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ORIGINAL ARTICLE

The mean platelet volume may predict the development of isolated bone metastases in patients with breast cancer: a retrospective study of the Young Researchers Committee of the Turkish Oncology Group (TOG)

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Summary

Purpose: *To determine the predictive value of the mean platelet volume (MPV) and the MPV/platelet count ratio on the development of isolated bone metastasis in patients with breast cancer.*

Methods: *A total of 121 previously untreated female patients with isolated bone metastases from breast cancer (group 1) were included in this retrospective cohort study. The patients enrolled in this study had similar age, biological subtypes, and duration of follow-up after diagnosis. Group 1 was compared with both 71 previously untreated women with breast cancer with no metastases at all (group 2) and 39 healthy women (group 3). Demographic data, laboratory tests and histological features of all of the patients in groups 1 and 2 were recorded and the study variables from each of the three groups were compared.*

Results: *In group 1, the cut-off value (9.2 fL) for the MPV was determined and patients were stratified into 4 subgroups. The MPV was higher in group 1 than in either group 2 or group 3. Group 1 patients had a MPV of 8.8±3.1 fL (mean 5.1, range: 6.1-15.6) and the cut-off value for MPV was 9.2 fl. For patients in group 1, the MPV distribution was stratified into 4 groups as follows: group A included MPV values <6.08 fL, in group B values ranged from 6.09 to 8.46 fL, group C included values from 8.47 to 10.05 fL, and group D included patients with MPV values >10.06 fL. MPV and the presence of lymphovascular invasion were found to be independent risk factors for the development of isolated bone metastases.*

Conclusion: *We concluded that MPV can be used to predict the development of isolated bone metastases.*

Key words: *bone metastases, breast cancer, mean platelet volume, platelet count*

Introduction

Bone cancer is the most common form of metastasis [1]. It is often observed in patients with breast and prostate cancer and is clinically significant in these two diseases [1]. However, thyroid

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cancer, kidney cancer, lung cancer, and gastrointestinal cancer rarely metastasize to the bone. In an autopsy series, nearly 70% of patients dying from prostate and breast cancer also had bone metastases [1-3]. The axial skeleton is clinically important because it contains the red marrow in the adult [1,3]. Blood circulation in extracellular regions is important in bone metastasis formation due to the possibility of circulating tumor cells and proper matrix properties [4]. Approximately 25-40% of metastases in breast cancer patients are found in the bones [4-6]. In patients with recurrent breast cancer, approximately 60-80% have skeletal metastases [4]. Circulating breast cancer cells show a high affinity for bone, and in 30-40% of early-stage breast cancer there are also circulating tumor cells in the bone marrow [4-6]. The majority of these cells escape apoptosis, and sometimes develop micro-metastatic proliferation [4]. Previous studies of bone metastases in breast cancer patients obtained results via silent cruising [4-7]. Therefore, patients with bone metastases may have a better prognosis than those with visceral metastasis [7]. Morbidity, including fracture risk in the skeletal system, pain, and spinal instability, are associated with clinical outcomes such as invasion and compression of the spinal cord [1,4-7].

In previous studies, several risk factors such as positive estrogen receptors, nodal metastases and younger age have been reported for bone metastases in patients with breast cancer [8-10]. Additionally, in the analysis of 7 studies where adjuvant therapy was administered including over 6,000 patients with breast cancer, the authors identified factors indicating a high-risk of bone metastases such as positive estrogen receptors and lymphovascular invasion [11]. In the International Breast Cancer Study Group's analysis, increased bone metastasis rate was related to estrogen receptor expression [1]. In another study, first recurrence with bone metastases after surgical treatment was associated with positive estrogen receptors in patients with luminal A molecular subtype [9]. In more recent studies in breast cancer patients with bone metastases, molecular markers that could predict the likelihood of metastasis to the bone have reported [12-15]. Epidermal growth factor receptor-2, parathyroid hormone related protein, osteopontin, interleukin-8, interleukin-11, interleukin-6 receptor activator of nuclear factor kappa-beta (RANK) and RANK ligand, bone sialoprotein, Fas/Fas ligand tumor cell surface integrin, and the CXC chemokine receptor type 4 were the most important to predict of bone metastases development [12-17]. However, the predictive power of these risk factors for breast cancer patients with bone metastases remains unclear [4-7]. Therefore, in the coming years researchers will continue to work towards a better definition of the predictive value of bone metastases and the identification of new markers.

