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ORIGINAL RESEARCH

Combination of the preoperative albumin to globulin ratio and neutrophil to lymphocyte ratio as a novel prognostic factor in patients with triple negative breast cancer

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Qijia Xuan[1,*]
Yan Yang[1,*]
Hongfei Ji[2]
Shuli Tang[1]
Juan Zhao[1]
Jiayue Shao[1]
Jingxuan Wang[1]

[1]Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang Province 150081, People's Republic of China; [2]Department of Cancer Molecular and Biology, Cancer Institute, Harbin Medical University, Harbin, Heilongjiang Province 150081, People's Republic of China

*These authors contributed equally to this work

Background: The pretreatment albumin to globulin ratio (AGR) and neutrophil to lymphocyte ratio (NLR) were the inflammation-associated factors which were related to the disease-free survival in various malignancies. The aim of this study was to evaluate the clinical significance of the pretreatment AGR combined with NLR for patients with triple negative breast cancer (TNBC).

Method: This retrospective study included 286 cases of pathologically diagnosed patients with TNBC. The relationships of AGR and NLR with clinicopathologic characteristics and prognosis were analyzed by Kaplan–Meier and Cox regression methods.

Results: An AGR of 1.63 and a NLR of 2.93 were identified as the optimal cut-off points for distinguishing patients with good versus poor prognosis. The area under the receiver operating characteristic curves of combined with AGR and NLR (CO-AN) was increased compared with AGR and NLR individually. Kaplan–Meier analysis showed that low AGR/high NLR was related to poor survival. The prognosis of patients can be predicted well by the CO-AN. Univariate and multivariate analyses revealed that high AGR levels, low NLR levels, and CO-AN<1 were significantly and independently associated with favorable disease-free survival.

Conclusions: Our study suggested that AGR and NLR levels can be prognostic biomarkers for disease-free survival in patients with TNBC. The CO-AN may have greater predictive value than AGR and NLR in patients with TNBC.

Keywords: triple negative breast cancer, neutrophil–lymphocyte ratio, albumin-to-globulin ratio, prognostic factor

Introduction

Triple negative breast cancer (TNBC) is defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), which occupies 12–17% of newly diagnosed breast cancer.[1] The long-term outcomes of TNBCs are poorer than that of other subtypes as a result of early recurrences and a propensity for distant visceral metastases.[2] To individualize systemic therapy and also to select well patients who may derive benefit from treatment, prognostic factors have been tried to classify patients with TNBC at low and increased risk of disease recurrence. The traditional prognostic markers for TNBC include tumor size, tumor histological grade, clinical stage, and lymphatic

Correspondence: Jingxuan Wang
Department of Medical Oncology, Harbin Medical University Cancer Hospital, 150 Haping Road, Harbin, Heilongjiang Province 150081, People's Republic of China
Tel +86 451 8629 8681
Fax +86 451 8629 8681
Email wjxilywendy@126.com

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metastasis. In an attempt to clearly estimate the TNBC patients' outcomes, many prognostic factors have been investigated.

Lately, increasing studies focus on the identification of several inflammation-based indexes in several cancers,[3,4] such as the neutrophil–lymphocyte ratio (NLR) and the albumin-to-globulin ratio (AGR).[5] However, only a few studies have systematically investigated the relationship between TNBC and AGR. Moreover, the NLR and prognostic value of the combined AGR and NLR remain unclear.

Material and methods

Patient population

From a prospectively collected Tumor Hospital of Harbin Medical University surgical database, patients were identified who underwent mastectomy between January 2006 and December 2008. Eligible patients were those with no metastatic lesions before surgery, infiltrating ductal carcinoma, and TNBC (ER, PR, and HER2 negative). These patients were treated with standard therapy. No patients were lost to follow-up. Patients who developed disease relapse were confirmed by adequate diagnostic examinations during the follow-ups. Disease-free survival (DFS) was calculated from the date of surgery to the date of disease recurrence, death or last follow-up.

Clinical data collection

Baseline characteristics were collected, including age, menopause status, tumor size, nodal status, histological grade, Ki-67 status, P53 status, and laboratory data (neutrophil count, lymphocyte count, serum ALB value, and serum GLB value on the first hospitalization day). NLR values were obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. AGR was defined as the serum ALB value divided by the serum GLB value.

