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ORIGINAL ARTICLE

Prospective Study

Postoperative decrease of serum albumin predicts short-term complications in patients undergoing gastric cancer resection

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Abstract

AIM

To find an accurate and simple predictor for post-operative short-term complications after gastrectomy.

METHODS

Two hundred and twenty-three patients undergoing gastric cancer resection between October 1, 2015 and September 30, 2016 were enrolled in this study. Univariate and multivariate analyses were used to

identify risk factors for complications after gastrectomy. The cutoff values and diagnostic accuracy were examined by receiver operating characteristic curves.

RESULTS

Sixty-two (27.8%) patients had short-term complications after gastric cancer resection. The postoperative decrease in serum albumin (ΔALB) was an independent risk factor for complications (OR = 17.957, 95%CI: 6.073-53.095, $P < 0.001$). The cutoff value was 14.0% and the area under the curve was higher than that of C-reactive protein on postoperative day 3 (area under the curve: 0.806 *vs* 0.709). Patients with ΔALB ⩾ 14.0% were more likely to have short-term complications after gastrectomy (46.7% *vs* 5.0%, $P < 0.001$), prolonged hospital stay (17.2 ± 10.8 d *vs* 14.1 ± 4.2 d, $P = 0.007$) and higher comprehensive complication index ($P < 0.001$) than those with ΔALB < 14.0%.

CONCLUSION

Postoperative ΔALB with a cutoff of 14.0% can be used to recognize patients who have high risk of short-term complications following gastric cancer resection.

Key words: Gastric cancer; Postoperative complications; Gastrectomy; Serum albumin; Predictor

Core tip: In this work, we investigated whether postoperative decrease of serum albumin can predict short-term complications following gastric cancer resection. Results indicate that the decrease of serum albumin could be more accurate than postoperative C-reactive protein in predicting complications after gastrectomy. Surgeons are warned of potential postoperative complications in patients whose serum albumin levels reduce by more than 14.0%. This is the first evaluation of the relationship between decrease in albumin and postoperative complications in gastric cancer resection.

Liu ZJ, Ge XL, Ai SC, Wang HK, Sun F, Chen L, Guan WX. Postoperative decrease of serum albumin predicts short-term complications in patients undergoing gastric cancer resection. *World J Gastroenterol* 2017; 23(27): 4978-4985 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i27/4978.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i27.4978

INTRODUCTION

Gastric cancer is one of the most common malignancies and is the third leading cause of cancer-related mortality in China. Surgery provides the only possibility of cure in patients with gastric cancer. Despite improvements in perioperative care and surgical procedures, postoperative complications remain a major impediment and threat to survival after gastric cancer surgery[1-3]. Therefore, it is crucial to specify a reliable and simple risk assessment index to indicate the possibility of postoperative complications, and the likelihood of early and safe patient discharge.

Many preoperative or postoperative indexes, such as C-reactive protein (CRP; a proinflammatory cytokine increasing in parallel with postoperative surgical stress), white blood cell count and albumin (ALB), have been identified as risk factors for complications after gastrectomy[4-8]. There are many studies revealing the association between serum ALB and postoperative outcomes. For example, preoperative hypoalbuminemia can predict surgical site infections[9]. Ryan *et al*[10] found that postoperative hypoalbuminemia on postoperative day (POD) 1 was associated with complications following esophagectomy. Sang *et al*[11] also found that hypoalbuminemia on POD 2 was an independent risk factor for acute kidney injury in patients with living donor liver transplantation. However, these studies mainly focused on the impact of serum ALB on nutritional status of patients[12,13].

ALB is also a negative acute phase protein and decreases after surgery, because of trauma and increased capillary leakage[14]. Norberg *et al*[15] observed an immediate and sharp decrease of serum ALB level (ΔALB) by 33% after major abdominal surgery, which occurred even earlier than the change in CRP. Unfortunately, few studies have identified the change in serum ALB level as a marker in predicting the outcomes of gastrectomy.

This study aimed to clarify whether the reduction of ALB level after surgery could be a predictor for short-term complications following gastric cancer resection. Therefore, the ΔALB on POD 1 was examined and its diagnostic accuracy in gastric cancer was investigated.