Recently, MPV has been identified as an important indicator of inflammation [18]. In patients with inflammation and atherosclerosis, a growing number of platelets increases the MPV [18]. In particular, studies of cardiovascular and cerebrovascular diseases indicate that MPV is an important predictive factor of mortality associated with cardiovascular events [18-21]. Furthermore, events in the skeletal system associated with malignancies are also associated with the microenvironment of inflammation [12]. Therefore, in many diseases associated with inflammation, MPV may have predictive value for some clinical events. Based on this knowledge, MPV may also be an important predictive factor for the development of metastatic bone disease [12].

This study determined the MPV level and the MPV/ platelet count ratio in order to understand their predictive value in the development of isolated bone metastasis in patients with breast cancer.

Methods

In this study, a total of 2,645 women histologically diagnosed with breast cancer were assessed retrospectively from 2006 to 2014. A total of 121 breast cancer patients with isolated bone metastases were then included in the study.

Group 1 was formed from the 121 women diagnosed with isolated bone metastases from breast cancer. A total of 71 women with breast cancer but without metastases of similar age and with similar biological subtypes (when compared to patients in group 1) were enrolled in group 2 of this study. Lastly, 39 healthy women were enrolled in group 3. Groups 2 and 3, served as control groups. Prior to any oncological treatment, the following data were recorded for group 1 and 2 patients: demographic features (age, gender, smoking habits, and body surface area), clinical characterizations (performance status, weight loss, menopausal status, stage of disease, bone metastasis development time, and bone metastasis sites), laboratory tests (hemoglobin, thrombocytes, neutrophils, and leukocyte count, MPV values, corrected serum calcium, serum alkaline phosphatase levels, lactate dehydrogenase levels, carcinoembryonic antigen, and carbohydrate antigen 15-3 levels), and histological features (histological

type, tumor grade, lymphovascular invasion, nodal status, hormone receptor status, presence of ductal carcinoma *in situ*, and Ki67 status). The following data were registered and analyzed from patients in group 3: age, body surface area, smoking habits, hemoglobin, neutrophils, leukocyte counts, thrombocyte counts, and levels of MPV. Data from across the variables listed above were used to compare healthy inidividuals with breast cancer patients in each of the 2 groups. Then, the cut-off values for the MPV were determined for patients in group 1. Using these values, patients were then stratified into 4 groups according to their MPV.

Exclusion criteria

For all groups, the patients with the following health-related issues were excluded from this study: diabetes mellitus, metabolic syndrome, hypertension, chronic renal failure, atherosclerotic cardiovascular and cerebrovascular disease, rheumatic disease, chronic systemic disease (such as chronic liver disease and alcoholism), second primary carcinoma or sarcoma in patients with hematological malignancy, patients with breast carcinoma infiltrating the bone marrow, visceral and lymph node metastasis, patients talking anticoagulants and anti-thrombotic drugs, as well as patients with neoadjuvant chemotherapy and/or radiotherapy during the last 6 months.

Inclusion criteria

The inclusion criteria for group 1 were as follows: initial diagnosis of isolated bone metastases, at least 6 months after adjuvant chemotherapy with or without adjuvant radiotherapy. This was determined at least 6 months after the patients developed isolated bone metastases.

Laboratory tests

Laboratory tests included hemoglobin (g/dl), haematocrit (%), number of leukocytes (10^3), neutrophil count (K/ml), thrombocyte count (10^3), MPV (fl), serum lactate dehydrogenase (LDH, U/L), alkaline phosphates (U/L), calcium (Ca, mg/dl), albumin (g/dl), carcinoembryonic antigen (CEA, ng/mL) and carbohydrate antigen-15-3 (CA-15.3, U/mL) levels. Blood samples were obtained for analysis after 8-12 hrs fasting. Serum LDH, albumin, and calcium measurements were performed on a Cobas 8000® modular analyzer series (Roche Diagnostics, Jersey, USA). A Pentra DF Nexus SPS (HORIBA Medical, Kyoto, Japan) was used to measure leukocytes, neutrophils, hemoglobin, thrombocytes, and MPV.

