

# Preoperative Serum Hypersensitive-c-Reactive-Protein (Hs-CRP) to Albumin Ratio Predicts Survival in Patients with Luminal B Subtype Breast Cancer

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**Objective:** To evaluate the clinical prognostic significance of preoperative serum hypersensitive-c-reactive-protein (Hs-CRP) to albumin ratio (CAR) in patients with luminal B subtype breast cancer.

**Methods:** A total of 199 patients with luminal B subtype breast cancer enrolled in this study were analyzed retrospectively. The optimal cutoff value of CAR was performed by the receiver operating characteristic curve (ROC). The associations between luminal B subtype breast cancer and clinicopathological variables by CAR were performed by chi-square test. Kaplan–Meier and log rank method were used for survival analysis. The independent prognostic factors were determined by univariate and multivariate Cox's proportional hazards regression model.

**Results:** The patients were divided into low CAR group (CAR<0.044) and high CAR group (CAR≥0.044) by ROC. CAR was the independent factor by univariate and multivariate analysis, and the mean DFS and OS in the low CAR group survived longer than those in the high CAR group (p<0.05). According to the endocrine therapy with aromatase inhibitors, the mean survival time of DFS and OS in the low CAR group was significantly higher than that in the high CAR group (p<0.05). Moreover, patients with pathological I+II stage survived longer than those with pathological III stage, and the mean survival time of DFS and OS in the low CAR group was significantly higher than that in the high CAR group (p<0.05). Patients without lymph vessel invasion survived longer than those with lymph vessel invasion (p<0.05), and the mean survival time of DFS and OS in low the CAR group was significantly higher than that in the high CAR group (p<0.05).

**Conclusion:** Preoperative CAR was significantly associated with survival and prognosis of breast cancer, and it can be used as a routine prognostic indicator to predict the prognosis of luminal B subtype breast cancer.

**Keywords:** hypersensitive-c-reactive-proteins, Hs-CRP, albumin, ALB, breast cancer, prognosis

## Introduction

Breast cancer is a disease with multi-gene involvement, multi-stage pathological changes and development, and long-term effects of many factors.<sup>1</sup> It is the most common malignancy in females, and the incidence and mortality rate are rising rapidly; it is also the leading cause of cancer deaths all over the world.<sup>2</sup> According to the global cancer statistics in 2020, about 19.3 million cases were diagnosed with new cancers, and 10 million cases died; breast cancer has surpassed lung cancer as the most common malignant tumor, with 2.3 million new cases and 680,000 deaths

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due to breast cancer.<sup>2</sup> According to data from cancer centers in China, there are 270,000 new cases of breast cancer and 70,000 deaths due to breast cancer; and the incidence and mortality rates in cities are higher than in the countryside.<sup>3</sup> Hormone receptor positive breast cancer is the most common type in breast cancer molecular type, accounting for about 70–75%; endocrine therapy is the main adjuvant treatment for this subtype, and can reduce the mortality by 25–30%.<sup>4</sup> Moreover, the luminal B subtype breast cancer mainly includes two types: 1) HER2 positive, ER/PR positive, Ki-67 in any condition; 2) HER2 negative, ER/PR positive, Ki-67 high or PR low expression.<sup>5</sup> Endocrine therapy usually lasts for a long time; however, these patients will appear drug resistant or experience other side effects. Tumor associated inflammatory response (TAIR) has attracted much attention in the occurrence, development and treatment of malignant tumors.<sup>6,7</sup> C-reactive protein (CRP) is an acute phase reaction protein synthesized by liver, and plays an important role in the occurrence and development of inflammatory reaction, and acts an inflammatory marker.<sup>8</sup> Nevertheless, hypersensitive-c-reactive protein (Hs-CRP) can be used to detect the low concentration of CRP by hypersensitive detection technology, and is a sensitive marker of inflammation.<sup>9</sup> Albumin (ALB) is an important indicator of the nutritional state of the body, and low concentration of ALB can destroy the immune system and inhibit the cellular immune function. Moreover, hypo-proteinemia is a reliable indicator to reflect the malignant liquid and malnutrition of malignant tumors.<sup>10</sup> Some studies have shown that the preoperative serum Hs-CRP to albumin ratio (CAR) is associated with the prognosis of tumors; however, there are few studies on breast cancer.<sup>11,12</sup> The aim of this study was to explore the predictive value and clinical significance of CAR for luminal B breast cancer, and provide some reference for the treatment of luminal B breast cancer.

## Materials and Methods

### Patients

A total of 199 patients with luminal B subtype breast cancer between January 2011 and December 2015 from Bayan Nur Hospital were enrolled into this study. All enrolled patients were diagnosed by histopathology and analyzed retrospectively. This retrospective study received approval from Institutional Review Board of Bayan Nur Hospital and was performed in accordance with the

Declaration of Helsinki. All patients signed informed consent forms. All treatments were carried out according to relevant guidelines and regulations.

