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Original Article

CD45RO positive expression correlates with lower histological grade, less lymph node metastasis and prolonged overall survival in surgical patients with breast cancer

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Abstract: To evaluate the correlation of tumor tissue CD45RO expression with clinicopathological features and overall survival (OS) in surgical breast cancer (BC) patients, 297 BC patients receiving breast surgery were retrospectively reviewed in this cohort study. Tumor tissue samples were obtained during the operation. CD45RO expression was assessed by immunofluorescent staining assay. The median follow-up duration was 115.0 months and the last follow up date was Sep 2016. 147 (49%) patients with CD45RO positive expression ($CD45RO^+$) and 150 (51%) patients with CD45RO negative expression ($CD45RO^-$) were observed. $CD45RO^+$ was negatively correlated with histological grade (P=0.028), N stage (P=0.001) and tumor-node-metastasis (TNM) stage (P=0.005), while it was positively correlated with ER^+ (P=0.014). Kaplan-Meier (K-M) curves showed that $CD45RO^+$ was associated with prolonged OS (P<0.001) in all BC patients. And subgroup analysis also revealed $CD45RO^+$ associated with better OS in ER^+ (P=0.008), ER^- (P=0.010), PR^+ (P=0.021), PR^- (P=0.002), $HER2^+$ (P=0.026) or $HER2^-$ (P<0.001) groups. Furthermore, multivariate Cox analysis indicated that $CD45RO^+$ (P=0.007) was an independent factor for prolonged OS, while higher histological grade (P=0.001) was an independent factor for worse OS. $CD45RO^+$ was negatively correlated with histological grade and lymph node metastasis, and it could be regarded as a novel and promising biomarker for prolonged OS in surgical BC patients.

Keywords: $CD45RO^+$, predict, prognosis, breast cancer, clinicopathological features

Introduction

Breast cancer (BC) is one of the most frequently diagnosed malignancies worldwide, which accounts for estimated 30% of all cancer cases and 15% of all cancer deaths among female. In 2012, approximately 1.7 million cases and 521,900 deaths occurred due to BC [1, 2]. Although the death rate dropped 38% from 1989 to 2014 for female BC due to great improvements of early diagnosis, targeted treatment as well as patients' care, BC is still the first leading cause of cancer-related mortality among female worldwide and its prognosis is still far more from satisfaction [3]. Therefore, exploring effective and reliable biomarkers for BC patients to monitoring tumor progression and prognosis timely are greatly needed.

Tumor infiltrating lymphocytes (TILs), a kind of heterogeneous cells, could infiltrate tumor tissue to directly reflect immune response state [4]. A large amount of TILs, especially cluster of differentiation 45 (CD45), have been proven to devote themselves into the process of tumorigenesis and tumor progress in ovarian cancer, lung cancer, as well as bowel cancer and so on [4-6]. CD45 molecules, known as protein tyrosine phosphatase receptor C type, is considered as a marker to classify subgroups of T lymphocyte, among which $CD45RO^+$ memory T cells, one of the most common T cell subtypes, are characterized by strong self-renewal [7]. These $CD45RO^+$ cells could generate abundant immune responses when they exposure to antigens again, thereby contributing to the antitumor progress [8, 9]. Although the predictive

Table 1. Baseline characteristics

Items	Breast cancer patients (N=297)
Age (years)	53.51±13.18
Tumor size (cm)	3.38±1.81
Histologic grade	
I (n/%)	57 (19)
II (n/%)	226 (76)
III (n/%)	14 (5)
T stage	
I (n/%)	70 (24)
II (n/%)	200 (67)
III (n/%)	27 (9)
N stage	
0 (n/%)	112 (38)
I (n/%)	92 (31)
II (n/%)	76 (26)
III (n/%)	17 (6)
M stage	
0 (n/%)	297 (100)
I (n/%)	0 (0)
TNM stage	
I (n/%)	26 (9)
II (n/%)	172 (58)
III (n/%)	99 (33)
ER positive (n/%)	198 (67)
PR positive (n/%)	172 (58)
HER2 positive (n/%)	99 (33)
CD45RO positive (n/%)	147 (49)

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

value of CD45RO in the progress of various carcinomas have been proven [5, 10, 11], few studies about the role of CD45RO in the prognosis of BC patients is explored. Hence, the aim of the present study was to evaluate the correlation of tumor tissue CD45RO expression with clinicopathological features and overall survival (OS) in surgical BC patients.

