

Prognostic impact of the pretreatment albumin to alkaline phosphatase ratio for nonmetastatic breast cancer patients

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Zhi-Qing Long^{1,*}
Xin Hua^{1,*}
Wen-Wen Zhang¹
Shao-Wen Lv¹
Jia-Peng Deng¹
Ling Guo²
Zhen-Yu He¹
Huan-Xin Lin¹

¹Department of Radiotherapy, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, People's Republic of China; ²Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, People's Republic of China

*These authors contributed equally to this work

Introduction: Albumin and alkaline phosphatase have been previously demonstrated as independent prognostic factors for various types of cancer. Here, we aimed to explore the potential value of pretreatment albumin to alkaline phosphatase ratio (AAPR) on overall survival (OS) in nonmetastatic breast cancer patients.

Methods: A total of 746 nonmetastatic breast cancer patients were enrolled in this study. Receiver characteristic curve was used to analyze the AAPR threshold. Survival analysis was conducted using the Kaplan–Meier method and compared with the log-rank test. Both univariate and multivariate analyses were performed using Cox proportional hazards regression methodology.

Results: The optimal cutoff value of AAPR in predicting OS in nonmetastatic breast cancer patients was 0.525. Increased pretreatment AAPR level was related to age at diagnosis (≥ 60 years vs < 60 years, $P=0.000$), tumor size ($T \leq 2$ cm vs $T > 2$ cm, $P=0.034$), estrogen receptor (positive vs negative, $P=0.022$), progesterone receptor (positive vs negative, $P=0.025$), carcino-embryonic antigen (abnormal vs normal, $P=0.016$), surgery (lumpectomy vs mastectomy, $P=0.002$), chemotherapy (yes vs no, $P=0.004$), radiotherapy (yes vs no, $P=0.013$), endocrine therapy (yes vs no, $P=0.027$) but not with lymph node involvement, HER-2 status or CA-153. The 5-year OS rate was 80.16% for the low AAPR group and 92.66% for the high AAPR group. Kaplan–Meier analysis indicated that patients with low-AAPR levels had shorter OS than patients with high-AAPR levels ($P=0.001$). N classification ($P<0.05$), Ki-67 (HR=3.603, 95% CI=1.046–12.414, $P=0.042$) and AAPR (HR=0.447, 95% CI=0.205–0.976, $P=0.043$) were related to OS in multivariate analyses, respectively.

Conclusion: AAPR is an independent prognostic factor for OS in nonmetastatic breast cancer patients. Further prospective studies are required to confirm our findings.

Keywords: nonmetastatic breast cancer, prognosis, pretreatment albumin, alkaline phosphatase

Introduction

Breast cancer is one of the most malignant tumors that poses a significant threat to female health.¹ Despite a number of effective treatments including surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy, it remains the second most prevalent lethal cancer in women all over the world.² Currently, tumor size, lymph node status, and metastasis are conventionally described as prognostic factors. Furthermore, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) status are broadly applied in clinic to recognize the different molecular subtypes of breast cancer for

Correspondence: Huan-Xin Lin; Zhen-Yu He
Department of Radiotherapy, Sun Yat-sen University Cancer Center, No. 651, Dongfeng East Road, Guangzhou, Guangdong 510060, People's Republic of China
Tel +86 208 734 3543; +86 20 87343392
Fax +86 208 734 3543; +86 20 87343392
Email linhx@susucc.org.cn; hezhy@susucc.org.cn

accurate treatment. However, a simpler and more economic index to assess the clinical outcomes for early breast patients effectively is required.