### Inclusion Criteria and Exclusion Criteria

The inclusion criteria of this study were as follows: 1) patients were confirmed by histopathology, and classified as luminal B subtype breast cancer; 2) ECOG <2 scores and KPS  $\geq$ 70 scores, and can bear the risk of the treatment; and 3) patients with complete clinical, pathological, and follow-up data. The exclusion criteria of this study were as follows: 1) patients diagnosed with unresectable or metastatic breast cancer or with other malignant tumors by imaging or pathological methods; 2) patients with acute or chronic infection; 3) patients receiving anti-tumor therapy, such as chemoradiotherapy, targeted therapy, immunotherapy, and so forth; and 4) the clinicopathological and follow-up information were incomplete.

### Patients with Endocrine Therapy

Endocrine therapy is the main adjuvant treatment for hormone receptor positive breast cancer, and mainly includes:<sup>13,14</sup> 1) selective estrogen receptor modulator (SERM), such as tamoxifen and toremifene; 2) aromatase inhibitors (AIs), such as letrozole, anastrozole, and exemestane; and 3) estrogen receptor antagonist, such as fulvestrant. All enrolled patients received endocrine therapy after operation.

### Follow Up

All patients were regularly followed up after operation. And the patients were reexamined every three months in the first two years, every six months in the third to fifth years; and then every year. Disease-free survival (DFS) was defined as the time from surgery to recurrence or progression. Overall survival (OS) was defined as the time from surgery to death or last follow up.

### Statistical Analysis

All statistical analyses were performed by SPSS Statistics software 22.0 and GraphPad prism software 8.0. The optimal cutoff value of CAR was performed by the receiver operating characteristic curve (ROC). The associations between luminal B subtype breast cancer and clinicopathological variables by CAR were performed by Chi-square test. The Kaplan–Meier method and Log rank test were constructed to determine the DFS and OS, and the survival curve. The hazard ratio (HR) and 95% confidence interval

(CI) for the risk of recurrence were associated with the DFS. The independent factors were performed by univariate and multivariate Cox proportional hazard regression analyses. A two-tailed  $p < 0.05$  was considered to indicate statistical significance.

## Results

### Baseline Clinicopathologic Characteristics

One hundred and ninety-nine Luminal B subtype breast cancer patients were enrolled into this study. The optimal cutoff value of CAR was performed by ROC, and divided into: low CAR group ( $CAR < 0.044$ ) and high CAR group ( $CAR \geq 0.044$ ). All patients were females, and the mean age was 48 years, and with the range from 25 years to 72 years. The histologic type included ductal carcinoma and lobular carcinoma, respectively. The baseline clinicopathological characteristics are listed in Table 1. Comparing the two groups, there were significant differences in age ( $p < 0.001$ ), BMI ( $p < 0.001$ ), menopause ( $p < 0.001$ ), type of surgery ( $p = 0.001$ ), and tumor size ( $p = 0.001$ ), respectively (Table 1).

### Relationship Between CAR and Pathological Data in Luminal B Breast Cancer

In our study, 156 patients received total mastectomy and 43 patients received breast-conserving surgery. Comparing the two groups, there were significant differences in pathological T stage ( $p = 0.020$ ), pathological TNM stage ( $p = 0.030$ ), CK ( $p = 0.013$ ), lymph vessel invasion ( $p < 0.001$ ), and neural invasion ( $p = 0.045$ ), respectively (Table 2).

### Associations Between CAR and Inflammation or Nutritional Indexes

The blood parameters were obtained before operation. Comparing the two groups, there were significant differences in ALT ( $p < 0.001$ ), AST ( $p < 0.001$ ), CEA ( $p < 0.001$ ), and FIB ( $p = 0.003$ ), respectively (Table 3).

### Univariate and Multivariate Analysis

We analyzed the independent factors, and the univariate and multivariate analysis revealed that age, family history, menopause, CAR, CA153, neutrophil, pathological TNM stage, total lymph nodes, ER, HER2, lymph vessel invasion, post-chemotherapy were the prognostic factors for DFS (Table 4) and OS (Table 5).

## Survival and Prognosis

In this study, the mean DFS and OS were 45.68 and 71.75 months, respectively. According to the univariate and multivariate analysis, CAR was the prognostic factor on DFS ( $p = 0.005$ , HR: 2.836, 95% CI: 1.093–8.099;  $p = 0.008$ , HR: 4.346, 95% CI: 1.477–12.786, respectively) and OS ( $p = 0.002$ , HR: 2.009, 95% CI: 1.283–3.148;  $p = 0.004$ , HR: 1.874, 95% CI: 1.226–2.864, respectively). In the low CAR group, the mean DFS and OS were 49.25 and 73.91 months, respectively. In the high CAR group, the mean DFS and OS were 41.77 and 66.20 months, respectively. Compared with the high CAR group, the mean DFS and OS in the low CAR group were survival longer ( $\chi^2 = 8.788$ ,  $p = 0.003$ ;  $\chi^2 = 7.426$ ,  $p = 0.006$ , respectively) (Figure 1).

