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ORIGINAL ARTICLE

CD14 macrophage and IL-10 levels in the peripheral blood of breast cancer patients and their diagnostic value*

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Abstract

Objective To explore the correlation between macrophages and interleukin-10 (IL-10 in the peripheral blood of breast cancer (BC) patients and the diagnostic value of joint detection.

Methods BC patients (n = 50) and healthy controls (n = 40) were prospectively recruited. The percentage of circulating cluster of differentiation 14 (CD 14) macrophage cells was analyzed by flow cytometry, and an enzyme-linked immunosorbent assay (ELISA) was used to detect IL-10 expression levels. Receiver operating characteristic (ROC) curves were used to verify the diagnostic value of the models based on the expression of CD14 macrophage cell populations and IL-10. In addition, the association between model expression and clinicopathological characteristics was investigated. Another 30 patients with BC and 30 with benign breast disease were selected to validate the IL-10 and CD14 macrophage joint detection model using the same method.

Results CD14 macrophage and IL-10 expression levels in BC patients were higher than those in healthy controls (P < 0.05). The ROC curve showed that the area under the curve (AUC) of CD14+ macrophages combined with IL-10 was 0.830, the sensitivity was 72.0%, and the specificity was 87.5%. Its diagnostic efficiency was better than all other single and joint detections. Correlation analysis of clinicopathological features showed that IL-10 and CD14+ macrophage joint detection was significantly correlated with tumor size, tumor-node-metastasis (TNM) stage, and lymph node, estrogen receptor (ER), and Ki-67 expression (P < 0.05). The validation analysis results were consistent with the test results.

Conclusion Peripheral blood macrophages can be an independent diagnostic marker for BC. Joint detection of CD14- macrophages and IL-10 suggests poor prognosis, which has unlimited potential to guide BC development and provides a new theory for studying tumor-associated macrophages in BC.

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Key words: breast cancer; macrophage; IL-10; peripheral blood; diagnostic value

Breast cancer (BC) is the primary cause of cancer-associated death in women [1]. Therefore, research on the BC tumor microenvironment (TME) has recently focused on new diagnostic and treatment methods. Macrophages are the dominant immune cell population in the TME [2]. Tumor-associated macrophages (TAMs) can help cancer cells enter the blood to form new tumors. Not only that, TAMs can migrate via the lymphatic system or intravasate across intratumor capillary barriers into peripheral circulation with circulating tumor cells (CTCs) and further turn into cancer-associated macrophage-like cells (CAMLs) [3–4], meaning macrophage expression in peripheral blood may be crucial in the TME.

As a classic anti-inflammatory cytokine, interleukin-10 (IL-10) induces macrophage maturation and polarization [5]. IL-10-stimulated macrophages can further generate IL-10 and matrix remodeling factors, such as matrix metalloproteinases (MMPs), involved in tumor cell

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proliferation, migration, invasion, metastasis, and apoptosis. Additionally, IL-10 expression is closely associated with the pathological stage and prognosis [6]. Therefore, this study used the macrophage-specific marker cluster of differentiation 14 (CD14) for screening and grouping, compared and analyzed the expression levels of CD14 macrophage cell populations and IL-10 in the peripheral blood of patients in different groups, and explored the application value of CD14 macrophages and IL-10 as prognostic indicators of BC by establishing a joint detection model of CD14 macrophages and IL-10.

Materials and methods

Clinical data

We selected 50 treatment-naive patients with BC admitted to Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, between January 2020 and December 2020 as the research participants. All BC diagnoses were confirmed via histological examination. Tumor-node-metastasis (TNM) classification was performed per the UICC-American Combined Committee on Cancer Staging (7^{th} edition). None of the patients received therapy prior to blood sampling. All patients were women aged 31–72 years, with a median age of 55 years. There were 48 cases of invasive ductal carcinoma (96.0%) and two cases of invasive lobular carcinoma (4.0%). We selected 40 healthy female volunteers as normal controls and obtained written informed consent from all the patients and healthy subjects. Table 1 lists the clinicopathological features (age, TNM stage, tumor size, clinical stage, lymph node metastasis, and information on estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) expression). Another 30 patients with BC and 30 with benign breast disease in our hospital from January 2021 to June 2021 were selected for the validation analysis. Fig. 1 illustrates the experimental design.

