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Original Article

High preoperative serum globulin in rectal cancer treated with neoadjunctive chemoradiation therapy is a risk factor for poor outcome

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Abstract: An elevated serum albumin (ALB) and albumin/globulin ratio (AGR) has been reported to be associated with a favorable prognosis for certain malignancies; however, little is known about the prognostic significance of globulin (GLB) in rectal cancer treated with neoadjuvant chemoradiation therapy (NCRT). The purpose of this study was to evaluate whether GLB analysis could predict the prognosis of patients received NCRT. A retrospective cohort of 293 locally advanced rectal cancer patients receiving NCRT followed by radical surgery was recruited between January 2006 and December 2012 at Fudan University Shanghai Cancer Center. Levels for preoperative GLB and ALB were obtained and used to calculate the AGR. Survival analysis was used to evaluate the predictive value of GLB. X-tile program determined 28.50, 36.20 and 1.20 as optimal cut-off value for GLB, ALB and AGR in terms of survival. Univariate and multivariate analysis revealed that low GLB levels were significantly associated with favorable rectal cancer-specific survival (RCSS) ($P < 0.05$). Conversely, low ALB levels were associated with a significantly worse RCSS ($P = 0.010$). Collectively, high preoperative GLB level was a significantly unfavorable factor for rectal cancer patients treated with NCRT. This easily obtained variable may serve as a valuable marker to predict the outcomes of such patient population.

Keywords: Rectal cancer, globulin, albumin, neoadjuvant chemoradiotherapy therapy, survival analysis

Introduction

About 50-60% of rectal carcinomas are considered to be locally advanced tumors with clinically staged T3/4 or node-positive disease, which are characterized by poor prognosis due to high incidence of systemic and local recurrence and low possibility of long-term survival [1]. Neoadjuvant chemoradiation therapy (NCRT) following curative resection has become a standard method to treat locally advanced rectal cancer because of its lowered local recurrence rates [2, 3]. However, in most cases, it appears that treatment failure was eventually caused by distant metastasis, failing to improve overall prognosis [4, 5]. So the identification of a simple and cost-effective indicator for predicting patient prognosis is of vital importance. Measurements of serum albumin (ALB) and globulin (GLB) are routinely performed in medical laboratories, in addition to the albumin/globulin ratio (AGR), which is calculated spontaneously by most clinical chemistry autoanalyzers. Prior studies demonstrated that low serum ALB is an independent predictor of poor survival in several types of cancer including lung cancer, nasopharyngeal carcinoma, ovarian cancer, breast cancer, as well as colorectal cancer [6-8]. In contrast to the considerable amount of researches on ALB, the impact of the globulin and A/G ratio on tumor metastasis and mortality in rectal cancer patients treated with NCRT has not yet been addressed. The purpose of this study was to assess the prognosis role of preoperative globulin and A/G ratio on rectal cancer treated with NCRT.

Materials and methods

Study population

We used the data from patients treated with NCRT at Fudan University Shanghai Cancer Center (FUSCC) between January 2006 and

December 2012. As we previously described, the FUSCC rectal cancer dataset was built prospectively to take records of the rectal cancer patients treated at FUSCC, Shanghai, China since January, 2006 [9, 10]. Patients aged 18 years or older with histologically confirmed clinical stage T3/4 or node-positive disease, located within 10 cm of the anal verge, rectal cancer as a single primary tumor, completed NCRT and received radical surgery were eligible for inclusion. Patients who had preexisting liver diseases, received immunosuppressive therapies including recent steroid exposure or with chronic inflammatory disease including autoimmune disorder and infection, received local resection, died with 30 days after surgery were excluded from this study. All patients received intensity-modulated radiation therapy to the pelvis of 45-50 Gy and a concomitant boost of 5 Gy to the primary tumor in 25 fractions, concurrent with capecitabine or 5-FU based chemotherapy. Radical surgery was scheduled 6-8 weeks after NCRT.

The research protocol was reviewed and approved by the Ethical Committee and Institutional Review Board of the FUSCC. All patients in FUSCC provided written informed consent.

