



# Preliminary study on the role of serum PECAM-1 in metastatic breast cancer

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**Background:** The metastatic breast cancer (MBC) is yet incurable with high mortality, thereby requiring improved biomarkers for predicting the outcome of palliative therapy in patients. The present study evaluated the correlation of serum platelet and endothelial cell adhesion molecule-1 (PECAM-1) with the prognosis of MBC patients.

**Methods:** Thirty women initially diagnosed as MBC before any palliative treatment, were divided according to the median value of serum PECAM-1 level, Group A (<4,058.89 pg/mL) and Group B (>4,058.89 pg/mL). After median 78 months follow-up from the preliminary surgery, 15 patients died of breast cancer. The Kaplan-Meier method and Cox regression analysis were used to determine progression-free survival (PFS) and overall survival (OS) rates. Other data were analyzed by the Chi-square test and *t*-test.

**Results:** The 3-year survival of MBC patients in Group A was higher than Group B. More patients in Group B accepted the adjuvant endocrine therapy than Group A. The serum CA125 level was higher in Group A than Group B. The serum total cholesterol (TC), low-density lipoprotein (LDL), and fasting glucose were significantly higher in Group A than Group B patients ( $P=0.02$ ,  $P<0.001$ , and  $P<0.001$ , respectively). Cox regression analysis of OS showed that the fasting glucose was an independent prognosis factor in MBC patients. No significant differences were seen between Group A and B either in PFS or OS ( $P>0.05$ ).

**Conclusions:** High serum level of PECAM-1 is related to a decline in 3-year survival of MBC. Whether serum PECAM-1 could predict the long-term survival of MBC necessitates additional clinical trials.

**Keywords:** Metastatic breast cancer (MBC); platelet and endothelial cell adhesion molecule-1 (PECAM-1); prognosis

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## Introduction

Breast cancer takes the highest prevalence and the second cause of mortality in all types of female malignant tumors (1). Despite advanced treatments, metastatic breast cancer (MBC) patients continue to exhibit poor survival. The alleviated rate of the first-line therapy for MBC patients is distinct, which depends on several factors. Thus, identifying

highly sensitive and specific biomarkers for predicting the outcome of the palliative therapy would be beneficial in clinical decisions for MBC patients.

The development of early relapse or metastasis of malignant tumors partially relies on the abnormal activity of vessels in the body. Platelet and endothelial cell adhesion molecule-1 (PECAM-1), also commonly known as CD31,

is a protein encoded by this gene and has been found on the surface of platelets, monocytes, neutrophils, and some types of T-cells, constituting a large portion of endothelial cells' intercellular junctions. It is a member of the immunoglobulin superfamily and is likely involved in leukocyte migration, angiogenesis, and integrin activation (2). PECAM-1 is one of the vital factors participating in cell adhesion and angiogenesis during tumor metastasis. Several studies demonstrated that the high expression of PECAM-1 in tumors could be related to the poor outcome in malignant tumors, such as non-small-cell lung cancer, colorectal cancer (3,4), and breast cancer (5,6). The heterogeneity of tumor angiogenesis and progression have been demonstrated in transgenic mice during mammary cancer progression (7). However, little has been reported on the evaluation of the serum level of PECAM-1 in MBC patients.

Our preliminary study found that the serum level of PECAM-1 and IGF-1 would decrease after the treatment with bisphosphonates (BPs) in MBC patients; the reduction of IGF-1 was more significant in breast cancer patients who received hormone therapy previously (8). Based on the properties of PECAM-1 and our findings of the changes in the serum level of PECAM-1 in MBC patients, we speculated an association of the serum level of PECAM-1 with the prognosis of MBC patients. We examined the serum level of PECAM-1 in those patients just diagnosed as MBC, before any-palliative therapy. The correlation between the serum level of PECAM-1 and pathological and physiological factors of MBC patients have also been studied.