### Endocrine Therapy After Operation

In this study, all patients were receiving endocrine therapy after operation. We defined the patients who received tamoxifen and toremifene as A group (60 cases), who received letrozole, anastrozole, and exemestane as B group (101 cases), and who received fulvestrant as C group (38 cases), respectively. In A group, the mean DFS and OS were 52.67 and 74.89 months in the low CAR group, and the mean DFS and OS were 41.77 and 70.97 months in the high CAR group, respectively. Compared with the high CAR group, the mean DFS and OS in the low CAR group were survival longer, and with no significant difference ( $p > 0.05$ ). In B group, the mean DFS and OS were 52.43 and 72.30 months in the low CAR group, and the mean DFS and OS were 49.92 and 64.55 months in the high CAR group, respectively. Compared with the high CAR group, the mean DFS and OS in the low CAR group were survival longer, and with significant difference ( $p < 0.05$ ). In C group, the mean DFS and OS were 42.03 and 63.44 months in the low CAR group, and the mean DFS and OS were 16.59 and 61.82 months in the high CAR group, respectively. Compared with the high CAR group, the mean DFS and OS in the low CAR group were survival longer, and with no significant difference ( $p > 0.05$ ) (Figure 2).

### Associations Between CAR and Pathological TNM Stage

According to the univariate and multivariate analysis, pathological TNM stage was the prognostic factor on DFS ( $p = 0.037$ , HR: 4.013, 95% CI: 1.182–23.065;

**Table I** Baseline Clinicopathological Characteristics

Parameters		Low CAR<0.044	High CAR≥0.044	$\chi^2$	p-value
Cases (n)	164	104	95		
Age (years)				16.199	<0.001
<48	103	68	35		
≥48	96	36	60		
BMI				27.978	<0.001
<24.66	116	79	37		
≥24.66	83	25	58		
Family history				0.531	0.466
No	139	75	64		
Yes	60	29	31		
Menopause				14.824	<0.001
No	116	74	42		
Yes	83	30	53		
Type of surgery				10.794	0.001
Mastectomy	156	72	84		
Breast-conserving surgery	43	32	11		
Tumor size				13.638	0.001
≤2cm	100	62	38		
>2 and <5cm	84	40	44		
≥5cm	15	2	13		
Histologic type				3.142	0.076
Ductal	193	103	90		
Lobular	6	1	5		
Histologic grade				5.299	0.071
I	22	15	7		
II	121	66	55		
III	56	23	33		
Post-chemotherapy				0.565	0.452
Yes	133	72	61		
No	66	32	34		
Post-radiotherapy				2.324	0.127
Yes	152	84	68		
No	47	20	27		
Post-endocrine therapy				0.752	0.386
Yes	170	91	79		
No	29	13	16		

p=0.022, HR: 2.485, 95% CI: 1.138–5.425, respectively) and OS (p=0.006, HR: 11.698, 95% CI: 2.045–66.917; p=0.007, HR: 4.415, 95% CI: 1.510–12.909, respectively). In this study, 115 cases were diagnosed with pathological I+II stage and 84 cases were diagnosed with pathological III stage, respectively. Patients with pathological I+II stage survived longer than those with pathological III stage

(p=0.028 and p=0.019, respectively). In pathological I+II stage, patients with low CAR survived longer than those with high CAR, and with no significant difference (p=0.125 and p=0.190, respectively). In pathological III stage, patients with low CAR survived longer than those with high CAR, and with significant difference (p=0.019 and p=0.026, respectively) (Figure 3).

**Table 2** Relationship Between CAR and Pathological Data in Luminal B Breast Cancer

Parameters		Low CAR<0.044	High CAR≥0.044	$\chi^2$	p-value
Cases (n)	164	104	95		
Pathological T stage				11.690	0.020
T1	88	54	34		
T2	91	46	45		
T3	13	2	11		
T4	7	2	5		
Pathological N stage				4.653	0.325
N0	73	44	29		
N1	48	26	22		
N2	36	17	19		
N3	42	17	25		
Pathological TNM stage				7.033	0.030
I	53	35	18		
II	62	33	29		
III	84	36	48		
Total lymph nodes				3.114	0.078
<22	101	59	42		
≥22	98	45	53		
Positive lymph nodes				2.741	0.098
<5	133	75	58		
≥5	66	29	37		
ER status				0.026	0.871
Negative	12	6	6		
Positive	187	98	89		
PR status				1.188	0.276
Negative	26	11	15		
Positive	173	93	80		
HER2 status				1.820	0.177
Negative (0--++)	147	81	66		
Positive (+++)	52	23	29		
Ki-67 status				2.726	0.099
Negative (≤14%)	39	25	14		
Positive (>14%)	160	79	81		
CK status				6.150	0.013
Negative	182	100	82		
Positive	17	4	13		
E-cad status				0.661	0.416
Negative	80	39	41		
Positive	119	65	54		
EGFR status				0.443	0.506
Negative	169	90	79		
Positive	30	14	16		

(Continued)

Table 2 (Continued).

