Breast Cancer (2019) 26:712–718
https://doi.org/10.1007/s12282-019-00976-1

ORIGINAL ARTICLE

Preoperative mean platelet volume predicts survival in breast cancer patients with type 2 diabetes

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Received: 1 October 2018 / Accepted: 6 May 2019 / Published online: 13 May 2019

Abstract

Purpose Patients with type 2 diabetes mellitus (T2DM) have an increased risk of breast cancer (BC). Furthermore, growing evidence suggests that activated platelets play a crucial role in tumor and T2DM. Mean platelet volume (MPV) is a platelet index and is altered in patients with malignancies. The aim of this study was to determine whether preoperative MPV could predict survival in BC patients with T2DM.

Methods The clinical data of 266 female BC patients with T2DM and 264 female BC patients without T2DM between January 2011 and December 2011 in our center were retrospectively analyzed. Survival analysis was performed using the log-rank test and Cox proportional hazards regression analysis.

Results The patients with T2DM had higher MPV levels than the patients without T2DM. Furthermore, MPV was found to be significantly associated with differentiation T2DM from non-T2DM. In addition, survival analysis revealed that the disease-specific survival and overall survival of patients with MPV ≤ 8.0 fL were significantly shorter than that of those with MPV > 8.0 fL in diabetic patients. Multivariate analysis identified MPV as an independent poor prognostic factor for survival only in patients with T2DM not in patients without T2DM.

Conclusions Our study first established a connection between MPV and BC patients with T2DM, suggesting that MPV was an independent prognostic factor and could be the biomarker for prognosis.

Keywords Breast cancer · Type 2 diabetes mellitus · Mean platelet volume · Prognosis

Introduction

Breast cancer (BC) is one of the most commonly diagnosed cancers and the fourth leading cause of cancer death in females worldwide [1]. Recent studies revealed that preexisting diabetes is independently associated with poor overall survival in BC [2]. In addition, compared with their nondiabetic counterparts, BC patients with pre-existing diabetes have a greater risk of death and tend to present at later stages [3]. Therefore, identifying biomarkers for prognosis in BC patients with diabetes is helpful in the choice of proper therapeutic strategies.

Platelets play a key role in cancer progression and metastasis. There is emerging evidence to suggest that platelets mediate tumor cell growth, angiogenesis, and dissemination [4]. Elevated platelets are correlated with a decrease in overall survival and poorer prognosis in various types of cancer, such as pancreatic cancer, gastric cancer, colorectal cancer, endometrial cancer, and ovarian cancer [5–9]. However, platelet number is determined by

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the balance between the rate of production and consumption of platelets. A normal platelet count could conceal the presence of highly hypercoagulative and pro-inflammatory cancer phenotypes in the presence of efficient compensatory mechanisms [10].

Mean platelet volume (MPV), the most commonly used measure of platelet size, is a surrogate marker of platelet activation [11]. Altered MPV levels were found in gastric cancer, ovarian cancer, lung cancer, and breast cancer [12–15]. Moreover, there was significantly higher MPV levels in diabetic patients than in the nondiabetic subjects [16]. However, the clinical implication of MPV in BC patients with diabetes has not been well defined.

In the present study, we aimed to determine whether preoperative MPV could predict survival in BC patients with diabetes.

Methods

Study population

This is a retrospective study at Harbin Medical University Cancer Hospital (Harbin, China). We performed a search of the information about the BC patients in the database of the Harbin Medical University Cancer Hospital. A total of 266 female BC patients with T2DM and 264 BC patients without T2DM who underwent surgery from January 2011 to December 2011 were selected for the present study. All of these patients were histologically confirmed BC by two experienced pathologists. No patient underwent preoperative radiotherapy, chemotherapy, or any other treatment. Exclusion criteria included hematological disorders, and medical treatment with anticoagulant, statins, and acetylic salicylic acid. Diagnosis of T2DM was based on American Diabetes Association criteria such as fasting plasma glucose $\geq$ 7.0 mmol/L, current treatment with a hypoglycemic agent, or casual glucose $\geq$ 11.1 mmol/L. For the patients with impaired fasting glucose, T2DM was diagnosed if a 2-h post-glucose level after a 75-g oral glucose tolerance test $\geq$ 11.1 mmol/L. The disease-specific survival (DSS) was defined as the time from the date of the diagnosis to the date of the death from breast cancer. Overall survival (OS) was calculated from the date of surgery to the date of death from breast cancer or last follow-up. Follow-up was completed on December 31, 2016. The median follow-up duration was 60 months.