Table 1. Comparison of the study variables for all groups

Characteristics	*Group 1 (N=121) N (%)*	*Group 2 (N=71) N (%)*	*Group 3 (N=39) N (%)*	*p value**
Age, years , mean ± SD	49±14	55±12	51±9	0.298
Body mass index(kg/m^2), mean ± SD	29±7	27±11	28±7	0.318
Smoking				
Yes	38 (21)	18 (25)	11(28)	
No	83 (69)	53 (75)	28 (72)	0.397
Menopausal status				
Postmenopausal	76 (63)	45 (63)	24 (62)	0.218
Premenopausal	45 (37)	26 (37)	15 (38)	
Weight				
Obesity (>30 kg/m^2)	33 (27)	22 (30)	13 (33)	
Overweight (25-30 kg/m^2)	47 (39)	26 (38)	15 (36)	0.297
Normal (<25 kg/m^2)	41 (34)	23 (32)	11 (31)	
Histological type				
Invasive ductal	90 (74)	57 (80)		
Invasive lobular	15 (12)	9 (13)	-	0.196
Inflammatory	9 (7)	2 (3)		
Other	7 (7)	3 (4)		
Tumor grade				
1	8 (6)	6 (9)		
2	81 (67)	46 (65)	-	
3	24 (21)	16 (23)		0.147

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Unknown	8 (6)	3 (3)		
Tumor size (cm)				
<2	24 (20)	18 (25)	-	
2-5	73 (60)	42 (59)		0.318
>5	24 (20)	11 (16)		
Nodal status				
N0	33 (27)	18 (25)		
N1	31 (26)	16 (23)	-	0.211
N2	35 (29)	24 (34)		
N3	22 (18)	13 (18)		
Lymphovascular invasion				
Yes	86 (71)	34 (48)	-	0.024
No	14 (12)	26 (37)		
Unknown	21 (17)	11 (15)		
Stage (TNM)				
I	-	8 (12)		
II	-	18 (25)	-	N/A
III	-	45 (63)		
IV	121 (100)	0 (0)		
Estrogen receptor status				
Positive	75 (62)	43 (61)	-	0.247
Negative	46 (28)	28 (29)		
Progesterone receptor status				
Positive	58 (48)	31 (44)	-	0.118
Negative	63 (52)	40 (56)		
Her2/neu status				
Positive	22 (21)	19 (27)	-	0.164
Negative	95 (79)	52 (73)		
Biological subtype				
Luminal A	89 (74)	45 (63)		
Luminal B	16 (13)	16 (23)	-	0.109
Her2/neu- positive	6 (5)	7 (10)		
Triple negative	10 (8)	3 (4)		
Ki67 score (%)				
<20	33 (27)	22 (31)		
20-50	31 (26)	16 (23)	-	0.243
>50	24 (20)	11 (56)		
Unknown	33 (27)	23 (24)		
Bone metastasis sites				N/A
Cervical vertebral column	4 (3)			
Thoracic vertebral column	5 (4)			
Lumbar vertebral column	4 (3)			
Thoracic and lumbar column	6 (5)			
Cervical and thoracic column	4 (3)			
Cervical and lumbar column	3 (3)			
Whole vertebral column	11 (9)			

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Upper extremities, long bone	8 (7)			
Lower extremities, long bone	6 (5)			
Costae	9 (7)			
Pelvis	4 (3)			
Sacroiliac	3 (3)			
Other areas in the vertebral column	21 (17)			
Multiple sites	33 (27)			
Hemoglobin (g/dL), mean±SD	9.2±2.4	9.4±2.6	9.9±3.1	0.187
Leukocyte count (10^3), mean±SD	7245±1320	6800±1150	5800±1240	0.032
Neutrophil count (K/ml), mean±SD	3450±795	3100±450	2950±125	0.041
Thrombocyte count (10^3), mean±SD	495±295	385±165	354±148	0.027
Platelet volume (fL), mean±SD	8.8 ± 5.1	7.1±2.1	7.3±2.3	0.018
Mean platelet volume/thrombocyte counts ratio (fL/(10^9/L)	0.0398	0.0321	0.0308	0.026
Serum LDH (U/L), mean±SD	247±24	218±19	174±16.	0.314
Serum calcium (mg/dl), mean±SD	8.8±2.3	8.1±1.4	8.3±0.8	0.289
Serum alkaline phosphatase (U/L), mean±SD	247±86	189±49	164±21	0.041
CEA (ng/mL), mean±SD	6.9±3.7	3.2±1.1	-	0.032
CA 15-3 (U/mL), mean±SD	34±23	21±9	-	0.029

