoperative treatment. The blood testing was performed one week before surgery. White blood cell, hemoglobin, and platelet indices were detected using an autoanalyzer (Sysmex XE-2100, Kobe, Japan). The inter- and intra-assay coefficients of variation of all these assays were below 5%. Estrogen receptor (ER) and progesterone receptor (PR) status were defined based on immunohistochemistry (IHC) results. Human epidermal growth factor receptor-2 (HER-2) positivity was defined as IHC 3+or fluorescence in situ hybridization (FISH) positive of the primary tumor.

This study was approved by the ethics committees of the Harbin Medical University Cancer Hospital (KY2022-10).

Statistical analysis

Continuous variables were presented as mean±standard deviation (SD), and categorical variables were expressed as percentages of the number. Continuous variables with normal distribution were compared by the Student's t test, and categorical variables were compared by the Chi-square test. Bone metastasis incidence curves were drawn by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression models were used to examine the potential predictors of bone metastasis. Variables associated with $p < 0.05$ in the univariate analysis were included in the multivariate Cox regression analysis. The optimal cutoff value of PDW was defined by analyzing the receiver operating characteristic curve in terms of bone metastasis incidence after surgery. The statistics were analyzed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 15.0. All analyses were two-sided, and $p < 0.05$ was considered significant.

Results

A total of 515 BC patients who underwent complete surgical resection were included in this study. The median age was 46 years (range from 27 to 73 years). 239 participants had no lymph node metastasis, whereas 276 people were present. 432 (83.9%) and 83 (16.1%) patients were classified as stages I-II, and III, respectively.

The clinicopathological characteristics between bone metastasis and non-bone metastasis groups are summarized in Tables 1 and 2. Platelet count, mean platelet volume, PDW, hemoglobin, multifocal disease, tumor size, lymph node status, PR status, histologic type, clinical stage, and adjuvant hormonal therapy were significantly associated with bone metastasis. No significant associations were found between bone metastasis and other clinical features.

The ROC curve was used to calculate the AUC and evaluate the predictive ability of PDW for bone metastasis. The AUC for predicting bone metastasis by preoperative PDW was 0.650 (0.607–0.692), the best cut-off value

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Table 1 Baseline characteristics of BC patients according to bone metastasis status

Variables	Without bone metastasis(*n* = 441)	Bone metastasis(*n* = 74)	*P*-value
Age (years)	50.1 ± 8.5	52.2 ± 9.5	0.062
BMI (kg/m^2)	24.8 ± 13.6	24.6 ± 5.0	0.922
WBC (×10^9/L)	6.6 ± 2.6	6.4 ± 1.2	0.148
Haemoglobin (g/L)	133.5 ± 15.2	134.9 ± 11.9	**< 0.001**
Platelet count (×10^9/L)	246.1 ± 62.8	262.5 ± 69.6	**0.041**
MPV (fL)	9.8 ± 1.4	10.3 ± 1.4	**0.002**
PDW (%)	14.9 ± 2.3	13.6 ± 2.5	**< 0.001**

BC, breast cancer; BMI, body mass index; WBC, white blood cell; PDW, platelet distribution width; MPV, mean platelet volume

was 15.0, the sensitivity was 67.6%, and the specificity was 59.3% (Fig. 1). The patients were divided into two groups according to the optimal cut-off value of PDW. 286 cases (55.5%) had PDW > 15.0%, and 229 (44.5%) had PDW ≤ 15.0%.

Table 3 summarizes the relationships between PDW and patients' clinicopathological characteristics. There was a strong correlation between PDW and histologic type, multifocal disease, and lymph node status. Nevertheless, no significant correlations between PDW and other clinical characteristics were found.

The median follow-up time was 65 months (interquartile range, 62–69 months). There were a total of 74 events of bone metastasis that occurred during the follow-up period. Patients with lower PDW had a greater risk of bone metastasis incidence than those with higher PDW (21.8% vs. 8.4%, respectively; *p* < 0.001). The Kaplan-Meier curve of PDW identified a significant difference between PDW > 15.0 and ≤ 15.0 in BC (Fig. 2).

Cox univariate and multivariate regression analyses were performed to identify the predictors for bone metastasis in BC patients. On univariate analysis, age, platelet count, mean platelet volume, PDW, multifocal disease, tumor size, lymph node status, PR status, histologic type, clinical stage, and adjuvant hormonal therapy were associated with bone metastasis. On multivariate analysis, age, PDW, multifocal disease, tumor size, histologic type, and adjuvant hormonal therapy were the independent predictors for bone metastasis (Table 4). Patients with reduced PDW had a hazard ratio (HR) of 0.835 (95% CI: 0.745–0.937, *p* = 0.002) for bone metastasis.