Parameters		Low CAR<0.044	High CAR≥0.044	$\chi^2$	p-value
P53 status				0.766	0.381
Negative	86	48	38		
Positive	113	56	57		
Lymph vessel invasion				12.001	<0.001
Negative	133	81	52		
Positive	66	23	43		
Neural invasion				4.008	0.045
Negative	166	92	74		
Positive	33	12	21		

## Associations Between CAR and Lymph Vessel Invasion

According to the univariate and multivariate analysis, lymph vessel invasion was the prognostic factor on DFS ( $p=0.010$ , HR: 3.860, 95% CI: 1.377–10.821;  $p=0.001$ , HR: 2.025, 95% CI: 1.311–3.127, respectively) and OS ( $p=0.003$ , HR: 5.975, 95% CI: 1.850–19.296;  $p<0.001$ , HR: 3.527, 95% CI: 2.188–5.685, respectively). In this study, 133 cases were diagnosed with lymph vessel invasion and 66 cases were diagnosed without lymph vessel invasion, respectively. Patients without lymph vessel invasion survived longer than those with lymph vessel invasion ( $p=0.0002$  and  $p<0.001$ , respectively). In patients without lymph vessel invasion, patients with low CAR survived longer than those with high CAR, and with significant difference ( $p=0.042$  and  $p=0.041$ , respectively). In patients with lymph vessel invasion, patients with low CAR survived longer than those with high CAR, and with significant difference ( $p=0.035$  and  $p=0.140$ , respectively) (Figure 4).

## Discussion

The molecular type of breast cancer by the driving gene is divided into Luminal A type, Luminal B type (HER2 negative), HER2 positive type (HR positive), HER2 negative type (HR negative), and Triple-negative type; and about 75% of breast cancers belong to the estrogen receptor positive (ER+) or progesterone receptor positive (PR+) type.<sup>15</sup> Endocrine therapy is an important part of comprehensive therapy for HR (+) breast cancer, and can reduce the risk of recurrence by about 50%. Whether to reduce or inhibit the growth dependent hormones or their receptors, endocrine therapy can inhibit the proliferation of tumor cells; the majority of HR (+) breast cancers can benefit

from this treatment.<sup>16</sup> Inflammation is closely related to tumorigenesis, affecting tumor cell proliferation, cell invasion and apoptosis, angiogenesis, and inhibiting cell-mediated immune function.<sup>17,18</sup> CRP is a sensitive indicator to reflect the inflammatory state or tissue damage. In recent years, some studies have shown that CRP has increased in varying degrees of cancer patients, releasing inflammatory factors to further aggravate the progress of tumor, and affecting the prognosis of tumor.<sup>19,20</sup> CRP is positively correlated with tumor patients' condition and recurrence degree of tumor; it can be used to determine the severity of the disease and tumor invasiveness, and to guide the treatment of breast cancer in order to improve the overall survival rate.<sup>21,22</sup> Albumin is mainly used for tissue repair and carrier protein, and to assess organism metabolism and immunity. Moreover, patients with low protein will destroy the immune system and inhibit immune function, and patients with hypoproteinemia will aggravate the occurrence of tumor cachexia, and make a worse prognosis.<sup>23,24</sup> Inflammatory biomarkers, such as fibrinogen (FIB), interleukin-6 (IL-6), carcinoembryonic antigen (CEA), neutrophils/lymphocytes ratio (NLR), and monocytes/lymphocytes (MLR), were used to study the prognosis of breast cancer.<sup>25–27</sup> CAR has been proven to be associated with prognosis in many solid tumors, such as non-small cell lung cancer, pancreatic cancer, and colorectal cancer, and was an important prognostic factor.<sup>28–30</sup> However, there are few studies on CAR in breast cancer, especially in HR (+) breast cancer. Therefore, it is of great significance to study the clinical prognosis of CAR in luminal B breast cancer.

In this study, 199 luminal B subtype breast cancer patients were enrolled and analyzed. The optimal cutoff value of CAR was 0.044 by ROC, and patients with low

**Table 3** Associations Between CAR and Inflammation or Nutritional Indexes

Parameters		Low CAR<0.044	High CAR≥0.044	$\chi^2$	p-value
Cases (n)	164	104	95		
CRP				2.763	0.096
<1.80	127	72	55		
≥1.80	72	32	40		
ALB				0.668	0.414
<44.77	94	52	42		
≥44.77	105	52	53		
ALT				17.283	<0.001
<20.00	141	87	54		
≥20.00	58	17	41		
AST				17.579	<0.001
<20.00	130	82	48		
≥20.00	69	22	47		
CEA				15.906	<0.001
<2.35	140	86	54		
≥2.35	59	18	41		
CA125				0.546	0.460
<19.67	146	74	72		
≥19.67	53	30	23		
CA153				1.049	0.306
<19.65	155	84	71		
≥19.65	44	20	24		
FIB				9.096	0.003
<2.94	106	66	40		
≥2.94	93	38	55		
Platelet (P)				1.313	0.252
<247.00	111	54	57		
≥247.00	88	50	38		
Neutrophil (N)				0.001	0.982
<3.92	107	56	51		
≥3.92	92	48	44		
Lymphocyte (L)				1.183	0.277
<1.84	103	50	53		
≥1.84	96	54	42		
Monocyte (M)				0.001	0.987
<0.39	113	59	54		
≥0.39	86	45	41		

CAR were significantly associated with baseline clinico-pathological characteristics, such as age, BMI, menopause, type of surgery, and tumor size. We also analyzed the relationship between CAR and pathological data, and the results indicated that low CAR was related to pathological T stage, pathological TNM stage, CK, lymph vessel

invasion, and neural invasion, respectively. Moreover, the results also indicated that CAR was associated with ALT, AST, CEA and FIB, respectively.

