

ORIGINAL ARTICLE

Low Serum Albumin Correlates with Poor Survival in Gastric Cancer Patients

Xiaojuan Ouyang^{*}, Yuan Dang^{*}, Fan Zhang, Qiaojia Huang

^{*}Xiaojuan Ouyang and Yuan Dang contributed equally to this article
Department of Experimental Medicine, Fuzhou General Hospital, Fuzhou City, Fujian Province, China

SUMMARY

Background: Preoperative nutritional status as evidenced by serum albumin measurement is associated with cancer prognosis but the clinical significance of this for patients with gastric cancer (GC) is unclear. Therefore, we evaluated an association between preoperative serum albumin and GC patient survival in the Fujian area which has a higher incidence for GC in China.

Methods: GC patients (n = 309) who underwent surgical treatment at Fuzhou General Hospital between 2010 and 2013 were retrospectively assessed using a Kaplan-Meier method and log-rank test, as well as univariate and multivariate Cox model analyses, to confirm a correlation between patient survival and preoperative serum albumin.

Results: Data show that low serum albumin was associated with poorer survival. Preoperative serum CEA, CA19-9, and albumin and tumor size, T staging, and lymph node metastases (LNM) were significantly associated with overall survival according to univariate analysis. Lower serum albumin (HR: 2.018, 95% CI [1.204 - 3.381], p = 0.008) and advanced cancers with deeper invasion (T3 + T4 stages) and with lymph node metastases were significantly associated with increased death risk according to multivariate analysis. Preoperative serum total protein, patient age, tumor size, T staging, and LNM were correlated with serum albumin according to chi-squared analysis.

Conclusions: Preoperative serum albumin may be related to GC patient survival and may hold promise as a prognostic predictor for such survival.

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Correspondence:

Professor Qiaojia Huang
Department of Experimental Medicine
Fuzhou General Hospital
156 North Xi-er Huan Road
Fuzhou City, Fujian Province, 350025
China
Email: huangqj100@126.com

KEY WORDS

preoperative serum albumin, gastric cancer, survival, predictor

LIST OF ABBREVIATIONS

GC - gastric cancer
CEA - carcino-embryonic antigen
OS - overall survival

INTRODUCTION

Gastric cancer (GC) is a major digestive malignant tumor [1] and complete surgical resection or partial tumor removal is the main treatment. Still, some patients live only a short while after surgery; the 5-year survival for advanced GC patients is persistently low. Thus, a predictor of GC patient survival would be useful. Most cancer survival predictors are based on tumor characteristics, and lymph node invasion and metastases but better prognostic factors that account for multiple cancer aspects may allow more tailored therapeutic choices. To this end, preoperative serum albumin is often measured to document the patient's nutritional status and may indicate future survival [2] as it is often associated with the severity of malignancy [3-5].

Cancer patients, for various reasons, often experience poor nutrition and cachexia which can interfere with therapy and be fatal [6,7]. Serum albumin can assist with estimating nutrition [8] and studies suggest that preoperative serum albumin may offer prognostic value for cancer patients' survival [6-10]: serum albumin of 35 - 52 g/L is considered normal and albumin < 35 g/L is hypoalbuminemia [11]. Cancer patients with hypoalbuminemia have a greater risk of death, especially when albumin < 20 g/L. Thus, exogenous albumin is offered to maintain appropriate protein (> 30 g/L).

Therefore, we evaluated serum albumin and associated this measurement with GC patient survival for 309 patients with the hopes of establishing a rapid and reliable prognostic marker.

MATERIALS AND METHODS

Study subjects

GC patients were histopathologically diagnosed at the Department of Pathology of Fuzhou General Hospital, and all data including patients' clinicopathological features and laboratory information were retrospectively collected from medical records (n = 309 cases) from patients who underwent surgical resection of a primary tumor between January 2010 and December 2013.

Blood biochemistry data collected included serum total protein and albumin which were analyzed on an Olympus AU2700 and serum tumor markers (AFP, CEA, and CA19-9) were analyzed with a quantitative tumor chip (Protein Chip-Chemiluminescence) (HealthDigit, Huzhou, China) and an HD-2001A ChipReader System (HealthDigit). Reference ranges for serum AFP, CEA, and CA19-9 were < 20 ng/mL, < 5.0 ng/mL, < 35.0 U/mL, respectively.

