Breast Cancer: Targets and Therapy

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ORIGINAL RESEARCH

The Prognostic Value of Serum Albumin to Globulin Ratio in Patients with Breast Cancer: A Retrospective Study

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Objective: This study examined the potential risk value of the serum albumin to globulin ratio (AGR) in patients with breast cancer (BC).

Methods: This study employed a retrospective design, enrolling 332 patients with BC and 38 patients without BC treated at Taizhou People's Hospital between September 2015 and May 2021. Multivariate Cox proportional hazard regression models were used to identify potential risk factors. A prognostic nomogram was developed based on the multivariate analyses. The receiver operating characteristic curve determined the optimal cutoff value for AGR.

Results: The results indicated a statistically significant decrease in AGR among patients with BC. Significant disparities were observed in globulin and AGR levels between the two cohorts. AGR was significantly associated with tumor size and stage, with a marked decline in advanced stages of BC. Additionally, AGR and aspartate transaminase/Alanine aminotransferase (AST/ALT) emerged as significant diagnostic indicators for invasive carcinoma and advanced stages (II–IV) of BC. Specifically, AGR exhibited an area under the curve of 0.645 ($P < 0.003$), highlighting the discriminatory capacity of serum globulin levels in distinguishing between BC and non-BC cohorts.

Conclusions: The AGR, routinely assessed due to its simplicity, objectivity, and cost-effectiveness, holds promise as a potential risk factor for BC and may have practical implications in clinical settings.

Keywords: albumin to globulin ratio, risk factor, breast cancer, retrospective study

Introduction

Breast cancer (BC) is the leading cause of death among women, with an estimated 43,700 deaths in the United States in 2023.[1] BC classification depends on molecular typing, resulting in subtypes such as Lumina A, Lumina B, Her2-positive (Her2, human epidermal growth factor receptor 2-positive), and triple-negative BC.[2] The diverse treatment approaches and prognoses for these subtypes have been widely recognized.

Survival rates of patients with cancer are influenced by various biological factors. Notably, gamma globulin levels are significantly correlated with the recurrence of nonmuscle-invasive bladder cancer.[3] Low pretreatment serum globulin levels may indicate a favorable prognosis in patients with gastric cancer.[4] Additionally, the albumin-to-globulin ratio (AGR) has been linked to an unfavorable prognosis in surgically treated patients with invasive cervical cancer.[5] AGR is also an independent prognostic factor for overall survival (OS) in patients with metastatic gastric cancer.[6] In patients with cervical cancer undergoing radiotherapy, a low AGR may predict a poor prognosis.[7] Previous studies have also indicated elevated plasma levels of D-dimer and fibrinogen in patients with BC.[8]

Peripheral blood biomarkers are widely recognized as convenient predictors of cancer. Serum tumor markers have gained unanimous approval from researchers for their diagnostic significance in BC. Among these markers, carbohydrate antigen 153

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(CA153) is considered a leading indicator for BC despite its limited sensitivity and specificity. The detection of carbohydrate antigen 125 (CA125) is highly sensitive and specific for bone metastasis in BC.[9] Serum levels of CA125 and CA199 can be used to evaluate the impact of neoadjuvant chemotherapy on patients with BC.[10] Preoperative levels of CA153 and CEA vary among different molecular subtypes of BC and are associated with prognosis.[11] Ki67 has long been favored as a biomarker for assessing tumor proliferation, especially in BC.[12] In addition, the combination of pretreatment plasma HSP90AA1 with other markers provides a convenient method for predicting the risk of BC development and metastasis.[13] Cathepsin D was proposed as a tumor marker in human BC many years ago.[14] Potentially harmful mutations in the BC susceptibility genes 1 and 2 (BRCA1/2) are associated with an increased risk of BC.[15] The risk of BC is 57% for BRCA1 mutation carriers and 49% for BRCA2 mutation carriers.[16] Mutations in the BRCA1/2 genes are frequently observed in BC, particularly in triple-negative BC.[17] BCs with BRCA1 mutations typically exhibit high-grade characteristics and unfavorable prognoses.[18] Triple-negative BC often includes subpopulations with BRCA1/2 mutations, which are hypothesized to be particularly sensitive to platinum-based therapies.[19] The consideration of albumin and globulin as noninvasive prognostic factors for BC has garnered significant attention. Elevated urinary albumin excretion has been noted in patients with BC.[20] Additionally, the fibrinogen-to-albumin ratio has been identified as a potential prognostic factor for both BC[21] and triple-negative patients with BC.[22] The low fibrinogen-to-albumin ratio group demonstrated longer median disease-free survival and OS compared to the high ratio group.[22] However, another study concluded that albumin is not a reliable indicator for predicting disease aggressiveness or recurrence in BC.[23] Prognostic and treatment-predictive factors in BC can effectively forecast clinical outcomes and aid in treatment decision-making.[24]