Materials and methods

Patients

297 breast cancer patients consecutively underwent breast surgery at Department of Thyroid and Breast Surgery, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, between January 2004 and December 2007 were retrospectively reviewed in this cohort study. The inclusion criteria were as follows: (1) Diagnosis as primary breast cancer demonstrated by clinical evaluation, radiographic examination and pathological proofs. (2) Underwent breast operation. (3) Completed clinicopathological data existed including histologic grade, TNM stage, immunohistochemistry (IHC) results of estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). (4) Tumor tissue section during the surgery was fixed in formalin and embedded in paraffin appropriately and able to perform immunofluorescent staining assay. This study was approved by the Ethics Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology. We acquired written informed consents or oral agreements of informed consents by phone with record from all patients.

Patients screening

A total of 805 patients were retrospectively reviewed, among which 47 cases were secondary breast cancer patients, 272 case did not receive surgery, the remaining 486 patients were preliminarily selected. While in the 486 patients, 85 cases lack confirmed histologic grade or TNM stage information, 37 cases lost at least one of the status of ER, PR or HER2 and tumor tissue section which was able to perform immunofluorescent staining assay was not obtained in other 67 cases, thus the remaining 297 patients were included in our study.

Data collection and definitions

Baseline clinical and pathological data was collected including age, gender, histologic grade, TNM stage as well as status of ER, PR and HER2. TNM stage was evaluated according to the 6th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual. Positive expression of ER, PR or HER2 was defined as above 10% staining by IHC of each parameter

Follow-ups

The median follow-up duration was 115.0 months (1/4 to 3/4 quarter: 94.5-135.0 months) and the last follow up date was Sep 2016. OS was calculated from the time of the surgery to date of death from any cause.

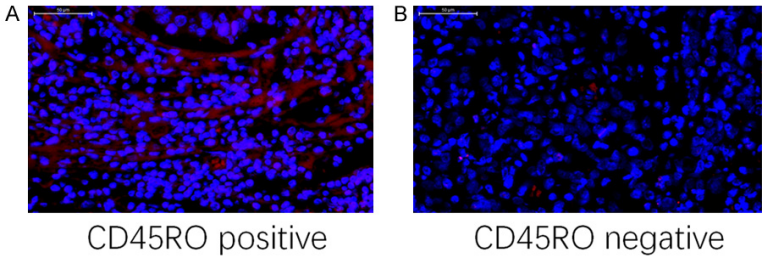

Figure 1. CD45RO expression in tumor tissue. Immunofluorescent staining results revealed that CD45RO was mainly expressed on cancer nests and stromal areas near the cancer cells. A: CD45RO positive expression; B: CD45RO negative expression.

Sample collection and immunofluorescent staining

Tumor tissue samples were obtained from all patients during the operation and then fixed in formalin and embedded in paraffin. After embedding and dehydrating at 65°C for 3 h, the section was washed with phosphate buffered saline (PBS) of pH 7.3, and then incubated over-night at 4°C with primary antibody for CD45RO (mouse antibody against CD45RO with dilution 1:400 (CST, UCHL1, USA)) in compliance with the manufacturer's instructions. After washing three times with PBS, the slide was subsequently stained with Alexa Fluor® 594 Conjugate labelled (red) antibody against mouse IgG with dilution 1:500 (CST, 8890, USA) as secondary antibody, and then the piece was counterstained with Hoechst 33342.