Statistical analysis

Detailed information regarding patient- and tumor-related variables was retrieved from the FUSCC rectal cancer database. Patient-related variables consisted of age, gender, serum ALB level, GLB level and CEA (Carcinoembryonic Antigen) level. The patients were divided into two groups due to age: ≤ 60 years (young) and > 60 years (old). CEA level > 5 ng/ml was defined as abnormal. Tumor-related factors consisted of location, size, morphology, histology, degree of differentiation and stage. Tumor stages were determined according to the AJCC TNM staging system (7th edition, 2010). Tumor regression of the primary tumor was semiquantitatively determined by the amount of viable tumor versus the amount of fibrosis, ranging from no evidence of any treatment effect to a complete response with no viable tumor identified, as described by Dworak et al. [11] The characteristics of each grade were as follow: grade 0, no regression; grade 1, minor regression (dominant tumor mass with obvious fibrosis in 25% or less of the tumor mass); grade 2, moderate regression (dominant tumor mass with obvious fibrosis in 26% to 50% of the tumor mass); grade 3, good regression (dominant fibrosis outgrowing the tumor mass; [i.e., more than 50% tumor regression]); and grade 4, total regression (no viable tumor cells, only fibrotic mass) [12].

The AGR was calculated [AGR = Albumin/(Total protein - Albumin)], and X-tile program [13] was performed to select the most appropriate cut-off points for the ALB level, GLB level and AGR to stratify patients at a high risk of cancer-related death. The primary endpoint of this study was rectal cancer cause specific survival (RCSS), which was calculated from the date of cancer diagnosis to the date of cancer caused death. Deaths attributed to the rectal cancer were treated as events and deaths from other causes were treated as censored observations. Survival curves were generated using Kaplan-Meier estimates, differences between the curves were analyzed by log-rank test. Multivariable Cox regression models were built for analysis of risk factors for survival outcomes in rectal cancer patients treated with NCRT. Chi-square test was used for categorical variables. 5-year RCSS was estimated from Kaplan-Meier curves. All statistical analyses were performed using the statistical software package SPSS for Windows, version 17 (IBM Corp, Armonk, NY, USA). Statistical significance was set at two-sided $P < 0.05$.

Results

Patient characteristics

A total of 293 eligible patients were identified from January 2006 to December 2012. There were 205 men (70.0%) and 88 women (30.0%) with an average age of 54 years (range, 22-78 years). Of these, 58 (19.8%) were pathological completed response (pCR), 66 (22.5%) were stage I, 69 (23.5%) were stage II, and 100 (34.1%) were stage III. 102 (34.8%) patients underwent Dixion procedure and 176 (60.1%) underwent Miles procedure, and 15 (5.1%) underwent Hartmann procedure. Patient demographics and pathological features are summarized in **Table 1**.

During follow-up, 64/293 patients (21.8%) experienced tumor recurrence after surgical treatment, including 9 (3.07%) who developed local or regional recurrence and 55 (18.77%)

Table 1. Demographic and clinical features of patients with rectal cancer treated with preoperative chemoradiation therapy from Fudan University Shanghai Cancer Center

	n	%
Age	54 (22-78)	
Sex		
male	205	70.0%
female	88	30.0%
Histotype		
Adenocarcinoma	277	94.5%
Mucinous/Signet ring cell	16	5.5%
Surgical Approach		
Dixion	102	34.8%
Miles	176	60.1%
Hartmann	15	5.1%
AJCC stage		
0	58	19.8%
I	66	22.5%
II	69	23.5%
III	100	34.1%
LNs retrieval		
< 12	182	62.1%
≥ 12	111	37.9%
Lymphovascular invasion		
Negative	265	90.4%
Positive	28	9.6%
Perineural invasion		
Negative	249	85.0%
Positive	44	15.0%
TRG		
0	24	8.2%
1	46	15.7%
2	71	24.2%
3	88	30.0%
4	64	21.8%

who developed distant metastasis. By the end of follow-up, 48/295 patients (16.3%) had died of rectal cancer.