## Methods

### *Study population and design*

Thirty female patients with initial diagnosis of relapse or MBC at the Zhejiang Cancer Hospital were enrolled in our study. The blood samples from patients were withdrawn from April 2010 to December 2014 and followed-up until October 2016. The median follow-up was 78 months. MBC was diagnosed according to the pathological biopsy, and the peripheral blood samples and history were assimilated simultaneously. Patients complicated with the presence of diabetes accepted the hypoglycemic therapy regularly. The peripheral blood tests included a complete blood count and serum blood biochemistry, i.e., fasting glucose, serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), and tumor markers (CEA,

CA125, and CA153). The first-line palliative therapy included chemotherapy, endocrine therapy, anti-Her-2-overexpression therapy, local radiation for chest lesion, and BPs for bone metastasis. The follow-up was conducted by regular-outpatient-review and telephone calls to each patient since the diagnosis of relapse or metastasis post-surgery. Progression-free survival (PFS) was defined as the time of diagnosis of MBC until progress from first-line palliative therapy. Overall survival (OS) was defined as the time of MBC diagnosis until death from any cause, or the end of follow-up, whichever occurred first. The study was approved by an independent Ethics Committee.

### *Serum PECAM-1, glucose, and lipid estimations*

Peripheral venous blood samples (5 mL) were collected before any treatment and maintained at room temperature (approximately 25 °C) for 30 min to allow clotting. Then, the samples were immediately (within 5 min) centrifuged at 3,000 ×g for 5min. The obtained serum supernatants were aliquoted and stored at -80 °C until further assessment. Serum levels of PECAM-1 were assayed using a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA, Quantikine Immunoassays R&D Systems, France) in duplicate, according to the manufacturer's instructions.

### *Statistical analysis*

The data were analyzed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). The Kaplan-Meier method and Cox regression analysis were used for determining PFS and OS rates. Other data were analyzed by the Chi-square test and *t*-test.

## Results

### *Patients' information*

*Table 1* summarizes the characteristics of patients enrolled in the present study. Thirty female MBC patients were included: 27 patients (90%) exhibited invasive ductal breast carcinoma, and 9 patients (30%) were menopausal. Three patients (10%) presented diabetes mellitus and administered medication regularly. Half of the patients had visceral metastases. All patients accepted adjuvant therapy after surgery, according to the NCCN guidelines for breast cancer. The study was approved by the medical ethics committee of Zhejiang Cancer Hospital, Hangzhou. Written informed consent was obtained from all patients prior to enrollment.

**Table 1** Patient characteristics (N=30)

Characteristics	n [%] or [range]
Median age (years) (range)	47 [30–78]
BMI (kg/m <sup>2</sup> )	23.8 [17.6–28.0]
PFS (months) (range)	12.5 [2–96]
Smoking history	1 [3]
Alcohol history	2 [7]
Menopause status	
Pre-menopause	21 [70]
Menopause	9 [30]
Diabetes mellitus	3 [10]
Tumor size (>20 mm)	24 [80]
Lymph node metastatic status	21 [70]
ECOG performance score	
0	6 [20]
1	23 [76]
2	1 [4]
Subtypes of pathology	
IDC	27 [90]
ILC	3 [10]
Clinical stages	
1	5 [17]
2	12 [40]
3	13 [43]
ER status	
Positive	20 [67]
Negative	10 [33]
PR status	
Positive	16 [53]
Negative	14 [47]
HER-2 status	
Positive	11 [37]
Negative	19 [63]
p53 status	
Positive	10 [33]
Negative	20 [67]

**Table 1** (continued)**Table 1** (continued)

Characteristics	n [%] or [range]
Abnormal tumor markers	
CA125 (>35 U/mL)	8 [27]
CA153 (>28 U/mL)	11 [37]
Accepted new adjuvant chemotherapy	6 [20]
Adjuvant chemotherapy	29 [97]
Adjuvant radiotherapy	11 [37]
Adjuvant endocrine therapy	16 [53]
Visceral metastases	15 [50]

BMI, body mass index; IDC, invasive ductal breast cancer; ILC, invasive lobular breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epithelial growth factor receptor-2; PFS, progression-free survival after first palliative therapy.

The trial is registered through the Hospital Pharmaceutical Research Fund Project of Zhejiang Provincial Pharmaceutical Association, number 2016ZYY12.

### **Comparison between subgroups of serum PECAM-1 level in MBC patients**

According to the median serum level of PECAM-1, patients were divided into two subgroups, Group A (<4,058.89 pg/mL) and Group B (>4,058.89 pg/mL).