Main instruments and reagents

The main reagent, PM-2 K macrophage antibody, was purchased from Abcam (Cambridge, UK). Other reagents and instruments included goat anti-mouse IgG-FC SureLight (SBA company), human IL-10 enzyme-linked immunosorbent assay (ELISA) kits (Shanghai Senxiong Technology Co., Ltd.), and PerCP anti-human CD3, PE anti-human CD19, and APC anti-human CD14 antibodies from BioLegend.

Flow cytometric analysis of CD14 macrophage cells in peripheral blood

Anticoagulant whole blood (5 mL) was added to 15 mL Ficoll (Tianjin Haoyang) and centrifuged at 800 × g for 20 min, after which the white membrane layer was removed and washed once to separate peripheral blood mononuclear cells (PBMCs). The samples were blocked with 10% human plasma for 10 min. One test of PM-2 K anti-macrophage antibody (Abcam ab58822) was added to every 106 cells and incubated at 4°C for 30 min. We added 5 mL phosphate-buffered saline (PBS), centrifuged (400 × g) for 5 min, and discarded the supernatant. The cells were resuspended, and one test of goat anti-mouse LGG FC and human/bovine/horse Spads FTC (Southern Biotech 1013-02) was added to every 106 cells and incubated at 4°C for 30 min. We resuspended the antibody, added 5 ml PBS, centrifuged (400 × g) for 5 min, discarded the supernatant, and repeated the previous step. We resuspended the cells, added one test of PerCP anti-human CD3 (BioLegend 300427), one test PE anti-human CD19 (BioLegend 302207), and one test of APC anti-human CD14 (BioLegend 325608) to every 106 cells, and incubated them at 4°C for 30 min. In another tube of cells, the same type of control was added as described above. The incubated samples were washed off with unbound antibodies and analyzed by flow cytometry. A gate was set to circle the cell population of CD3–CD19 and detect PM-2k+ CD14+ and PM-2k+ CD14- macrophage levels.

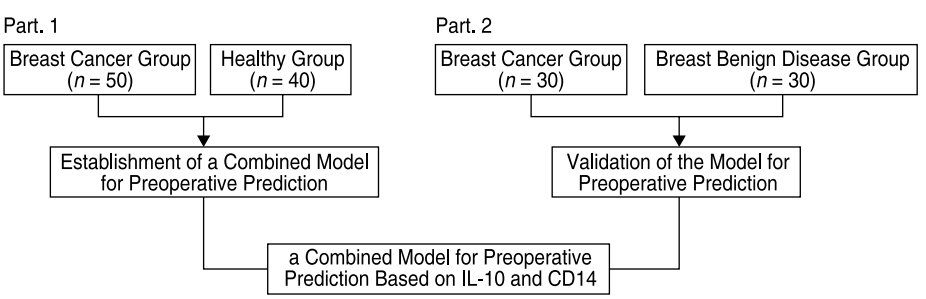

Fig. 1 Basic roadmap for the establishment and validation of IL-10 and CD14 macrophage joint detection model

Table 1 Clinicopathological features of BC group and control group [*n* (%)]

Items	BC group (*n* = 50)	Control group (*n* = 40)
Age (years, $\bar{\chi}\pm s$)	54.0±12.2	39.5±9.2
≤50	18 (36.0)	32 (80.0)
>50	32 (64.0)	8 (20.0)
Tumor size (cm, $\bar{\chi}\pm s$)	2.8±1.8	-
≤2	22 (44.0)	-
>2	28 (56.0)	-
Lymph node metastasis		
0	15 (30.0)	-
1–3	21 (42.0)	-
≥4	14 (28.0)	-
Ki-67		
>30%	29 (58.0)	-
≤30%	21 (42.0)	-
Vascular invasion		
No	33 (66.0)	-
Yes	17 (34.0)	-
TNM stage		
I	15 (30.0)	-
II	24 (48.0)	-
III	11 (22.0)	
ER		
Negative	27 (54.0)	-
Positive	23 (46.0)	-
Her-2		
Negative	20 (40.0)	-
Positive	30 (60.0)	-

