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ORIGINAL RESEARCH

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# Study on diagnostic efficacy of combined detection of serum CCL-18, p185 and SDF-1 in breast cancer

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## Abstract

This study aims to investigate the diagnostic efficacy of combined detection of serum C-C Motif Chemokine 18 (CCL-18), p185 and Stromal cell derived factor 1 (SDF-1) in breast cancer. 88 breast cancer patients admitted to our hospital were selected as study subjects. 88 healthy women who visited for a physical examination during the same period were selected as controls. Serum CCL-18, p185 and SDF-1 levels were measured. Combined detection and single detection in breast cancer diagnosis were compared in terms of sensitivity, specificity, accuracy, positive predictive value and negative predictive value. ROC (receiver operating characteristic) curves were drawn to further compare the differences between combined detection and single detection methods. CCL-18, p185 and SDF-1 in the cancer group were significantly higher than in the control group ($p < 0.05$). The area under the ROC curve of CCL-18, p185, SDF-1 and combined detection were 0.786 (95% Confidence Interval (CI): 0.717–0.854), 0.852 (95% CI: 0.788–0.916), 0.921 (95% CI: 0.883–0.958) and 0.962 (95% CI: 0.925–0.999), respectively. Sensitivity of combined detection was significantly higher than CCL-18 and p185 ($p < 0.05$). Specificity, accuracy and positive predictive value of combined detection were significantly higher than CCL-18, p185 and SDF-1 ($p < 0.05$). Compared with CCL-18 and p185, combined detection had a higher negative predictive value, which was statistically significant ($p < 0.05$). Combined detection of serum CCL-18, p185 and SDF-1 is more effective at diagnosing breast cancer and is worth clinical application.

## Keywords

CCL-18; p185; SDF-1; Combined detection; Breast cancer; Diagnostic efficacy

## 1. Introduction

Breast cancer has no known etiology. The exploration of high risk factors for breast cancer, such as abnormal estrone and estradiol secretion, parental inheritance, overnutrition and excessive alcohol consumption [1] has led to certain results after numerous studies and clinical diagnosis. Breast cancer has a long cycle, generally lasting 1 to 10 years. A long-time span makes early-stage symptoms unobvious and easy to ignore. Symptoms include breast lumps, tingling pain, skin depression and other phenomena. At the middle and late stages of breast cancer, tumor cells have spread throughout the body, causing loss of appetite, weight loss and anorexia, among other symptoms. In severe cases, life will be at risk [2]. Due to the common nature of early-stage symptoms, breast cancer is prone to being missed and neglected, delaying diagnosis and treatment, which reduces the probability of cure. It is therefore essential to cure breast cancer at the appropriate time, in the appropriate way, and with the correct technology [3].

C-C Motif Chemokine 18 (CCL-18) is a regulatory chemokine produced by the innate immune system, primarily dendritic cells, monocytes and macrophages. According to clinical microscopic observation, breast cancer stroma contains excessive numbers of M2 macrophages [4]. Meanwhile, a number of domestic and foreign studies have found a positive correlation between human epidermalgrowth factorreceptor-2 (HER-2) and breast cancer pathogenesis. The HER-2 gene product, p185 also plays a crucial role in pathogenesis, while SDF-1 (Stromal Cell Derived Factor 1) speeds up tumor cell metastasis during the process [5]. CCL-18, p185 and SDF-1 can be combined in early breast cancer screening to determine the incidence of patients with their comprehensive indicators. However, only a few relevant studies have been published [6]. Therefore, this study examined the diagnostic efficacy of combined detection of serum CCL-18, p185 and SDF-1 for breast cancer.

## 2. Materials and methods

### 2.1 Clinical data

A total of 88 breast cancer patients admitted to our hospital were selected as the cancer group. 88 healthy women who

visited for a physical examination during the same period were selected as controls. Clinical data did not differ significantly between both groups. Table 1 shows the result.

Inclusion criteria: (1) Cancer group diagnosed with breast cancer by pathological diagnosis. (2) Complete clinical data. (3) No cognitive dysfunction. (4) Informed consent is signed.

Exclusion criteria: (1) Infectious diseases. (2) Liver, kidney, and other organ dysfunction. (3) Other breast diseases.

## 2.2 Method

Serum CCL-18, p185 and SDF-1 levels were measured. Combined detection and single detection in breast cancer diagnosis were compared in terms of sensitivity, specificity, accuracy, positive predictive value and negative predictive value. ROC curve (Receiver Operating Characteristic Curve) was used to evaluate diagnostic efficacy.