Additionally, the AGR has been identified as an independent and significant predictor of long-term mortality in patients with BC.[25] However, research into AGR as a risk factor in BC patients has been limited. Consequently, the objective of our study was to examine the significance of AGR in patients diagnosed with BC and other non-BC conditions. We also constructed predictive nomogram models to evaluate the likelihood of BC, invasive carcinoma, and advanced stages of BC. The receiver operating characteristic (ROC) curve was used to determine the optimal cutoff value for AGR.

Materials and Methods

Ethics Approval and Informed Consent

The study design was approved by the Ethics Committee of Jiangsu Taizhou People's Hospital, and written informed consent was obtained from all participants. This study adhered to the principles outlined in the Declaration of Helsinki and its subsequent amendments, along with other similar ethical standards.

Study Population

A total of 332 patients diagnosed with BC and 38 patients without BC were treated at Taizhou People's Hospital between September 2015 and May 2021. All patients underwent histological confirmation of their diagnoses. Clinicopathologic characteristics and detailed treatment information were obtained from the patients' medical records. The inclusion criteria for patient selection were as follows: (1) confirmation of BC or non-BC through pathology; (2) availability of complete medical records; (3) blood samples obtained before the initiation of treatment. The exclusion criteria were as follows: (1) individuals with synchronous or metachronous tumors; (2) those diagnosed with acute or chronic inflammatory diseases; (3) patients undergoing antitumor therapy; (4) individuals administered anti-inflammatory medications. The Tumor Node Metastasis (TNM) stage classification was determined based on the eighth edition of the American Joint Committee on Cancer.[26]

Peripheral Venous Blood Parameters

Peripheral venous blood samples were obtained before treatment. The AGR was calculated using the pretreatment counts of peripheral albumin and globulin.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 27.0; IBM Corp., Armonk, NY, USA). Chi-square or Fisher's exact test was used to evaluate clinicopathologic categorical variables. Multivariate Cox proportional hazards regression models were employed to identify independent prognostic factors.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to assess the recurrence risk associated with AGR. A prognostic nomogram was developed from these multivariate analyses. ROC curve was employed to identify the optimal AGR cutoff. Predictive accuracy was assessed via calibration curves. A $P < 0.05$ indicated a statistically significant difference.

Results

Patient Clinicopathologic Characteristics

Table 1 presents the demographic and clinicopathologic characteristics of a cohort of 332 pathologically-diagnosed female patients with BC. The median age was 54 years, ranging from 26 to 90 years.

AGR Expression Was Significantly Lower in BC

No significant differences were observed in total protein and albumin levels between the BC and non-BC cohorts. However, patients with BC exhibited significantly higher globulin levels compared to patients without BC (30.77 ± 4.35 vs 29.01 ± 2.76, P = 0.001). Additionally, AGR expression was significantly lower in patients with BC (1.43 ± 0.21 vs 1.53 ± 0.19, P = 0.005).