Table 2 Comparison of macrophages and IL-10 expression levels between BC and control group in peripheral blood ($\bar{\chi}\pm s$)

Items (%)	BC (*n* = 50)	Control (*n* = 40)	*t*	*P*
CD14+ macrophages	4.766±1.899	2.985±1.123	5.239	0.000
CD14- macrophages	18.981±8.276	11.233±7.819	1.604	0.112
Total macrophages	16.867±8.216	13.318±8.128	2.048	0.043
IL-10(pg/mL)	17.324±5.0473	14.028±3.554	3.493	0.001

Detecting IL-10 in peripheral blood

We drew 5 mL of anticoagulant whole blood, placed it in an ethylenediaminetetraacetic acid (EDTA) anticoagulant tube, and let it stand for 1 h at 3600 × g. The serum was separated by centrifugation for 10 min and stored at -80°C until needed. ELISA was used to quantitatively detect IL-10 in the serum. The manufacturer's instructions were strictly followed.

Statistical analysis

SPSS 22.0 statistical software was used for the statistical analysis. A *t*-test was used to compare the level of peripheral blood macrophages between BC patients and healthy controls, and binary logistic regression was used to establish the joint detection formula. A receiver operating characteristic (ROC) curve was used to analyze the diagnostic efficiency of each index, and the best critical value of the test items was obtained. Clinicopathological indices, other immunohistochemical indices, molecular subtypes, and clinicopathological indices of patients with macrophages and BC were analyzed using a chi-square test and the Fisher exact probability method. Correlation analysis was performed using Spearman's rank correlation coefficient ($P < 0.05$).

Results

Comparison of peripheral blood macrophage cell populations and IL-10 expression between BC patients and healthy controls

The expression of CD14+ macrophages, CD14- macrophages, total macrophages, and IL-10 in BC patients and healthy controls was tested using a *t*-test. Although CD14- levels were higher in the BC group than in the control group, this difference was not statistically significant ($P = 0.112$). IL-10 and CD14+ were higher in the BC patients than the controls, and this difference was statistically significant ($P < 0.01$). Table 2 describes this in detail, and Fig. 2 shows the flow cytometry gating strategies.

Evaluating the diagnostic efficacy of CD14+ macrophages, CD14- macrophages, total macrophages, and IL-10 in BC

ROC curve analyses showed that the areas under the ROC curve (AUC) were 0.778, 0.596, 0.599, and 0.688, respectively. Based on the logistic regression model, we established a combined diagnosis of CD14+, CD14-, and total macrophages with IL-10 and found that the IL-10 CD14+ macrophage joint detection AUC was 0.830, which was significantly higher than the AUCs of the four indicators separately and other joint detections. It also had significant advantages because of its high sensitivity (72.0%) and specificity (87.5%) for diagnosing BC. Table 3 and Fig. 3 present the results.

Correlation analysis between clinicopathological features and CD14+ macrophages, IL-10 and CD14+ joint detection, and IL-10 and CD14- joint detection in peripheral blood

Based on the above results, we selected three detectors with relatively optimal test efficiency for the correlation analysis with clinicopathological features. The optimal cutoff values of CD14+ macrophages, IL-10 and CD14+ joint detection, and IL-10 and CD14- joint detection calculated by the ROC curve were 4.655%, 22.161%, and 29.300%, respectively. We divided the BC patients into the high score or low score groups based on the cutoff values. The results indicated that CD14+ expression