Ethics statement

Permission for this study was obtained from the Ethics Committee of Fuzhou General Hospital and all individual participants.

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 software (SPSS, Chicago, IL, USA). Survival variations were evaluated using the chi-squared test, Kaplan-Meier curve, and log-rank test as well as Cox's proportional hazards model (p-value < 0.05 was statistically significant).

RESULTS

Identification of correlations with preoperative serum albumin

Patients' clinical pathological features are shown in Table 1. Albumin reference ranges are 35 - 52 g/L. Of the 309 patients studied, there were two groups: low (< 35 g/L) and normal-high serum albumin (\geq 35 g/L). Of these, 48 patients had low albumin and 261 patients had normal albumin (35 - 52 g/L). Preoperative albumin ranged from 22 - 53 g/L (median 39.3 ± 4.93 g/L) in this cohort of patients.

Chi-squared analysis showed that patient age (< 60 vs. \geq 60 years-of-age, p = 0.002), tumor size (< 3 vs. \geq 3 cm, p = 0.006), invasion/T stages (T1 + T2 vs. T3 + T4, p = 0.033), lymph node metastases (LNM) (negative vs. positive, p = 0.009), and total protein (p = 0.000) were associated with preoperative serum albumin (Table 2). Older patients (\geq 60 years), larger tumors (\geq 3 cm), more serious invasion (T3 + T4), more serious lymph node metastases (positive), and low total protein were tied to less preoperative serum albumin (Table 2). Preoperative serum albumin was not associated with gender, nor with vascular and nerve invasion, TNM stage or serum AFP, CEA, and CA19-9.

Identification of correlations with overall survival

As shown in Table 3, preoperative serum albumin (p = 0.000), tumor size (p = 0.014), invasion/T stages (T1 + T2 vs. T3 + T4, p = 0.000), lymph node metastases (negative vs. positive, p = 0.000), and serum CEA (p = 0.014) and CA19-9 (p = 0.02) were associated with overall survival according to univariate analyses. Table 3 also shows that serum albumin (p = 0.008), invasion/T stages (T1 + T2 vs. T3 + T4, p = 0.003) (p = 0.003), lymph node metastases (LNM) (negative vs. positive, p = 0.016) were associated with overall survival according to multivariate analyses. GC patients with low albumin had a greater risk of death than those with normal albumin (HR: 2.018, 95% CI 1.204 - 3.381, p = 0.008). Albumin, T stages, and LNM were also independent prognostic factors for GC patients. Patients with deeper invasion (T3 + T4 stages) (HR: 2.156, 95% CI 1.309 - 3.550, p = 0.003) and more serious LNM (HR: 1.894, 95% CI 1.128 - 3.179, p = 0.016) were at greater risk of death compared to those at T1 + T2 stages or without LNM.

Kaplan-Meier curve and log-rank data confirm that patients with low serum albumin had shorter survival (mean overall survival was 38.262 months), whereas,

Table 1. Patient's clinical pathological features.

Variable		Case (n = 309)	
		n	%
Gender	Male	229	74.11
	Female	80	25.89
Age	< 60	154	49.84
	≥ 60	155	50.16
Tumor size	< 3cm	119	38.51
	≥ 3cm	190	61.49
T	T1 + T2	140	45.31
	T3 + T4	169	54.69
Lymph node metastases	Negative	116	37.54
	Positive	193	62.46
Vascular invasion	Negative	300	97.09
	Positive	9	2.91
Nerve invasion	Negative	264	85.44
	Positive	45	14.56
TNM stages	0 (I)	3	0.97
	1 (II)	224	72.49
	2 (III)	82	26.54
AFP	Normal	304	98.38
	High	5	1.62
CEA	Normal	272	88.03
	High	37	11.97
CA199	Normal	268	86.73
	High	41	13.27
Total protein	Normal	277	89.64
	Low	32	10.36
Serum albumin	Normal	261	84.5
	Low	48	15.50
Survival time (months)	< 48	98	32.00
	≥ 48	211	68.00

mean overall survival of patients with normal serum albumin was 49.098 months (49.098 months vs. 38.262 months, $p = 0.000$; Figure 1A). Figure 1B and 1C show data obtained from T stages and LNM, respectively. Mean overall survival was 53.237 months and 41.939 months for those with T1 + T2, and patients with T3 + T4, respectively ($p = 0.000$). Mean overall survival times were 53.424 months and 43.974 months for patients without LNM and patients with LNM, respectively ($p = 0.000$).

