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Study on the Diagnostic Value of Serum Tumor Markers CEA, CA153, and CYFRA21 in Invasive Breast Cancer

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Abstract: *Objective:* To explore the diagnostic value of serum tumor markers CEA, AFP, CA199, CA125, CA153, CYFRA21, CA724, and NSE in invasive breast cancer. *Methods:* A total of 314 patients with invasive breast cancer from Baoding First Central Hospital between January 2021 and December 2022, and 31 patients with benign breast diseases (including mastitis, breast fibroadenoma, breast adenosis, adenoma of the breast, benign phyllodes tumor of the breast, and intraductal papilloma) were randomly selected as the control group. The levels of CEA, AFP, CA199, CA125, CA153, CYFRA21, CA724, and NSE were measured using electrochemiluminescence. *Results:* The serum concentrations of CEA, CA153, and CYFRA21 showed significant statistical differences between the invasive breast cancer group and the benign breast disease group ($P < 0.01$). ROC curve analysis revealed that CA153 had the highest sensitivity for diagnosing invasive breast cancer, while CEA had the highest specificity, at 84.4% and 77.4%, respectively. When multiple tumor markers were used for the diagnosis of invasive breast cancer, the combination of CEA and CA153 showed the highest specificity at 90.3%, while the combination of CEA and CYFRA21 had the highest sensitivity at 88.2%. The combined detection of CEA, CYFRA21, and CA153 had the largest area under the curve (AUC) on the ROC curve, at 0.802, indicating that the combination of these three markers provided the best diagnostic performance for invasive breast cancer. *Conclusion:* CEA, CA153, and CYFRA21 can be used for the diagnosis of invasive breast cancer, and the combined detection of these three markers offers the best diagnostic efficacy for invasive breast cancer.

Keywords: Invasive breast cancer; Serum tumor markers; CEA; CA153; CYFRA21

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1. Introduction

According to the latest global cancer data released by the International Agency for Research on Cancer (IARC)

in 2020, the incidence of breast cancer in women has rapidly increased to 2.26 million cases, accounting for 11.7% of all newly diagnosed cancers, surpassing lung cancer for the first time and ranking first globally [1]. In China, there were 420,000 new breast cancer cases in 2020, making it the country with the highest absolute number of cases globally, while breast cancer ranked fourth in the overall cancer incidence in China. Despite the high incidence, breast cancer's mortality rate is relatively low, ranking fourth in cancer-related deaths. Early diagnosis of breast cancer is key to its treatment, as the five-year survival rate for early-detected breast cancer patients exceeds 90%, and the ten-year survival rate for patients in stages II and III is about 70%. Although targeted therapies can extend survival in advanced cases, the five-year survival rate for stage IV breast cancer patients is only 21%. Compared to the breast cancer screening rate of over 70% in Western countries, the screening rate in China is only 21.7% [2]. Therefore, early screening is crucial for breast cancer treatment and improving survival rates [3].

Current methods for early breast cancer screening primarily include mammography (X-ray) and ultrasound (B-ultrasound) combined with magnetic resonance imaging (MRI) screening. The Chinese breast cancer treatment guidelines recommend screening every two years, or annually, for women over 40. These tests involve the use of radioactive elements and are costly, limiting large-scale breast cancer screening. It is well-known that biomarkers are effective tools for cancer diagnosis. Currently, clinical cancer screening in Chinese hospitals commonly uses 13 types of tumor markers [4,5]: carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), cancer antigen 199 (CA199), cancer antigen 724 (CA724), cancer antigen 153 (CA153), cancer antigen 50 (CA50), alpha-fetoprotein (AFP), alpha-L-fucosidase (AFU), human chorionic gonadotropin (HCG), neuron-specific enolase (NSE), squamous cell carcinoma antigen (SCC), soluble fragment of cytokeratin 19 (CYFRA21-1), and prostate-specific antigen (PSA), among others [6]. However, clinical application results have shown that the sensitivity and specificity of these tumor markers are not high, despite their widespread use in tumor screening [7]. Therefore, this study systematically investigated the levels of CEA, AFP, CA199, CA125, CA153, CYFRA21, CA724, and NSE in the serum of patients with invasive breast cancer, in order to explore the diagnostic value of individual or combined tumor marker indicators in invasive breast cancer.