Immunohistochemistry

All the TNBC tissues were formalin-fixed and paraffin-embedded. For each sample, a 4 μm-thick tissue section was provided on a slide. Immunohistochemical method was executed as depicted previously.[6] The tumors from 2006–2008 in the study were re-tested the status of ER, PR and HER2 by two different pathologists. ER, PR, and HER2 were considered negative according to the ASCO/CAP guidelines.[7,8] Samples were considered positive for Ki-67 with more than 20% stained of the breast cancer cells examined. Any staining of the cancer cells was seen as P53 positive.

Statistical analyses

Statistical analyses were performed with SPSS, version 20.0 (IBM, USA). The primary end point of the study was DFS. We determined the optimal cutoff levels for the AGR and NLR by applying receiver operating curve (ROC) analysis. Sensitivity and specificity were calculated by the optimal cutoff points on the ROC curves, which decided the maximum value (sensitivity+specificity−1) of Youden index.[9]

The Chi-square test or Fisher's exact test was used to calculate the association between patients' and tumor's categorical characteristics and AGR and NLR. The impact of AGR and NLR on DFS was analyzed using Kaplan–Meier method. Survival data between groups were compared with the two-tailed Log-rank test. We performed the Cox proportional hazard model for the univariate and multivariate analysis to assess the variables under the prognostic factor section to evaluate their impact on DFS. A P value of <0.05 was considered statistically significant.

Results

TNBC patient characteristics

A total of 286 patients met all inclusion criteria and were included in the study. Patient demographics, TNBC characteristics at diagnosis, and correlation of these characteristics with AGR and NLR are shown in Table 1. The median age at the time of surgery for the enrolled patients with TNBC was 50 years (range 24–76 years). Over half of the patients with TNBC (51.4%) were postmenopausal, and 53.1% had no lymph node metastases. The median tumor size was 4 cm. The majority (86.4%) had histological grade Ⅱ tumors. Among these figures, 171 breast cancers Ki-67 were ≥20% (59.8%), and 87 patients P53 status was positive (30.4%).

Optimal cutoff point of AGR and NLR in patients with TNBC

The median value of ALB was 45.3 g/L (interquartile range, 26.9–56.8), and the median value of GLB was 27.7 g/L (interquartile range, 16.3–44.9). The median value of AGR was 1.70, and the optimal cut-off value for DFS was 1.63 (area under the curve [AUC]=0.586, P=0.043) according to the ROC curve plotted in Figure 1.

Table 1 Characteristics of triple negative breast cancer according to albumin-to-globulin ratio and neutrophil–lymphocyte ratio

Characteristic	Overall (%)	AGR		*P*-value	NLR		*P*-value
		<1.63	≥1.63		<2.93	≥2.93	
Age				0.551			0.196
≤50	124(43.4)	60	64		92	32	
>50	162(56.6)	85	77		131	31	
Menopause status				0.557			0.086
No	139(48.6)	73	66		102	37	
Yes	147(51.4)	72	75		121	26	
Tumor size(cm)				0.152			0.386
≤2	61(21.4)	36	25		45	16	
>2	225(78.6)	109	116		178	47	
Nodal status				0.814			0.253
N0	152(53.1)	76	76		123	29	
N+	134(46.9)	69	65		100	34	
Histological grade				0.185			0.318
I	6(2.1)	1	5		5	1	
II	247(86.4)	129	118		189	58	
III	33(11.5)	15	18		29	4	
Ki 67status				0.718			0.111
<20%	115(40.2)	60	55		84	31	
≥20%	171(59.8)	85	86		139	32	
P53 status				0.443			0.539
Positive	87(30.4)	41	46		70	17	
Negative	199(69.6)	104	95		153	46	

Abbreviations: AGR, albumin-to-globulin ratio; NLR, neutrophil–lymphocyte ratio.

