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Original article

Prognostic Significance of CRP and CA 15-3 Levels in the Diagnosis of Breast Cancer: A Comparative Study

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Abstract: *Background* — C-reactive protein (CRP) and cancer antigen 15-3 (CA 15-3) are commonly studied biomarkers in breast cancer, but their prognostic significance at diagnosis remains unclear.
Aim: Our study aimed to assess the prognostic value of serum CRP and CA 15-3 levels in newly diagnosed breast cancer patients.
Methods — We enrolled 39 patients with primary breast cancer in our single-center study. Serum CRP and CA 15-3 levels were measured at diagnosis. Receiver operating characteristic (ROC) analysis was employed to determine optimal cut-off values. Survival outcomes were analyzed.
Results — Elevated CRP and CA 15-3 levels were associated with shorter progression-free survival and overall survival. In particular, CRP demonstrated significant prognostic value. However, due to the critically small sample size, the obtained results should be considered preliminary.
Conclusion — Serum CRP and CA 15-3 levels may serve as potential prognostic markers in breast cancer. These results are hypothetical and require confirmation in larger cohorts.

Keywords: Breast cancer, CA 15-3, CRP, prognostic markers, PFS, OS.

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Introduction

Breast cancer (BC) remains a major global health problem, representing the most frequently diagnosed cancer and the leading cause of cancer-related deaths among women worldwide [1, 2]. Reliable biomarkers predicting disease progression and patient outcomes are needed for personalized treatment strategies [3].

C-reactive protein (CRP) is an acute-phase reactant, and its elevated levels are associated with poor prognosis in patients with BC [4-7]. Cancer antigen 15-3 (CA 15-3) is widely used to monitor treatment response and disease recurrence, with higher levels associated with advanced disease and worse outcomes [8, 9].

While CRP and CA 15-3 have been studied separately, limited data are available on their combined prognostic efficacy at the time of initial diagnosis, particularly in Middle Eastern populations. Few studies have included survival analyses using ROC-derived cutoff values for both markers in treatment-naïve patients.

The aim of this study was to compare the prognostic value of CRP and CA 15-3 levels at diagnosis in patients with BC, hypothesizing that both markers are associated with progression-free survival (PFS) and overall survival (OS) and may aid in risk stratification.

Material and Methods

Study population

A total of 39 patients with histopathologically confirmed BC were recruited from the Department of Oncology at Tishreen University Hospital. Serum samples were collected at diagnosis, before the start of any treatment.

The demographic and clinical characteristics of the study cohort are presented in *Table* 1. These include age, cancer stage, tumor grade, receptor status (ER/PR/HER2), and treatment types.

Sample collection and analysis

CRP was measured using a high-sensitivity immunoturbidimetric assay (Mindray BS-380; kit lot number 20240101); intra-assay coefficient of variation (CV)=3.5%, inter-assay CV=4.2%. CA 15-3 was measured using the Immunoassay 360 analyzer (Autobio Diagnostics, kit lot number 20240115); manufacturer's reference range <30 U/mL.

Statistical analysis

SPSS v.26 software was employed for statistical analysis. Receiver operating characteristic (ROC) curves were used to assess the predictive accuracy of CRP and CA15-3 levels. The area under the curve (AUC), cutoff values, sensitivity, and specificity were

calculated. Kaplan-Meier survival curves were constructed to estimate PFS and OS. Statistical significance was set at $P<0.05$. The Shapiro-Wilk test was conducted to assess normality of distribution, and Spearman correlation analysis was performed to assess the relationship between CRP and CA 15-3 levels.

Results

Sample characteristics

The study included 39 female BC patients from whom samples were collected at diagnosis, before the start of any treatment. The patients' ages ranged from 37 to 76 years, with a mean age of 57±8.9 years. The mean CRP level among patients was 39.05±22.9 mg/L, and the mean CA 15-3 level was 47.91 U/mL. Given the small sample size of 39 patients, the results should be interpreted with caution. These data are preliminary and primarily hypothetical in nature. Due to the small sample size (n=39), we were unable to reliably perform multivariate Cox regression analysis with adequate adjustment for clinicopathological covariates. This limitation reduces our ability to confirm whether CRP and CA 15-3 are independent prognostic markers. The median follow-up time for all patients was 17 months.