The 3-year survival of MBC patients was higher in Group A than Group B (P=0.044). A significant difference was not seen in Groups A and B either with respect to PFS or OS (P>0.05). More patients in Group B accepted the adjuvant endocrine therapy as compared to Group A patients (P=0.001). The serum TC, LDL, and fasting glucose were higher in Group A than Group B patients (P=0.02, P<0.001, and P<0.001, respectively). The serum CA125 level was higher in Group A than Group B patients (P=0.03) (Table 2). After adjusting the values of TC, LDL, and fasting glucose in the groups, Cox regression analysis showed that fasting glucose was an independent factor influencing the prognosis of MBC patients (P=0.019) (Table 3).

### **Discussion**

Here, we explored the preliminary role of serum PECAM-1 levels in the initial recurrence or metastasis of breast cancer

**Table 2** Comparison of clinical characteristics and outcome between subgroups of serum PECAM-1 level in MBC patients

Parameters	Group B (N=16)	Group A (N=14)	P	$\chi^2$
3-year survival	13	14	0.044	2.917
5-year survival	12	10	0.395	0.536
Progression after first-line therapy	11	10	0.596	0.026
Death	6	9	0.136	2.143
Smoking history	0	1	0.467	1.182
Alcohol history	1	1	0.724	0.010
Lymph node metastatic status	11	10	0.596	0.026
Tumor size (>20 mm)	10	11	0.290	0.918
Stage			0.439	2.086
1	4	1		
2	5	7		
3	7	6		
ECOG performance score			0.657	1.584
0	4	2		
1	12	11		
2	0	1		
Menopause status			0.150	2.066
Pre-menopause	13	8		
Menopause	3	6		
Subtypes of pathology			0.448	0.536
IDC	15	12		
ILC	1	2		
ER positive	12	8	0.259	1.071
PR positive	11	5	0.074	3.274
HER-2 positive	4	7	0.150	2.010
P53 positive	4	6	0.259	1.071
Abnormal serum CA125	2	6	0.030	3.519
Abnormal serum CA153	4	7	0.150	2.010
Accepted neoadjuvant chemotherapy	3	3	0.605	0.033
Accepted adjuvant chemotherapy	16	13	0.467	1.182
Accepted adjuvant radiotherapy	5	6	0.390	0.433
Accepted adjuvant endocrine-therapy	13	3	0.001	10.736
Visceral metastases	9	6	0.358	0.536
Diabetes mellitus	1	2	0.448	0.536
TC (mmol/L)	4.75	5.28	0.02	–

Table 2 (continued)

Table 2 (continued)

Parameters	Group B (N=16)	Group A (N=14)	P	$\chi^2$
LDL (mmol/L)	2.62	3.51	<0.001	–
Fasting-glucose (mmol/L)	5.47	5.87	<0.001	–

PECAM-1, platelet and endothelial cell adhesion molecule 1; MBC, metastatic breast cancer; IDC, invasive ductal breast cancer; ILC, invasive lobular breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epithelial growth factor receptor-2; TC, total cholesterol; LDL, low-density lipoprotein.

Table 3 Cox regression analysis results of subgroups of PECAM-1 and metabolic factors' impact on the OS

Parameters	P	Risk ratio	$\beta$	SE	Wald
TC	0.278	0.540	-1.602	1.135	1.994
LDL	0.084	4.082	1.906	0.818	5.437
Fasting-glucose	0.019	7.404	1.849	0.902	4.205
Subgroups of PECAM-1	0.125	0.161	-0.841	0.8478	0.987

PECAM-1, platelet and endothelial cell adhesion molecule 1; TC, total cholesterol; LDL, low-density lipoprotein; OS, overall survival.

patients. A high level of serum PECAM-1 was found to be correlated with a poor 3-year survival in patients with MBC. Since the treatment of MBC is rather challenging, the prognosis is rather unsatisfactory. In addition, factors such as molecular subtypes and characteristics of the primary tumor, the postoperative systematic adjuvant therapies, and response to palliative therapy could impact the outcome of MBC. Therefore, the prediction and evaluation of the prognosis of MBC poses a pressing concern for clinicians.

