Combination of Lymphocyte Count and Albumin Concentration as a New Prognostic Biomarker for Gastric Cancer

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Abstract

Aim: This research links systemic inflammation and nutritional status with gastric cancer prognosis and postoperative outcomes.

Methods: Patients undergoing total gastrectomy for gastric adenocarcinoma (2015-2018) were categorized into two: Low Lymphocyte–Albumin(LA) score (Group 1) and High Lymphocyte-Albumin score (Group 2). Demographics, clinical data, operative outcomes, and survival rates were compared. The LA score's predictive ability for lymph node positivity was assessed.

Results: Using a cut-off value of 6069.7, Group 1 had 59 patients (low value) and Group 2 had 45 (high value). Hospital readmissions due to wound infections were higher in Group 1 (16.9% vs. 2.2%, p=0.041). Both groups had similar tumor localization and total lymph nodes removed, but Group 1 had more positive lymph nodes (4 vs. 2, p=0.026). Survival rates were comparable (32.59 vs. 31.32 months, p=0.390).

Conclusions: Low LA scores correlate with a higher number of positive lymph nodes, serving as a postoperative quality assessment indicator.

Keywords: Gastric Cancer, prognosis, complication, albumin, lymphocyte count

Main Points

· Gastric cancer is the fifth most prevalent cancer worldwide, with a low 5-year survival rate of 20-40%. Its prognosis largely depends on the disease stage at diagnosis.

· A composite index called LA, derived from lymphocytes and albumin levels, has emerged as a potential prognostic marker in other cancers, yet its relevance in gastric cancer remains unexplored.

· This retrospective study analyzed 82 patients who underwent gastrectomy for gastric cancer, assessing the predictive ability of the LA score for metastatic lymph nodes and overall prognosis.

· While the LA score did not directly correlate with survival rates in gastric cancer patients, a low LA score was associated with a higher number of positive lymph nodes.

· The LA score, though not a direct predictor of survival, can be a valuable marker in assessing lymph node metastasis in gastric cancer and warrants further research.

1. Introduction

Gastric cancer is the fifth most common form of cancer worldwide, and the third leading cause of cancer-related death after lung and colorectal cancers. In 2018, 1.033.701 new cases were reported globally as well as 782.685 gastric cancer-related deaths.[1] Despite the use of multidisciplinary treatments, 5-year survival in gastric cancer is still low, reported in the range of 20–40%.[2]

While the prognosis of gastric cancer is determined based on such parameters as tumor localization, histological type, degree of differentiation and lymphovascular invasion, the leading prognostic factor is still disease stage at the time of diagnosis.[3,4] These parameters, however, remain insufficient for gastric cancer patients due to the search for individualized diagnosis and medical treatment. It is, therefore, necessary to identify prognostic markers that can accurately predict the prognosis of gastric cancer.

It would be erroneous to attribute the progression or metastasis of cancer solely to the behavior of tumor cells, as the nutritional and immune statuses of the host also play an important role, and can be assessed through a hematological examination.[5,6]

For instance, lymphocytes induce cytotoxic cell death and play an important defensive role against cancer by inhibiting the proliferation and migration of cancer cells.[7] Serum albumin level, one of the most used parameters for the prediction of nutritional status in patients, is also used for the assessment of cancer progression and prognosis – a decreased albumin level has been

linked to a shorter survival span in cancer patients.[8]

A recent research introduced the LA index, determined by the equation: (LA) = lymphocytes (/L) × albumin (g/L). This index was linked to lower survival rates in rectal cancer.[5] However, its correlation with gastric cancer hasn't been explored yet.

In the present study we assess the ability of a combined LA approach to predict the rate of metastatic lymph nodes and prognosis in gastric cancer patients who had undergone curative resection.

2. Materials and methods

The research encompassed 120 patients who received total gastrectomy for gastric cancer at the General Surgery Clinic of xxx University's Faculty of Medicine from January 2015 to December 2018. The Ethics Committee of xxx University Faculty of Medicine granted approval for this study. Informed consent was taken from all the patients. A database was created through a prospective review of patient files and hospital information system records, and this database was used to make a retrospective analysis of the patients. The study excluded patients who had palliative surgery, were diagnosed with Stage IV gastric cancer, were below 18 years old, were pregnant, had chronic inflammatory diseases like tuberculosis or sarcoidosis, suffered from autoimmune or hematological conditions, were on steroids for any purpose, or had unavailable records. Remaining 82 patients were included in the study.