LDH: lactate dehydrogenase, CEA: carcinoembryonic antigen, CA-15.3: carbohydrate antigen 15.3, SD: standard deviation. *two-tailed p value by Student's t-test

Statistics

The data were expressed as mean with standard deviation (SD), median plus range, and/or interquartile range (25-75%). The distribution of variables was analyzed with the Kolmogorov-Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed, independent Student's t-test. Nonparametric variables were analyzed with the Mann-Whitney U test. At least 6 months after the last chemotherapy or radiotherapy, operating variables were identified during follow-up and the patients were assessed by Student's t-test for repeated variables. The area under the curve (AUC) of the cut-off value was determined and the MPV value for predicting bone metastases was determined based on the sensitivity, accuracy, and specificity of the data. Qualitative parameters were analyzed using x^2 test and Fisher's exact test. The Kruskal-Wallis test was used for comparisons between clinical and demographic variables. In addition, univariate and multivariate analyses were used to determine independent risk factors. In the context of this study, $p<0.05$ was considered statistically significant.

Results

The mean age of group 1 patients was 49 ± 14 years (median 63, range 41-79). There was no significant difference in age (p=0.298) among patients in group 1, group 2 (mean 55±12) and group 3 (mean 51±9). The other demographic characteristics of the patients in each of the 3 groups are shown in Table 1. Group 1 patients had a higher lymphovascular invasion rate (p=0.024). Also, in group 1 patients the following results were obtained in blood/serum assessed factors: leukocyte count (p=0.032), neutrophil count (p=0.041), and thrombocyte count (p=0.027) compared with patients in groups 2 and 3. For group 1, the MPV was significantly higher when compared to groups 2 and 3 (p=0.018, Table 2). Similarly, the MPV/platelet count ratio in group 1 was significantly higher when compared to groups 2 and 3 (p=0.026, Table 2). The serum CEA and CA-15.3 values were also higher in group 1 compared to group 2 (p=0.032 and p=0.029, respectively). Comparisons of other histopathological and laboratory variables are presented in Table 2.

The MPV of group 1was 8.8 fL (SD=5.1, range 6.1-15.6) and the cut-off value was 9.2 fL. The patients in group 1 were stratified according to the MPV for study variables and the data are presented in Table 3. The 4 groups were defined as follows: group A had a MPV >6.08 fL (lowest quartile), group B had MPVs ranging from 6.09 to 8.46 fL, group C had MPVs ranging from 8.47 to 10.05 fL, and group D had MPV ≥10.06 fL (high-

Table 2. Stratification according to the cut-off level of mean platelet volume

Characteristics	*Group A <6.08 fL N (%)*	*Group B 6.09-8.46 fL N (%)*	*Group C 8.47-10.05 fL N (%)*	*Group D >10.06 fL N (%)*	*p value**
N	11	25	49	36	-
Age (years), mean±SD	45±12	47±11	48±12	47±12	0.215
Body mass index(kg/m2), mean±SD	28±8	28±7	28±9	29±7	0.246
Smoking					
Yes	7 (63)	19 (76)	33 (67)	24 (67)	0.197
No	4 (37)	6 (24)	16 (33)	12 (33)	
Menopausal status					
Postmenopausal	6 (55)	16 (64)	32 (65)	22 (61)	0.207
Premenopausal	5 (45)	9 (36)	17 (35)	14 (39)	
Histological type					
Invasive ductal	8 (73)	20 (78)	34 (69)	28 (78)	
Invasive lobular	2 (18)	3 (12)	7 (14)	3 (10)	0.392
Inflammatory	1 (9)	1 (5)	3 (7)	4 (11)	
Other	0	1 (5)	5 (10)	1 (1)	
Tumor grade					
1	1 (9)	1 (4)	4 (8)	2 (5)	
2	6 (55)	19 (76)	30 (61)	26 (72)	0.211
3	3 (27)	4 (16)	11 (23)	6 (18)	
Unknown	1 (9)	1 (4)	4 (8)	2 (5)	
Tumor size (cm)					
<2	3 (27)	4 (16)	11 (22)	6 (17)	0.274
2-5	5 (46)	18 (72)	25 (51)	25 (69)	
>5	3 (27)	3 (12)	13 (27)	5 (14)	
Nodal status					
N0	2 (18)	8 (32)	16 (34)	7 (19)	
N1	2 (18)	5 (20)	17 (35)	7 (19)	0.037
N2	5 (46)	6 (24)	12 (25)	12 (33)	
N3	2 (18)	6 (24)	4 (6)	10 (29)	
Lymphovascular invasion					
Present	7 (64)	15 (60)	33 (67)	31 (86)	0.032
Absent	2 (18)	7 (28)	4 (8)	1 (3)	
Unknown	2 (18)	3 (12)	12 (25)	4 (11)	
Estrogen receptor status					
Positive	6 (54)	15 (60)	35 (71)	19 (53)	0.191
Negative	5 (46)	10 (40)	14 (29)	17 (47)	
Progesterone receptor status					
Positive	5 (46)	17 (68)	31 (63)	5 (4)	0.074
Negative	6 (54)	8 (32)	18 (37)	31 (86)	
Her2/neu status					
Positive	2 (18)	4 (16)	11 (22)	5 (14)	
Negative	9 (82)	21 (84)	38 (78)	31 (86)	0.209
Biological subtype					
Luminal A	5 (46)	16 (64)	42 (86)	27 (75)	
Luminal B	5 (46)	6 (24)	3 (6)	2 (5)	0.104
Her2-positive	1 (8)	1 (4)	2 (4)	2 (5)	
Triple negative	0	2 (8)	2 (4)	5 (15)	