DISCUSSION

Serum albumin is an important serum protein which confers colloidal stability. Low albumin can cause changes of the albumin: globulin ratios that alter protein metabolism which can be fatal. Also, serum albumin is a critical cellular nutrient and offers essential amino acids via protein decomposition, and albumin is an important transport protein. Cancer patients' tumors are characterized by rapid cell proliferation which elevates cell metabolism and consumes albumin to the point that stores are critically decreased and prognosis worsens. Thus, serum albumin may be a biomarker for patient survival. A prospective study by Lam's group indicated

Table 2. Relationship between clinical pathological features and preoperative serum albumin levels.

Clinical or molecular feature	Preoperative serum albumin levels				p
	< 35 g/L		≥ 35 g/L		
	No.	%	No.	%	
Total no. of patients	48	15.5	261	84.5	
Gender					
Male	35	15.3	194	84.7	0.837
Female	13	16.3	67	83.8	
Age					
< 60	14	9.1	140	90.9	0.002
≥ 60	34	21.9	121	78.1	
Tumor size					
< 3cm	10	8.4	109	91.6	0.006
≥ 3cm	38	20	152	80	
T					
T1 + T2	15	10.7	125	89.3	0.033
T3 + T4	33	19.5	136	80.5	
Lymph node metastases (LNM)					
Negative	10	8.6	106	91.4	0.009
Positive	38	19.7	155	80.3	
Vascular invasion					
Negative	45	15	255	85	0.135
Positive	3	33.3	6	66.7	
Nerve invasion					
Negative	43	16.3	221	83.7	0.376
Positive	5	11.1	40	88.9	
TNM stages					
0 (I)	0	0	3	100	0.069
1 (II)	29	12.9	195	87.1	
2 (III)	19	23.2	63	76.8	
AFP					
Negative	48	15.8	256	84.2	0.334
Positive	0	0	5	100	
CEA					
Negative	39	14.3	233	85.7	0.116
Positive	9	24.3	28	75.7	
CA199					
Negative	42	15.7	226	84.3	0.864
Positive	6	14.6	35	85.4	
Total protein					
Normal	28	10.1	249	89.9	0.000
Low	20	62.5	12	37.5	
Survival time (months)					
< 48	27	27.6	71	72.4	0.000
≥ 48	21	10	190	90	

Table 3. Univariate and multivariate Cox Model analysis of the factors related with survival.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age				
< 60	1	0.061	1	0.633
≥ 60	1.474 (0.983 - 2.210)		1.113 (0.718 - 1.725)	
Gender				
Female	1	0.839	1	0.502
Male	1.048 (0.665 - 1.651)		1.173 (0.736 - 1.867)	
Tumor size				
< 3cm	1	0.014	1	0.895
≥ 3cm	1.746 (1.121 - 2.721)		1.033 (0.635 - 1.681)	
T				
T1 + T2	1	0.000	1	0.003
T3 + T4	2.906 (1.853 - 4.557)		2.156 (1.309 - 3.550)	
Lymph node metastases				
Negative	1	0.000	1	0.016
Positive	2.686 (1.657 - 4.356)		1.894 (1.128 - 3.179)	
Vascular invasion				
Negative	1	0.307	1	0.713
Positive	1.600 (0.650 - 3.940)		1.197 (0.460 - 3.119)	
Nerve invasion				
Negative	1	0.111	1	0.726
Positive	1.530 (0.906 - 2.584)		1.109 (0.622 - 1.978)	
AFP				
Negative	1	0.112	1	0.328
Positive	2.541 (0.804 - 8.033)		1.872 (0.533 - 6.572)	
CEA				
Negative	1	0.014	1	0.426
Positive	1.896 (1.136 - 3.164)		1.277 (0.669 - 2.334)	
CA199				
Negative	1	0.020	1	0.805
Positive	1.817 (1.099 - 3.005)		1.078 (0.592 - 1.965)	
Total protein				
Normal	1	0.205	1	0.625
Low	1.459 (0.814 - 2.618)		0.847 (0.432 - 1.648)	
Serum albumin				
Normal or high (≥ 35 g/L)	1	0.000	1	0.008
Low (< 35 g/L)	2.341 (1.499 - 3.655)		2.018 (1.204 - 3.381)	