The (LA) score was calculated using the formula of lymphocytes (/L) × albumin (g/L) using the blood samples collected when the patient was admitted for the operation. Based on the determined cut-off value using ROC curve, patients were categorized into two groups: Group 1 (Low LA) and Group 2 (High LA). The demographic characteristics, Body Mass Index (BMI), comorbidities, ASA score, neoadjuvant treatments, type and nature of the operation, tumor localization, and pathological stage of the tumor of the patients in both groups were recorded. The pathological tumor stage, total number of lymph nodes and the number of metastatic lymph nodes, duration of operation, mean blood loss, complications after surgery as classified by the Clavien-Dindo system.[9], rate of anastomotic leak, length of postoperative hospital stay, 30-day mortality, postoperative 30-day rate of unplanned hospital readmission and overall survival rate were recorded and compared between the two groups. The clinical value of the LA score in predicting postoperative lymph node positivity was calculated.

The tumor-node-metastasis (TNM) staging system 2016 was used for tumor staging.

An anastomotic leak was identified as a breach in the anastomotic connection, determined through a mix of clinical, radiological, and surgical methods.

The depth of tumor invasion was assessed preoperatively by endoscopic ultrasound in suspected cases. All patient records contained contrast-enhanced thoracic and upper and lower abdominal computed tomography imaging for staging purposes.

2.1.Statistical evaluation

IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) package program has been used for statistical analysis of the data. While evaluating the study data, besides the descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), Student's t test was used to compare quantitative data, and Mann Whitney U test was used to evaluate parameters that did not show normal distribution. Pearson's Chi-squared test and Fisher's Exact test have been used to compare qualitative data, Patients were divided into two groups according to the mortality, and roc analysis was performed according to these

groups. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) curve analysis to assess the association of LA with gastric cancer overall survival, multivariate Cox's proportional hazard model was conducted to estimate Hazard ratios (HRs) and their 95% confidence intervals (CIs). Kaplan-Meier analysis and Log Rank test were used for survival analysis. The $p<0.05$ value was considered statistically significant in the results.

3. Results

A ROC analysis was performed, producing a ROC curve to set a threshold for the LA score, resulting in a 56.4% area under the curve. Based on the established LA cut-off value of ≤6069.7, patients were deemed to have positive lymph nodes, showing a sensitivity of 51.85% and a specificity of 68%. These findings are detailed in Table 1 and Figure 1.

Using the 6069.7 cut-off value, the patients were classified as lower and higher group. Group 1 comprised 59 patients (n = 59) and Group 2 comprised 45 patients (n =45).

Table 1

Proposed cut-off values for significant parameters in lymph node positivity

	LA
AUC	0.564
95% CI (%)	0.463–0.661
Cut-off	>6069.7
Specificity	51.85
95% CI (%)	37.8–65.7
Sensitivity (%)	68.0
95% CI (%)	53.3–80.5
PPV	63.6
NPV	56.7
+LR	1.62
-LR	0.71
P	0.262

Figure 1

ROC analysis of LA analysis and positive lymph nodes
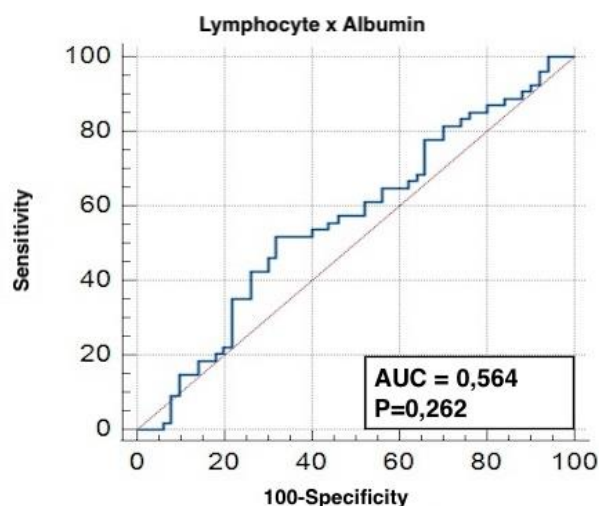
In comparing the groups, the average age (p=0.77), female proportion (p=0.313), and ASA score distribution (p=0.946) were consistent. However, Group 2 had a notably higher BMI (p=0.005). These findings are detailed in Table 2.

The rate of minimally invasive surgeries (p = 0.785), the distribution of complications in accordance with the Clavien-Dindo classification (p = 0.523), the rate of anastomotic leaks (p = 0.66) and the length of postoperative hospital stay (p = 0.080) were similar in the two groups (Table 3).