The Institutional Ethics Review Board of Harbin Medical University Cancer Hospital approved this study and waived the need for informed consent because this was a retrospective study.

Statistical analysis

Continuous data are presented as means ± SD or medians (interquartile range) (IQR), and categorical data are presented as numbers (percentages). Normally distributed continuous variables were compared with the Student's *t* test and skewed-distributed with the Mann–Whitney *U* test. Comparisons of dichotomized variables were performed with the χ^2 test. DSS and OS were calculated and plotted with Kaplan–Meier method with the log-rank test for the comparison between the groups. Cox proportional hazard model was used to evaluate the effects of clinicopathologic variables on DSS and OS. All statistical analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). *P* values < 0.05 were considered as significant.

Results

266 BC patients with T2DM, and 264 BC patients without non-T2DM were included in this study. The mean age was 50.5 ± 9.6 years in non-T2DM patients and 57.5 ± 9.6 years in T2DM patients. The baseline characteristics of both T2DM and non-T2DM patients are presented in Table 1. Patients with T2DM were older, more likely to have a higher WBC count, BMI, MPV, and CEA levels than patients without T2DM. Post-menopausal women, larger tumor size, advanced *N* stage, and HER-2 positive, had a higher prevalence in T2DM group. There were no significant differences in T staging, cancer staging, ER status, and PR status. The discrepancy between diabetes patients and non-diabetes patients in differentiation grade was also found.

Cut-off value of 8.0 for MPV had a 36.1% sensitivity and 85.2% specificity for OS rate (AUC = 0.642, 95% CI 0.581–0.699, $p = 0.007$) (Fig. 1).

For patients with T2DM, with a median follow-up of 60 months, 65 (24.6%) patients had death events. Patients with MPV $\leq$ 8.0 fL exhibited significantly shorter OS compared to those with MPV > 8.0 fL (72.3% vs. 89.5%, $p = 0.002$). The Kaplan–Meier DSS and OS curves of the reduced versus elevated MPV showed a significant separation (Fig. 2). For patients without T2DM, with a median follow-up of 60 months, 36 (13.5%) patients had death events. Patients with MPV $\leq$ 8.0 fL did not exhibit shorter OS compared to those with MPV > 8.0 fL (74.9% *vs*. 78.0%, p = 0.775). The Kaplan–Meier DSS and OS curves of the reduced versus elevated MPV did not show a significant difference (Fig. 3).

Logistic regression analysis was performed to evaluate the risk factors for distinguishing T2DM from non-T2DM.

Table 1 The clinicopathological characteristics in BC patients according to T2DM status

Variables	With T2DM	Without T2DM	P value
N	266	264	
Age (years)	57.5 ± 9.6	50.5 ± 9.6	< 0.001
BMI (kg/m^2)	26.0 ± 3.5	23.6 ± 3.5	< 0.001
Smoker (n, %)	20 (7.5)	16 (6.1)	0.505
FPG (mmol/L)	7.76 (6.20–9.42)	5.19 (4.80–5.58)	< 0.001
Albumin (g/L)	45.4 ± 4.7	44.9 ± 5.4	0.305
WBC (× 10^9/L)	7.22 ± 1.77	6.10 ± 1.74	< 0.001
Hemoglobin (g/dl)	137.8 ± 12.4	134.8 ± 12.3	0.005
Platelet count (× 10^9/L)	245.2 ± 64.2	236.9 ± 50.9	0.097
MPV (fL)	9.5 ± 1.5	9.1 ± 1.4	0.003
CEA (ng/ml)	1.88 (1.24–3.19)	1.30 (0.86–1.98)	< 0.001
Menopausal status			< 0.001
Pre	55 (20.7)	107 (40.5)	
Post	211 (79.3)	157 (59.5)	
Tumor size			< 0.001
< 2.5 cm	112 (42.1)	202 (76.5)	
≥ 2.5 cm	154 (57.9)	62 (23.5)	
Differentiation grade			< 0.001
G1	64 (24.1)	163 (61.7)	
G2	159 (59.8)	27 (10.2)	
G3	43 (16.2)	74 (28.0)	
T stage			0.836
T1 + T2	251 (94.4)	248 (93.9)	
T3 + T4	15 (5.6)	16 (6.1)	
N stage			< 0.001
N0	116 (43.6)	203 (76.9)	
N1-3	150 (56.4)	61 (23.1)	
TNM stage			0.202
I + II	233 (87.6)	221 (83.7)	
III	33 (12.4)	43 (16.3)	
ER	0.124		
Positive	186 (69.9)	168 (63.6)	
Negative	80 (30.1)	96 (36.4)	
PR			0.643
Positive	159 (59.8)	163 (61.7)	
Negative	107 (40.2)	101 (38.3)	
HER-2 status			< 0.001
Positive	177 (66.5)	123 (46.6)	
Negative	89 (33.5)	141 (53.4)	
T2DM duration (years)	4.1 ± 3.4	–	
Insulin, *n* (%)	72 (17.5)	–	
Metformin, *n* (%)	34 (17.5)	–	