Identification of GLB, ALB, and AGR optimal cut-off points

The mean GLB and ALB were 27.09 g/L (range, 17.60-43.60 g/L) and 40.75 g/L (range, 24.90-52.30 g/L), respectively. The mean AGR was 1.54 (range, 0.83-2.51). X-tile program was used to determine the optimal cut-off value for GLB. The GLB cutoff point for RCSS was 28.50 g/L with maximum χ^2 log-rank value of 6.146 (P = 0.013), and all patients were divided into either high (> 28.50 g/L) or low (≤ 28.50 g/L) GLB groups. Similarly, an ALB cutoff 36.2 g/L and an AGR cutoff 1.20 were selected as the optimal cutoff points for survival analyses (χ^2 = 5.745, P = 0.017, and χ^2 = 4.308, P = 0.038, respectively) to divide the patients into high and low risk subsets in terms of RCSS (**Figure 1**).

Association among GLB, ALB and the clinical features of rectal cancer treated with preoperative

The distribution of the GLB level differed significantly when the patients were stratified by gender and age (**Table 2**). Significantly more patients were male in the low GLB group than patients in higher GLB group (P = 0.042), and 150/198 (75.76%) patients were at young age (< 60) in low GLB group compared to 55/95 (57.89%) patients at young age in high GLB group (P = 0.002). Conversely, there were higher percentage of young patients in high ALB group (186/256, 72.66%) than in low ALB group (19/37, 51.35%) (P = 0.008). The patients in the low GLB group seemed to have a higher ALB level than those in the high GLB group, although the *P* value just failed its significance (P = 0.060) (**Table 2**).

Prognostic value of GLB, ALB, and AGR

The high GLB level, low ALB level and AGR, and other clinicopathological factors, including mucinous and signet-ring cancer (P = 0.003), high CEA level (> 5 ug/ml) (P < 0.001), advanced AJCC stages (P < 0.001), poor TRG score (P < 0.001), present with lymphovascular invasion (P = 0.001) and perineural invasion (P < 0.001) were significant risk factors for poor survival according to univariate analysis (**Table 3**).

Multivariate analysis with Cox regression was performed, and consistent with the univariate analysis, GLB and ALB levels were independent prognostic factors for RCSS (**Table 3**), and a higher GLB demonstrated a negative effect on survival (hazard ratio [HR] 2.015; 95% confidence interval [CI] 1.019-3.985, P = 0.044). Conversely, a higher ALB demonstrated a positive effect on survival (HR 0.375; 95% CI 0.169-0.832, P = 0.016). However, the AGR was not a significant predictive factor for RCSS in multivariate analysis (HR 1.008; 95% CI 0.372-2.730, P = 0.988) (**Table 3**).