Table 2
Patient characteristics

		Group 1 Low LA	Group 2 High LA	p*
Age (mean ± SD)		61.3 ± 16.7	56.0 ± 11.8	0.077
Sex	Female	18 (30.5)	18 (40)	0.313
	Male	41 (69.5)	27 (60)	
ASA score	1	33 (55.9)	25 (55.6)	0.946
	2	17 (28.8)	14 (31.1)	
	3	9 (15.3)	6 (13.3)	
BMI (min–max)		23 (16–40.3)	25 (17.5–36)	0.050
Neoadjuvant CTx	Not received	42 (71.2)	33 (73.3)	0.829
	Received	17 (28.8)	12 (26.7)	

p < 0.05 ASA- The American Society of Anesthesiologists CTx -Chemotherapy

Table 3
Intraoperative and Postoperative Outcomes

		Group 1 Low LA	Group 2 High LA	p
Type of operation	Open	49 (83.1)	39 (86.7)	0.785
	Laparoscopic	10 (16.9)	6 (13.3)	
Duration of operation (min)		220 (170–500)	210 (160–480)	0.223
Complications (Clavien-Dindo)	1	10 (16.9)	8 (17.8)	0.523
	2	32 (54.2)	29 (64.4)	
	3A	10 (16.9)	6 (13.3)	
	3B	3 (5.1)	0 (0)	
	5	4 (6.8)	2 (4.4)	
Anastomotic leaks	None	53 (89.8)	40 (88.9)	0.666
	Stump leak	2 (3.4)	3 (6.7)	
	Esophagojejunostomy	4 (6.8)	2 (4.4)	
Length of postoperative hospital stay (days)		9 (4–46)	8 (2–40)	0.080
30-day hospital readmission	None	47 (79.7)	42 (93.3)	0.041
	Ileus	0 (0)	2 (4.4)	
	Impaired oral intake	1 (1.7)	0 (0)	
	Pneumonia	1 (1.7)	0 (0)	
	Wound site infection	10 (16.9)	1 (2.2)	

The two groups had a similar rate of neoadjuvant chemotherapy (p = 0.829); the most common tumor localization was the antrum in both groups (p = 0.607); the total number of lymph nodes removed, and the lymph node positivity rate were similar in the groups, while the number of positive lymph nodes was higher in Group 1 (p = 0.026). The most common pathological stage was Stage 2b in both groups (p = 0.084) (Table 4).

Group 1 saw a notably increased rate of readmissions to the hospital within 30 days (p=0.041). However, the overall survival rates between the groups were comparable (p=0.390), as illustrated in Table 5 and Figure 2.

Table 4
Tumor characteristics

		Group 1 Low LA	Group 2 High LA	p*
Tumor localization	Antrum	21 (35.6)	17 (37.8)	0.607
	Cardia	8 (13.6)	3 (6.7)	
	Corpus	19 (32.2)	14 (31.1)	
	Lesser curvature	5 (8.5)	8 (17.8)	
	Linitis Plastica	5 (8.5)	2 (4.4)	
	EGJ	1 (1.7)	1 (2.2)	
Total number of lymph nodes removed (mean) (min–max)		28 (3–63)	30 (7–60)	0.579
Number of positive lymph nodes (mean) (min–max)		4 (0–47)	2 (0–20)	0.026
Lymph node positivity	Negative	22 (37.3)	21 (46.7)	0.422
	Positive	37 (62.7)	24 (53.3)	
pSTAGE	1A	5 (8.5)	9 (20)	0.084
	1B	4 (6.8)	3 (6.7)	
	2A	0 (0)	5 (11.1)	
	2B	15 (25.4)	10 (22.2)	
	3A	7 (11.9)	4 (8.9)	
	3B	5 (8.5)	3 (6.7)	
	3C	23 (39)	11 (24.4)	
Pathological grade	Undifferentiated	7 (11.9)	11 (24.4)	0.342
	Poorly differentiated	24 (40.7)	18 (40.0)	
	Moderately differentiated	14 (23.7)	7 (15.6)	
	Well-differentiated	14 (23.7)	9 (20)	

p < 0.05 EGJ Esophagogastric junction

Figure 2
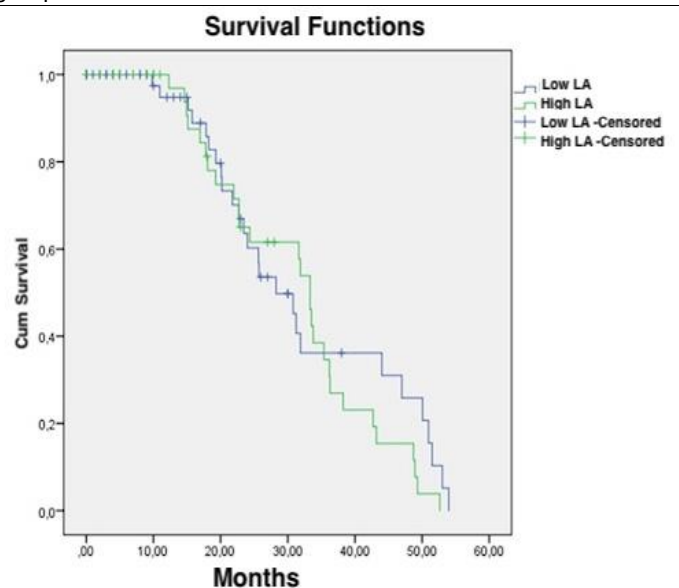Comparison of overall survival rates between low and high LA groups