MATERIALS AND METHODS

Patients

Written informed consent was obtained from all the patients enrolled in the investigation. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and the Ethics Committee of Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School, Nanjing, China.

Data collection

The data of 317 consecutive patients who underwent surgery for gastric cancer between October 1, 2015 and September 30, 2016 at the Department of Gastrointestinal Surgery, Nanjing Drum Tower Hospital, the Affiliated Hospital of Nanjing University Medical School were prospectively collected and standard ethnic audit was conducted. Patients with ALB infusion preoperatively or within POD 1, reoperation for postoperative complications, non-resection of the stomach, severe organ dysfunction or comorbidity, multivisceral resection, or incomplete laboratory data

were excluded. Finally, a total of 223 patients were enrolled in the study.

Data were collected based on the following factors: age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, initial clinical stage, comorbidity, surgical procedures (surgical approach, type of resection, degree of lymph node dissection), neutrophils, lymphocytes, hemoglobin, tumor makers such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, preoperative CRP and ALB, CRP on POD 3[16], ALB on POD 1[11], operation time, estimated blood loss during surgery and intraoperative blood transfusion.

Definition of outcomes

Relative ΔALB was calculated as: (preoperative ALB level - ALB level on POD 1)/preoperative ALB level × 100%[17]. Receiver operating characteristic (ROC) curve was used to calculate the cutoff values of ΔALB. The postoperative outcomes were analyzed which included length of postoperative hospital stay and postoperative complications before discharge or < 30 d after surgery. Postoperative complications was identified by Clavien-Dindo classification, which showed that the Grades Ⅰ and Ⅱ were mild complications and Grades Ⅲ and Ⅳ were major complications in patients[18]. The comprehensive complication index (CCI) is a score developed to include all complications after surgery and is based on the Clavien-Dindo system[18,19]. The CCI of each patient was calculated using the Website http://www.assessurgery.com[20].

Statistical analysis

SPSS version 19.0 (SPSS Inc., Chicago, IL, United States) was used for the analysis. Categorical data were expressed by counts and percentages, while continuous data were expressed by mean ± SD or median (range). Fisher's exact test or Pearson's χ^2 test was used to analyze categorical variables, while Student's *t*-test was used to analyze continuous variables. $P < 0.05$ was considered statistically significant. ROC curve analysis was used to assess the predictive accuracy. Significant correlations ($P < 0.05$) on univariate analysis were used to verify independent predictors for postoperative complications by multivariate logistic regression analysis.

RESULTS

Study population and baseline characteristics

There were 159 men and 64 women, with a mean age of 62.3 ± 9.9 years. The clinical characteristics are summarized in Table 1. The preoperative mean BMI, and CRP and ALB level were 23.0 ± 3.4 kg/m^2, 6.6 ± 10.3 g/L and 38.3 ± 3.2 g/L, respectively. One hundred and seventeen patients received total gastrectomy, 82 distal gastrectomy and 24 proximal gastrectomy. One hundred and eighty patients underwent D2 or more lymphadenectomy. The operation time was 239.1 ± 66.9 min, with blood loss of 228.6 ± 146.2 mL. The length of postoperative hospital stay was 15.8 ± 8.6. Sixty-two patients (27.8%) had postoperative complications. According to Clavien-Dindo classification, 40 patients (17.9%) had mild complications (Grade Ⅰ or Ⅱ), and 22 (9.9%) had major complications (Grade Ⅲ or greater).