2. Materials and methods

2.1. Patients

From January 2021 to December 2022, 314 patients with invasive breast cancer and 31 patients with benign breast diseases (including mastitis, breast fibroadenoma, breast adenosis, adenoma of the breast, benign phyllodes tumor of the breast, and intraductal papilloma) were randomly selected from Baoding First Central Hospital as the control group. All patients were pathologically confirmed. This experiment was approved by the ethics committee.

2.2. Methods

This study compared the test results and diagnostic roles of tumor markers CEA, AFP, CA153, CA125, CYFRA21, CA199, CA724, and NSE between patients with invasive breast cancer and those with benign breast diseases. The detection methods used were all electrochemiluminescence, with reagents provided by Roche Diagnostics (Shanghai) Co., Ltd., and the instruments used were COBAS 8000 e602 (for two tumor markers) and COBAS 8000 e601 (for six tumor markers). In this study, the optimal cutoff values for marker sensitivity and specificity were: CEA > 1.365 μg/L, CA153 > 6.45 U/mL, and CYFRA21 > 1.445 U/L.

2.3. Statistics analysis

The concentrations of tumor markers were described using the median and interquartile range (IQR). The Mann-Whitney test was used to compare serum concentrations between the two groups. For tumor markers with significant differences between the two groups, receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated. The maximum sum of sensitivity and specificity was considered the optimal cutoff value. Significant differences were determined when *P*-values were less than or equal to 0.01. All statistical analyses were performed using SPSS for Windows (version 19.0).

3. Results

Table 1 shows that the serum levels of CEA, CA153, and CYFRA21 in patients with invasive breast cancer were 1.82 (1.59) ng/mL, 10.49 (8.59) IU/mL, and 2.08 (1.88) ng/mL, respectively, which were significantly higher than those in the benign breast disease group, 1.05 (0.57) ng/mL, 6.44 (5.73) IU/mL, and 1.35 (1.36) ng/mL, with all differences being statistically significant ($P < 0.01$).

Table 1. Comparison of tumor marker concentrations between invasive breast cancer and benign disease groups [median (IQR)]

Serum tumor markers	Benign breast disease group	Invasive breast cancer group	Z-value	*P*
AFP (ng/mL)	2.63, 2.21	2.8, 2.1	-1.136	0.256
CEA (ng/mL)	1.05, 0.57	1.82, 1.59	-4.334	0.000
CA125 (IU/mL)	12.57, 9.9	11.93, 9.18	-0.543	0.587
CA153 (IU/mL)	6.44, 5.73	10.49, 8.59	-3.825	0.000
CA199 (IU/mL)	7.96, 6.00	11.32, 11.92	-2.275	0.023
CA724 (IU/mL)	1.6, 2.43	1.81, 3.06	-0.390	0.697
CYFRA21 (ng/mL)	1.35, 1.36	2.08, 1.88	-4.093	0.000
NSE (ng/mL)	18.35, 7.55	18.90, 8.43	-0.697	0.486

As shown in **Figure 1**, to better evaluate the diagnostic value of the three tumor markers in invasive breast cancer, we plotted the ROC curves for the serum tumor markers CEA, CA153, and CYFRA21, as well as their combined detection, in diagnosing invasive breast cancer, and calculated the AUC values.