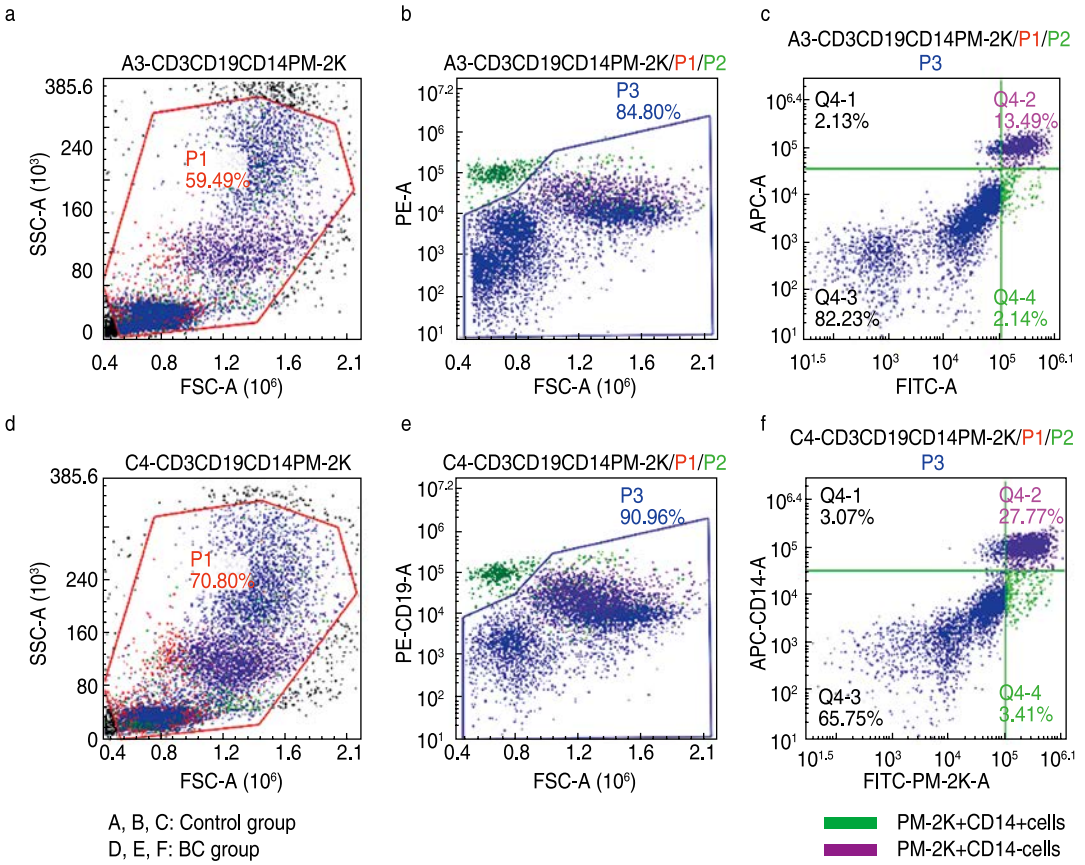

Fig. 2 Flow cytometry gating strategy for macrophages from peripheral blood of BC patients and healthy controls

Table 3 Comparison of the diagnostic value of single and combined detection of macrophages and IL-10 in breast cancer

Items	Cutoff value	AUC	95%CI	S_b	Sensitivity	Specificity
CD14+ macrophages	4.655	0.778	0.680–0.876	0.000	62.00	92.00
CD14- macrophages	19.980	0.596	0.490–0.723	0.083	34.00	66.00
Total macrophages	25.430	0.599	0.481–0.717	0.107	22.00	90.50
IL-10	19.025	0.688	0.580–0.795	0.002	40.00	82.50
IL-10 CD14+ macrophages combined detection	29.300	0.830	0.748–0.912	0.000	72.00	87.50
IL-10 CD14-macrophages combined detection	22.161	0.715	0.611–0.819	0.000	40.00	95.00
IL-10 total macrophages combined detection	17.089	0.712	0.607–0.816	0.001	62.00	65.00