Table 1 Demographic and Clinicopathologic Characteristics in Breast Cancer

Clinical Information	No.	%	Total Protein	Albumin	Globulin	AGR
Age (years)						
< 50	118	35.54				
≥ 60	214	64.46				
T			0.101	**0.006**	0.897	0.181
T1	132	39.76				
T2-3	187	56.33				
Lymph node			**0.024**	0.708	**0.001**	**0.004**
Negative	189	56.93				
Positive	123	37.05				
TNM			0.371	0.541	**0.045**	**0.012**
Tis-I	117	35.24				
II–IV	193	58.13				
Ki67			0.311	0.905	0.145	0.222
≤ 30	117	35.24				
> 30	211	63.55				
ER			0.845	0.303	0.522	0.15
Negative	176	53.01				
Positive	153	46.08				
PR			0.99	0.925	0.959	0.918
Negative	193	58.13				
Positive	137	41.27				
Her2			0.83	0.917	0.778	0.882
Negative	172	51.81				
Positive	155	46.69				
Pathological typing			0.821	0.152	0.091	**0.006**
In situ carcinoma	26	7.83				
Invasive carcinoma	306	92.17				
Molecular subtyping			0.649	0.46	0.981	0.503
Triple-negative	100	30.12				
Other	182	54.82				

Note: Bold values indicate P < 0.05.

Abbreviations: AGR, albumin to globulin ratio; T1, tumor diameter ≤ 2 cm; T2-3 tumor diameter > 2 cm; ER, estrogen receptor; PR, progesterone receptor; Her2, human epidermal growth factor receptor 2.

The Correlations Between AGR and Pathological Data in BC

At diagnosis, the pathological TNM stage indicated that 117 (35.24%) patients with BC were at stages Tis+ I, and 193 (58.13%) were at stages II–IV. Notably, significant differences in globulin levels and AGR expression between these two groups were observed (P = 0.045 and 0.012, respectively; Table 2).

The Liver Metabolic Changes Have Close Associations with Clinic Parameters

A correlation analysis was conducted to explore potential associations between liver metabolic parameters and variables such as age, tumor stage, and hormone-receptor expression (Table 3). This analysis revealed intriguing negative associations of liver metabolic parameters—including total protein, albumin, and AGR—with age. Furthermore, total

Table 2 Mean Difference in Liver Metabolic Parameters of Patients with Breast Cancer and the Control Group

		Cancer (332)	Non-Cancer (38)	P-value
Total protein	Mean ± SD	74.04 ± 6.69	73.04 ± 4.17	0.201
	Median	74.45	73.55	
	IR	8.9	6.65	
Albumin	Mean ± SD	43.27 ± 4.06	44.04 ± 3.20	0.26
	Median	43.85	44.15	
	IR	5.78	5.5	
Globulin	Mean ± SD	30.77 ± 4.35	29.01 ± 2.76	**0.001**
	Median	30.6	28.4	
	IR	5.75	4	
Albumin to globulin ratio	Mean ± SD	1.43 ± 0.21	1.53 ± 0.19	**0.005**
	Median	1.4	1.5	
	IR	0.3	0.3	

Note: Bold values indicate P < 0.05.
Abbreviations: SD, standard deviations; IR, interquartile range.

Table 3 Correlation Between Liver Metabolic Parameters and Clinic Features of Breast Cancer Patients

		Total Protein	Albumin	Globulin	Albumin to Globulin Ratio
Age	R	–0.132	–0.261	0.04	–0.183
	P	**0.016**	**0.001**	0.471	**0.001**
T	R	0.114	0.003	0.176	–0.174
	P	**0.042**	0.957	**0.002**	**0.002**
N	R	0.001	–0.034	0.033	–0.066
	P	0.988	0.55	0.559	0.249
TNM	R	0.022	–0.088	0.119	–0.184
	P	0.697	0.123	**0.035**	**0.001**
Ki67	R	0.054	0.02	0.063	–0.045
	P	0.333	0.714	0.253	0.42
ER	R	0.012	0.053	–0.029	0.067
	P	0.823	0.342	0.603	0.225
PR	R	–0.019	0.0001	–0.027	0.029
	P	0.737	1	0.624	0.6
Her2	R	0.064	0.041	0.06	–0.036
	P	0.247	0.462	0.279	0.52