## 2.3 Outcome measures

(1) Serum CCL-18, p185 and SDF-1

Patients fasted before sampling venous blood. Each time, 6 mL of blood was collected and stored in an anticoagulant tube. Next, serum supernatants were separated, centrifuged and layered by centrifuge (3000 r/min, 15 min). Supernatants were taken for refrigeration at −80 °C. Finally, serum samples were detected by ELISA assay kits (100189, Shanghai Hengyuan Biotechnology Co., Ltd., Shanghai, China). CCL-18, p185 and SDF-1 levels in serum were detected emphatically following the manual.

(2) Sensitivity = number of true positives/(number of true positives + number of false negatives) $>$ 100%;

(3) Specificity = number of true negatives/(number of true negatives + number of false positives) $>$ 100%;

(4) Accuracy = (number of true positives + number of true negatives)/total number of cases $>$ 100%;

(5) Positive predictive value = number of true positives/(number of true positives + number of false positives) $>$ 100%;

(6) Negative predictive value = number of true negatives/(number of true negatives + number of false negatives) $>$ 100%.

## 2.4 Data processing methods

Statistical analysis and data processing were performed with SPSS 27.0 (International Business Machines Corporation, Armonk, NY, USA). Normal distribution-conforming measurement data were presented as ($\bar{x} \pm s$). For measurement data that do not conform to a normal distribution was presented as median (upper and lower quartiles) (M (Q1, Q3)). The *t*-test (normal distribution) and rank sum test (non-normal distribution) were used. Enumeration data were presented as the number of cases and percentage (n (%)). The $\chi^2$ test was used to compare enumeration data between groups. Significant differences were indicated by $p < 0.05$.

For further comparison of diagnostic efficacy between different indicators, ROC (receiver operating characteristic) curves were plotted using SPSS 27.0.

# 3. Results

## 3.1 Comparison of CCL-18, p185 and SDF-1 between both groups

CCL-18, p185 and SDF-1 levels in the cancer group were significantly higher than that in the control group ($p < 0.05$) (Table 2, Figs. 1,2,3).

## 3.2 Results of ROC curve analysis

The area under ROC curves of CCL-18, p185, SDF-1, and combined detection was 0.786 (95% CI: 0.717–0.854), 0.852 (95% CI: 0.788–0.916), 0.921 (95% CI: 0.883–0.958), and 0.962 (95% CI: 0.925–0.999), respectively. Combined detection had the largest area under the ROC curve, suggesting the most significant diagnostic effect (Table 3 and Fig. 4).

**TABLE 1. Comparison of clinical data between both groups.**

| Group | N | Age (yr) | Weight (kg) | Height (m) | Menopause time (yr) |
|---|---|---|---|---|---|
| Control group | 88 | 65.23 ± 5.51 | 64.20 ± 5.33 | 1.59 ± 0.15 | 10.20 ± 2.24 |
| Cancer group | 88 | 65.26 ± 5.54 | 64.24 ± 5.41 | 1.61 ± 0.19 | 10.23 ± 2.27 |
| *t* value | —— | 0.036 | 0.049 | 0.775 | 0.088 |
| *p* value | —— | 0.971 | 0.961 | 0.439 | 0.930 |

**TABLE 2. Comparison of CCL-18, p185 and SDF-1 between both groups ($\bar{x} \pm s$), pg/mL.**

| Group | N | CCL-18 | p185 | SDF-1 |
|---|---|---|---|---|
| Control group | 88 | 5.23 ± 1.50 | 3.13 ± 1.33 | 5231.02 ± 552.35 |
| Cancer group | 88 | 7.78 ± 2.78 | 7.33 ± 3.53 | 6300.15 ± 565.14 |
| *t* value | | 7.580 | 10.452 | 172.932 |
| *p* value | | <0.001 | <0.001 | <0.001 |