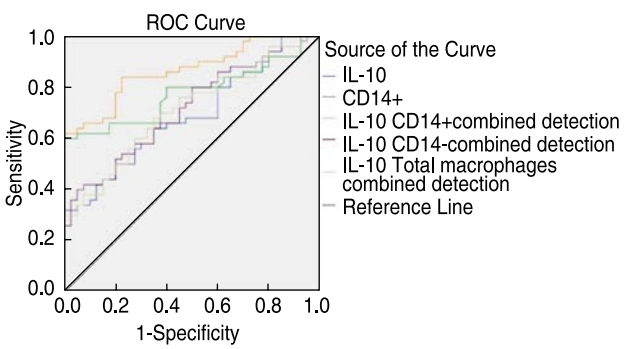

Fig. 3 Curve of CD14+ macrophages, IL-10 and their joint detections in breast cancer diagnosis

correlated with lymph node metastasis, TNM stage, and Ki-67 expression. IL-10 and CD14+ joint detection significantly correlated with tumor size, TNM stage, lymph node, ER expression, and Ki-67 expression ($P < 0.05$). IL-10 and CD14- joint detection was only related to TNM stage and lymph node metastasis. Age, vascular infiltration, and HER2 expression were not associated with any detection ($P > 0.05$) (Table 4).

Validation analysis of IL-10 and CD14+ joint detection in peripheral blood of BC patients and patients with benign breast diseases

We also collected 30 cases of breast cancer and benign breast diseases to test the diagnostic efficiency of the

Table 4 The correlation of CD14- macrophages, IL-10 and their joint detection with different clinicopathological features in BC patients [*n* (%)]

Items	CD14+ macrophages		IL-10 CD14-combined detection		IL-10 CD14+ combined detection	
	Low expression	High expression	Low expression	High expression	Low expression	High expression
Cases (*n*)	22	28	28	22	20	30
Age (years)						
≤50	9 (50.0)	9 (50.0)	12 (66.67)	6 (33.33)	9 (50.0)	9 (50.0)
>50	13 (40.6)	19 (59.4)	16 (50.00)	16 (50.00)	11 (34.4)	21 (65.6)
χ^2	0.411		1.299		1.172	
P	0.522		0.254		0.279	
r	0.091		0.161		0.153	
Tumor size (cm)						
≤2	12 (54.5)	10 (45.5)	15 (68.18)	7 (31.82)	13 (59.1)	9 (40.9)
>2	10 (35.7)	18 (64.3)	13 (46.43)	15 (53.57)	7 (25.0)	21 (75.0)
χ^2	1.773		2.366		5.966	
P	0.183		0.124		0.015	
r	0.188		0.218		0.345	
Lymph node metastasis						
0	11 (73.3)	4 (26.7)	13 (86.67)	2 (13.33)	10 (66.7)	5 (33.7)
1–3	6 (28.6)	15 (71.4)	9 (42.86)	12 (57.14)	4 (19.0)	17 (81.0)
≥4	5 (35.7)	9 (64.3)	6 (42.86)	8 (57.14)	6 (42.9)	8 (57.1)
χ^2	7.657		8.179		8.333	
P	0.022		0.017		0.016	
r	0.294		0.341		0.193	
Vascular invasion						
No	16 (48.5)	17 (51.5)	18 (54.55)	15 (45.45)	16 (48.5)	17 (51.5)
Yes	6 (35.3)	11 (64.7)	10 (58.82)	7 (41.18)	4 (23.5)	13 (76.5)
χ^2	0.792		0.083		2.911	
P	0.373		0.773		0.088	
r	0.126		-0.041		0.241	
TNM stage						
I	11 (73.3)	4 (26.7)	12 (80.00)	3 (20.00)	10 (66.7)	5 (33.7)
II+III	11 (31.4)	24 (68.6)	16 (45.71)	19 (54.29)	10 (28.6)	25 (71.4)
χ^2	7.483		5.009		6.349	
P	0.006		0.025		0.012	
r	0.387		0.317		0.356	
Her-2						
Negative	12 (60.0)	8 (40.0)	14 (70.00)	6 (30.00)	11 (55.0)	9 (45.0)
Positive	10 (33.3)	20 (66.7)	14 (45.67)	16 (53.33)	9 (30.0)	21 (70.0)
χ^2	3.463		2.652		3.125	
P	0.063		0.103		0.077	
r	0.263		-0.230		0.250	
ER						
Negative	15 (55.6)	12 (44.4)	17 (63.0)	10 (37.0)	15 (55.6)	12 (44.4)
Positive	7 (30.4)	16 (69.6)	11 (47.8)	12 (52.2)	5 (21.7)	18 (78.3)
χ^2	3.181		5.238		5.918	
P	0.075		0.022		0.015	
r	0.252		0.295		0.344	
Ki-67						
≤30	17 (58.6)	12 (41.4)	18 (62.07)	11 (37.93)	17 (58.6)	12 (41.4)
>30	5 (23.8)	16 (76.2)	10 (47.62)	11 (52.38)	3 (14.3)	18 (85.7)
χ^2	5.99		1.032		9.975	
P	0.014		0.310		0.002	
r	0.346		0.144		0.447	