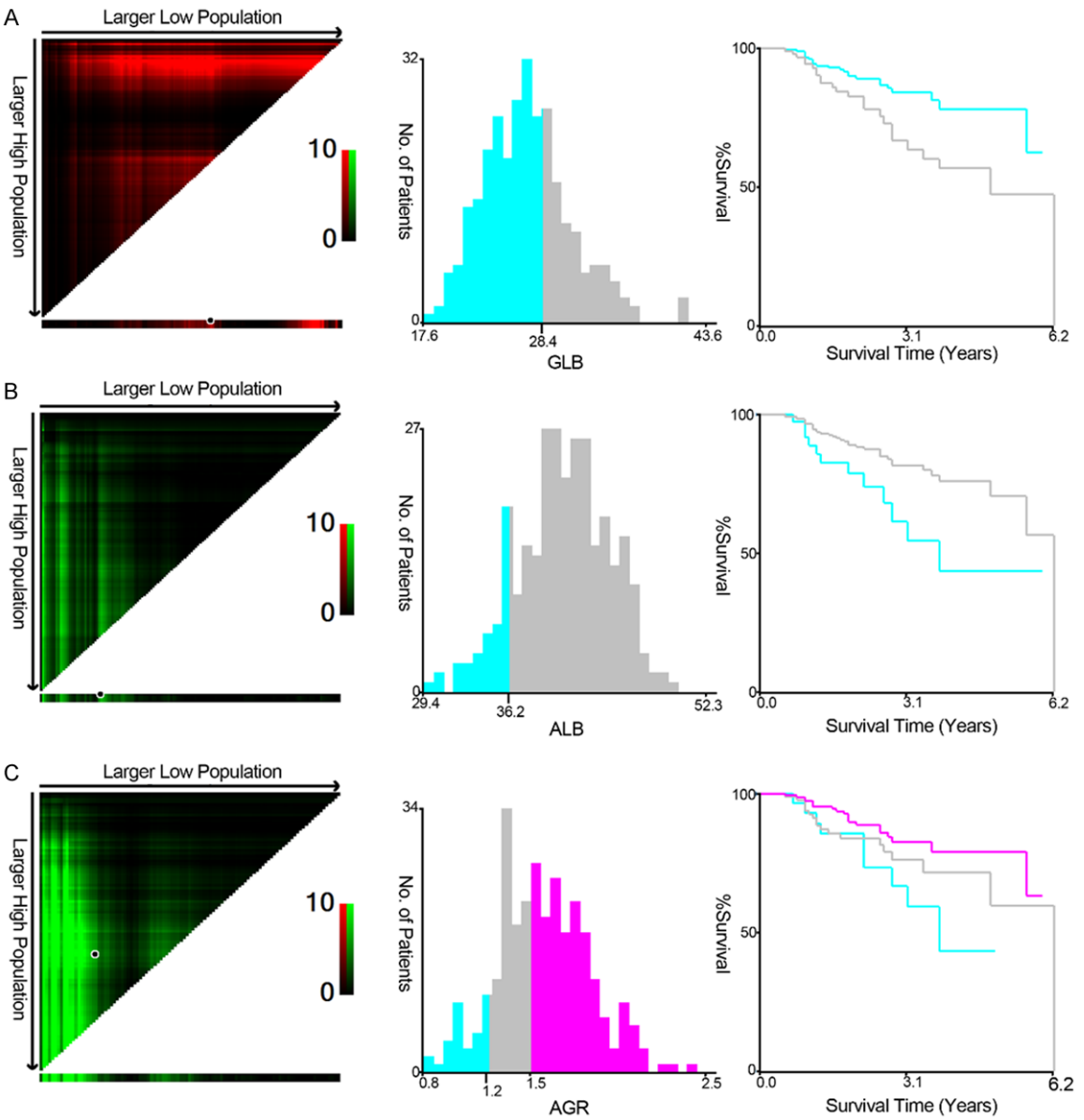

Figure 1. X-tile analysis of survival data of patients treated with preoperative chemoradiation therapy. X-tile analysis was performed using patient data, which were equally divided into training and validation sets. X-tile plots of the training sets are shown in the *left panels*, with plots of matched validation sets shown in the *smaller inset*. The optimal cut-point highlighted by the *black circle* in the *left panels* is shown on a histogram of the entire cohort (*middle panels*), and a Kaplan-Meier plot (*right panels*). *P* values were determined using the cutoff point defined in the training set and applying it to the validation set. A: Shows the optimal cutoff point for the GLB (28.50, χ^2 = 6.146, P = 0.013). B: Shows the optimal cutoff point for the ALB (36.20, χ^2 = 5.745, P = 0.017). C: Shows the optimal cutoff point for the AGR (1.20 and 1.460, χ^2 = 4.308, P = 0.038).

Discussion

Distant metastasis and local recurrence remain main concerns in patients with rectal cancer treated with NCRT [14, 15]. Factors known to be associated with decreased survival would provide the ability to pre-select those patients who would benefit most from more aggressive treatments. Pathologic stage is valuable for predicting prognosis in patients with rectal cancer; however, it is difficult to accurately determine the stage in patients after NCRT. Moreover, when predicting prognosis, both tumor and host related factors must be considered.