*CCL-18: C-C Motif Chemokine 18; SDF-1: Stromal Cell Derived Factor 1.*

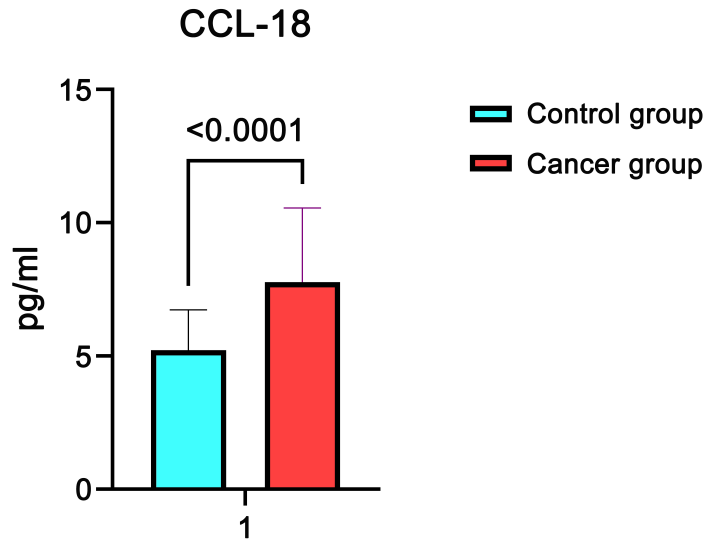


**FIGURE 1. Comparison of CCL-18 between both groups.** CCL-18: C-C Motif Chemokine 18.

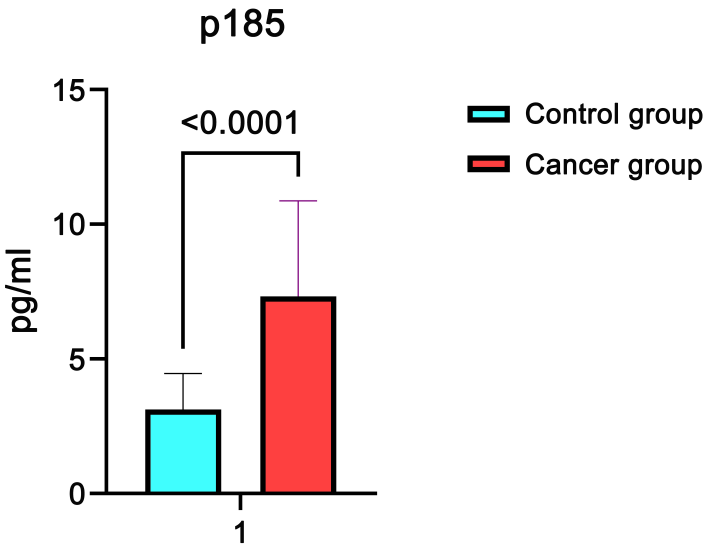


**FIGURE 2. Comparison of p185 between both groups.**

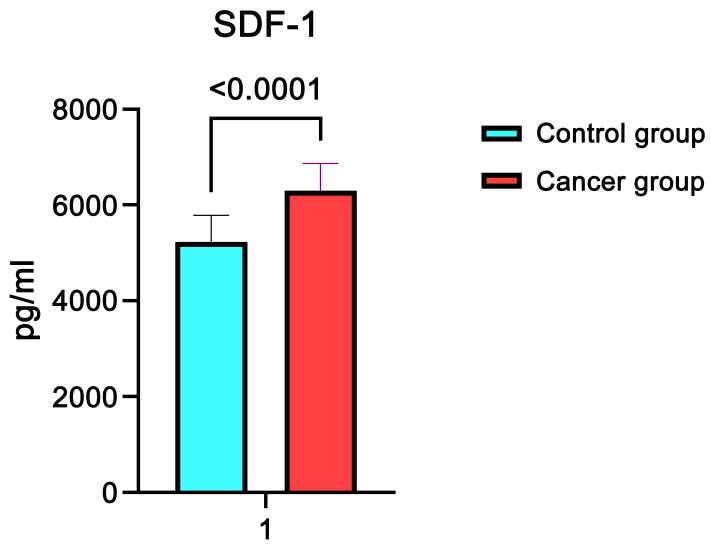


**FIGURE 3. Comparison of SDF-1 between both groups.** SDF-1: Stromal Cell Derived Factor 1.

**TABLE 3. ROC curve analysis results.**

| Indicators | AUC | 95% Confidence interval | | Critical value | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| | | Lower limit | Upper limit | | | |
| CCL-18 | 0.786 | 0.717 | 0.854 | 5.96 | 75.00 | 72.73 |
| p185 | 0.852 | 0.788 | 0.916 | 4.86 | 77.27 | 93.18 |
| SDF-1 | 0.921 | 0.883 | 0.958 | 5594.29 | 95.45 | 72.73 |
| Combined detection | 0.962 | 0.925 | 0.999 | - | 95.45 | 100.00 |

*CCL-18: C-C Motif Chemokine 18; SDF-1: Stromal Cell Derived Factor 1; AUC: Area Under Curve.*