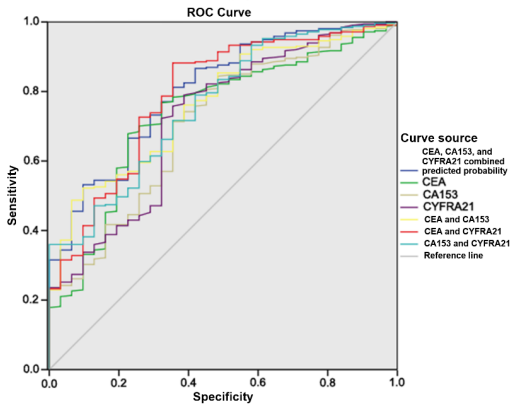

Figure 1. ROC analysis of serum tumor markers CEA, CA153, and CYFRA21 and their combined detection for diagnosing invasive breast cancer

As shown in **Table 2**, the AUC values for CEA, CA153, and CYFRA21 were 0.736, 0.708, and 0.723, respectively, with the highest ROC curve and AUC being obtained by CEA. When two tumor markers were combined, the highest AUC was achieved by the CEA and CYFRA21 combination (AUC = 0.790), while the lowest was the CA153 + CYFRA21 combination (AUC = 0.759).

Table 2. ROC area for serum tumor markers CEA, CA153, and CYFRA21 and their combined detection

Serum tumor marker	Area	*P*-value	95% Confidence interval
CEA	0.736	0.00	0.647–0.825
CA153	0.708	0.00	0.613–0.803
CYFRA21	0.723	0.00	0.627–0.819
CEA+CA153	0.763	0.00	0.685–0.841
CEA+CYFRA21	0.790	0.00	0.705–0.875
CA153+CYFRA21	0.759	0.00	0.675–0.843
CEA+CA153+CYFRA21	0.802	0.00	0.726–0.879

Further ROC curve analysis of the sensitivity and specificity of tumor markers for diagnosing invasive breast cancer, as shown in **Table 3** and **Figure 1**, indicates that CA153 had the highest diagnostic sensitivity for invasive breast cancer, while CEA had the highest diagnostic specificity, at 84.4% and 77.4%, respectively. When multiple tumor markers were used to diagnose invasive breast cancer, the combination of CEA and CA153 had the highest specificity (90.3%), while the combination of CEA and CYFRA21 had the highest sensitivity (88.2%). The combined detection of CEA, CYFRA21, and CA153 had the largest AUC on the ROC curve (0.802), indicating that the combination of these three markers had the best diagnostic efficacy for invasive breast cancer.

Table 3. Role of CEA, CA153, and CYFRA21 in diagnosing invasive breast cancer

Tumor marker	Sensitivity (%)	Specificity (%)	Youden index (%)
CEA	67.8	77.4	45.3
CA153	84.4	51.6	36.0
CYFRA21	79.0	61.3	40.3
CEA+CA153	52.2	90.3	42.6
CEA+CYFRA21	88.2	64.5	52.7
CA153+CYFRA21	79.0	58.1	37.0
CEA+CA153+CYFRA21	81.2	64.5	45.7

4. Discussion

Breast cancer ranks first globally in incidence and fourth in China, posing a serious threat to women's health. Compared to developed countries, the 5-year survival rate for breast cancer patients in China is relatively low, primarily due to low cancer screening rates and delayed medical consultations. Therefore, early screening for breast cancer is critical for its treatment and improving survival rates.

Currently, internationally accepted breast cancer screening methods include mammography combined with

ultrasound and MRI. However, these methods involve the use of radioactive elements and high costs, making them less suitable for large-scale early screening of breast cancer. The development of breast cancer-specific tumor markers has brought hope for early diagnosis. However, the accuracy of the commonly used breast cancer-specific tumor marker CA153 is not ideal in screening. Therefore, the development of combined tumor marker detection for early breast cancer diagnosis holds significant value and social importance.