Recently, inflammation and immunity are research hotspots in cancer.³ Various serum pretreatment markers have been analyzed to assess whether they offer more valuable information in diagnosis and prognosis in breast cancer. These include neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio,⁴ and pretreatment prognostic nutritional index (PNI).⁵ Serum albumin (ALB), produced by the liver, reflects body nutritional status and general physiological function by maintaining nitrogen balance, accelerating damage repair, and reducing inflammation.⁶ In addition, ALP, a hydrolase that participates in epithelial–mesenchymal transition (EMT)⁷ and ERK1/2 dephosphorylation and other bioprocesses,⁸ has been confirmed to be elevated and related to poor prognosis in multiple cancers, such as gastric cancer and prostate cancer.^{9,10}

The AAPR is defined as the serum ALB level divided by the serum ALP level. The AAPR was first used as a prognostic index for hepatocellular carcinoma in 2015.¹¹ In addition, AAPR has been trialled as a novel prognostic factor of OS for metastatic nasopharyngeal carcinoma and pancreatic ductal adenocarcinoma.^{12,13} However, the prognostic capability of the pretreatment AAPR value for early breast cancer patients still remains unknown. Thus, we examined the role of the AAPR for nonmetastatic breast cancer patients undergoing surgery and its relation with other clinical features.

Methods

Patients selection

We retrospectively reviewed female breast cancer patients who received surgical treatment in Sun Yat-Sen University Cancer Center (Guangzhou, People's Republic of China) from November 2011 to February 2013. The exclusion criteria were: 1) incomplete baseline data; 2) no surgery; 3) metastatic breast cancer patients; 4) synchronous malignancies; 5) ductal carcinoma in situ. All subjects enrolled provided their written informed consent and the clinic ethics committee approval was obtained from Sun Yat-sen University Cancer Center (Guangzhou, People's Republic of China). This study was conducted in accordance with the Declaration of Helsinki.

Data collection

All patient information was intensively reviewed and obtained from the hospital database. The overall survival

(OS) time was defined as the period from surgery to death or to the last follow-up date. Pathological staging was assessed using the TNM staging system of the AJCC 7th edition via both postoperative histopathological inspection and clinical assessment. According to pathological reports, we identified ER and PR positive if there were at least 1% positive heterologous tumor cell nuclei in the sample evaluated by immunohistochemistry (IHC). HER-2 status was assessed using a semiquantitative score (0–3+). Patients with 2+ IHC staining for HER2 underwent fluorescence in-situ hybridization (Fish) to confirm HER2 positivity or negativity. AAPR was calculated as follows: $AAPR = \text{pretreatment serum albumin level (g/L)} / \text{alkaline phosphatase level (U/L)}$.

Statistical analysis

The optimal cutoff value of the AAPR was determined by the receiver operating characteristic (ROC) curve analysis of OS for early breast cancer patients. Baseline characteristics were compared using Fisher's exact test or Chi-squared test. The Kaplan–Meier method was used for survival analyses and compared using the log-rank test. Univariate and multivariate analyses (Cox proportional hazards regression model) were conducted to assess the effect of potential confounding factors on OS. $P < 0.05$ was considered statistically significant. All statistical analyses were processed using Graphpad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA) and SPSS version 23.0 (SPSS, Inc., Chicago, IL) in this study.

Results

Patient clinic characteristics

We incorporated a total of 746 consecutive patients with surgery and histopathologically diagnosed early breast cancer in SYSUCC. The baseline characteristics of the patients are shown in Table 1. Pathological T stage was 301, 368, 39, 38 patients for T1, T2, T3 and T4 stage patients, respectively. There are 569 (76.3%) patients having invasive ductal carcinoma. Among 746 patients, there are 199 (26.7%) patients in stage I, 364 (48.8%) patients in stage II, 183 (24.5%) patients in stage III. ER status varied from positive ($n=522$, 70.0%), negative ($n=203$, 27.2%) to unknown ($n=21$, 2.8%). About 468 (62.7%) of all enrollees are positive for PR status. According to the ROC results, patients were divided into a AAPR-low group ($AAPR < 0.525$, $n=125$, 16.8%) and a AAPR-high group ($AAPR \geq 0.525$, $n=621$, 83.2%).