Immunofluorescent staining was assessed by histological score (HSCORE) which was defined as follows: HSCORE=∑Pi (i+1). Pi means the percentage of stained cells for each intensity scoring from 0% to 100%; i is the intensity of staining with a value at 1 (weak), 2 (moderate) and 3 (strong); 1 is a correction for optimal density [12]. HSCORE 0.7 was used as a threshold of a positivity status for the measurement of immunofluorescent staining based on the previous study [13].

Statistics analysis

Statistical analysis was carried out using SPSS 22.0 software (IBM, USA) and 2015 office software (Microsoft, USA). Data were mainly presented as mean value ± standard deviation, median (1/4 to 3/4 quarter value) or count (percentage). Comparison between two groups was determined by t test or Chi-square test. Kaplan-Meier (K-M) curves and log-rank test were used for OS analysis. Univariate Cox proportional hazard regression was used to evaluate factors affecting OS, all factors with *P* value below 0.1 were further evaluated by multivariate analysis. *P* Value <0.05 was considered significant.

Results

Baseline characteristics

In the current study, the mean age of 297 BC patients was 53.51±13.18 years. Mean value of tumor size was 3.38±1.81 cm. the numbers of patients with histological grade I, II, III were 57 (19%), 226 (76%) and 14 (5%) respectively (**Table 1**). There were 70 (24%), 200 (67%) and 27 (9%) patients in T stage I, II and III respectively. Moreover, 112 (38%), 92 (31%), 76 (26%) and 17 (6%) patients in N stage 0, I, II and III, and all of these 297 patients (100%) were in M0 stage. As to TNM stage, the number of patients in stage I, stage II and stage III were 26 (9%), 172 (58) and 99 (33%). Furthermore, 198 (67%) patients were with ER positive, 172 (58%) patients were with PR positive, 99 (33%) patients were with HER2 positive. The other characteristics of BC patients at baseline were shown in **Table 1**.

CD45RO expression in tumor tissue

Immunofluorescent staining was used to explore the role of CD45RO expression in tumor microenvironment, which showed that CD45RO was mainly expressed on cancer nests and stromal areas near the cancer cells (**Figure 1**). As listed in **Table 1**, 147 (49%) patients with CD45RO positive expression ($CD45RO^+$) and 150 (51%) patients with CD45RO negative expression ($CD45RO^-$) were observed.

Comparison of clinicopathological features between $CD45RO^+$ and $CD45RO^-$ groups

T test or Chi-square test was used to evaluate the difference of clinicopathological features between $CD45RO^+$ and $CD45RO^-$ groups (**Figure 2**). Compared with $CD45RO^-$ group, $CD45RO^+$ was negatively correlated with histological grade (P=0.028, **Figure 2B**), N stage (P=0.001, **Figure 2D**), TNM stage (P=0.005, **Figure 2E**), while it was positively associated with ER^+