GLB is the uppermost blood proteins. Levels of GLB arise high due to elevated accumulation of acute-phase proteins and immunoglobulins, as

Table 2. Association among GLB, ALB and the clinical features in rectal cancer patients treated with preoperative

Variable	GLB level (g/L)		χ^2 Value	P	ALB level (g/L)		χ^2 Value	P
	≤ 28.50	> 28.50			≤ 36.20	> 36.20		
Sex			4.134	0.042			2.225	0.136
Male	146	59			22	183		
Female	52	36			15	73		
Age			9.748	0.002			6.983	0.008
< 60	150	55			19	186		
≥ 60	48	40			18	70		
Histotype			0.199	0.655			< 0.001	0.987[a]
Adenocarcinoma	188	89			35	242		
Mucinous/signet ring cell	10	6			2	14		
CEA (ug/ml)			0.856	0.355			0.103	0.748
< 5	167	76			30	213		
≥ 5	31	19			7	43		
LNs retrieval			0.068	0.795			0.517	0.472
< 12	124	58			21	161		
≥ 12	74	37			16	95		
AJCC Stage			2.283	0.516			1.211	0.750
0	44	14			9	49		
I	43	23			6	60		
II	45	24			9	60		
III	66	34			13	87		
TRG score			0.146	0.703			0.229	0.632
0-1	46	24			10	60		
2-4	152	71			27	196		
Lymphovascular invasion			0.153	0.696			0.077	0.781
Negative	180	85			33	232		
Positive	18	10			4	24		
Perineural invasion			1.302	0.254			0.505	0.477
Negative	165	84			30	219		
Positive	33	11			7	37		
GLB (g/L)							3.354	0.060
≤ 28.50					20	178		
> 28.50					17	78		

[a]Fisher's exact test.

well as other serum proteins; these changes are reflective of an inflammatory state [6]. Increasing evidence shows that the presence of a systemic inflammatory response is associated with poor survival in patients with various malignancies, including colorectal cancer [16-18]. Several studies have shown that inflammation-based prognostic scores, including a combination of serum C-reactive protein and ALB as the Glasgow Prognostic Score, and a combination of neutrophils and lymphocyte counts as the neutrophil to lymphocyte ratio, are associated with survival in patients with colorectal cancer [16, 17, 19-21]. Our study demonstrated that the GLB is a significant predictor of RCSS in patients treated with NCRT. Although a low GLB was associated with a younger age and gender, the predictive GLB remained significant after adjustment for AJCC stage and other clinical characteristics in multivariate analysis. There was an absolute 15.5% improvement in the 5-year RCSS if ≤ 28.50 g/L GLB level was analyzed rather than > 28.5 g/L ($P < 0.05$).

So far, the prognostic significance of the marker of systematic inflammatory reaction to solid

Table 3. Univariate and multivariate survival analyses evaluating GLB, ALB, and AGR influencing RCSS in rectal cancer treated with preoperative chemoradiation therapy