Table 1 Basic characteristics of the enrolled patients

Characteristic	Group	N (%)
Age	≥60	127 (17.0)
	<60	619 (83.0)
Histopathological type	Invasive ductal carcinoma	569 (76.3)
	Others	177 (23.7)
T Classification	T1	301 (40.3)
	T2	368 (49.3)
	T3	39 (5.2)
	T4	38 (5.1)
N Classification	N0	407 (54.6)
	N1	182 (24.4)
	N2	86 (11.5)
	N3	71 (9.5)
Clinical stage	I	199 (26.7)
	II	364 (48.8)
	III	183 (24.5)
Histological grade	G1	20 (2.7)
	G2	480 (64.3)
	G3	146 (19.6)
	Unknown	100 (13.4)
Estrogen receptor	Positive	522 (70.0)
	Negative	203 (27.2)
	Unknown	21 (2.8)
Progesterone receptor	Positive	468 (62.7)
	Negative	256 (34.8)
	Unknown	22 (2.9)
Human epidermal growth factor receptor type 2 (HER-2)	Positive	219 (29.4)
	Negative	421 (56.4)
	Unknown	106 (14.2)
CEA	Normal	646 (86.6)
	Abnormal	67 (9.0)
	Unknown	33 (4.4)
CA-153	Normal	630 (84.5)
	Abnormal	81 (10.9)
	Unknown	35 (4.7)
Ki-67	≥14	463 (62.1)
	<14	243 (32.6)
	Unknown	40 (5.4)
Surgery	Mastectomy	570 (76.4)
	Lumpectomy	176 (23.6)
Chemotherapy	Yes	589 (79.0)
	No	157 (21.0)
Radiotherapy	Yes	212 (28.4)
	No	534 (71.6)
Endocrine therapy	Yes	384 (51.5)
	No	362 (48.5)
AAPR	<0.525	125 (16.8)
	≥0.525	621 (83.2)

Note: Clinical stage was according to the 7th edition of the American Joint Commission on Cancer staging system.

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor type 2; CEA, carcino-embryonic antigen; CA15-3, cancer antigen 15-3; AAPR, pretreatment albumin to alkaline phosphatase ratio.

Relationship between AAPR and patient characteristics

The clinicopathological features for each group are shown in Table 2.

Prognostic value of AAPR for OS

The 5-year OS rate was 80.16% and 92.66% for the low and high AAPR groups, respectively. The Kaplan–Meier curve showed that patients in the low-AAPR group had poorer OS survival rate than those in the high-AAPR group ($P=0.001$) (Figure 1).

In our study, based on univariate analysis, T classification, N classification, Ki-67, AAPR, ER, PR and HER-2 were important predictors of OS (all $P<0.05$). An AAPR<0.525 was statistically associated with inferior survival (HR=0.363; 95% CI=0.191–0.689; $P=0.001$). Neither the age nor the histopathological grade demonstrated any prognostic impact. In the Cox multivariate analysis model, the AAPR (HR=0.447, 95% CI=0.205–0.976, $P=0.043$) proved to be an independent prognostic factor of OS. Meanwhile, N classification and Ki-67 were independent prognostic factors (all $P<0.05$) (Table 3).

Discussion

In our study, we demonstrated that the AAPR was significantly related to the risk index of nonmetastatic breast cancer, including age, tumor size, ER, PR and carcino-embryonic antigen (CEA). The OS rate of the high AAPR group was significantly higher than that of the low AAPR group. Our findings were in accordance with previous studies of other type of cancers.^{11,12,14} The multivariate Cox proportional hazards regression model confirmed that the elevated pre-treatment serum level of AAPR can independently predict OS for early breast cancer patients. To our knowledge, this is the first time that AAPR has been reported as an independent predictor of OS for breast cancer patients.