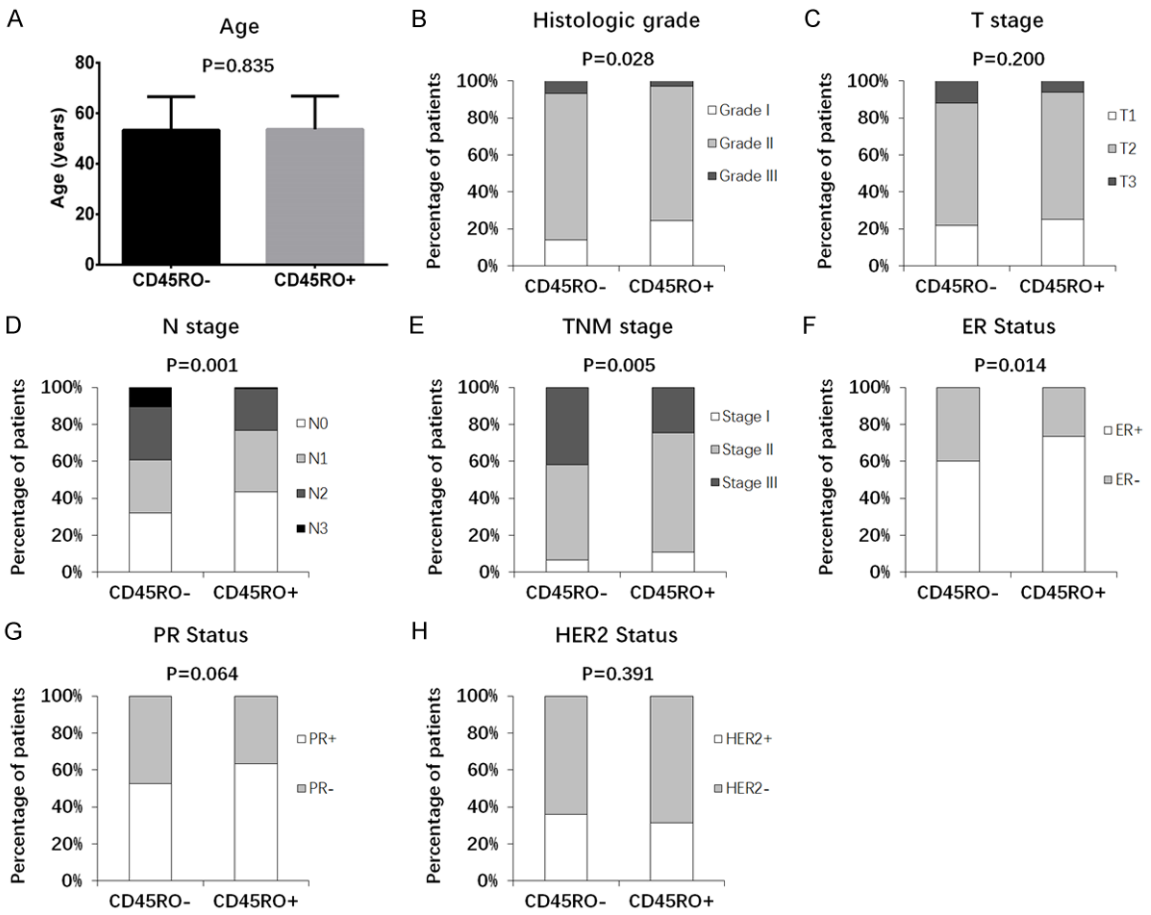

Figure 2. Comparison of clinicopathological features between CD45RO+ and CD45RO- groups. CD45RO+ was negatively correlated with histological grade (B), N stage (D), TNM stage (E), while positive correlation between CD45RO+ and ER+ (F) was observed. No difference of age (A), T stage (C), PR status (G) and HER2 status (H) between two groups was discovered. T test or Chi-square test was used to compare the difference between groups. P<0.05 was considered significant.

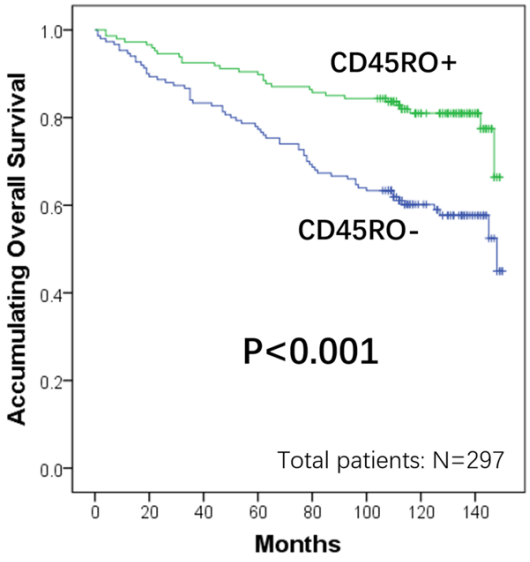

Figure 3. Association of CD45RO expression with OS. BC patients with OCT4RO+ had better OS than those with CD45RO-. Kaplan-Meier curves and log-rank test were used to compare OS according to CD45RO status in total BC patients. P<0.05 was considered significant.