Predictive factors for postoperative complications

The results of univariate analyses of various clinical factors are shown in Table 2, including age, sex, BMI, ASA grade, clinical stage, tumor makers (CA19-9, CEA), lymphocyte count, comorbidity, preoperative hemoglobin, operation time, intraoperative blood loss, surgical procedures (mode of approach, type of resection, degree of lymph node dissection), preoperative CRP and serum ALB, CRP on POD 3, and ΔALB. Among these, diabetes mellitus (OR = 3.259, 95%CI: 1.128-9.414, P = 0.029), preoperative serum ALB (OR = 1.048, 95%CI: 1.018-1.109, P = 0.015), clinical stage (OR = 1.798, 95%CI: 1.255-2.686, P = 0.009), type of resection (OR = 1.291, 95%CI: 1.006-1.896, P = 0.013), CRP on POD 3 (OR = 4.653, 95%CI: 2.435-8.889, $P < 0.001$) and ΔALB (OR = 16.837, 95%CI: 6.403-44.275, $P < 0.001$) were significantly associated with postoperative complications. Therefore, a multivariate analysis model was used to identify the independent predictive factors for complications after gastrectomy. As shown in Table 3, ΔALB (OR = 17.957, 95%CI: 6.073-53.095, $P < 0.001$) remained as an independent risk factor in predicting complications after surgery. However, it was not strong enough for us to draw the conclusion that ΔALB can be an accurate predictor for complications after gastrectomy.

Predictive accuracy of ΔALB and CRP on POD 3 for complications after gastrectomy

CRP on POD 3 was identified as a practical predictor for complications after gastric cancer surgery in recent studies[7,16]. In this study, the predictive accuracy of ΔALB and CRP on POD 3 was analyzed by ROC curve. Figure 1 shows the ROC curve parameters. The area under the curve (AUC) of CRP on POD 3 was 0.709, sensitivity was 0.785, specificity was 0.661, Youden's index was 0.446, and the cutoff point was 131.9; comparatively, the AUC of ΔALB was 0.806, sensitivity was 0.808, specificity was 0.675, Youden's index was 0.483, and the cutoff point was 14.0%. Therefore, ΔALB was a better predictive index than CRP on POD 3 for postoperative complications in patients undergoing gastric cancer surgery.

Use of ΔALB to predict complications after gastrectomy

Based on the cutoff value of ΔALB, we divided patients into two groups. As shown in Table 4, patients with ΔALB ⩾ 14.0% had more complications after gastrectomy than those with ΔALB < 14.0% (46.7% *vs* 5.0%, P

Table 1 Patient characteristics

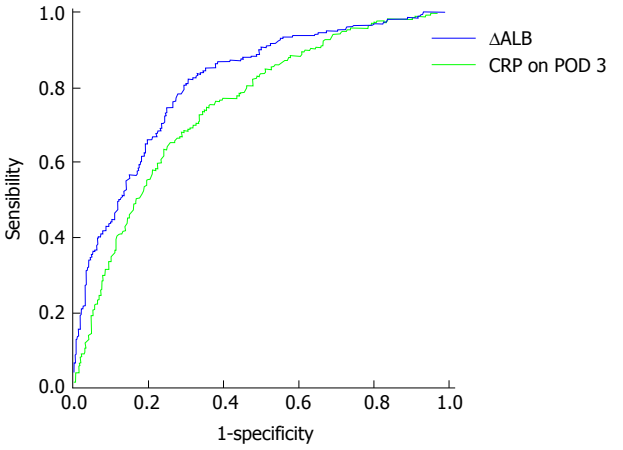
Characteristic	*n* = 223
Age in yr	62.3 ± 9.9
Sex, *n*	
Male	159
Female	64
BMI in kg/m^2	23.0 ± 3.4
Comorbidities, *n*	
Diabetes mellitus	15
Hypertension	72
Preoperative serum albumin in g/L	38.3 ± 3.2
Preoperative hemoglobin in g/L	123.4 ± 24.9
Preoperative CRP in g/L	6.6 ± 10.3
CA 19-9 in ng/mL	
≥ 37	43
< 37	180
CEA in ng/mL	
≥ 5	26
< 5	197
Lymphocyte count as × 10^9/L	
≥ 3	9
< 3	214
CRP on POD 3 in mg/L	99.7 ± 60.9
ALB on POD 1 in g/L	32.7 ± 3.6
ASA ≥ 3, *n*	122
Clinical stage Ⅰ / Ⅱ / Ⅲ / Ⅳ, *n*	67/44/103/9
Mode of surgical approach, *n*	
Laparoscopic	18
Open	205
Type of resection, *n*	
Distal gastrectomy	82
Proximal gastrectomy	24
Total gastrectomy	117
Degree of lymph node dissection ≥ 2, *n*	180
Operation time in min	239.1 ± 66.9
Blood loss in mL	228.6 ± 146.2
Postoperative complications as Clavien-Dindo grade, *n*	
Ⅰ and Ⅱ	40
≥ Ⅲ	22
Postoperative stay in d	15.8 ± 8.6

ALB: Albumin; ASA: American Society of Anesthesiologists; BMI: Body mass index; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CRP: C-reactive protein; POD: Postoperative day.