Data are expressed as means ± SD or median (inter-quartile range) or number (percentage)

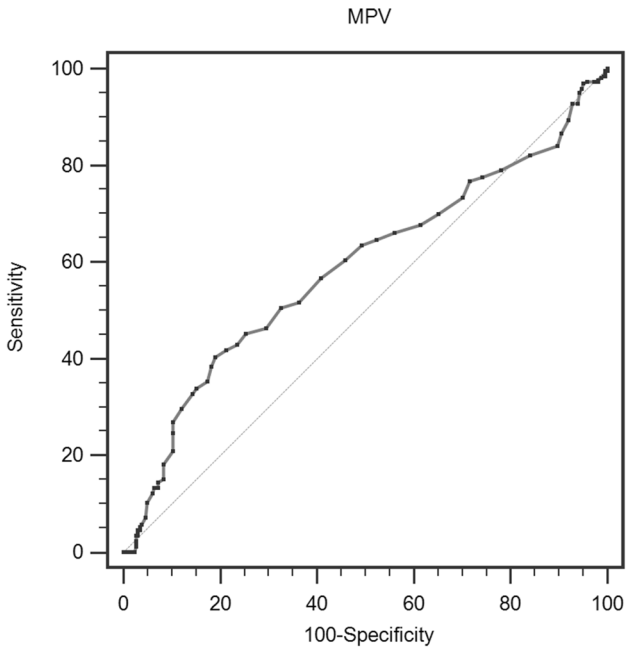

Fig. 1 Optimized cutoff value was determined for MPV using standard ROC curve analysis

The risk factors found to be significantly associated with differentiation in the regression analysis included age, BMI, MPV, WBC, tumor size, N stage, HER2 status, and differentiation grade (Table 2). Notably, MPV was a significant factor in the multivariate model ($\beta = 1.340$; $p = 0.026$).

We entered these clinicopathological data into multiple Cox regression models of DSS and OS as covariates in BC patients. For patients with non-T2DM, tumor size, TNM stage, and ER status were determined to be significant in univariate analyses (Table 3). For patients with T2DM, tumor size, TNM stage, ER status, and MPV were determined to be significant in univariate analyses (Tables 4, 5). The significant factors in univariate survival analysis were enrolled into a multivariate Cox proportional regression for the test of independent factors. The statistical analysis data indicated that TNM stage was an independent prognostic factor for OS in patients with non-T2DM (Table 3). Pretreatment MPV, ER status, and TNM stage were independent prognostic factors for DSS and OS in patients with T2DM (Tables 4, 5).

Discussion

This study showed that patients with T2DM had higher MPV levels than patients without T2DM. MPV was found to be significantly associated with differentiation T2DM from