(P=0.014, **Figure 2F**). No difference of age (P=0.835, **Figure 2A**), T stage (P=0.200, **Figure 2C**), PR status (P=0.064, **Figure 2G**) and HER2 status (P=0.391, **Figure 2H**) was discovered between CD45RO+ and CD45RO- groups.

Association of CD45RO expression with OS

K-M curve showed that compared to CD45RO-, OCT4RO+ was associated with prolonged OS in total BC patients (P<0.001) (**Figure 3**). Subsequently, OS analysis in subgroups divided by ER, PR or HER2 status was performed. As listed in **Figure 4**, CD45RO+ was correlated with better OS than that in CD45RO- group in all sub-

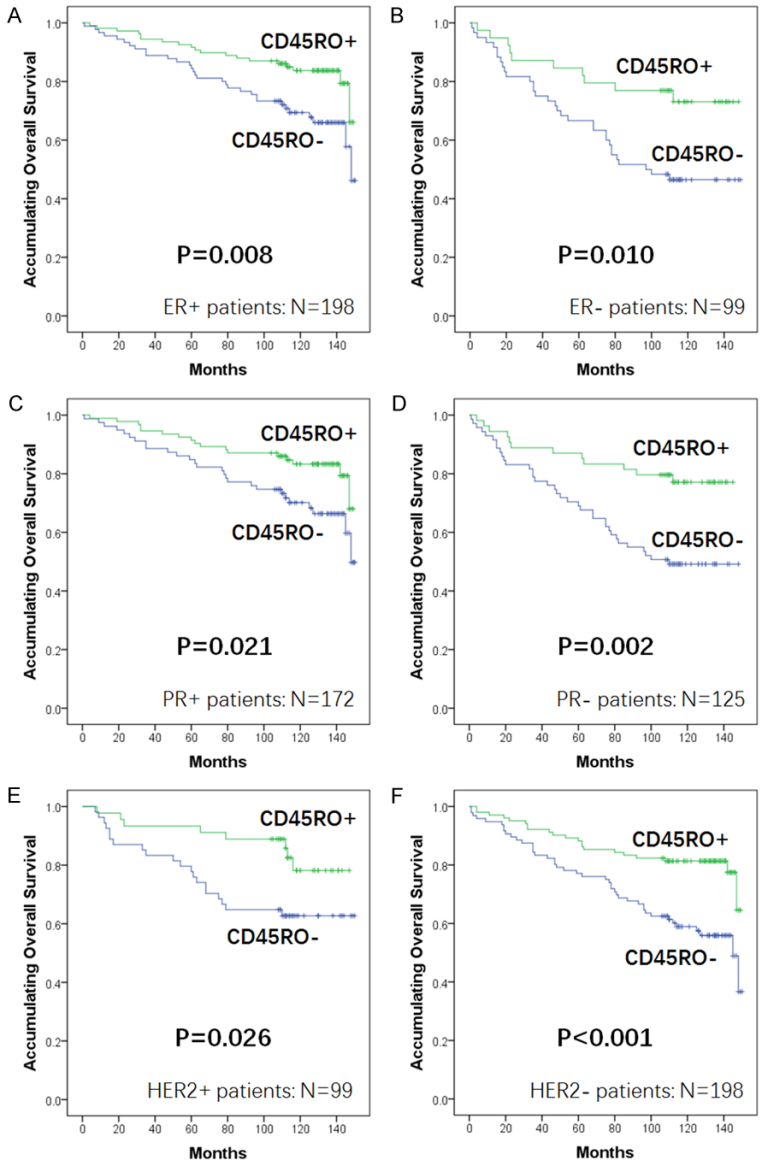

Figure 4. Correlations of CD45RO expression with OS in subgroups. Correlations of CD45RO expression with OS in ER+ patients (A), ER- patients (B), PR+ patients (C), PR- patients (D), HER2+ patients (E) and HER2- patients (F). CD45RO+ was correlated with better OS in all subgroups. Kaplan-Meier curves and log-rank test were used to analyse the correlation of CD45RO expression with OS in each subgroup. P<0.05 was considered significant.

groups, including ER+ (P=0.008, **Figure 4A**) and ER- (P=0.010, **Figure 4B**), PR+ (P=0.021, **Figure 4C**) and PR- (P=0.002, **Figure 4D**), as well as HER2+ (P=0.026, **Figure 4E**) and HER2- (P< 0.001, **Figure 4F**) groups.

Analysis of baseline factors affecting OS

Baseline factors affecting OS in BC patients were evaluated by univariate Cox's proportional hazards regression. As disclosed in **Table 2**, CD45RO+ (P<0.001), ER+ (P<0.001) and PR+ (P<0.001) were correlated with prolonged OS, while higher histological grade (P<0.001), higher T stage (P=0.046), N stage (P=0.01) and TNM stage (P< 0.001) were associated with shorter OS in BC patients. Multivariate Cox proportional hazard regression was performed to analyse the factors with a *P* value below 0.1 in univariate model, which indicated that CD45RO+ (P=0.007) was an independent factor for prolonged OS, while higher histological grade (P=0.001) was an independent factor for worse OS (**Table 3**).