that albumin can indicate survival for those with advanced cancer [8]. Siddiqui and coworkers reported that serum protein predicts early mortality in pancreatic cancer patients [9,10]. Several lines of evidence also suggest that low serum albumin is related to prognosis or survival for ovarian cancer patients whose primary can-

cers occur at unknown sites [2,12]. Because GC can influence digestion and compromise protein synthesis, low albumin is especially important for patients with GC [11]. However, the relationship between preoperative serum albumin and GC prognosis is still unclear. Thus, we studied a cohort of 309 patients

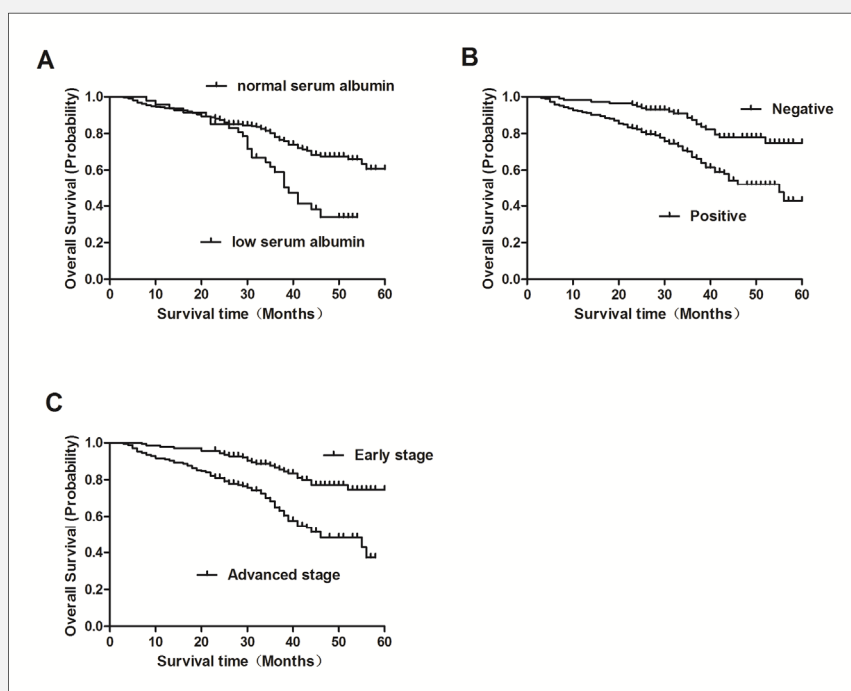


Figure 1. Kaplan-Meier survival curves and log rank test results for serum albumin, lymph node metastases, and invasion (T stages), respectively.

A: Mean overall survival time (months) for GC patients with hypoalbuminemia (< 35 g/L) was shorter than for those with normal albumin (≥ 35 g/L) ($p = 0.000$); **B:** Mean overall survival time (months) for GC patients with lymph node metastases (positive) was shorter than for those with no metastases (negative) ($p = 0.000$); **C:** Mean overall survival time (months) for GC patients with advanced stages (T3 + T4) was significantly shorter than for GC patients at early stages (T1 + T2) ($p = 0.000$).

from the Fujian area, which has a high incidence of GC and we noted that for those with low serum albumin mean survival was 38.262 months, much less than the mean survival for those with normal serum albumin (49.098 months). These data agree with previous studies of other cancers [2,8-15]. Also, our data showed that tumor's invasion/T stages, lymph node metastases, and serum albumin were independent prognostic factors for overall survival.

CONCLUSION

Data from the multivariate cox regression results revealed that serum albumin and invasion/T stage and lymph node metastases were associated with death, and low serum albumin, deeper tumor invasion, and lymph node metastases were independent prognostic factors for poor survival in GC patients. Increasing serum albumin may improve the health of GC patients with hypoalbuminemia, but our sample size was small. Larger studies may confirm these preliminary assertions and establish a true

clinical value for this measurement. Thus, preoperative serum albumin is closely associated with GC patient survival and may have enormous clinical utility.

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Declaration of Interest:

The authors declare that they have no conflicts of interests.

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