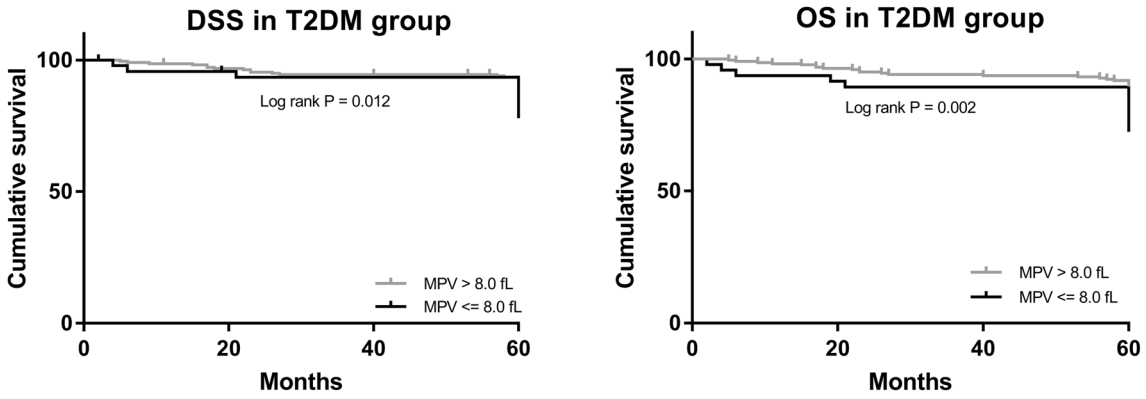

Fig. 2 Kaplan–Meier analysis of DSS and OS in BC patients with T2DM

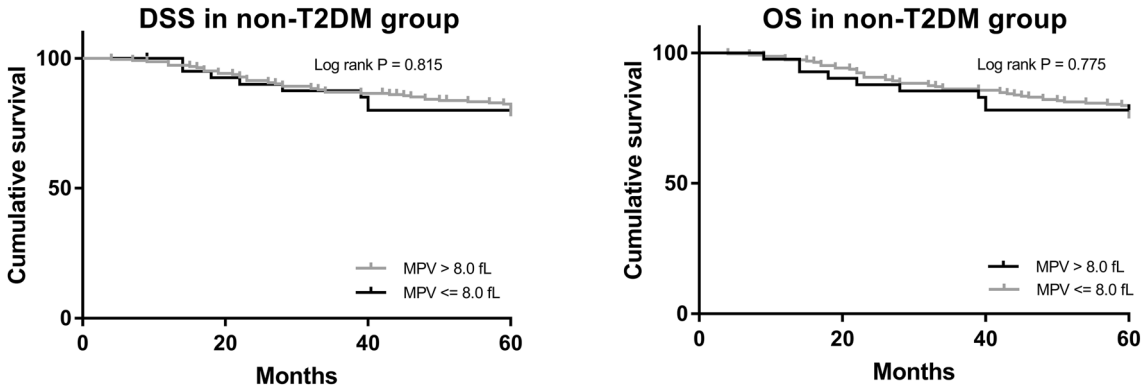

Fig. 3 Kaplan–Meier analysis of DSS and OS in BC patients without T2DM

Table 2 Multivariable logistic regression analysis on baseline variables associated with T2DM

Variables	β	OR (95% CI)	*P* value
Age (years)	1.093	1.040–1.150	**0.001**
Menopausal status	0.630	0.217–1.827	0.395
BMI (kg/m^2)	1.242	1.120–1.376	**< 0.001**
WBC ($\times 10^9$/L)	1.500	1.230–1.829	**< 0.001**
Hemoglobin (g/dl)	1.015	0.988–1.043	0.271
MPV (fL)	1.340	1.036–1.734	**0.026**
CEA (ng/ml)	1.081	0.931–1.256	0.305
Tumor size	2.436	1.152–5.151	**0.020**
N stage	17.301	7.080–42.275	**< 0.001**
HER-2 status	2.341	1.159–4.731	**0.018**
Differentiation grade	0.190	0.118–0.306	**< 0.001**

Bold indicates statistically significant difference ($P<0.05$)

non-T2DM. In addition, MPV is an independent risk factor that influences prognosis in BC patients with T2DM.

Despite best current medical and surgical treatment, the overall prognosis of BC patients with diabetes remains poor. Therefore, it is of great importance in identifying novel prognostic factors.

There is a complex interplay between platelet-induced tumor growth and tumor cell-induced platelet activation [17]. In breast cancer, platelet-derived growth factor (PDGF) expression is associated with biological aggressiveness via NFkappaB signaling pathway [18, 19]. Moreover, platelet-derived lysophosphatidic acid accelerates osteolytic bone metastases [20]. These discoveries make the PDGFR/PDGF system an attractive oncologic therapeutic target [21]. A recent study demonstrated that combinations of anti-platelet drugs inhibit breast cancer cell-induced platelet aggregation [22]. In agreement with the studies above, our study indirectly confirmed the findings using a simple platelet index. Moreover, our study can form the basis for further mechanistic studies and ultimately aid in patient-tailored selection of therapeutic strategies.