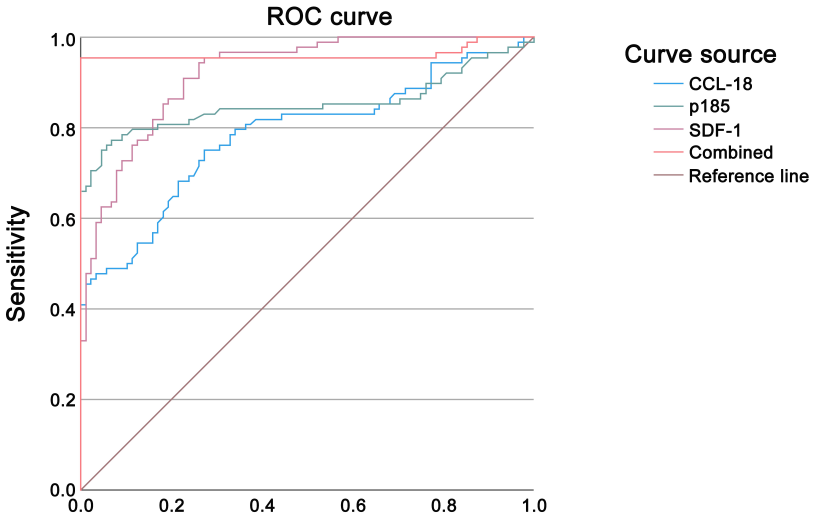


**FIGURE 4. ROC curves of CCL-18, p185, SDF-1 and combined detection.** CCL-18: C-C Motif Chemokine 18; SDF-1: Stromal Cell Derived Factor 1; ROC: receiver operating characteristic.

### 3.3 Comparison of diagnostic efficacy indicators of CCL-18, p185, SDF-1 and combined indicators

Sensitivity of combined detection was significantly higher than CCL-18 and p185 ($p < 0.05$). Specificity, accuracy and positive predictive value of combined detection were significantly higher than CCL-18, p185 and SDF-1 ($p < 0.05$). Compared with CCL-18 and p185, combined detection had a higher negative predictive value, which was statistically significant ($p < 0.05$) (Table 4).

## 4. Discussion

Breast cancer, known as the "pink killer", is more common among women and is a malignant solid tumor. Recent incomplete statistics indicate that breast cancer sufferers has gradually risen worldwide. Incidence has gradually exceeded that of cervical cancer, also known as the "hidden killer" [7]. Multiple organ lesions may occur as a result of breast. It negatively affects patients' lives and production, but also seriously endangers them. Therefore, early diagnosis and treatment can greatly improve breast cancer cure probability.

Breast cancer is diagnosed in approximately 300,000 women in China every year, with a higher incidence on the eastern coast and in developed areas. This is the first malignant tumor to pose a health risk to women. Numerous studies have been conducted in China and overseas in response to its concerns [8]. Since its early-stage symptoms are similar to common gynecological diseases, it is often misdiagnosed by doctors and patients during diagnosis. Consequently, patients miss out on the most appropriate time for treatment, affecting their lives and health. During the late stage of cancer, there are many factors that contribute to tumor cells metastasizing to multiple organs in the body, resulting in organ failure and serious life-threatening situations' [9]. Therefore, early screening, detection, diagnosis and treatment are imperative to reduce breast cancer incidence or even cure breast cancer. Presently, breast cancer is screened and diagnosed primarily using ultrasound and pathological biopsy. Breast cancer screening has limited value because of its low efficiency, accuracy and other disadvantages. Researchers in various countries have, however, gradually clarified an alternative methodological path with the deepening of biomolecular research [10].

Biological factor research has focused on ligands for chemokine receptor 4 over the past few years. Early and late breast cancer formation is significantly influenced by SDF-1 [11]. SDF-1 has a small molecular weight and high specific binding degree. It acts on neural and vascular development, hematopoiesis and immunity. After binding to chemokine receptor 4, SDF-1 directly acts on G protein-coupled receptors to guide immune cells or tumor cells to migrate throughout the body. It has been demonstrated in numerous studies that blocking SDF-1 from binding to chemokine receptor 4 can

**TABLE 4. Comparison of diagnostic efficacy of DWI and DCE-MRI for cervical invasion (%).**

| Method | Sensitivity | Specificity | Accuracy | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|
| CCL-18 | 75.00 (66/88)* | 72.73 (64/88)* | 73.86 (130/176)* | 73.33 (66/90)* | 74.42 (64/86)* |
| p185 | 77.27 (68/88)* | 93.18 (82/88)* | 85.23 (150/176)* | 91.89 (68/74)* | 80.39 (82/102)* |
| SDF-1 | 95.45 (84/88) | 72.73 (64/88)* | 84.09 (148/176)* | 77.78 (84/106)* | 94.12 (64/68) |
| Combined detection | 95.45 (84/88) | 100.00 (88/88) | 97.73 (172/176) | 100.00 (84/84) | 95.65 (88/92) |

*Note: *Compared with combined detection, $p < 0.05$ showed significant differences. CCL-18: C-C Motif Chemokine 18; SDF-1: Stromal Cell Derived Factor 1.*

cure breast cancer tumor cells.