< 0.001). Patients with Δ < 0.001). Patients with Δ ALB ≥ 14.0% were found to have more mild or severe complications than those with ΔALB < 14.0% (30.3% *vs* 3.0%, *P* < 0.001 or 16.4% *vs* 2.0%, *P* < 0.001, respectively). In addition, patients who had Δ ALB ≥ 14.0% were suggested to have prolonged postoperative stay (17.2 ± 10.8 *vs* 14.1 ± 4.2, *P* = 0.007) and higher CCI (*P* < 0.001).

DISCUSSION

In this study, serum ALB was mainly considered as an acute phase protein. The ΔALB was an independent risk factor for prolonged hospital stay and complications after gastrectomy. Patients were distinguished as having low or high risk of complications after gastrectomy by the cutoff value of 14.0% in ΔALB, which was more accurate than CRP level on POD 3.



	ΔALB	CRP on POD 3
Cutoff point	0.140	131.9
AUC	0.806	0.709
Sensitivity	0.808	0.785
Specificity	0.675	0.661
Youden's index	0.483	0.446

Figure 1 Receiver operating characteristic curve showing decrease in serum albumin levels and C-reactive protein levels on postoperative day 3 predictive of postoperative overall complications. ROC: Receiver operating characteristic; CRP: C-reactive protein; ΔALB: (Albumin level before surgery-albumin on POD 1)/albumin level before surgery × 100%; POD: Postoperative day; AUC: Area under the curve.

Numerous studies have shown that preoperative and postoperative hypoalbuminemia are risk factors for complications after surgery[9-12], while few have specifically focused on the relationship between decreased serum ALB after surgery and clinical outcomes. Hübner *et al*[21] reported that stress response led to a reduction in postoperative albumin levels, which was consistent with the findings in our study. After major abdominal surgery, the albumin synthesis rate remained the same, whereas the fractional synthesis rate increased, leading to a decrease in plasma ALB[15]. However, sequestration into the interstitial space may contribute most to a postoperative drop in ALB level[14,21]. Capillary leakage is especially common in some malnourished patients with surgical trauma followed by an increased transcapillary escape rate of ≥ 100%[14,22,23]. To summarize, multiple factors affect the reduction in serum ALB after surgery and the stress response plays an important role in the change[23].

Nevertheless, increasing evidence shows that postoperative CRP level, as a risk factor for postoperative inflammation, can be used to predict complications after gastrectomy[7,24]. For instance, Kim *et al*[16] found that the CRP level on POD 4 was one of the most reliable predictors for complications following gastric cancer resection, when compared to many systematic inflammatory markers (white blood cells, neutrophils, platelet counts and CRP on POD 1). However, in previous studies, certain drawbacks were found by using postoperative CRP as a marker of

Table 2 Univariate analysis of risk factors associated with postoperative complications

Characteristic	OR	95%CI	*P* value
Age ⩾ 75 yr	1.330	0.476-3.715	0.586
Sex	0.642	0.342-1.202	0.166
BMI of < 18.5 kg/m^2	0.277	0.034-2.232	0.228
Comorbidities			
Diabetes mellitus	3.259	1.128-9.414	0.029
Hypertension	0.728	0.382-1.389	0.336
Preoperative serum albumin of < 35 g/L	1.048	1.018-1.109	0.015
Preoperative hemoglobin of < 120 g/L	1.487	0.817-2.705	0.194
Preoperative CRP of ⩾ 10 g/L	1.336	0.512-3.486	0.553
CA 19-9 of ⩾ 37 ng/mL	1.328	0.647-2.723	0.439
CEA of ⩾ 5 ng/mL	1.177	0.483-2.865	0.720
Lymphocyte count of ⩾ 3 × 10^9/L	0.314	0.038-2.560	0.279
CRP on POD 3 in mg/L	4.653	2.435-8.889	< 0.001
△ALB of ⩾ 14.0%	16.837	6.403-44.275	< 0.001
ASA of ⩾ 3	1.007	0.559-1.815	0.981
Clinical stage of ⩾ Ⅱ	1.798	1.255-2.686	0.009
Mode of surgical approach	1.206	0.588-2.475	0.610
Type of resection	1.291	1.006-1.896	0.013
Degree of lymph node dissection ⩾ 2	2.263	0.948-5.399	0.066
Operation time of ⩾ 250 min	1.621	0.896-2.931	0.110
Blood loss of ⩾ 200 mL	1.417	0.758-2.651	0.275