At the same moment, the Cox proportional hazard regression analyses showed that age, family history, menopause, CAR, CA153, neutrophil, pathological TNM stage, total

**Table 4** Univariate and Multivariate Analysis of Disease-Free Survival in Luminal B Breast Cancer

Parameters	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age (<48 vs ≥48 years)	4.461(1.784–11.160)	0.001	2.393(1.085–5.279)	0.031
Family history (No vs Yes)	11.264(4.078–31.115)	<0.0001	2.701(1.530–4.770)	0.001
Menopause (No vs Yes)	7.521(2.559–22.101)	<0.001	9.577(3.135–29.261)	<0.001
CAR (<0.044 vs ≥0.044)	2.836(1.093–8.099)	0.005	4.346(1.477–12.786)	0.008
CA153 (<19.65 vs ≥19.65 U/mL)	2.732(1.155–6.461)	0.022	2.619(1.278–5.369)	0.009
Neutrophil (<3.92 vs ≥3.92)	1.790(1.134–2.825)	0.012	2.025(1.274–3.217)	0.003
Pathological TNM stage (I+II vs III)	4.013(1.182–23.065)	0.037	2.485(1.138–5.425)	0.022
Total lymph nodes (<22 vs ≥22)	3.062(1.221–7.680)	0.017	3.221(1.528–6.789)	0.002
ER status (Negative vs Positive)	3.969(1.226–12.850)	0.021	4.489(1.063–8.415)	<0.0001
HER2 status (Negative vs Positive)	4.192(1.466–11.983)	0.007	1.719(1.008–2.932)	0.047
Lymph vessel invasion (Negative vs Positive)	3.860(1.377–10.821)	0.010	2.025(1.311–3.127)	0.001
Post-chemotherapy (No vs Yes)	0.273(0.103–0.724)	0.009	0.296(0.148–0.592)	0.001

**Table 5** Univariate and Multivariate Analysis of Overall Survival in Luminal B Breast Cancer

Parameters	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Age (<48 vs ≥48 years)	11.935(3.626–39.285)	<0.0001	3.965(1.557–10.098)	0.004
Family history (No vs Yes)	11.458(3.716–35.322)	<0.0001	2.560(1.450–4.523)	0.001
Menopause (No vs Yes)	3.673(1.539–8.765)	0.003	1.968(1.213–3.194)	0.006
CAR (<0.044 vs ≥0.044)	2.009(1.283–3.148)	0.002	1.874(1.226–2.864)	0.004
CA153 (<19.65 vs ≥19.65 U/mL)	2.208(1.050–4.642)	0.037	1.785(1.105–2.883)	0.018
Neutrophil (<3.92 vs ≥3.92)	3.284(1.882–12.233)	0.026	1.789(1.137–2.814)	0.012
Pathological TNM stage (I+II vs III)	11.698(2.045–66.917)	0.006	4.415(1.510–12.909)	0.007
Total lymph nodes (<22 vs ≥22)	4.069(1.482–11.172)	0.006	2.610(1.227–5.551)	0.013
ER status (Negative vs Positive)	2.931(1.437–5.978)	0.003	3.350(1.322–8.494)	0.011
HER2 status (Negative vs Positive)	3.746(1.159–12.105)	0.027	2.949(1.401–6.207)	0.004
Lymph vessel invasion (Negative vs Positive)	5.975(1.850–19.296)	0.003	3.527(2.188–5.685)	<0.0001
Post-chemotherapy (No vs Yes)	0.248(0.093–0.661)	0.005	0.234(0.111–0.496)	<0.001