CCL-18 is a lung-derived, activation-regulated chemokine produced by antigen-presenting cells of the innate immune system that affects human autoimmunity and allergy [12]. Clinical practice has shown that abnormal CCL-18 expression can affect breast cancer, leukemia and other cancer pathogenesis. Besides, it can play a role in attracting cells and enhancing attachment, accelerating the migration of tumor cells, and transmitting and expressing tumor cell information to a certain extent [13].

As an oncogene-encoded product, p185 activates multiple information transduction pathways through its own activity under carcinogenic factors. Gene expression is accelerated to make cytopathic lesions into breast cancer and promote rapid metastasis [14]. In serum testing, abnormal expression of p185 indicates an increasing degree of tumor infiltration. According to current clinical research practice, the detection of Carbohydrate Antigen 153 (CA153) content in patients' serum combined with the detection of p185 expression can diagnose and prevent early breast cancer with considerable probability [15].

This study demonstrated that combined detection had the largest area under the ROC curve, suggesting the most significant diagnostic effect. Meanwhile, sensitivity of combined detection was significantly higher than CCL-18 and p185 ($p < 0.05$). Specificity, accuracy, and positive predictive value of the combined test diagnosis were significantly higher than CCL-18, p185 and SDF-1 ($p < 0.05$). Compared with CCL-18 and p185, combined detection had a higher negative predictive value, which was statistically significant ($p < 0.05$). This result suggests that the combined detection of serum CCL-18, p185 and SDF-1 levels improves breast cancer diagnostic efficacy. According to domestic and foreign research reports [16–18], this result is consistent.

Combined detection of serum CCL-18, p185 and SDF-1 has a higher diagnostic efficacy for breast cancer and offers comparative advantages over the traditional gold standard method, which are as follows. Diagnostic methods for breast cancer traditionally rely on clinical manifestations, imaging examination and histopathology. However, these methods have certain limitations, including atypical clinical manifestations, inaccurate imaging examination results, and surgical sampling for histopathological analysis. Combined detection of CCL-18, p185 and SDF-1 in serum can diagnose breast cancer by detecting biomarkers in serum, with high accuracy and sensitivity. It is often necessary to wait until the tumor forms a significant mass or other obvious symptoms before it can be diagnosed using traditional diagnostic methods. Combined detection of serum CCL-18, p185 and SDF-1 can detect abnormalities before tumor forms a significant mass or other obvious symptoms to achieve an early diagnosis. This is a noninvasive diagnostic method that does not require surgical sampling but instead collects serum from patients for detection. Patients who are unable to undergo surgical sampling, such as the elderly, frail patients, *etc.*, benefit greatly from this technique. It requires only the patient's serum and does not require complex equipment or technology. This can be very beneficial for primary care institutions in diagnosing breast cancer.

Combined detection of CCL-18, p185 and SDF-1 in serum is of substantial significance in breast cancer and oncology diagnosis. It can provide a valuable reference for breast cancer treatment. Results from the test can assist doctors with determining the type, stage, and prognosis of the tumor and thus develop more personalized treatment plans. Breast cancer is a tumor that tends to recur and metastasize. Combined detection of serum CCL-18, p185 and SDF-1 helps monitoring breast cancer recurrence and metastasis. In this case, doctors can determine whether the tumor has recurred or metastasized to take appropriate treatment measures at the right time. Additionally, it is useful for doctors to evaluate breast cancer therapeutic effects. Using test results, doctors can determine whether treatment plans are effective and modify them accordingly.

Study limitations include the number and source of cases as well as some limitations. The diagnostic efficacy of different indicators has not been studied for different pathological types. Patients' survival analysis was also not conducted. For future research, we should expand the scope of the research subjects, deepen the study connotation to draw a more objective conclusion, and develop a reference for breast cancer clinical diagnosis.

## 5. Conclusions

In summary, combined detection of serum CCL-18, p185 and SDF-1 is more effective at diagnosing breast cancer and is worth clinical application.

### AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be

obtained from the corresponding author upon request.

## AUTHOR CONTRIBUTIONS

JBY, ZG, BW and YLW—designed the study and carried them out; prepare the manuscript for publication and reviewed the draft of the manuscript. JBY, ZG, BW—supervised the data collection. JBY, ZG—analyzed the data, interpreted the data. All authors have read and approved the manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Zhanjiang Central People's Hospital (Approval no. PJ (IIT-2023-025-P02)). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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