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Ki67 score (%)					
<20	3 (27)	8 (32)	16 (33)	6 (17)	
20-50	2 (19)	6 (24)	13 (27)	10 (28)	0.241
>50	3 (27)	6 (24)	12 (25)	3 (8+)	
Unknown	3 (27)	5 (20)	8 (15)	17 (47)	
Bone metastasis sites					
Cervical vertebral column	0	1	2	1	
Thoracic vertebral column	0	1	2	2	
Lumbar vertebral column	0	1	1	2	
Thoracic and lumbar column	1	1	3	1	
Cervical and thoracic column	0	1	1	2	
Cervical and lumbar column	1	0	2	0	
Whole vertebral column	1	2	6	2	0.032
Upper extremities, long bone	1	2	6	2	
Lower extremities, long bone	0	3	2	1	
Ribs	2	1	3	3	
Pelvis	1	1	2	0	
Sacroiliac	0	1	2	0	
Other areas in the vertebral column	2	6	7	6	
Multiple sites	2	4	10	17	
Hemoglobin level (g/dL)**	9.1±2.2	9.2±2.4	9.3±2.3	9.1±2.1	0.298
Leukocyte count (10^3)**	6750±1250	7150±1100	6850±1200	6900±1150	0.297
Neutrophil count (K/ml)**	3200±750	3250±850	3400±650	3500±700	0.345
Thrombocyte count (10^3)**	400±250	425±225	450±230	495±250	0.098
Serum LDH level (U/L)**	235±25	230±28	225±25	226±24	0.379
Serum calcium level (mg/dl)**	8.7±2.6	8.7±2.4	8.6±2.8	8.8±2.3	0.213
Serum alkaline phosphates level** (U/L)	239±74	215±66	227±64	234±57	0.357
CEA level (ng/mL)**	6.4±3.2	6.6±2.8	6.8±2.8	6.9±2.7	0.145
CA 15-3 level (U/mL)**	34±21	34±14	36±17	35±18	0.211

*two-tailed p value by Student's t-test; **values are given as mean±standard deviation

est quartile). Based on this comparison, MPV <10.06 fL was observed in the majority of N3 disease (p=0.041), with lymphovascular invasion (p=0.039) and bone metastasis in multiple areas (p=0.034) (Table 3).

In patients (N=31) who developed isolated bone metastases at least 6 months after the end of chemotherapy or radiotherapy, MPV was found to be significantly increased in non-metastatic patients at the time of diagnosis (8.3 ± 4.8 and 7.9 ± 3.2, respectively; p=0.015). Similarly, the MPV/ thrombocyte count rate in patients with isolated bone metastases was increased significantly when compared to the previous values (0.0241 and 0.0297, respectively; p=0.029).