ΔALB: (Albumin level before surgery-albumin on POD 1)/albumin level before surgery × 100%; ASA: American Society of Anesthesiologists; BMI: Body mass index; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CRP: C-reactive protein; POD: Postoperative day.

Table 3 Multivariate analysis of risk factors associated with postoperative complications

Characteristic	OR	95%CI	*P* value
Age ⩾ 75 yr	1.053	0.248-4.470	0.945
Sex	0.572	0.237-1.380	0.214
BMI of < 18.5 kg/m^2	0.147	0.013-1.666	0.122
Comorbidities			
Diabetes mellitus	1.234	0.322-4.726	0.759
Hypertension	0.989	0.397-2.463	0.981
Preoperative serum albumin of < 35 g/L	0.914	0.897-1.067	0.093
Preoperative hemoglobin of < 120 g/L	1.804	0.748-4.353	0.189
Preoperative CRP of ⩾ 10 g/L	1.008	0.210-4.840	0.993
CA 19-9 of ⩾ 37 ng/mL	1.197	0.431-3.327	0.730
CEA of ⩾ 5 ng/mL	0.794	0.233-2.706	0.713
Lymphocyte count of ⩾ 3 × 10^9/L	0.192	0.018-2.048	0.172
CRP on POD 3 in mg/L	4.296	1.887-9.780	0.001
△ALB of ⩾ 14.0%	17.957	6.073-53.095	< 0.001
ASA of ⩾ 3	0.929	0.406-2.127	0.861
Clinical stage of ⩾ Ⅱ	1.198	0.355-2.286	0.109
Mode of surgical approach	1.737	0.576-5.235	0.327
Type of resection	0.791	0.506-1.896	0.063
Degree of lymph node dissection ⩾ 2	3.485	1.163-10.446	0.026
Operation time of ⩾ 250 min	1.448	0.624-3.355	0.389
Blood loss of ⩾ 200 mL	1.418	0.636-3.160	0.393

ΔALB: (Albumin level before surgery-albumin on POD 1)/albumin level before surgery × 100%; ASA: American Society of Anesthesiologists; BMI: Body mass index; CA 19-9: Carbohydrate antigen 19-9; CEA: Carcinoembryonic antigen; CRP: C-reactive protein; POD: Postoperative day.

complications after gastrectomy, which lacks accuracy in certain conditions[16,21,25]. Rettig *et al*[5] discovered that increased CRP levels after surgery were not early enough to identify patients at high risk for postoperative complications. In our study, ΔALB was an independent predictive marker for complications after gastrectomy in multivariate analysis. The AUC of ΔALB was larger than that of CRP on POD 3, suggesting ΔALB was a better positive predictive marker. According to these findings, ΔALB had a higher predictive value and tended to be more precise than CRP.

ΔALB could be more precise than CRP in predicting complications after gastrectomy because it is more accurate in reflecting the stress response after surgical trauma. As previously mentioned, the serum ALB level decreases earlier than CRP level after major abdominal surgery. The postoperative reduction in ALB level is associated with systemic inflammatory

Table 4 Univariate analysis of postoperative complications associated with median value of ΔALB

Characteristic	All, n = 223	ΔALB < 14.0%, n = 101	ΔALB ⩾ 14.0%, n = 122	P value
Overall[1,3]	62 (27.8)	5 (5.0)	57 (46.7)	< 0.001
Mild complications[1,3]	40 (17.9)	3 (3.0)	37 (30.3)	< 0.001
Major complications[1,3]	22 (9.9)	2 (2.0)	20 (16.4)	< 0.001
Postoperative stay in d[2]	15.8 ± 8.6	14.1 ± 4.2	17.2 ± 10.8	0.007
CCI all patients[4]	0 (0-20.9)	0 (0-0)	8.7 (0-26.2)	< 0.001