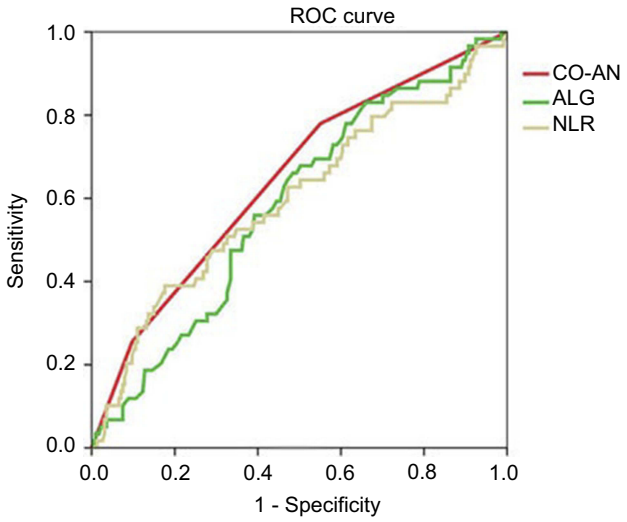

Figure 1 ROC curves assessing the cut-off of AGR and NLR for predicting the occurrence of disease events in the study.
Abbreviations: AGR, albumin-to-globulin ratio; NLR, neutrophil–lymphocyte ratio; CO-AN, combination of decreased AGR and increased NLR.

Among the 286 patients with TNBC, the mean counts of neutrophil were 3.70×10^9/L (range, 1.49–7.1×10^9/L), and the mean counts of lymphocytes were 1.88×10^9/L (range, 0.4–5.4×10^9/L). The median value of NLR was 2.83. We also determined the optimal cutoff levels for the NLR by ROC analysis. Regarding NLR, the value of 2.93 was chosen as the cut-off level as associated with a high sensitivity and specificity for DFS.

CO-AN was defined as the combination of decreased AGR and increased NLR. CO-AN was scored between 0 and 2 according to the number of decreased AGR and increased NLR. For example, patients with 1 decreased AGR and 1 increased NLR were scored 2, whereas patients with one or zero decreased AGR or increased NLR were scored 1 or 0, respectively. Finally, by comparing the AUC, the association between AGR, NLR, and CO-AN with reoccurrence rate was assessed. CO-AN exhibited greater

predictive significance (AUC, 0.647; *P*=0.001; 95% confidence interval [CI], 0.568–0.726) compared with AGR or NLR.

All patients with TNBC were divided into either low-(<1.63) or high-(≥1.63) AGR groups (Table 1). Similarly, the patients also dissolved into the low-NLR (<2.93) group and the high-NLR (≥1.63) group (Table 1). As demonstrated in Table 1, no statistically significant difference was observed in clinicopathologic characteristics between patients with TNBC with low and high AGR/NLR.

Survival in terms of AGR and NLR status in patients with TNBC

During the follow-up, 227 patients (79.4%) did well without any evidence of disease progression, whereas 59 patients (20.6%) experienced progressive diseases or death.

The optimal cut-off value was 1.63 for the AGR by ROC analysis. We tested AGR<1.63 or AGR≥1.63 for DFS by using Kaplan–Meier survival analysis. We observed that patients infused an AGR<1.63 compared with patients infused with an AGR≥1.63 experienced superior DFS (*P*=0.025) (Figure 2A).

Conversely, patients with a low NLR (<2.93) enjoyed a longer DFS compared with those with high NLR (≥2.93) values (*P*=0.000) (Figure 2B).

To further investigate the prognostic significance of CO-AN, we tested the whole cohort by Kaplan–Meier survival curves. The prognostic significance is shown in Figure 3. The DFS of the three groups was significantly different (*P*=0.000). The patients with CO-AN=0 had a significantly higher survival probability than the other two groups. Conversely, the survival rate of the patients with CO-AN=2 was the lowest among the three groups.

Predictors for DFS in patients with TNBC

We determined the association of clinicopathologic factors with DFS by univariable analysis. We found that AGR (HR: 0.549, 95% CI=0.322–0.936, *P*=0.028), NLR (HR: 2.524, 95% CI=1.495–4.261, *P*=0.001), CO-AN (HR: 2.013, 95% CI=1.3898–2.900, *P*=0.000), and lymph node status (HR: 3.840, 95% CI=2.136–6.903, *P*=0.000) were significant prognostic indications for DFS (Table 2). Similarly, multivariate analysis identified AGR, NLR, CO-AN, and lymph node status as independent prognostic factors (Table 2). The menopause status, age, tumor size, and histological grade status had no significant association with DFS in either univariate or multivariate analysis.