Table 5 Comparison of the diagnostic value of single and combined detection of macrophages and IL-10 between patients with breast cancer and breast benign diseases

Items	AUC	95%CI	S_b	Sensitivity	Specificity
CD14+ macrophages	0.653	0.512–0.794	0.041	36.70	95.00
CD14- macrophages	0.612	0.469–0.794	0.135	98.50	26.70
Total macrophages	0.690	0.557–0.823	0.011	36.70	96.70
IL-10	0.659	0.517–0.801	0.035	46.70	90.00
IL-10 CD14+macrophages combined detection	0.779	0.660–0.896	0.000	83.30	72.30
IL-10 CD14-macrophages combined detection	0.668	0.527–0.809	0.026	40.00	96.70
IL-10 total macrophages combined detection	0.687	0.549–0.824	0.013	40.00	98.50

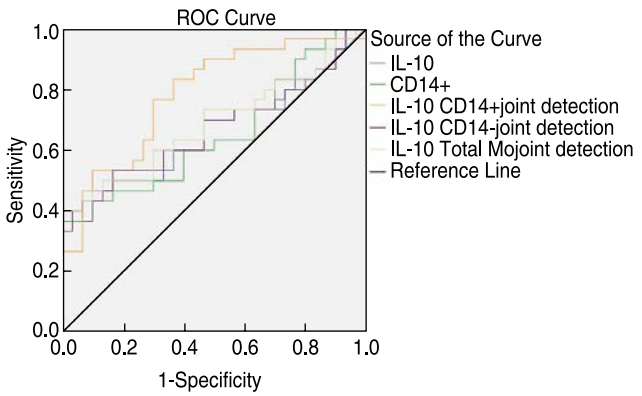

Fig. 4 Curve of CD14+ macrophages, IL-10 and their joint detections in validation analysis

above joint detection model. The analysis results of the ROC curve suggested that in the validation population with benign breast diseases as the control, the efficacy level of IL-10 and CD14+ joint detection was still higher than that of single detection and other joint detections. The AUC was 0.779, and the sensitivity and specificity were 83.3% and 72.3%, respectively. The results of the validation analysis were consistent with the test results, and the difference was statistically significant ($P < 0.001$) (Fig. 4).

Discussion

In recent years, TAMs have become well known because of their plasticity and diversity [7]. After naive monocytes in peripheral circulation are recruited to the TME, they are polarized into two phenotypes: classic M1 macrophages and alternative M2 macrophages [8]. TAMs with the M1 phenotype show proinflammatory activity and better prognosis [9], whereas the M2 phenotype is associated with increased angiogenesis and tumor aggressiveness [10–11]. M2 TAMs are also key players in tumor immune escape and angiogenesis [12]. In addition, except for macrophages in tumor tissues, TAMs were found to escape from tumor tissue, migrate via the lymphatic system, or intravasate across intratumor capillary barriers into peripheral circulation with CTCs and other blood cells, and further turn into CAMLs [13]. Therefore, future research into the BC TME should focus on the specific mechanism of M2 TAMs *in vivo*.