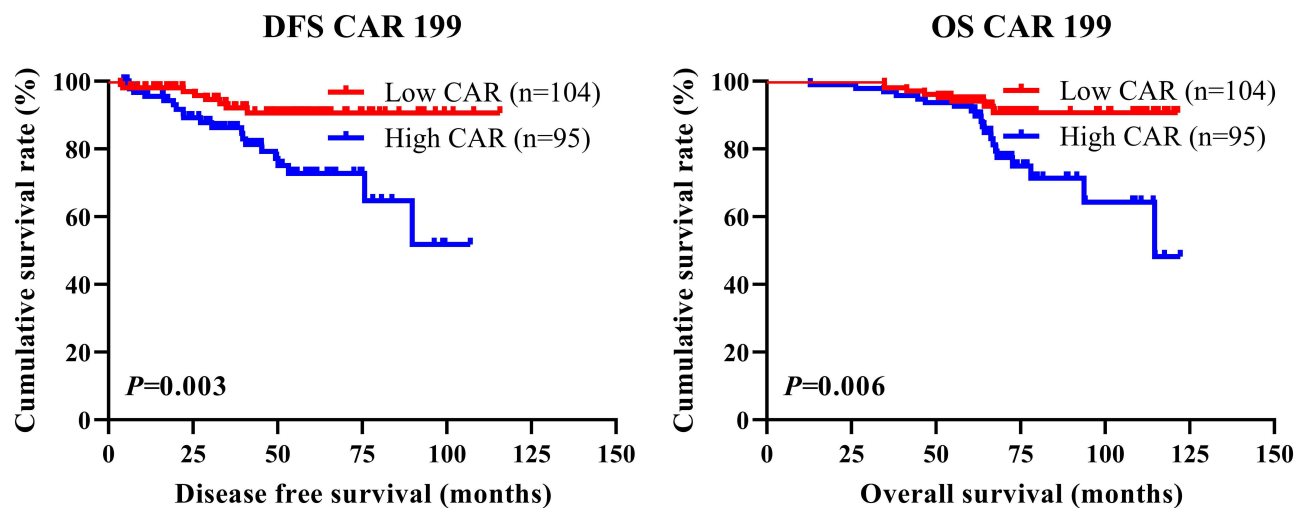
lymph nodes, ER, HER2, lymph vessel invasion, post-chemotherapy were the prognostic factors for DFS and OS with univariate and multivariate analysis. Our results indicated that CAR was the prognostic factor, and the mean DFS and OS in the low CAR group were survival longer than those with high CAR. One study by Zhou L showed that 200 patients with non-metastatic breast cancer receiving modified radical mastectomy used the CAR to predict the prognosis, and CAR was significantly associated with reduced DFS and OS, and proved that an increased CRP to albumin ratio was an independent risk factor for long-term outcome and predicted reduced DFS and OS.<sup>31</sup>

Yubo Liu's study found that patients with high CRP/Alb had poor overall survival compared to those with low CRP/Alb, and CRP/Alb was an independent prognostic factor for overall survival.<sup>32</sup>

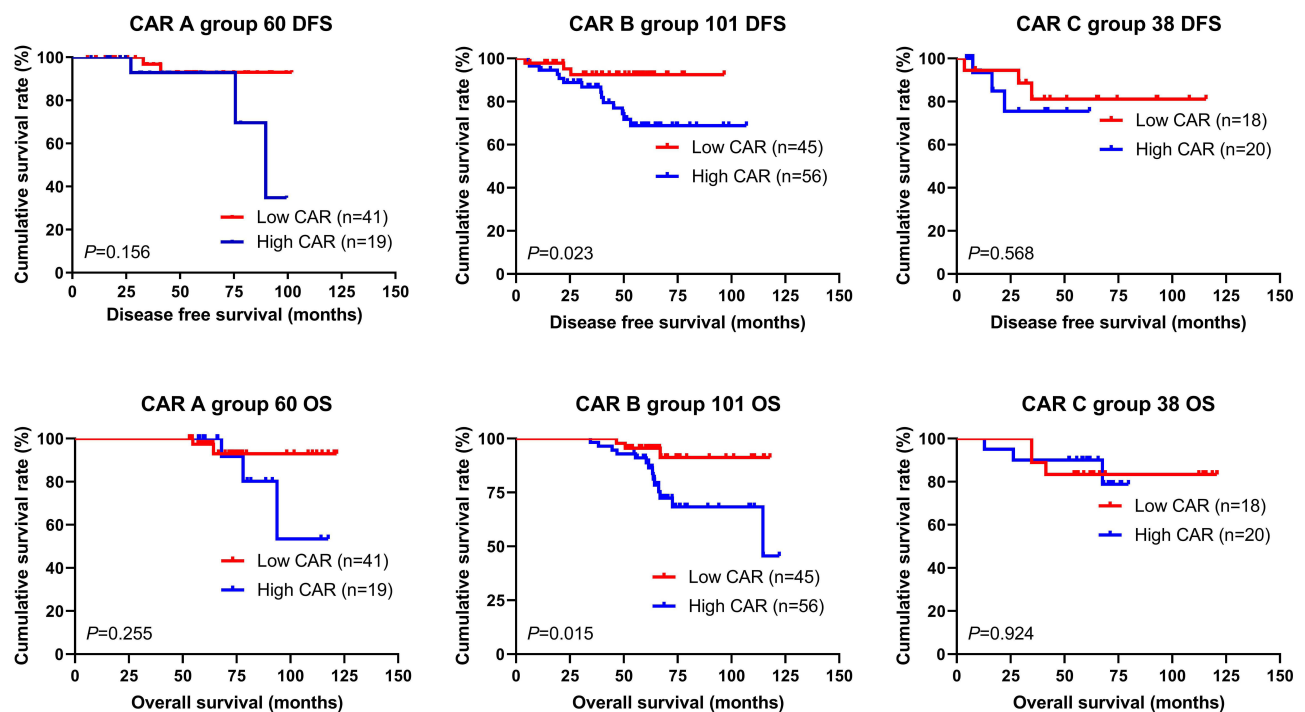
Endocrine therapy represents an important strategy in the management of hormone positive breast cancer. And this treatment was to block the effect of estrogen at the receptor level or by inhibiting estrogen production.<sup>33</sup> In our study, the results indicated that the mean DFS and OS in the low CAR group were survival longer than those in the high CAR group, and with significant difference, especially in patients receiving letrozole, anastrozole, and exemestane therapy. We also analyzed the relationship between CAR and pathological TNM stage, and the results showed that those patients with pathological I+II stage survived longer than those with pathological III stage, and patients with low CAR survived longer than those with high CAR, especially in pathological III stage.