Luo *et al.* studied the levels of CA153, CA125, and CEA in 100 breast cancer patients and 110 benign breast tumor patients and found that the levels of CA153, CA125, and CEA were significantly higher in the breast cancer group compared to the benign breast tumor group and the control group. CA153 had the highest positive rate in single detection, followed by CA125, and CEA had the lowest. The sensitivity of the combined detection of the three markers was significantly increased, reaching 53.00%, although specificity decreased [8]. Qiu *et al.* studied the value of the combined detection of CA153 and CEA in diagnosing breast cancer, finding that the combination improved diagnostic accuracy [9]. Wang *et al.* studied the diagnostic value of CA125, CA153, CYFRA21, and CEA for triple-negative breast cancer, finding that CEA had the lowest diagnostic efficiency, while CA125 was an effective diagnostic marker for triple-negative breast cancer. The combination of CA125, CA153, and CYFRA21 significantly enhanced diagnostic specificity [10]. Hing *et al.* explored the relationship between CEA and CA153 and breast cancer recurrence, finding that exceeding the critical values for CEA and CA153 was an important predictor of recurrence [11]. Zhang *et al.* investigated the diagnostic differences between different combinations of TPS, CA125, CA153, and CEA for distant metastasis and non-metastasis in breast cancer, revealing that combined detection was more valuable than single marker detection [12]. Uygur and Gümüş found similar results, showing that the combination of CEA and CA153 as tumor markers was useful in early diagnosis, with elevated levels associated with unfavorable clinical pathological parameters in cancer patients [13].

In recent years, combinations of CA153, CA125, CEA, and new tumor markers such as HER-2, microRNA-335 (miR-335), and human epididymal protein 4 (HE4) have gained attention. Rong *et al.* explored the diagnostic value of CA153, CA125, and HER-2 levels in breast cancer, finding that serum levels of these markers were elevated in breast cancer patients, and their combined detection improved positive detection rates, sensitivity, and specificity [14]. Wan studied the value of the combined detection of serum tumor markers CA153, CA125, CEA, and HER-2 in diagnosing breast cancer, concluding that it reduced false-negative rates and improved sensitivity [15]. Fu found that the combination of CEA, CA125, CA153, and HER2 increased sensitivity in breast cancer diagnosis [16]. Wei *et al.* discovered that the combined detection of CA153, CEA, and HE4 achieved higher diagnostic rates in breast cancer compared to individual tests [17]. Liu *et al.* also found similar results [18]. Liu *et al.* showed that the combined detection of CA153 and miR-335 provided higher sensitivity, specificity, and accuracy in diagnosing early breast cancer than either marker alone [19]. Wang *et al.* examined the diagnostic value of CEA, CA199, CA125, CA153, and TPS for metastatic cancer, finding that CEA had the highest sensitivity, CA125 had the highest specificity, and the combination of CEA and TPS had the highest sensitivity for metastatic cancer [20]. These findings suggest that different tumor marker combinations have varying diagnostic values.

5. Conclusion

In summary, the combined use of multiple serum tumor markers offers significant clinical value for the early

diagnosis of different types of breast cancer. However, no studies have been reported on the combined use of CEA, CA153, and CYFRA21 for diagnosing invasive breast cancer. This study investigated the serum levels of CEA, AFP, CA19-9, CA125, CA153, CYFRA21, CA724, and NSE in patients with invasive breast cancer. The findings revealed that the serum levels of CEA, CA153, and CYFRA21 were higher in the invasive breast cancer group than in the benign breast disease group, with statistically significant differences. CA153 had the highest diagnostic sensitivity for invasive breast cancer, while CEA had the highest diagnostic specificity. When multiple tumor markers were used for diagnosis, the combination of CEA and CA153 had the highest specificity, while the combination of CEA and CYFRA21 had the highest sensitivity. The combined detection of CEA, CYFRA21, and CA153 had the largest AUC on the ROC curve, indicating that the combination of these three markers had the best diagnostic performance. CEA, CA153, and CYFRA21 can be used in the diagnosis of invasive breast cancer, and their combined detection provides the best diagnostic efficacy for this condition.

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Disclosure statement

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