Discussion

Our study found that patients with lower PDW were more likely to develop bone metastasis. Moreover, PDW was significantly correlated with histologic type, multifocal disease, and lymph node status. Multivariate Cox regression revealed that PDW was an independent predictor for bone metastasis.

A growing body of literature recognizes the importance of activated platelets in tumor growth and metastasis [22]. Platelets play pivotal roles in cancer progression via direct interactions with cancer cells and indirect interactions mediated by platelet releasates [23]. Platelets can promote the endothelial arrest of tumor cells by directly bridging the endothelium with circulating cancer cells [24]. The interaction between GPIb-IX-V receptors on platelets and von Willebrand factor exposed to vascular endothelium is crucial to this process [25]. Platelets also release chemokine CXC motif ligand 5 (CXCL5), CXCL7, and lysophosphatidic acid to directly recruit granulocytes that promote the transendothelial migration of tumor cells [26, 27]. Moreover, in a BC mouse model with bone metastasis, platelets were observed to secrete lysophosphatidic acid to induce metastatic foci formation [28]. PDW reveals variations in platelet size and indicates platelet activation. It is well known that malignant tumors are accompanied by an inflammatory response throughout the body. Numerous inflammatory cytokines can promote the proliferation of macrophages, further result in platelet activation, and enhance the release of larger platelets [29]. Activated platelets can coat circulating tumor cells, and tumor cells can escape from shear-induced damage, which facilitates and accelerates tumor colonization, tumor growth, angiogenesis, and metastasis [30].

It is unknown how PDW contributes to the pathophysiology of bone metastases. Instead of bone resorption, BC cells' overexpression of osteoclasts disrupts the dynamic balance between osteoclasts and osteoblasts, leading to BC bone metastases [31]. The epithelial-to-mesenchymal transition (EMT) and bone metastases in BC are facilitated by the transforming growth factor-β (TGF-β) and WNT signaling pathways [32]. Previous studies have demonstrated that the TGF-β1/Smad pathway in cancer cells is activated in a synergistic manner by both platelet-derived TGF-β1 and direct platelet-tumor cell interaction [33]. According to another report, the direct interaction between platelets and BC cells leads to WNT-β-catenin activation and promotes metastasis [34]. Furthermore, TGF-β1 autocrine and BC cell metastasis are accelerated by activated WNT-β-catenin [34].

An increased PDW level indicates a large disparity in platelet volume and can be a sign of activated platelet production. Baseline PDW reflects accelerated platelet turnover and will reduce after treatment in diseases such as sepsis, deep venous thrombosis, atrial fibrillation, and acute myocardial infarction [35–39]. In patients with lung cancer, breast cancer, and colorectal cancer, antitumor therapy is associated with a decrease in PDW levels [40–42]. However, changes in PDW before and after treatment had no effect on progression-free survival or overall survival in cervical cancer, lung cancer, breast

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Table 2 Baseline characteristics of BC patients according to bone metastasis status

Variables	Without bone metastasis($n=441$)	Bone metastasis($n=74$)	P-value
Menopausal status			0.119
Pre	222 (50.3)	30 (40.5)	
Post	219 (49.7)	44 (59.5)	
Histologic type			**< 0.001**
IDC	387 (87.8)	51 (68.9)	
ILC	39 (8.8)	21 (28.4)	
Others	15 (3.4)	2 (2.7)	
Multifocal disease			**< 0.001**
Yes	61 (13.8)	24 (32.4)	
No	380 (86.2)	50 (67.6)	
Tumor size (cm)			**< 0.001**
≥ 2.5	151 (34.2)	44 (59.5)	
< 2.5	290 (65.8)	30 (40.5)	
Lymph node status			**0.019**
Negative	214 (48.5)	25 (33.8)	
Positive	227 (51.5)	49 (66.2)	
Clinical stage			**0.016**
I-II	377 (85.5)	55 (74.3)	
III	64 (14.5)	19 (25.7)	
Ki-67 (%)			0.161
< 20%	131 (29.7)	28 (37.8)	
≥ 20%	310 (70.3)	46 (62.2)	
ER			0.195
Positive	313 (71.0)	47 (63.5)	
Negative	128 (29.0)	27 (36.5)	
PR			**0.010**
Positive	289 (65.5)	37 (50.0)	
Negative	152 (34.5)	37 (50.0)	
HER2 status			0.111
Positive	129 (29.3)	15 (20.3)	
Negative	312 (70.7)	59 (79.7)	
Molecular subtype			0.660
Luminal-A	149 (33.8)	26 (35.1)	
Luminal-B	123 (27.9)	16 (21.6)	
HER2-enriched	87 (19.7)	15 (20.3)	
TNBC	82 (18.6)	17 (23)	
Adjuvant radiotherapy			0.438
Yes	114 (25.9)	16 (21.6)	
No	327 (74.1)	58 (78.4)	
Adjuvant hormonal therapy			**< 0.001**
Yes	222 (50.3)	21 (28.4)	
No	219 (49.7)	53 (71.6)	
Adjuvant chemotherapy			0.215
Yes	413 (93.7)	72 (97.3)	
No	28 (6.3)	2 (2.7)	

BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma
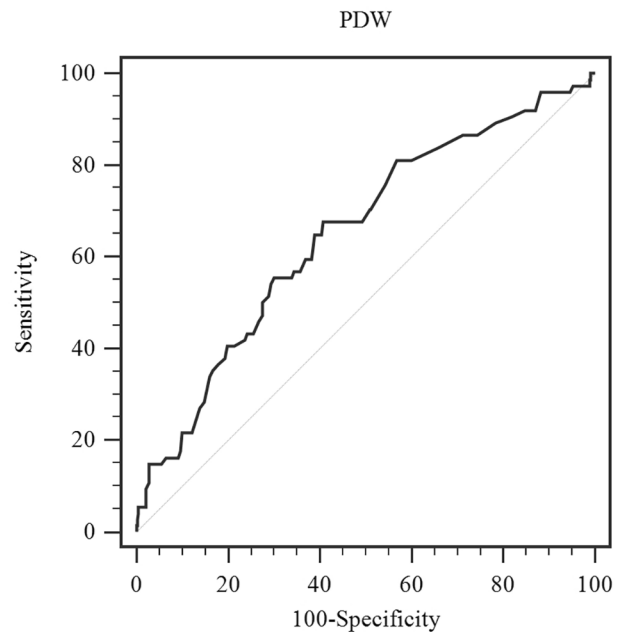

Fig. 1 An optimized cut-off value was determined for PDW using ROC curve analysis

cancer, or colorectal cancer [40–43]. To fully understand the impact of various treatment modalities on the kinetics of platelet indices, more research is required.

Our findings might be valuable in the prevention of bone metastasis in BC patients. Patients with reduced PDW may need closer follow-up and more active therapy. PDW may be a useful predictive parameter to identify patients at higher risk for bone metastasis.

PDW is a simple and cheap laboratory parameter and is easy to use in daily practice. Our research has laid a preliminary foundation for further investigation of activated platelets in the occurrence of bone metastasis. However, our study has some limitations. First of all, this was a retrospective study at a single center. Second, the potential mechanistic role of PDW was not investigated in this study. Third, we are not able to extrapolate the results to different ethnic groups because only Chinese participants were included in this study.

In summary, PDW is an independent predictor for bone metastasis in BC. Our findings underscore the importance of PDW in the mechanism of bone metastasis in BC patients.

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Table 3 Baseline clinico-pathological parameters of BC patients according to PDW levels