Note: Bold values indicate P < 0.05.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; Her2, human epidermal growth factor receptor 2.

protein and globulin revealed positive correlations with tumor size. AGR exhibited significant correlations with tumor size and stage, with notably reduced levels in advanced stages of BC.

Multivariate Cox Regression Survival Analyses

Multivariate Cox regression survival analyses identified total protein and globulin as significant diagnostic factors for BC (Table 4). Additionally, AGR and AST/ALT were significant diagnostic indicators for invasive carcinoma (Table 5). Similarly, AGR and AST/ALT were significant diagnostic factors for advanced stages (II–IV) of BC (Table 6).

Table 4 Multivariate Analyses of Factors Associated with Breast Cancer

Variables	HR (95% CI)	P-value
Total bilirubin	0.956 (0.864, 1.058)	0.382
Direct bilirubin	1.128 (0.656, 1.939)	0.663
Total protein	0.713 (0.508, 1)	**0.0499**
Globulin	2.29 (1.019, 5.142)	**0.045**
AGR	1332.409 (0.171, 1.04E+07)	0.116
ALT	0.958 (0.895, 1.025)	0.211
AST	1.058 (0.968, 1.157)	0.211
AST to ALT ratio	0.792 (0.292, 2.15)	0.648
Gamma-glutamyl transferase	1.004 (0.984, 1.025)	0.666

Note: Bold values indicate P < 0.05.
Abbreviations: AGR, albumin to globulin ratio; ALT, alanine transaminase; AST, aspartate aminotransferase; HR, hazard ratio.

Table 5 Multivariate Analyses of Factors Associated with Invasive Carcinoma

Variables	HR (95% CI)	P-value
Total protein	0.971 (0.905, 1.043)	0.426
AGR	0.046 (0.006, 0.356)	**0.003**
AST	1.014 (0.955, 1.077)	0.651
AST to ALT ratio	0.454 (0.225, 0.919)	**0.028**
Gamma-glutamyl transferase	1.006 (0.972, 1.040)	0.738

Note: Bold values indicate P < 0.05.
Abbreviations: AGR, albumin to globulin ratio; ALT, alanine transaminase; AST, aspartate aminotransferase; HR, hazard ratio.

Table 6 Multivariate Analyses of Factors Associated with Later-Stage Breast Cancer

Variables	HR (95% CI)	P-value
Total bilirubin	0.974 (0.904, 1.049)	0.482
Direct bilirubin	1.190 (0.847, 1.672)	0.316
Total protein	0.993 (0.955, 1.033)	0.722
AGR	0.210 (0.060, 0.727)	**0.014**
AST	1.027 (0.997, 1.058)	0.082
AST to ALT ratio	0.531 (0.324, 0.869)	**0.012**
Gamma-glutamyl transferase	0.996 (0.988, 1.004)	0.307

Note: Bold values indicate P < 0.05.
Abbreviations: AGR, albumin to globulin ratio; ALT, alanine transaminase; AST, aspartate aminotransferase; HR, hazard ratio.

Establishment of the Nomogram

Using a multivariate Cox proportional hazards model, a novel nomogram was developed for diagnosing BC, invasive carcinoma, and advanced-stage BC (Figure 1). The analysis revealed that higher patient grades were significantly associated with an increased likelihood of diagnosing BC, invasive carcinoma, and advanced-stage BC.