Tumor-related immune responses and nutritional assumption are associated with tumor development and progression.¹⁵ First, tumor growth, invasion and metastasis all require nutrition and the induction of an immunological response. Tumor cells can consume nutrients leading to cachexia. Then, to resist and kill cancer cells, the body may expend more nutrients and produce numerous inflammatory cytokines, such as tumor necrosis factor- α and vascular endothelial growth factor.^{16,17} The types of

Table 2 Association between AAPR and clinicopathological factors in patients with nonmetastatic breast cancer

Variable	Total	AAPR value		P
		Low	High	
Age (year)				
<60	127	45	82	0.000
≥60	619	80	539	
Tumor size				
T≤2 cm	302	41	261	0.034
T>2 cm	444	84	360	
N				
Positive	339	59	280	0.369
Negative	407	66	341	
ER				
Positive	522	76	446	0.022
Negative	203	43	160	
PR				
Positive	468	67	401	0.025
Negative	256	52	204	
HER-2				
Positive	219	41	178	0.117
Negative	421	62	359	
CEA				
Abnormal	67	18	49	0.016
Normal	646	99	547	
CA-153				
Abnormal	81	17	64	0.156
Normal	630	100	530	
Surgery				
Lumpectomy	176	17	159	0.002
Mastectomy	570	108	462	
Chemotherapy				
Yes	589	87	502	0.004
No	157	38	119	
Radiotherapy				
Yes	212	25	187	0.013
No	534	100	434	
Endocrine therapy				
Yes	384	54	330	0.027
No	362	71	291	

Note: Significant *P*-values are shown in bold.

Abbreviation: AAPR, pretreatment albumin to alkalinephosphatase ratio.

nutritional and inflammatory parameters have been reported to predict prognosis in breast cancer, including the pretreatment NLR, platelet to lymphocyte ratio,¹⁸ and PNI. Albumin and alkaline phosphatase are more direct

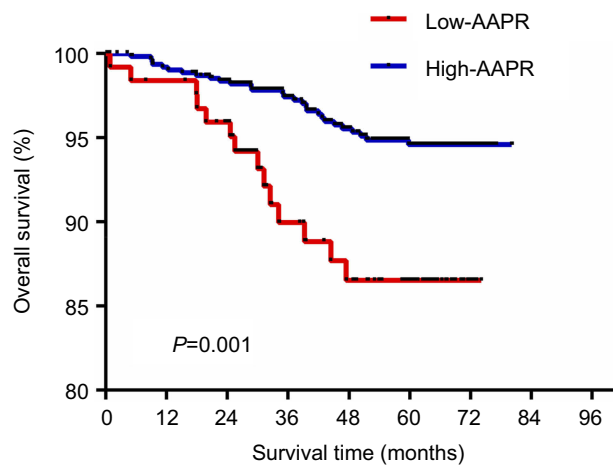


Figure 1 Overall survival based on the AAPR cutoff point of 0.525 in nonmetastatic breast cancer patients.

serum biochemical factors that reflect nutritional status of patients. Some abnormal conditions can affect the level of serum albumin, such as alcohol abuse, trauma, liver disease and hypermetabolism.¹⁹ Hypoalbuminemia may suppress immune responses, affecting both granuloma formation and macrophage activation. Consequently, some studies have demonstrated that a pretreatment ALB decrease is associated with poor outcome in several cancers due to malnutrition and an imbalanced tumor micro-environment, including renal cell carcinoma and colorectal cancer.^{20,21} The level of ALP may be associated with bile duct obstruction, bone disease, hepatitis and malnutrition. Jaundice typically appears when ALP increases. According to previous studies, evaluation of ALP might manifest as a heavy tumor burden and thus relate to a poorer prognosis in esophageal carcinoma, colorectal cancer, and nasopharyngeal carcinoma.^{22–24}

AAPR, obtained from the combination of albumin and alkaline phosphatase, may reflect nutritional state, and inflammatory and immune responses in cancer patients. Due to cancer development and progression, the body assumes an abnormal physiological status, such as nutritional decline and inflammatory activation, thus ultimately resulting in poor survival. Nei et al reported that AAPR may serve as a novel prognostic factor of OS for patients with metastatic nasopharyngeal carcinoma and consequently received cisplatin-based chemotherapy.¹² Besides, a prior study indicated that AAPR was a useful prognostic factor for advanced HCC patients treated with non-standard anti-cancer regimens.¹⁴ It should be noted that the optimal cutoff values of the AAPR are not the same for different cancers.