Lymph vessel invasion (LVI) was a pathological determination and thought to lead to cancer dissemination





**Figure 1** Disease-free survival and overall survival in luminal B subtype breast cancer.

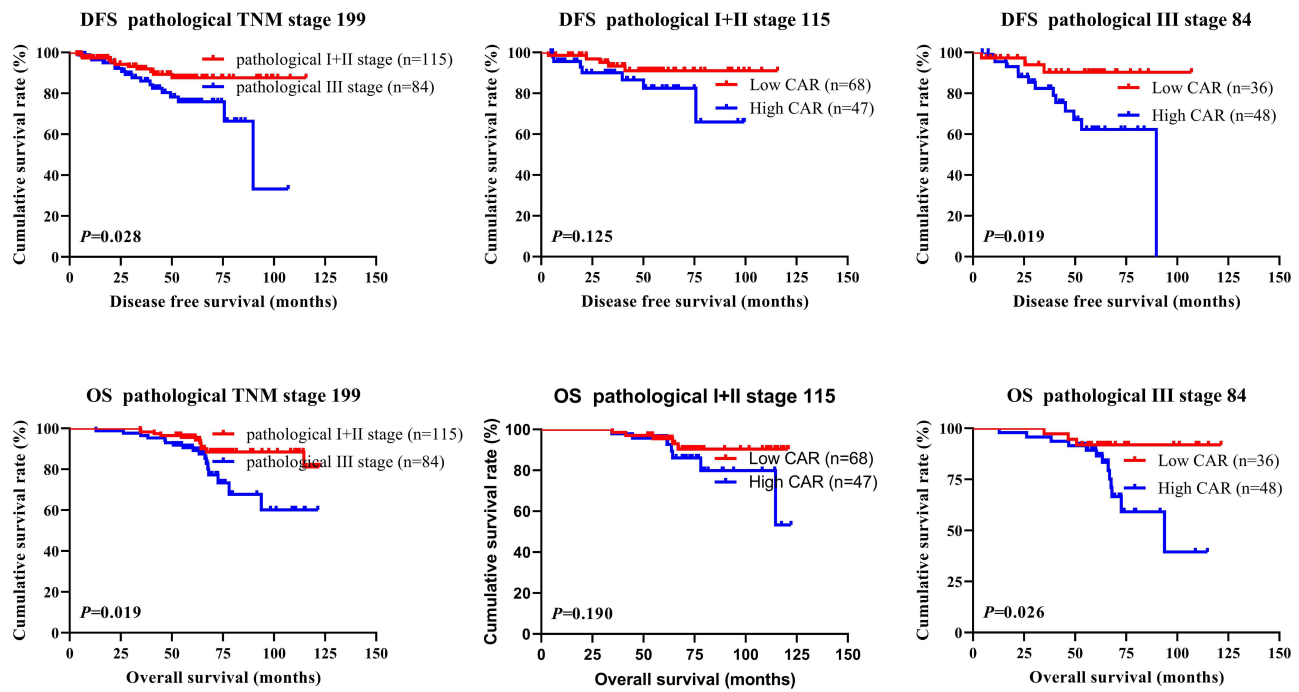


**Figure 2** Disease-free survival and overall survival by endocrine therapy in luminal B subtype breast cancer.

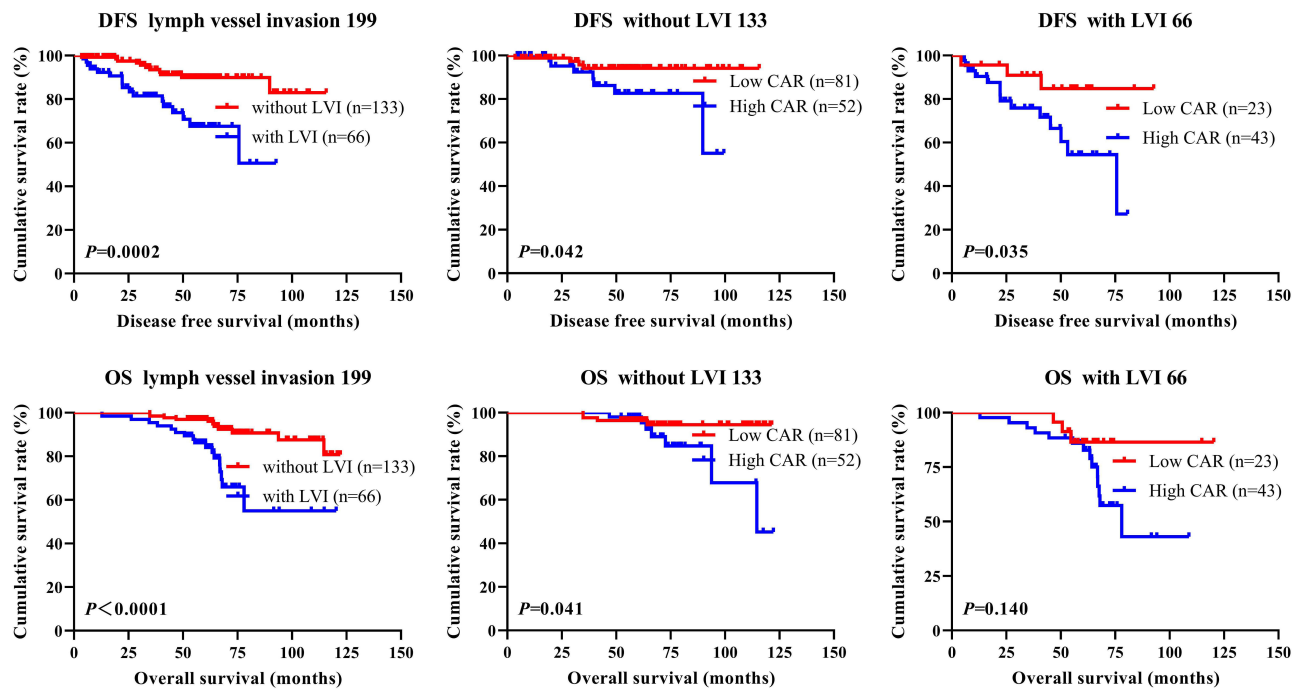
through lymphatic vessels, and was related to worse pathological features and clinical prognosis.<sup>34,35</sup> In Hamy's study, the results showed that LVI is a strong independent prognostic factor, and associated with impaired DFS.<sup>36</sup> Another study showed that LVI was strongly associated with both breast cancer-specific survival (BCSS) and distant metastasis-free survival (DMFS), provided a strong predictor of outcome in patients with invasive breast cancer and should be incorporated into

breast cancer staging systems.<sup>37</sup> Our results indicated that patients without lymph vessel invasion survived longer than those with lymph vessel invasion, and patients with low CAR survived longer than those with high CAR, especially in patients without lymph vessel invasion.

There are some potential mechanisms to explain the clinical significance of CAR in breast cancer. CRP increased the levels of vascular growth factor and interleukin to



**Figure 3** Disease-free survival and overall survival by pathological TNM stage in luminal B subtype breast cancer.



**Figure 4** Disease-free survival and overall survival by lymph vessel invasion in luminal B subtype breast cancer.

accelerate angiogenesis, and combined with integrin in inflammatory microenvironment to promote tumor cell invasion and metastasis.<sup>38,39</sup> Moreover, the increased serum CRP level may indicate the degree of tumor invasion and relate to treatment resistance and poor prognosis of breast cancer