ROC curve analysis for CRP

The ROC curve for CRP levels at diagnosis for predicting disease relapse showed an AUC of 0.753 (P=0.009) at a cutoff of 10.95 mg/L, yielding a sensitivity of 73.3% and a specificity of 79.2% (*Figure 1*). *Figure 1* depicts Receiver Operating Characteristic (ROC) for CRP levels at diagnosis. The x-axis represents (1 – specificity), i.e., false positive rate, while the y-axis represents sensitivity (true positive rate). Each point on the curve corresponds to a cutoff CRP value. The area under the curve (AUC) indicates the overall ability of CRP to discriminate between patients with and without disease relapse.

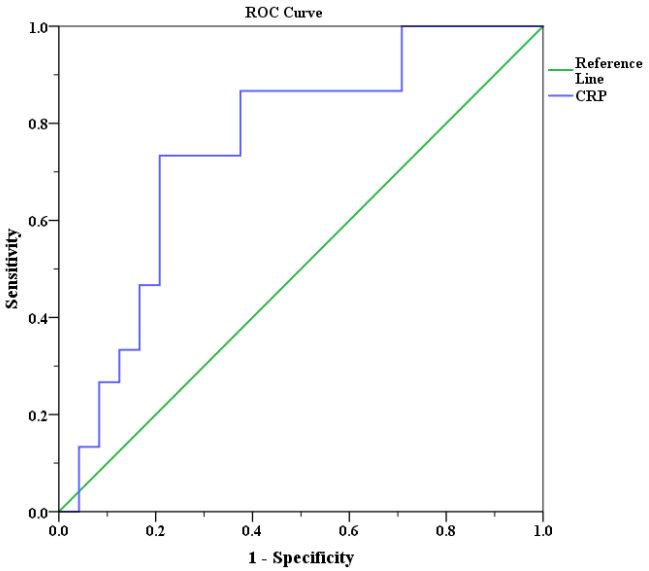

Figure 1. ROC curve for C-reactive protein (CRP) levels.

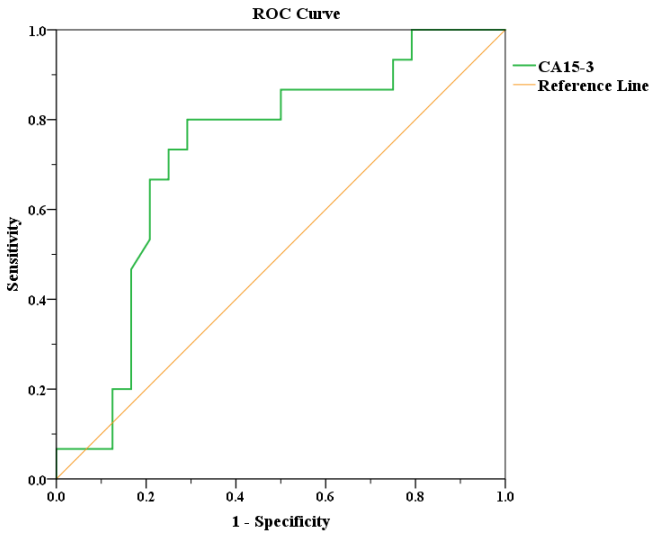

Figure 2. ROC curve for CA 15-3.