Of the numerous cytokines associated with the TME, IL-10 and M2 TAMs are closely related. M2 phenotype macrophages are activated in the microenvironment by IL-10, glucocorticoids, and immune complexes. They can generate auxiliary IL-10 and matrix-remodeling factors, such as MMPs [14]. Several studies have identified that IL-10 secreted by macrophages can induce endothelial cell proliferation and participate in the epithelial-to-mesenchymal transition to promote apoptosis in BC cells through their related pathways, including the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway [15–16]. In addition, previous research has shown that the double-labeling of IL-10 and CD14+ can screen "M2-like macrophages" in peripheral blood, which is significantly correlated with malignant clinicopathological characteristics and poor prognosis [17]. Thus, IL-10 and M2 TAMs are inextricably associated with cancer-promoting processes. CD14 macrophages and IL-10 in peripheral blood may also be critical in BC.

This study is the first to show that patients with BC have higher levels of IL-10, CD14+ macrophages, and total macrophages than healthy individuals. This implies that the *in vivo* environment, which shows the presence of more macrophages, can confer a survival advantage to tumor cells. Simultaneously, BC patients also had significantly higher IL-10 expression levels, suggesting a certain effect of M2 macrophages in BC patients. Therefore, based on these analyses, we established a joint detection model of IL-10 and CD14 macrophage expression by binary logistic regression. ROC curve analysis confirmed that the joint detection of CD14+ and IL-10 was more valuable and effective as a potential diagnostic method of BC than the single detection of IL-10 and CD14 macrophages and other joint detections (AUC = 0.830, $P < 0.001$). In the validation analysis, we found that the joint detection of CD14+ and IL-10 still showed advantageous diagnostic efficiency (AUC = 0.779,

$P < 0.001$), and the result was consistent with the test results.

This study also analyzed the relationship between macrophages and BC clinicopathological features. CD14+ macrophage expression was correlated with stage, lymph node metastasis, and high Ki-67 expression ($P < 0.05$), suggesting a significant relationship between macrophage expression in the peripheral blood and poor prognosis in BC patients. TAMs are always expressed at low levels in patients with early-stage and luminal BC and early-stage BC, whereas triple-negative BC (TNBC) mostly shows TAM overexpression [18–19]. The results of this study were consistent with these findings. The joint detection results of IL-10 and CD14+ macrophages were significantly correlated with tumor size, TNM stage, lymph node metastasis, ER expression, and Ki-67 expression ($P < 0.05$). ER-positive patients have lower macrophage expression levels in the peripheral blood. The faster tumor cells proliferate, the later the tumor stage and the stronger the expression of macrophages in the peripheral blood of BC patients. This confirmed that jointly detecting IL-10 and CD14+ macrophages could suggest tumor burden and the invasive ability of BC cancer cells, and they may be potential BC biomarkers.

However, the present study only analyzed macrophages and IL-10 in the peripheral blood, and different subtypes of macrophages were not further classified. There is a lack of intuitive data on the independence and interaction of M1 and M2 macrophages in the peripheral blood. The level difference of peripheral blood in different molecular types of breast cancer is also unclear. We need to expand the sample size to confirm this observation in future research.

In summary, this study found that the expression of total macrophages, CD14+ macrophages, and IL-10 were significantly increased in BC patients. Jointly detecting CD14+ macrophages and IL-10 can also indicate a poor prognosis, guide BC development and monitoring, and provide new ideas for research on BC-related macrophages.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

Conception and design: K Jiang; Administrative support: X Xue; Provision of study materials or patients: J Sheng; Collection and assembly of data: M Dong, C Li, P·Jiapaer, X Li, M Yuan; Data analysis and interpretation: M Dong, K Jiang, J Sheng; Manuscript writing: all authors; Final approval of manuscript: all authors.

Data availability statement

Not applicable.

Ethical approval

The authors are accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in accordance with the Declaration of Helsinki (revised in 2013). This study was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine. All the patients signed an informed consent form before inclusion in the study.

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