Discussion

Growing interest is observed in the interaction between cancer cells and the host immune system. Breast cancer has a rather unique and complex microenvironment, which is rich in growth factors, proteinases, and inflammatory cytokines that are of benefit to proliferation, invasion, and metastasis of breast cancer cells.[10,11] Increased serum levels of inflammatory cytokines are also related to the poor clinical features of breast cancer.[12] Consequently, cancer-associated inflammation is a key molecular feature in breast cancer.

ALB and GLB are two important components of systemic inflammatory response. The combination of these two indexes (AGR) has been reported to be significant in several types of cancers, including hepatocellular carcinoma, small-cell lung cancer, and nasopharyngeal carcinoma.[13,14] In our study, we included 289 cases, and the pretreatment AGR was an independent prognostic factor for patients with TNBC. To the best of our knowledge, this work is the first study to report the prognostic value of preoperative AGR in patients with TNBC.

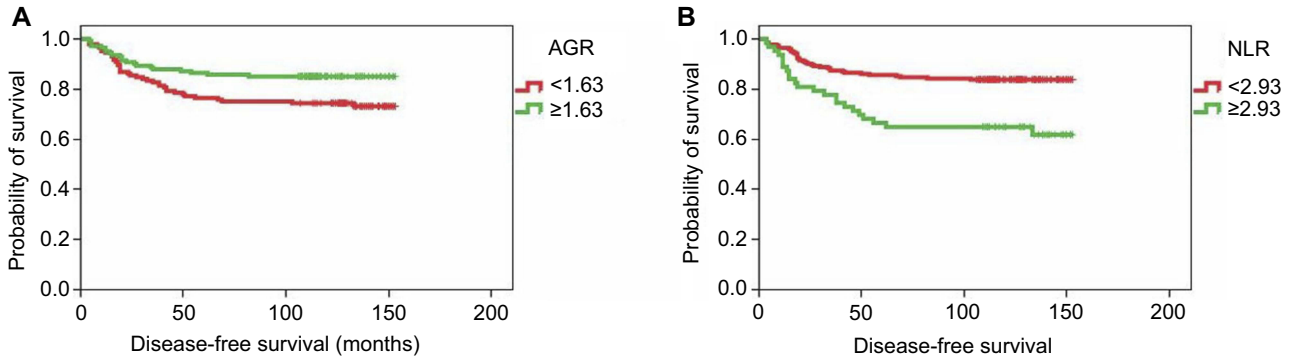

Figure 2 Kaplan-Meier curves for DFS according to optimal cutoff points of AGR and NLR. (**A**) AGR. (**B**) NLR.
Abbreviations: DFS, disease-free survival; AGR, albumin-to-globulin ratio; NLR, neutrophil–lymphocyte ratio.

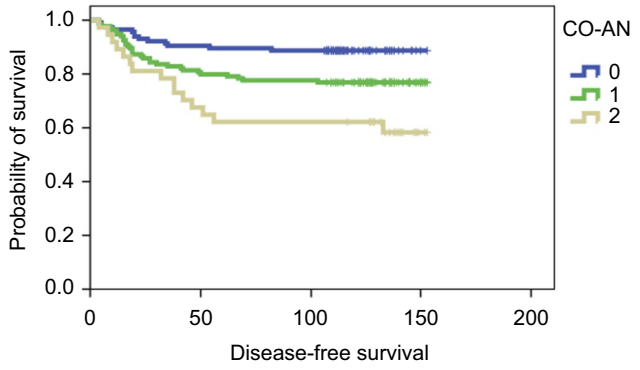

Figure 3 Kaplan-Meier curves for DFS according to optimal cutoff points of CO-AN.
Abbreviation: DFS, disease-free survival; CO-AN, combination of AGR and NLR.

Table 2 Univariate and multivariate analyses of clinicopathologic characteristics for DFS in triple negative breast cancer