ROC Analysis

The ROC curve was used to evaluate the performance of serum globulin levels in distinguishing between BC and non-BC groups (Figure 2). The AUC for globulin was 0.637 (95% P < 0.006), with sensitivity and specificity of 63% and 68.4%, respectively, at a cutoff value of 29.45 g/L (Figure 2A). Figure 2B depicts the ROC curve for the AGR, which had an AUC of 0.645 (95% P < 0.003). The AGR exhibited a sensitivity and specificity of 84.2% and 39.2%, respectively, at a cutoff value of 1.35.

Discussion

Prompt and accurate detection of BC in its early stages is crucial for reducing mortality rates. Hepatic metabolism significantly influences the development and progression of tumors. Therefore, we investigated liver metabolism indicators in patients with BC.

Total protein and albumin are important indicators for assessing an individual's nutritional status and disease severity. In our research, total protein proved to be a significant diagnostic factor for BC. Both total protein and albumin can help identify cancer cachexia and cancer-related malnutrition, with patients with cachexia depicting lower levels of these proteins compared to those without cachexia.[27] Additionally, our study found a negative correlation between total protein and age and a positive correlation between total protein and tumor size.

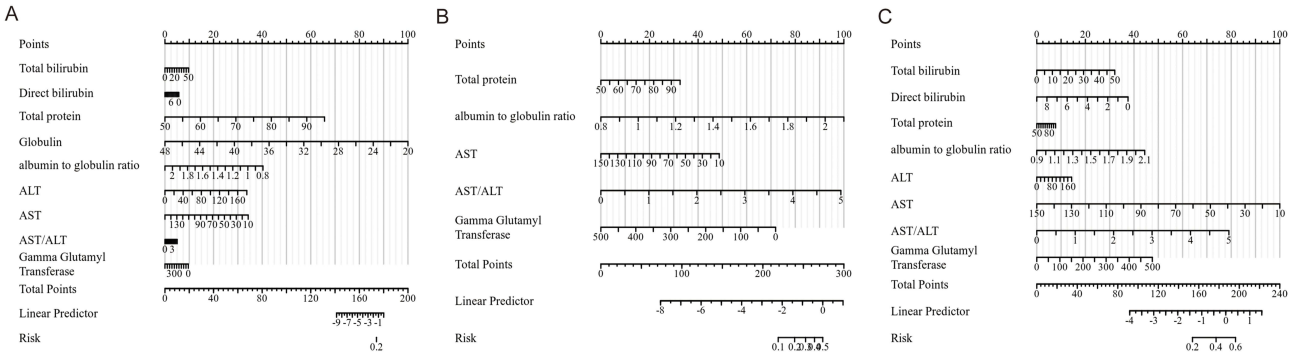

Figure 1 AGR-based nomogram for predicting breast cancer, invasive cancer, and late-stage breast cancer. (**A**) AGR-based nomogram for predicting breast cancer. (**B**) AGR-based nomogram for predicting invasive cancer. (**C**) AGR-based nomogram for predicting late-stage breast cancer.

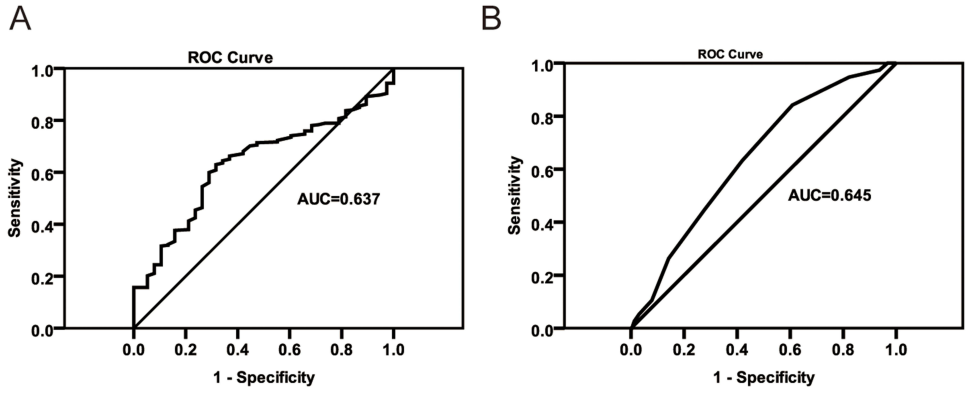

Figure 2 The ROC curves of different algorithms based on 10-fold cross-validation. (**A**) ROC curve of globulin. (**B**) ROC curve of AGR.