A cut-off <9.2 fL had significant predictive value according to receiver-operating curve analysis for MPV. This cut-off for MPV had a 91% positive predictive value and 94% negative predictive value in the prediction of isolated bone metastases. With a cut-off level of MPV of 9.2 fL, the accuracy, sensitivity, and specificity rates in predicting isolated bone metastases were 85, 96, and 93%, respectively. Additionally, a significant correlation was observed for the increase in serum calcium levels, LDH levels, progesterone receptor expression, low Ki67 ratio, and MPV (Table 4).The univariate analysis showed that the following variables were associated with the prediction of isolated bone metastases: nodal status, lymphovascular invasion, positive progesterone receptor, MPV, MPV/ platelet count rate, corrected serum calcium levels, alkaline phosphatase levels, thrombocyte count, and CA-15.3 value (Table 5). In multivariate analysis MPV and lymphovascular invasion were identified as independent risk factors for isolated bone metastasis in breast cancer (Table 4).

Table 3. Correlation analyses between study variables and mean platelet volume

Variables	*r*	*p value*
Age (<65 vs >65 years)	0.317	0.211
Smoking (Yes vs No)	0.254	0.342
Body mass index (obesity and overweight vs normal)	0.372	0.304
Histological type (invasive ductal carcinoma vs others)	0.293	0.274
Nodal status (N0-2 vs N3)	0.598	0.034
Tumor size (<2 vs 2-5 vs >5 cm)	0.308	0.274
Lymphovascular invasion (Yes vs No)	0.667	0.024
Tumor grade (1 vs 2-3)	0.457	0.144
Estrogen receptor status (positive vs negative)	0.245	0.417
Progesterone receptor status (positive vs negative)	0.297	0.245
Her2/neu status (positive vs negative)	0.274	0.314
Ki67 score (<20 vs >20%)	0.298	0.213
Biological type (luminal A vs other)	0.374	0.204
Serum LDH level	0.276	0.245
Serum calcium level	0.481	0.044
Serum alkaline phosphatase level	0.299	0.264
Leukocyte count	0.347	0.238
Thrombocyte count	0.574	0.031
Hemoglobin level	0.354	0.031
CEA level	0.448	0.137
CA- 15.3 level	0.548	0.191

LDH: lactate dehydrogenase, CEA: carcinoembryonic antigen, CA-15.3: carbohydrate antigen-15.3

Discussion

In the analysis, the MPV and MPV/thrombocyte count ratio of isolated bone metastatic breast cancer patients were significantly higher than in the other groups. In these patients, the MPV cut-off value was 9.2 fL, and the accuracy, sensitivity and specificity rates for the predictive value of bone metastases were 85, 96, and 93%, respectively.

Predictive and prognostic values of MPV were demonstrated in previous studies, particularly in atherosclerotic coronary and cerebral diseases together with systemic inflammation and thromboembolism [18,20,21]. Similarly, an increased MPV/thrombocyte count ratio in non-ST-elevation acute myocardial infarction predicts subsequent mortality [21]. These findings indicate a role for platelets in the pathogenesis of inflammation and thrombosis [19,21]. Platelets with increased mean volume are highly reactive and aggregate. However, the effects of pro-inflammatory cytokines in patients with cancer remain unclear. Tumor necrosis factor-α, interleukin [IL] -1, and IL-6 activate thrombopoiesis in the bone marrow of cancer patients, resulting in thrombocytosis [22]. For bone metastases the direct effect of cancer cells may play a role in inflammation in the microenvironment [22].

Studies on cancer patients suggest that increased MPV and thrombocytosis are independent prognostic factors of poor prognosis. Osada et al. [22] assessed gastric cancer patients and healthy controls and reported that the MPV was significantly increased in patients with gastric cancer. In studies of esophageal, ovarian, breast, and hepatocellular cancer, the MPV, platelet count, platelet distribution, neutrophil/lymphocyte ratio, and the platelet count/lymphocyte ratio were determined as predictive factors in peripheral blood prior to surgical treatment or prior to systemic therapy [23-26]. However, the relationship between poor prognosis and increased mortality in cancer patients and the MPV remains uncertain [24]. In another study by Karagoz et al. [25] with 71 lung cancer patients, no significant difference was noticed in MPV between lung cancer patients and the control group (p=0.517).