Discussion

In this present study, we found: 1) CD45RO+ was negatively associated with histological grade, N stage and TNM stage. 2) K-M curves suggested that CD45RO+ was correlated with prolonged OS compared to CD45RO-, and multivariate Cox analysis indicated that CD45RO+ could predict better OS independently in surgical BC patients.

CD45 is a group of transmembrane proteins with similar structures, encoded by the PRPRC gene, which has various isoforms, such as CD45RA, CD45RO, CD45RB and CD45RC [14, 15]. Among these subtypes, CD45RA and CD45RO are mainly located on T cells, which belong to TILs that contribute to tumorigenesis and tumor progresses by specific recognition and elimination of tumor cells [16-18]. In terms of CD45RO+ T cells, they could quickly produce strong immune responses, eliminating tumor cells when they were exposed to tumor cells again [17]. Previous study indicates that CD45RO could target interleukin-2 (IL-2), interferon-gamma (IFN-gamma) and tumor necrosis factor (TNF-alpha) to inhibit the proliferation

Table 2. Univariate analysis of factors affecting OS

	Univariate Cox proportional hazard regression			
	P value	HR	95% CI	
			Lower	Higher
CD45RO+ (vs. CD45RO-)	<0.001	0.411	0.264	0.638
Age (≥50 years)	0.196	1.323	0.865	2.021
Histologic grade	<0.001	2.362	1.481	3.766
T stage	0.046	1.484	1.007	2.185
N stage	0.001	1.434	1.160	1.773
TNM stage	<0.001	1.930	1.352	2.757
ER positive	<0.001	0.481	0.319	0.726
PR positive	0.003	0.533	0.352	0.807
HER2 positive	0.713	0.920	0.589	1.436

Univariate Cox proportional hazard regression was performed to analyzed the factors affecting OS which was performed based on the following definitions: Histologic grade was scored as 1-grade I, 2-grade 2, 3-grade 3; T stage was scored as 1-T1, 2-T2, 3-T3; N stage was scored as 0-N0, 1-N1, 2-N2 and 3-N3; TNM stage was scored as 1-Stage I, 2-Stage II and 3-Stage III. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 3. Multivariate analysis of factors affecting OS