patients.<sup>40,41</sup> Serum albumin was a common indicator of nutritional status and related to immune status, and malnutrition and hypoproteinemia were commonly found in cancer patients.<sup>42</sup> Preoperative serum albumin levels were associated with the prognosis of breast cancer, and TNF- $\alpha$

selectively inhibits ALB gene expression and reduces ALB level ultimately.<sup>43</sup> The CAR was a more comprehensive serum marker that reflected the inflammation and nutritional status of cancer patients, and identified as a novel promising prognosis marker. A meta-analysis assessed the CAR in cancer and indicated that high CAR was related to increased risk of relapse and mortality in cancer patients.<sup>44</sup> Moreover, compared with other inflammation-based prognostic scoring systems, CAR showed more effective prognostic value and more accurate differentiation ability.<sup>45</sup>

This study has several limitations. Firstly, this study was a retrospective study, and selection bias might exist. Secondly, a small number of patients were included in the study, and more patients should be enrolled into a study. Thirdly, this study included many factors that were associated with systemic inflammation and nutritional status, and further comparative studies should determine the best predictors of prognosis in patients with breast cancer. Therefore, large-scale, multicenter, and prospective studies should be conducted to further evaluate the prognostic role of CAR and determine the high-risk population of breast cancer patients.

## Conclusions

This study showed that CAR was significantly associated with survival and prognosis, and was an objective, simple, and economical biomarker that is routinely available from a routine laboratory blood test. It might be used as a routine prognostic indicator for preoperative clinical evaluation, and is helpful to improve the prognosis of patients with luminal B subtype breast cancer.

## Disclosure

The authors report no conflicts of interest in this work.

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