The mechanisms to explain the association between MPV and survival remains unclear. Inflammation may be responsible for the association. Activated platelets play an essential role in inflammation and cancer. MPV is an early parameter of activated platelets and associates with inflammatory

Table 3 The univariate and multivariate analyses of overall survival in BC patients without T2DM

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years) (> 50 versus ≤ 50)	1.250 (0.768–2.036)	0.370		
Menopausal status (post versus pre)	0.767 (0.471–1.248)	0.285		
BMI (kg/m^2)	1.035 (0.970–1.105)	0.301		
Smoking status (Yes versus No)	0.435 (0.107–1.779)	0.247		
Tumor size (cm) (≥ 2.5 versus < 2.5)	2.057 (1.236–3.421)	0.005	1.218 (0.723–2.054)	0.459
Differentiation	1.160 (0.870–1.547)	0.313		
TNM stage (III versus I + II)	18.267 (10.897–30.621)	< 0.001	17.295 (10.167–29.418)	**< 0.001**
ER (positive versus negative)	0.658 (0.404–1.074)	0.094	0.870 (0.530–1.428)	0.582
PR (positive versus negative)	1.535 (0.899–2.620)	0.116		
HER-2 (positive versus negative)	0.923 (0.566–1.506)	0.750		
FPG (mmol/L) (log-value)	1.364 (0.187–9.956)	0.760		
Albumin (g/L)	1.017 (0.975–1.061)	0.436		
CEA (ng/ml) (log-value)	1.396 (0.702–2.777)	0.342		
Hemoglobin (g/dl)	0.998 (0.979–1.018)	0.870		
WBC (× 10^9/L)	1.015 (0.887–1.163)	0.824		
Platelet count (× 10^9/L)	1.004 (0.999–1.008)	0.121		
MPV (fL) (≤ 8.0 versus > 8.0)	0.903 (0.447–1.826)	0.777		

Bold indicates statistically significant difference ($P<0.05$)

Table 4 The univariate and multivariate analyses of DSS in BC patients with T2DM

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years) (> 50 versus ≤ 50)	0.671 (0.312–1.443)	0.307		
Menopausal status (post versus pre)	0.686 (0.304–1.549)	0.364		
BMI (kg/m^2)	0.897 (0.797–1.009)	0.071	0.916 (0.813–1.034)	0.155
Smoking status (Yes versus No)	0.421 (0.057–3.092)	0.395		
Tumor size (cm) (≥ 2.5 versus < 2.5)	2.399 (1.025–5.617)	0.044	1.697 (0.711–4.050)	0.233
Differentiation	0.849 (0.473–1.521)	0.581		
TNM stage (III versus I + II)	4.211 (1.958–9.058)	< 0.001	3.613 (1.642–7.952)	**0.001**
ER (positive versus negative)	0.287 (0.137–0.601)	0.001	0.380 (0.175–0.825)	**0.014**
PR (positive versus negative)	0.789 (0.380–1.640)	0.526		
HER-2 (positive versus negative)	1.264 (0.560–2.853)	0.573		
FPG (mmol/L) (log-value)	1.905 (0.617–5.882)	0.262		
Albumin (g/L)	0.994 (0.922–1.072)	0.878		
CEA (ng/ml) (log-value)	1.156 (0.620–2.153)	0.648		
Hemoglobin (g/dl)	0.983 (0.957–1.010)	0.211		
WBC (× 10^9/L)	0.854 (0.680–1.073)	0.175		
Platelet count (× 10^9/L)	1.000 (0.995–1.006)	0.907		
MPV (fL) (≤ 8.0 versus > 8.0)	2.551 (1.186–5.485)	0.017	2.231 (1.017–4.894)	**0.035**
T2DM duration (years)	0.988 (0.977–1.000)	0.057	0.994 (0.983–1.004)	0.236
Insulin (yes versus no)	1.712 (0.809–3.626)	0.160		
Metformin (yes versus no)	0.040 (0.000–4.076)	0.172		