Table 1. Demographic and clinical characteristics of breast cancer patients included in this study

Characteristic	*n (%) or mean±SD*
Number of patients	39
Age (years)	57±8.9
Cancer stage	Stage I: 5 (12.8%), Stage II: 18 (46.2%), Stage III: 16 (41%)
Tumor grade	Grade 1: 7 (18%), Grade 2: 20 (51%), Grade 3: 12 (31%)
Estrogen receptor (ER) status	Positive: 28 (71.8%), Negative: 11 (28.2%)
Progesterone receptor (PR) status	Positive: 26 (66.7%), Negative: 13 (33.3%)
HER2 status	Positive: 15 (38.5%), Negative: 24 (61.5%)
Treatment type	Surgery: 35 (89.7%), Chemotherapy: 33 (84.6%), Hormonal therapy: 26 (66.7%)

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

Progression-free survival vs. CRP level

Based on the established CRP cutoff value, BC patients were divided into two groups: those with a low CRP level (≤10.95 mg/L) and those with a high CRP level (>10.95 mg/L). Patients with a CRP level ≤10.95 mg/L had significantly higher median PFS (16.7 months) and rates (82.6%) compared with those with a CRP level >10.95 mg/L (10.56 months and 31.3%, respectively) (P=0.00027). The log-rank test confirmed a significant difference in PFS between the two groups (*Table 2*).

Overall survival vs. CRP level

Patients with CRP≤10.95 mg/L also had significantly higher mean OS (17.2 months) and mortality (91.3%) vs. patients with CRP>10.95 mg/L (12.1 months and 50%, respectively) (P=0.001) (*Table 3*).

ROC curve analysis for CA 15-3

The ROC curve for CA 15-3 levels at diagnosis to predict disease recurrence showed an AUC of 0.726 (P=0.019) with a cutoff value of 47.8 U/mL, a sensitivity of 80%, and a specificity of 70.8% (*Figure 2*).

Table 2. Comparison of progression-free survival (PFS) rates and relapses by CRP level.

	CRP level	Number of relapses	Number of PFS cases	PFS rate, %	PFS mean (standard error)	Confidence interval for the mean, 95% CI		Log- rank chi-square	P-value
						Maximum	Minimum		
Group 1, n=23	CRP≤10.95 mg/L	4	19	82.6	16.73 (0.628)	17.96	13.25	13.25	0.00027
Group 2, n=16	CRP>10.95 mg/L	11	5	31.3	10.56 (1.378)	13.26	7.86		

Table 3. Analysis of overall survival (OS) and mortality rates by CRP level

	CRP level	Number of deaths	Number of OS cases	OS rate, %	OS mean (standard error)	Confidence interval for the mean, 95% CI		Log- rank chi-square	P-value
						Maximum	Minimum		
Group 1, n=23	CRP≤10.95 mg/L	2	21	91.3	17.2 (0.56)	18.3	16.1	10.69	0.001
Group 2, n=16	CRP>10.95 mg/L	8	8	50	12.1 (1.47)	14.9	9.18		

Table 4. Progression-free survival (PFS) rates and relapses by CA 15-3 level

	CA 15-3 level	Number of relapses	Number of PFS cases	PFS rate	PFS mean	Confidence interval for the mean, 95% CI		Log- rank chi-square	P-value
						Maximum	Minimum		
Group 1, n=23	CA 15-3≤47.8 U/mL	3	17	85%	16.9 (0.655)	18.18	15.6	10.6	0.001
Group 2, n=16	CA 15-3>47.8 U/mL	12	7	36.8%	11.3 (1.272)	13.86	8.87		

Table 5. Overall survival (OS) rates and mortality by CA 15-3 level

	CA 15-3 level	Number of deaths	Number of OS cases	OS rate, %	OS mean (standard error)	Confidence interval for the mean, 95% CI		Log- rank chi-square	P-value
						Maximum	Minimum		
Group 1, n=23	CA 15-3≤47.8 U/mL	2	18	90	17.1 (0.64)	18.3	15.8	6.5	0.011
Group 2, n=16	CA 15-3>47.8 U/mL	8	11	57.9	13.1 (1.33)	15.6	10.4		

Table 6. Spearman correlation analysis between CRP and CA 15-3 levels

Spearman correlation test		
		CA15-3
CRP	Correlation coefficient	0.676**
	Significance (two-tailed test)	2.36726131719618E-06

** The correlation is significant at the 0.01 level (two-tailed test); * The correlation is significant at the 0.05 level (two-tailed test).