Historically, albumin has been recognized as an indicator of the inflammatory response and is widely acknowledged as a highly sensitive marker for assessing a patient's nutritional status.[28] Historically, albumin has been recognized as an indicator of the inflammatory response and a highly sensitive marker for assessing nutritional status. In our study, we observed a negative correlation between albumin levels and age. Albumin serves as a marker for hepatocyte protein synthesis,[29] which aligns with the prevailing understanding that advanced age is associated with reduced liver protein synthesis capacity. Additionally, serum albumin levels may have prognostic value in predicting treatment outcomes and compliance in patients with advanced disease.[30]

Serum globulin, synthesized by immune organs, is widely recognized as an indicator of the body's immune and inflammatory status. Our study identified globulin levels as significant diagnostic factors for BC, depicting a positive correlation with tumor size. Higher globulin levels suggest an overactive immune system, indicating that larger tumors trigger a stronger immune response. Globulin demonstrated moderate diagnostic accuracy for BC, with a sensitivity of 63% and specificity of 68.4%. It has also been extensively reported as an independent prognostic indicator for various diseases.[7] Therefore, composite variables such as the AGR are considered to have superior prognostic capabilities compared to singular markers. CA153 has been reported to have a sensitivity of 59.2% and a specificity of 94.1% in BC, while CA125 depicts a sensitivity of 49% and a specificity of 87.4%.[31] AGR has a higher sensitivity than these tumor markers, suggesting it is a valuable primary screening indicator. By calculating the AGR value in women during routine physical examinations, high-risk individuals can be identified. Further diagnosis using ultrasound or mammography can then confirm BC, enabling early detection and treatment.

AGR has been extensively studied as a potential prognostic indicator in various cancers, including Triple-negative BC,[32] glioblastoma,[33] gastric cancer,[6] renal cell carcinoma,[34] and multiple myeloma.[35] Our study found that AGR is significantly lower in BC. However, we could not establish AGR as a predictive factor for patients in the TNBC subgroup. We observed a significant negative correlation between AGR and both tumor size and stage, suggesting that as the tumor grows and progresses, a decrease in AGR may be due to ongoing protein loss. The findings indicate a significant correlation between reduced AGR and the presence of invasive carcinoma and advanced stages of BC. An AGR cutoff value of 1.35 was identified as a superior predictor in terms of the hazard ratio, demonstrating the highest levels of sensitivity and specificity.

This study has several limitations. First, it was retrospective and involved a limited number of patients, highlighting the necessity for larger sample sizes in future investigations. Second, the study did not incorporate a power calculation to determine the necessary sample size. Lastly, the absence of follow-up data may have limited the ability to establish AGR as a predictor of outcomes for patients with BC in this study. Therefore, it is recommended that large-scale, multicenter, prospective studies be undertaken to thoroughly assess the prognostic significance of AGR and to identify high-risk populations among patients with BC.

Conclusion

In conclusion, the AGR, routinely tested due to its simplicity, objectivity, and cost-effectiveness, is a potential diagnostic factor for BC. Liver function tests, including AGR, may be used for the initial screening of patients with BC. By calculating the AGR value during routine physical examinations, high-risk individuals can be identified. Subsequent diagnosis with ultrasound or mammography can then confirm BC, enabling early detection and treatment. This approach requires further validation through large-scale clinical cohorts to confirm its applicability in clinical practice.

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Disclosure

Chi Pan and Yawen Gu are co-first authors for this study. The authors report no conflicts of interest in this work.

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