Bold indicates statistically significant difference ($P<0.05$)

conditions. In low-grade inflammatory conditions, such as dyslipidemia, hypertension, and diabetes, higher MPV levels were observed. High-grade inflammatory diseases, such as active rheumatoid arthritis or attacks of familial Mediterranean fever, present with low levels of MPV, which reverse in the course of anti-inflammatory therapy [11]. In accord

Table 5 The univariate and multivariate analyses of overall survival in BC patients with T2DM

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years) (> 50 versus ≤ 50)	0.707 (0.354–1.414)	0.327		
Menopausal status (post versus pre)	0.681 (0.328–1.411)	0.301		
BMI (kg/m^2)	0.931 (0.840–1.031)	0.168		
Smoking status (Yes versus No)	0.336 (0.046–2.453)	0.282		
Tumor size (cm) (≥ 2.5 versus < 2.5)	2.285 (1.075–4.860)	0.032	1.722 (0.797–3.720)	0.167
Differentiation	0.734 (0.434–1.243)	0.251		
TNM stage (III versus I + II)	3.989 (1.995–7.978)	< 0.001	3.658 (1.795–7.455)	< **0.001**
ER (positive versus negative)	0.363 (0.189–0.699)	0.002	0.400 (0.207–0.774)	**0.006**
PR (positive versus negative)	0.641 (0.334–1.232)	0.182		
HER-2 (positive versus negative)	0.759 (0.388–1.483)	0.419		
FPG (mmol/L) (log-value)	1.651 (0.594–4.592	0.337		
Albumin (g/L)	1.002 (0.947–1.102)	0.584		
CEA (ng/ml) (log-value)	1.169 (0.643–2.124)	0.608		
Hemoglobin (g/dl)	0.980 (0.957–1.004)	0.101		
WBC (× 10^9/L)	0.879 (0.718–1.075)	0.209		
Platelet count (× 10^9/L)	1.001 (0.996–1.006)	0.787		
MPV (fL) (≤ 8.0 versus > 8.0)	2.737 (1.386–5.403)	0.004	2.721 (1.369–5.408)	**0.004**
T2DM duration (years)	0.994 (0.986–1.002)	0.124		
Insulin (yes versus no)	0.040 (0.001–2.544)	0.129		
Metformin (yes versus no)	1.582 (0.802–3.124)	0.186		

Bold indicates statistically significant difference ($P<0.05$)

with our results, a study found that solid tumors with bone marrow metastasis were more likely to have low MPV levels [23]. In addition, low MPV levels were associated with poor prognosis in renal cell carcinoma, and invasive bladder cancer [24, 25]. However, Gu et al. revealed that higher MPV associates with worse clinicopathologic features and prognosis in patients with invasive breast cancer [26]. Moreover, MPV is also increased in T2DM patients, especially in the presence of micro-vascular complications [27]. An increase in MPV is one of the risk factors for macro-vascular complications, such as myocardial infarction, ischemic stroke and venous thromboembolism [28]. The biggest difference between past studies and our study is study population. Diabetes was excluded in past reports which investigated the associations between MPV and cancer prognosis [24–26]. Previous studies confirmed that diabetes mellitus is associated with an increased risk of breast cancer and poorer prognosis of breast cancer [2, 29]. Furthermore, dysregulated glucose metabolism, which concurs with a chronic pro-inflammatory condition and an associated oxidative stress promote tumor initiation and progression in T2DM patients with breast cancer [30]. The release rate of small size platelets from the bone marrow increased since excessive pro-inflammatory cytokines interfere with megakaryopoiesis [31]. Therefore, lower MPV values could be suggestive of an enhanced consumption of large platelets in inflammatory states [11].

Several limitations should be acknowledged in the present study. First, this was a single-center retrospective study and additional larger validation studies are needed to confirm our results. Second, the mechanisms underlying the involvement of MPV in BC patients with T2DM, to which further investigation should be addressed. Third, the patients were composed of Chinese. The application to other ethnic groups needs further investigation.

In conclusion, our study first established a connection between MPV and BC patients with T2DM, suggesting that MPV was an independent prognostic factor and could be the biomarker for prognosis.

Funding This work was supported by Natural Science Foundation of Heilongjiang Province of China (ZD2017017) and Science Foundation of Heilongjiang Academy of Medical Science (Grant no. 201811).

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

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