Progression-free survival by CA 15-3 level

Patients with CA 15-3≤7.8 U/mL had significantly higher mean PFS (16.9 months) and rates (85%) vs. patients with CA 15-3>47.8 U/mL (11.3 months and 36.8%, respectively) (*P*=0.001) (*Table 4*).

Overall survival by CA 15-3 level

Patients with CA 15-3≤47.8 U/mL had significantly longer overall survival and survival rates (17.1 months, 90%) vs. patients with CA 15-3>47.8 U/mL (13.1 months, 57.9%) (*P*=0.011) (*Table 5*).

Correlation between CRP and CA 15-3 levels

The Shapiro-Wilk test revealed a non-normal distribution; consequently, a Spearman correlation analysis was performed between CRP and CA 15-3 levels, revealing a moderate direct correlation, as shown in *Table 6*.

It is important to point out that the cutoff values obtained from the ROC analysis in this small cohort may reflect overfitting. These optimal cutoff values are likely overly optimistic and may not generalize to other populations. Therefore, these cutoff values should be validated in larger independent cohorts before being applied in clinical practice.

Discussion

Our study demonstrates that CRP and CA 15-3 levels at diagnosis are significant prognostic markers in patients with BC. Elevated CRP levels were associated with worse PFS and OS, which was consistent with previous studies linking higher CRP levels to worse outcomes in BC [1-3, 7].

Similarly, high CA 15-3 levels were associated with disease progression and decreased survival. This finding matched the results of previous studies [8-10]. CA 15-3 was used to monitor disease progression and recurrence, and our results support its utility in early risk stratification. AUC values indicate good predictive accuracy for both markers, with CRP slightly outperforming CA 15-3. This suggested that combining inflammatory and tumor-specific markers may improve prognostic assessment [9, 11-13]. Integration of CRP and CA 15-3 with traditional clinicopathological factors (tumor size, lymph node status) may improve the accuracy of prognostic models [14-18].

Furthermore, our previously published study demonstrated that serum hepcidin, CRP, and CA 15-3 levels increase with tumor stage progression, thereby confirming a link between systemic inflammation and disease progression [19]. These results highlight the potential of CRP and CA 15-3 as prognostic biomarkers at diagnosis.

Study novelty and its clinical implications

This study directly compares CRP and CA 15-3 levels measured simultaneously at diagnosis, enabling the identification of AUC-based cutoff values for early risk stratification. This approach is particularly relevant for low- and middle-income regions, offering a cost-effective and practical tool for treatment decision-making.

Conclusion

Baseline CRP and CA 15-3 levels measured at diagnosis were associated with PFS and OS in this study cohort. Their individual and combined prognostic value suggests potential utility in identifying patients with high-risk breast cancer and supporting personalized treatment strategies. However, these results require external validation in larger multicenter studies before they can be integrated into routine clinical practice, as well as the establishment of standardized cutoff values in different populations.

Implications for the Future

Based on our results, we recommend including CRP and CA 15-3 testing at breast cancer diagnosis as part of the initial prognostic assessment. Their integration into clinical protocols may improve decision-making, particularly in resource-limited settings. CRP, in particular, may be preferable due to its low cost, widespread availability, and independent association with systemic inflammation. Clinicians should consider both markers along with established histopathological factors to more accurately stratify patients. Further prospective studies involving various patient groups are needed to confirm optimal cutoff values and evaluate the feasibility of longitudinal monitoring of these markers during and after treatment.

Limitations

This is a single-center pilot study with a relatively small sample size (n=39) and a median follow-up period of 17 months, which limits the statistical power and generalizability of the results. We were unable to account for all potential confounders (e.g., BMI, active infections, chronic inflammatory diseases, and complete molecular subtype data) due to incomplete medical records. Therefore, residual confounding factors are possible. The predictive cutoff points obtained using ROC analysis are preliminary and require external validation. Finally, the observational nature of the study precludes the possibility of establishing causality.

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Ethical approval

This study was approved by the Ethics Committee of Tishreen University and Tishreen University Hospital. All participants provided written informed consent prior to their enrollment in the study.

Conflict of Interest

The authors declare no conflicts of interest.

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