Previous studies showed that PECAM-1 is a pivotal marker for assessing the density of microvessels and angiogenesis *in vivo* and *in vitro* (9,10). The blood vessel invasion was marked using PECAM-1 in tumor cells, thereby indicating a robust correlation of the aggressive subtypes and poor prognosis in breast cancer patients (11). A high PECAM-1 immunoreactivity was substantially related to the formation of tubules, histological grade of malignancy, and clinical stage (12). The tumor-associated macrophages (TAMs) accumulate in various cancers including breast cancer and promote tumor angiogenesis and metastasis with high specificity. PECAM-1 was reported as one of the significantly overexpressed proangiogenic factors in TAMs (13). The abnormal change in the density of microvessels was correlated to the tumor microenvironment, thereby inducing relapse or metastasis of the malignant tumor. In our study, since a limited number of biopsies were available from metastatic lesions of patients with MBC, tissue specimens

from only 11 patients could be utilized in IHC for analyzing the expression of CD31. Although the paraffin sections were found to be sensitive and superior in cancer research, the CD31 staining was affected by the inflammatory background of cells and frequent loss of antigen due to fixatives containing acetic acid. Furthermore, the anti-CD31 antibodies might incorrectly render a prominent inflammatory infiltration region, such as a rich vascular spot, at low magnification (14). Considering the defects associated with monitoring the tumor tissue markers and the heterogeneity of the tissue, identifying novel peripheral blood tumor markers for early diagnosis is imperative for the adequate palliative treatment of MBC patients.

Furthermore, we found that high serum PECAM-1 level in patients proposed their candidature for the adjuvant endocrine therapy. However, only a few studies emphasized the potential crosstalk between PECAM-1 and hormone therapy. Moreover, the putative effect of PECAM-1 in hormone receptor-positive breast cancer patients calls necessitates further exploration. According to the current results, PECAM-1 is not only related to the prognosis of MBC but also associated with the metabolisms of lipid and glucose. Blood lipid and glucose are closely linked to the development of breast cancer (15,16). Increasing evidence shows that the abnormal levels of serum lipids and glucose impact the survival of breast cancer patients (17-20). Metabolic syndrome could increase the risk of breast

cancer and influence the prognosis in patients (21). Also, the metabolic disturbances would impact the response and resistance to aromatase inhibitors (22). A mechanism underlying these associations might encompass chronic inflammation and insulin resistance that in turn, might drive atherogenesis, cellular proliferation, and angiogenesis (16). However, recent negative results on the fasting blood lipids or glucose might affect the survival of breast cancer patients (23,24). In the current study, fasting glucose was found to be an independent factor on the OS of the MBC patients. This conclusion was in agreement with the previous studies in MBC patients with diabetes; however, supplementary evidence should be assimilated before deeming that high fasting glucose was a negative prognostic factor for OS in MBC patients.

In the present study, a negative correlation was established between the serum level of PECAM-1 and TC, LDL, fasting glucose, and CA125. Serum PECAM-1 was considered to be involved in the inflammatory events, which induced diabetic complications, such as diabetic retinopathy (25). Furthermore, we speculated that PECAM-1 could potentially be an early marker that can indicate the blood lipid and glucose metabolism disorder and the difference in the levels of these biochemicals from that of the baseline. A previous study on the influence of microvessel density on ovarian carcinogenesis showed that the change in CA125 did not associate with the CD31 counts, thereby suggesting a sophisticated correlation between tumor vascularity, metastasis, and response to treatment (26). The recent ASCO guidelines recommended that CEA, CA15-3, and CA27.29, except CA125, could be employed as MBC biomarkers (27). Nevertheless, the value of CA125 in MBC diagnosis and prediction is yet obscure and controversial.

Although the present preliminary study consisted of a small sample size, it focused on the predictive value of serum PECAM-1 in the correction of the physiological and pathological factors in MBC patients. However, single-center and retrospective nature of the study in MBC patients are a few limitations. Therefore, in future studies, we would consider comparing the expression of PECAM-1 in the metastatic lesions with serum level of the protein. Additional combinations of peripheral biomarkers would be used to predict the prognosis of MBC patients, even integrating with PECAM-1 to establish a prognostic panel.

## Conclusions

High serum level of PECAM-1 is correlated to the decline of 3-year survival of MBC patients. Further research is

warranted for the evaluation of serum PECAM-1 as a prognostic biomarker in MBC patients.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2017.11.04>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Zhejiang Cancer Hospital Ethic Institution Office (ID was 2016ZYY12). Written informed consent was obtained from all patients prior to enrollment.

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