In hematologic malignancies and solid tumors, MPV may predict bone marrow infiltration and the MPV value in patients with bone marrow infiltration is usually lower than normal ranges

Table 4. Univariate and multivariate analysis of the factors for isolated bone metastasis in patients with breast cancer

Factors	*Odds ratios (95% CI)*	*p value*
Univariate analysis		
Age (<65 vs >65 years)	1.37 (0.44-2.97)	0.374
Smoking (Yes vs No)	1.41 (0.74-2.47)	0.239
Body mass index (obesity and overweight vs normal)	1.59 (0.47-2.31)	0.274
Histological type (invasive ductal carcinoma vs other)	1.46 (0.31-4.76)	0.229
Nodal status (N0-2 vs N3)	2.11 (1.71-6.61)	0.022
Tumor size (<2 vs 2-5 cm vs >5 cm)	1.24 (0.41-2.36)	0.245
Lymphovascular invasion (Yes vs No)	1.44 (1.18-4.79)	0.041
Tumor grade (1 vs 2-3)	1.71 (0.67-3.41)	0.211
Estrogen receptor status (positive vs negative)	1.49 (0.34-2.44)	0.171
Progesterone receptor status (positive vs negative)	2.46 (0.44-4.34)	0.178
Her2/neu status (positive vs negative)	1.91 (0.34-2.97)	0.192
Ki67 score (<20 vs >20%)	1.54 (0.39-3.14)	0.474
Biological type (Luminal A vs other)	1.48 (0.42-2.87)	0.408
Mean platelet volume (<9.4 vs >9.4 fL)	1.43 (1.15-6.54)	0.027
Mean platelet volume/thrombocyte count ratio	1.97 (1.64-3.41)	0.044
Serum LDH level	1.49 (0.31-2.98)	0.345
Serum calcium level	1.77 (1.46-2.74)	0.041
Serum alkaline phosphatase level	1.78 (1.24-5.14)	0.043
Leukocyte count	1.91 (0.35-3.78)	0.385
Thrombocyte count	2.14 (1.42-4.38)	0.034
Hemoglobin level	2.41 (0.79-3.18)	0.209
CEA level	1.91 (0.97-1.96)	0.117
CA- 15.3 level	1.71 (1.27-3.45)	0.037
Multivariate analysis		
Increased mean platelet volume	2.17 (1.24-5.11)	0.023
Presence of lymphovascular invasion	2.38 (1.745-6.18)	0.026

LDH: lactate dehydrogenase, CEA: carcinoembryonic antigen, CA-15.3: carbohydrate antigen-15.3

of MPV values [26,27]. Aksoy et al. [28] showed that the MPV in patients with cancer that has metastasized to the bone marrow was significantly reduced when compared to healthy controls. That study gave a MPV cut-off value of 7.4 fL, and for bone marrow metastasis a MPV below this value had a positive predictive value of 85%, a negative predictive value of 90%, a sensitivity of 82.7% and a specificity of 89.5%. Our study did not include bone marrow infiltration. In addition, the objective of this study was not to determine the prognostic value of MPV during the later stages of bone metastases in order to better predict metastasis to the bone. This is an important point for further studies.

Breast cancer is a heterogeneous disease and its molecular subtypes possess prognostic and predictive properties [29-37]. The luminal A subtype is associated with more frequent bone metastases [29-32]. In our study, we did not find a relationship between hormone receptor status and bone metastasis. The leukocyte, neutrophil, and thrombocyte counts are basic markers of inflammation [18], and we determined that patients with isolated bone metastases had a significantly increased risk for inflammatory processes. These results show that the role of inflammation in cancer is consistent with other studies, and emphasizes the inflammatory response in the microenvironment of bone metastases.

Previous studies on CEA and CA-15.3 in breast cancer patients tried to predict the development of distant metastases [38]. We recommend that these two markers be evaluated together [38]. While there is a limited number of positive predictive studies of CEA and CA-15.3 for bone metastases, similar studies are available for brain metastases. In our study, isolated bone metastases in breast

cancer patients had significantly higher CEA and CA15.3 values compared to non-metastatic patients. However, multivariate analysis identified these two markers as independent risk factors.

The most important limitation of our study is its retrospective nature. Moreover, the relatively small number of patients might negatively affect the statistical power. However, we believe that further studies should continue to shed light on this topic. For isolated bone metastases the MPV at diagnosis may be an important predictive factor. Yet, larger studies are necessary and additional biomarkers must be identified.

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Conflict of interests

The authors declare no confict of interests.

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