	Multivariate Cox proportional hazard regression			
	P value	HR	95% CI	
			Lower	Higher
CD45RO+ (vs. CD45RO-)	0.007	0.536	0.339	0.846
Histologic grade	0.001	2.247	1.375	3.671
T stage	0.728	1.081	0.697	1.678
N stage	0.170	1.688	0.799	3.566
TNM stage	0.969	0.992	0.658	1.495
ER positive	0.198	0.674	0.370	1.228
PR positive	0.336	0.748	0.415	1.351

Multivariate Cox proportional hazard regression was performed to analyzed the factors with a *P* value below 0.1 in univariate model which was performed based on the following definitions: Histologic grade was scored as 1-grade I, 2-grade 2, 3-grade 3; T stage was scored as 1-T1, 2-T2, 3-T3; N stage was scored as 0-N0, 1-N1, 2-N2 and 3-N3; TNM stage was scored as 1-Stage I, 2-Stage II and 3-Stage III. ER, estrogen receptor; PR, progesterone receptor.

and invasion of cervix cancer cells, thereby leading to the repression of tumor growth and migration [19]. Another interesting study in patients with colon carcinoma also suggests that CD45RO could decrease the secretion of high-mobility group box 1 (HMGB1), resulting in the repression of tumor cell proliferation and invasion [20]. Furthermore, overexpression of CD45RO has been identified to be negatively correlated with histological grade and TNM stage in patients with rental cancer [21]. Also its high expression is negatively associated with lymphatic metastasis and vessel invasion in patients with colorectal carcinoma [22]. As to the role of CD45RO expression in BC patients, pervious study reveals that upregulated CD45RO expression is negatively correlated with tumor size and lymphatic metastasis, while this study only enrolled 98 BC patients, which was relatively small sample size [23]. In the current study, a total of 297 BC patients receiving breast surgery were retrospectively reviewed. Partially in accordance with these results, we found the negative correlation between CD45RO+ with histological grade, N stage and TNM stage. The possible explanations are that CD45RO high expression could regulate multiple effector cells to produce cytokines, generating strong immune responses to inhibit the proliferation and migration of tumor cells, and induce tumor cell differentiation, thereby suppressing tumor growth and metastasis as well as promoting tumor differentiation [5, 7, 11, 17, 19, 20].

As for the predictive value of CD45RO, CD45RO+ is associated with lower recurrent rate in breast cancer [24]. Also CD45RO+ has been reported to be closely related to better DFS and OS of patients with various carcinomas, including ovarian carcinoma, rental cell cancer and gastric cancer [21, 25, 26]. In line with these previous studies, our study found that CD45RO+ could be an independent role to predict prolonged OS in total surgical BC patients. Subsequently, we divided these BC patients into the ER, PR or HER2 subgroups. We found that CD45RO+ was correlated with better OS in all subgroups, which was in line with previous studies [27, 28]. The two possible reasons are as follows. Firstly, CD45RO could target several genes and pathways, inhibiting the tumor progress, thereby affecting the prognosis in BC patients [19, 20, 29]. Secondly, CD45RO could increase the sensitivity to radiotherapy and chemotherapy, accordingly improving treatment effects and contributing to the recovery of BC patients [10, 30].

There were some limitations in this study as follows. 1) We retrospectively reviewed 297 BC

patients in TNM stage I to III (no patient in stage IV), thus he role of CD45RO in the prognosis of BC patients in stage IV was not explored in the present study. 2) Only tumor tissue sample was assessed in the present study, while blood sample was not evaluated, which was relatively more feasible to obtain. 3) Sample size was relatively small, which possibly could lead to lower statistical efficiency compared with larger sample size studies.

In conclusion, CD45RO+ was negatively correlated with histological grade and lymph node metastasis, and it could be regarded as a novel and promising biomarker for prolonged OS in surgical BC patients.

Disclosure of conflict of interest

None.

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