Table 3 Survival analyses of clinicopathological factors and AAPR

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.412 (0.676–2.951)	0.359	—	—
T Classification				
T1	I (reference)		I (reference)	
T2	2.741 (1.241–6.053)	0.013	2.152 (0.789–5.868)	0.134
T3	4.415 (1.329–14.665)	0.015	2.397 (0.533–10.775)	0.254
T4	4.617 (1.390–15.338)	0.013	1.715 (0.296–9.918)	0.547
N Classification				
N0	I (reference)		I (reference)	
N1	3.207 (1.290–7.974)	0.012	2.290 (0.785–6.683)	0.130
N2	6.019 (2.231–15.607)	0.000	4.405 (1.442–13.453)	0.009
N3	11.742 (4.924–28.003)	0.000	7.780 (2.670–22.670)	0.000
Ki-67	3.712 (1.452–9.492)	0.006	3.603 (1.046–12.414)	0.042
AAPR	0.363 (0.191–0.689)	0.001	0.447 (0.205–0.976)	0.043
ER	0.478 (0.255–0.896)	0.021	0.621 (0.194–1.992)	0.423
PR	0.467 (0.251–0.869)	0.016	1.149 (0.365–3.614)	0.831
HER-2	2.481 (1.261–4.883)	0.009	1.286 (0.580–2.851)	0.536
Histological grade	0.757 (0.334–1.714)	0.504	0.604 (0.254–1.438)	0.255
CEA	2.165 (0.960–4.885)	0.063	0.615 (0.201–1.881)	0.394
Surgery	6.135 (1.526–26.128)	0.011	—	—
Chemotherapy	1.362 (0.573–3.235)	0.484	—	—
Radiotherapy	1.272 (0.677–2.392)	0.455	—	—
Endocrine therapy	0.361 (0.190–0.688)	0.002	—	—

Note: Significant *P*-values are shown in bold.

Abbreviation: AAPR, pretreatment albumin to alkalinephosphatase ratio.

In our study, we initially investigated the relationship between AAPR and other clinical factors in nonmetastatic breast cancer patients and found that age, tumor size, ER, PR and CEA were related. A low-AAPR level was associated with poor OS in early breast cancer patients. A low-AAPR level may reflect the decline in both immunological function and anti-cancer ability. Furthermore, we first considered that pretreatment AAPR may independently and effectively predict OS in early breast cancer patients. As a low-cost, simple, accessible and non-invasive index, the AAPR could provide more information for clinicians and how best to treat. For example, low-AAPR value is associated with a poorer outcome in early breast cancer patients, therefore patients need to adequately increase their nutritional intake and receive proportionately more anti-inflammatory therapy according to clinical guidance. Immunotherapeutic drugs such as PD-1 inhibitors could provide a good therapeutic response in these patients.²⁵ Furthermore, those patients with low-AAPR status should have their cancer status and physical condition reviewed more carefully compared with the high-AAPR group.

The limitations of our study is that it is a retrospective analysis of a single-center design, leading to selection bias and a relatively small sample size. In addition, we focused on the pretreatment serum index but failed to analyze the dynamic changes in the AAPR value during the whole process. Finally, biological mechanisms between AAPR and inflammation remain unclear. Therefore, further large-scale prospective clinical trials and basic research studies are required to elucidate the molecular mechanisms of a low-AAPR value and poorer prognosis in patients with breast cancer.

In summary, we confirmed that the AAPR was related to OS of early breast cancer patients treated with surgery. A low-AAPR predicted poorer prognosis compared to the high-AAPR group. The AAPR was considered as an independent risk parameter in patients with nonmetastatic breast cancer. We provide more information for clinicians to determine treatment regimens through an easily accessible parameter of AAPR.

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Disclosure

The authors report no conflicts of interest in this work.

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