Variables	> 15.0% (*n* = 286)	≤ 15.0% (*n* = 229)	*P*-value
Menopausal status			0.472
Pre	144 (50.3)	108 (47.2)	
Post	142 (49.7)	121 (52.8)	
Histologic type			**0.046**
IDC	243 (85.0)	175 (76.4)	
ILC	36 (12.6)	44 (19.2)	
Others	7 (2.4)	10 (4.4)	
Multifocal disease			**0.004**
Yes	35 (12.2)	50 (21.8)	
No	251 (87.8)	179 (78.2)	
Tumor size (cm)			0.675
≥ 2.5	106 (37.1)	89 (38.9)	
< 2.5	180 (62.9)	140 (61.1)	
Lymph node status			**0.011**
Negative	147 (51.4)	92 (40.2)	
Positive	139 (48.6)	137 (59.8)	
Clinical stage			0.051
I-II	248 (86.7)	184 (80.3)	
III	38 (13.3)	45 (19.7)	
Ki-67 (%)			0.111
< 20%	80 (28)	79 (34.5)	
≥ 20%	206 (72)	150 (65.5)	
ER			0.858
Positive	199 (69.6)	161 (70.3)	
Negative	87 (30.4)	68 (29.7)	
PR			0.860
Positive	182 (63.6)	144 (62.9)	
Negative	104 (36.4)	85 (37.1)	
HER2 status			0.169
Positive	73 (25.5)	71 (31.0)	
Negative	213 (74.5)	158 (69.0)	
Molecular subtype			0.753
Luminal-A	102 (35.7)	73 (31.9)	
Luminal-B	73 (25.5)	66 (28.8)	
HER2-enriched	55 (19.2)	47 (20.5)	
TNBC	56 (19.6)	43 (18.8)	
Adjuvant radiotherapy			0.514
Yes	69 (24.1)	61 (26.6)	
No	217 (75.9)	168 (73.4)	
Adjuvant hormonal therapy			0.852
Yes	136 (47.6)	107 (46.7)	
No	150 (52.4)	122 (53.3)	
Adjuvant chemotherapy			0.803
Yes	270 (94.4)	215 (93.9)	
No	16 (5.6)	14 (6.1)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma
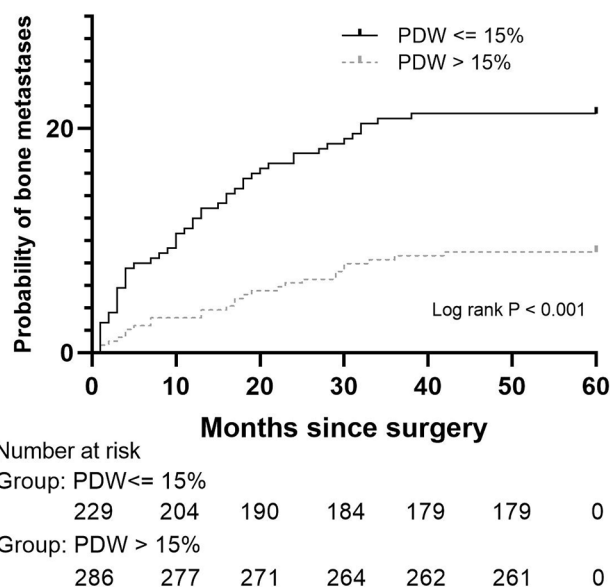

Number at risk
Group: PDW<= 15%

| 229 | 204 | 190 | 184 | 179 | 179 | 0 |

Group: PDW > 15%

| 286 | 277 | 271 | 264 | 262 | 261 | 0 |

Fig. 2 Incidence of bone metastasis based on PDW levels

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Table 4 The predictors of bone metastases in patients with breast cancer

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	1.026 (1.000–1.053)	**0.052**	1.030 (1.003–1.058)	**0.031**
BMI (kg/m^2)	0.999 (0.980–1.019)	0.928		
Menopausal status				
(Post vs. Pre)	1.449 (0.911–2.304)	0.117		
Ki-67 (%)				
(≥ 20 vs. < 20)	0.728 (0.455–1.164)	0.185		
Histologic type				
IDC	1		1	
ILC	0.633 (0.152–2.646)	0.531	1.042 (0.243–4.463)	0.955
Others	5.998 (1.450–24.815)	**0.013**	8.367 (1.968–35.581)	**0.004**
Multifocal disease				
(Positive vs. Negative)	2.603 (1.600–4.236)	**< 0.001**	1.828 (1.094–3.054)	**0.021**
Tumor size (cm)				
(≥ 2.5 vs. < 2.5)	2.555 (1.606–4.064)	**< 0.001**	2.053 (1.226–3.439)	**0.006**
Lymph node status				
(Positive vs. Negative)	1.793 (1.107–2.902)	**0.018**	1.104 (6.644–1.893)	0.718
Clinical stage				
(III vs. I-II)	1.914 (1.136–3.225)	**0.015**	0.669 (0.359–1.246)	0.205
PR				
(Positive vs. Negative)	0.557 (0.353–0.878)	**0.012**	1.221 (0.707–2.109)	0.474
HER2 status				
(Positive vs. Negative)	0.647 (0.367–1.140)	0.132		
Adjuvant chemotherapy				
(Yes vs. No)	2.307 (0.566–9.404)	0.243		
Adjuvant radiotherapy				
(Yes vs. No)	0.807 (0.464–1.403)	0.447		
Adjuvant hormonal therapy				
(Yes vs. No)	0.411 (0.248–0.681)	**0.001**	0.407 (0.224–0.740)	**0.003**
WBC (×10^9/L)	0.945 (0.833–1.071)	0.374		
Haemoglobin (g/L)	1.007 (0.989–1.026)	0.431		
Platelet count (×10^9/L)	1.004 (1.000–1.007)	**0.036**	1.000 (0.996–1.004)	0.966
MPV (fL)	1.285 (1.096–1.506)	**0.002**	1.159 (0.946–1.421)	0.153
PDW (%)	0.810 (0.737–0.889)	**< 0.001**	0.835 (0.744–0.937)	**0.002**

BMI, body mass index; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; WBC, white blood cell; MPV, mean platelet volume; PDW, platelet distribution width; HR, hazard ratio; CI, confidence interval

Declarations

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