		Univariate analysis		Multivariate analysis	
Variable	5-year RCSS	Log rank χ^2 test	P*	HR (95% CI)	P
Sex		0.217	0.641		NI
Male	66.3%				
Female	73.4%				
Age		0.036	0.850		NI
< 60	66.8%				
≥ 60	69.5%				
Histotype		8.707	0.003		0.173
Adenocarcinoma	68.4%			Reference	
Mucinous/signet ring cell	49.2%			1.823 (0.768-4.326)	
CEA (ug/ml)		17.520	< 0.001	Reference	0.011
< 5	72.7%			2.326 (1.213-4.459)	
≥ 5	38.1%				
LNs retrieval		0.908	0.341		NI
< 12	61.4%				
≥ 12	76.9%				
AJCC Stage		26.784	< 0.001		0.126
0	95.5%			Reference	
I	82.2%			4.913 (0.590-40.908)	0.141
II	64.3%			9.155 (1.155-72.557)	0.036
III	45.7%			9.993 (1.236-80.791)	0.031
TRG score		20.311	< 0.001		0.253
0-1	44.9%			Reference	
2-4	78.9%			0.666 (0.332-1.338)	
Lymphovascular invasion		10.489	0.001		0.220
Negative	72.7%			Reference	
Positive	26.9%			1.591 (0.757-3.341)	
Perineural invasion		13.230	< 0.001		0.085
Negative	70.8%			Reference	
Positive	51.3%			1.783 (0.923-1.344)	
GLB (g/L)		6.146	0.013		0.044
≤ 28.40	72.1%			Reference	
> 28.40	56.6%			2.015 (1.019-3.985)	
ALB (g/L)		5.745	0.017		0.016
≤ 36.20	41.9%			Reference	
> 36.20	72.2%			0.375 (0.169-0.832)	
AGR		4.308	0.038		0.988
≤ 1.20	42.2%			Reference	
> 1.20	72.3%			1.008 (0.372-2.730)	

NI: not included in multivariate survival analysis. *P values refer to the log-rank test of the differences between the two survival curves generated using Kaplan-Meier analysis.

tumors has been relatively ignored in the pursuit of tumor-based molecular evaluation of outcome [21]. The present study, to our knowledge, is the first research mainly focuses on the association between GLB and prognosis as well as clinicopathological parameters in rectal cancer treated with NCRT. There are several reasons why cancer-related inflammation is especially important in rectal cancer. First, The mutual relationship between chronic inflamma-

tion and colorectal cancer has been established by the observations showing that greatly increased risk of malignancy exists in patients with inflammatory bowel disease [21, 22], and that a decreased colorectal cancer risk is found in patients who take regular nonsteroidal anti-inflammatory drugs (NSAIDs) [23]. Postdiagnosis use of aspirin can reduce all-cause mortality among colorectal cancer patients, and patients with a mutant form of the PIK3CA gene might benefit more from the prescription of aspirin [24]. Second, inflammatory responses lead to chronic oxidative stress and generate oxygen free radicals, which have been shown to stimulate cancer initiation, promotion and progression [25, 26]. Third, systemic inflammation showed an inverse correlation with chemotherapy response. Adjuvant chemotherapy is generally used for patients treated with NCRT and total mesorectal excision surgery, which may improve overall survival and disease-free survival [27]. Previous studies have shown that neutrophils can suppress the T cell response through the production of reactive oxygen species (ROS), nitric oxide (NO) and arginase [28, 29]. This suggests that the presence of inflammatory response after NCRT may cause unfavorable effects on tumor response [30].

Serum ALB is considered an objective measure of nutritional status [31], and it is also a useful factor for predicting the prognosis of patients with cancer. A low ALB associated with an increased severity of disease, a high risk of disease progression and poor survival in several types of cancers [7, 32, 33]. Our study confirmed that a preoperative ALB $\leq$ 36.2 g/L is predictive of poor prognosis. Young patients are usually at good nutrition status and tolerate well to chemoradiotherapy [34], which may lead to relative high levels of ALB, thus leading to good survival outcomes.

There are several limitations associated with the present study. First, the study design is retrospective, and routine measurements of the preoperative cytokines and C-reactive protein levels were not performed, so we could not analyze the relationship among GLB, ALB with cytokines and C-reactive protein. Second, the number of patients included in the study is relatively small, after classified by ALB levels, there is relatively small number of patients in low ALB group, which may cause limited statistical power. A prospective study utilizing larger numbers of patients is required to further assess the prognostic significance of GLB, ALB in rectal cancer treated with NCRT.

Despite these limitations, this study is informative. We are the first to demonstrate that preoperative GLB is associated with patients' prognosis, and a low GLB level predicts favorable survival outcomes in rectal cancer treated with NCRT. Also, we confirmed ALB as an independent prognostic factor in our study population. This biomarker can be obtained directly from routine medical laboratories, and can be easily applied in the clinical setting.

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Disclosure of conflict of interest

None.

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