Table 5

Overall survival by LA groups

		Mean (Mean + SD (Min–Max))	Median (Mean + SD (Min–Max))	p
LA group	Low LA	32.59 ± 2.67	28.26 ± 3.13	0.390
	High LA	31.32 ± 2.18	33.32 ± 1.13	

4. Discussion

Although there are a growing number of studies highlighting the prognostic value of various inflammatory markers in different cancer types, the clinical significance of these markers remains unclear. Moreover, there is a lack of consensus on the cut-off values to be assigned to each marker. In the present study we assess the prognostic significance of the LA ratio – a combination of these inflammatory and nutritional parameters – in patients with gastric cancer, which is one of the gastrointestinal cancers.

Low preoperative serum albumin is known to be a strong predictor of postoperative morbidity and mortality.[10,11] In their study of gastric cancer patients, Ouyang et al. found a low albumin level to be associated with reduced survival[12], and it is important to note that an initial low albumin value may affect early surgical outcomes, regardless of albumin replacement.[10,11]

Preoperative serum albumin is also widely used to predict the lymph node metastasis of gastrointestinal tumors. Ouyang et al. found a low albumin level to be associated with reduced survival in gastric cancer[12]; Liu Q et al. detected more metastatic lymph nodes in patients with low albumin levels[13]; O Huamán et al. identified decreased albumin levels with increasing tumor stage in gastric cancer; while Kang et al. showed that low albumin levels were associated also with increased rates of postoperative complications in gastric cancer patients.[10,14]

The chronic inflammatory effect causes lymphocytes to enter the tumor, and consequently, the surrounding tissues, increasing the likelihood of metastasis. Lymphocyte plays an important role in tumor-related immunology, having a strong anti-tumor immune function that can inhibit tumor progression, while high lymphocyte levels have been reported to be associated with a favorable prognosis in various tumors.[15,16] Feng et al. reported a low lymphocyte count to be associated with poor prognosis in gastric cancer.[17] In their meta-analysis, Schroth found preoperative lymphopenia to be associated with more frequent mortality and complications, regardless of the type of surgery.[18] Xu et al. established that preoperative lymphocytopenia was associated with increased lymph node metastasis, increased stage, and serosal invasion (T3+T4) risk and poorer overall survival in gastric cancer.[19]

Building on this data, Yamamoto T and team analyzed 448 patients with stage II/III rectal cancer post-curative resection. They discovered that a diminished LA score was linked to both decreased overall and disease-free survival. The researchers suggested its potential use in pinpointing patients at greater risk of relapse and assisting in choosing post-surgery treatments to minimize recurrence chances.[5]

In the present study, we did not find LA score to be a survival-related factor in patients who had undergone curative resection for gastric cancer, but it was associated with the number of positive lymph nodes. In addition, a low LA score seems to increase the rate of unplanned hospital admissions, which is one of the postoperative

quality indicators. We believe that our failure to identify any relationship with survival in our study could be related to the small patient population. Low LA increased the number of positive lymph nodes, as expected. Impaired nutritional status appeared to be an important parameter affecting the postoperative period.

Our research comes with certain limitations. Being a retrospective analysis with a limited sample size, there's potential for selection bias. To truly understand LA's clinical significance, more extended observation studies are necessary. Nonetheless, we believe that this work pioneers the exploration of this topic in the literature.

5. Conclusion

Our research indicates that the LA score by itself isn't a definitive predictor of survival for gastric cancer patients. However, a lower LA score does correlate with an increased count of positive lymph nodes. LA score can be used as a quality indicator for assessment in the postoperative period and is a new marker that can easily be calculated through routine blood tests, suggesting opportunities for further research.

Author Contributions

OY,UT conceived and designed the study. OY,UT,İCE,AU,GS,CKP acquired data. OY and UT confirm the authenticity of all the raw data. UT,BY performed the statistical analysis. İCE,AU,GS,CKP,BY interpreted the results, analyzed the data and drafted the manuscript. All authors read and approved the final version of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Originality Assertion

The authors have not submitted this article to another journal previously.

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