	Univariate analysis		Multivariate analysis	
Variable	HR(95% CI)	*P*-value	HR(95% CI)	*P*-value
AGR	0.549 (0.322–0.936)	**0.028**	0.513 (0.288–0.913)	**0.023**
NLR	2.524 (1.495–4.261)	**0.001**	2.387 (1.385–4.114)	**0.002**
CO-AN	2.013 (1.398–2.900)	**0.000**	2.253 (1.331–3.812)	**0.002**
Lymph node status	3.840 (2.136–6.903)	**0.000**	3.669 (2.035–6.614)	**0.000**
Ki 67 status	0.956 (0.569–1.603)	0.956	1.818 (0.634–2.197)	0.601
Menopause status	0.970 (0.582–1.617)	0.908	1.069 (0.515–2.217)	0.858
Age	0.960 (0.574–1.605)	0.960	0.939 (0.447–1.971)	0.867
Tumor size	1.008 (0.534–1.904)	0.980	0.826 (0.430–1.588)	0.566
Histological grade status	1.312 (0.656–2.623)	0.442	1.682 (0.761–3.720)	0.199
P53 status	1.021 (0.587–1.778)	0.941	0.963 (0.503–1.843)	0.909

Note: Bold values are significant ($P<0.05$).
Abbreviations: DFS, disease-free survival; AGR, albumin-to-globulin ratio; NLR, neutrophil–lymphocyte ratio; HR, hazard ratio; CO-AN, combination of decreased AGR and increased NLR.

ALB is a major protective element that can stabilize DNA replication and cell growth, which can go against carcinogenesis by aflatoxins and nitrosamines.[15] Additionally, some research recommended that the high concentration of ALB can inhibit the growth of a variety of tumor cells.[15,16] ALB generation can be suppressed by inflammation and malnutrition, which are the pathogenic factors of many cancers.[17] Cytokines, such as TNF and IL-6, were produced by the inflammatory response, which can reduce the ALB synthesis by the liver cells.[18,19] Previous studies confirmed that low levels of ALB were associated with poor prognosis in multiple malignancies.[18–20] GLB was produced by immune organs and reflected the immune status,[21] which included a large number of acute reactive protein. Elevated globulin levels may reflect the inflammatory status marked by the immunoglobulins, acute phase proteins, and other serum proteins. This condition was also related to the poor prognosis in several malignant tumors.[21] As mentioned above, the inflammatory state may play an important role in the TNBC carcinogenesis.

In our study, the best cut-off for AGR was 1.63, which was determined by the ROC analysis. This value was close to the optimal cut-off value reported in the previous studies on esophageal squamous cell carcinoma.[22] The use of diverse AGR cut-off values in a diverse cohort of patients with breast cancer may lead to varied survival results. Therefore, the optimal and generalized AGR thresholds for patients with TNBC should be determined in the future with a large cohort.

Neutrophils play an important role both in systemic and local inflammatory responses. The upregulation of neutrophils can reflect the invasive characteristics of cancer cells as it was primarily stimulated by hematopoietic cytokines from tumor cells.[23] Neutrophils can produce the substances, such as arginase, reactive oxygen species, and nitric oxide, and inhibit the function of cytotoxic lymphocytes.[24,25] Meanwhile, lymphocytes had anticancer activity by inhibiting tumor growth or metastasis.[26] Lymphocyte counts can reflect endogenous cancer resistance of the immune system.[27,28] By the combination of neutrophils and lymphocytes, high NLR level has been shown to be a promising indicator of poor prognosis for patients with cancer.[29–31] In this study, the optimal cutoff value of 2.93 for the NLR was found to exhibit superior prognostic value for the DFS of TNBC. The threshold is similar to the results of some previous TNBC research.[32–34] However, this study also used the higher NLR thresholds compared to several previous TNBC studies.[35–37] This may due to the difference of the geographical area, race and the number of grouped patients.

Importantly, the results of the present study further demonstrated that CO-AN has improved predictive power compared with AGR and NLR, individually. The CO-AN may thus represent a more effective prognostic factor than the marker alone.

Conclusions

Our findings strongly suggest that the AGR and NLR are significantly associated with the survival time in patients with TNBC, and we moreover defined the specific AGR/NLR cut-off value restricted to patients with TNBC, considering the large heterogeneity of breast cancer. Furthermore, our results indicated that the prognosis of patients with CO-AN can be well predicted. Given that this work was a retrospective and single-center study, further investigations need to be performed to validate our conclusion.

Ethics approval and informed consent

This study, including the procedures for patient enrollment and recruitment, was approved by the Institutional Review Board of the Harbin Medical University Cancer Hospital, and all patients who participated in the study provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

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Author contributions

QJX and JXW designed the study. QJX and YY wrote the manuscript. YY, HFJ and SLT performed the experiments. JZ and JYS performed the statistical analysis of the data. JXW polished the manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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