[1]Clavien-Dindo's classification of surgical complications; [2]Values are expressed as the median ± SD; [3]Values are expressed as n (%); [4]Values are expressed as median (interquartile range); ΔALB: (Albumin level before surgery-albumin on POD 1)/albumin level before surgery × 100%; CCI: Comprehensive complication index.

response syndrome, which leads to increased fractional synthesis and pathological capillary leakage of serum ALB[14]. Besides, serum ALB has a series of significant physiological functions, including free radical scavenging, maintenance of colloid osmotic pressure, change of capillary membrane permeability, and anticoagulant effects[26]. Hypoalbuminemia inhibits the innate immune response by promoting granuloma formation and reducing collagen synthesis. As a result, the systemic immune status is more sensitive to infection and other postoperative complications[27]. In contrast, CRP is involved in innate immunity as an early defense against infection, enhancing phagocytosis by macrophages and assisting complement binding to damaged cells or foreign matter[28]. From the above, the finding that ΔALB could be more precise than CRP in predicting complications after gastrectomy is understandable, and serum ALB is a better predictor of both systemic inflammation and nutritional status.

However, it remains to be established whether ALB supplementation benefits patients with a large ΔALB after gastrectomy. Golub *et al*[29] reported that routine ALB infusion was not beneficial to patients in the surgical intensive care unit. For patients with postoperative hypoalbuminemia, ALB infusion was deemed to be useless after major gastrointestinal surgery[30]. No studies have ever demonstrated the benefit for patients with preoperative hypoalbuminemia. Instead, exogenous ALB administration might increase risks of edema, extravasation of albumin, or other postoperative complications[31]. More intensive perioperative care might relieve an early ΔALB following gastric cancer resection and improve patient outcomes by reducing postoperative generalized inflammation[9].

There were several limitations to the current study. First, it was a retrospective observational analysis, so the possibility of residual confounding factors could not be entirely excluded. Second, it was a single-center study and the outcome might have been influenced by the small number of patients enrolled and perioperative management strategies in our hospital. To verify the conclusions, multicenter prospective studies involving a large volume of data are needed. Third, whether the findings in our study could be applied to other operations, such as esophagectomy or liver resection, is not known for sure.

In conclusion, this study confirmed that a postoperative ΔALB can predict short-term complications following gastric cancer resection. The ΔALB could be more accurate than postoperative CRP in predicting complications after gastrectomy. Surgeons are warned of potential postoperative complications in patients whose serum ALB levels are reduced by > 14.0%.

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COMMENTS

Background

To find an accurate and simple predictor for postoperative short-term complications after gastrectomy. A reduction of serum albumin (ALB) level is observed in many patients after gastrectomy, but it remains uncertain whether it could be used as a predictor for short-term outcomes following gastric cancer resection.

Research frontiers

Many preoperative or postoperative indexes, such as C-reactive protein (CRP; a proinflammatory cytokine increasing in parallel with surgical stress after operation), white blood cell count and ALB, have been identified as risk factors for complications after gastrectomy. There are many studies revealing the association between serum albumin and postoperative outcomes. However, these studies mainly focused on the impact of serum albumin on nutritional status of patients.

Innovations and breakthroughs

The authors investigated whether the postoperative decrease of serum ALB can predict short-term complications following gastric cancer resection. The decrease of serum ALB could be more accurate than postoperative CRP in predicting complications after gastrectomy. This study involves the first evaluation of the relationship between decrease of ALB and postoperative complications in gastric cancer resection.

Applications

Surgeons are warned of potential postoperative complications in patients whose serum ALB levels are reduced by more than 14.0%.

Peer-review

The authors investigated serum ALB changes after gastrectomy and found a

correlation between the ALB change with short-term complication rates. Study results are interesting and have novel findings. They know colorectal surgery correlated with ALB changes, but gastric cancer is a new finding and may add some contribution to the literature.

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