COMBINATION OF LYMPHOCYTE COUNT AND ALBUMIN CONCENTRATION AS A NEW PROGNOSTIC BIOMARKER FOR COLORECTAL CANCER

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ABSTRACT

Purpose: *In this study, it is aimed to evaluate the prognostic importance of lymphocytexalbumin (LA) combination in patients having colorectal cancer who underwent curative resection*

Method: *Patients who underwent curative surgery for colorectal cancer between the dates of January 2015 and January 2019 were included in the study. We defined the LA as lymphocyte count (/L)×albumin (g/L). The cut-off point was determined by ROC curves. The patients were divided into two groups according to the cut-off point: Group 1 (Low LA) and Group 2 (High LA). Demographic, clinical and pathological characteristics and survival times were compared between the two groups.*

Results: *Patients are divided into two groups based on the cut off point of 4413 Groups were comparable with respect to age, gender, ASA score, The rate of rectal tumor location was higher in Group 1 (60% vs 32.9 p<0.001). Rates of postoperative complications, unplanned readmission, and reoperation were similar in the groups. Low LA was found to be an independent risk factor with regards to decreased survival in multivariate analysis. (HR(95%-Cl) 2.840 (1.332-6.057) p:0.007). Overall and disease free survival rates were lower in Group 1 compared to Group 2 (44.2 vs 51.02 p:0.005; 47.1 vs 52.18 p:0.025, respectively).*

Conclusion: *This study indicated decreased overall and Disease-free survival (DFS) associated with low LA index in patients managed with curative treatment for colorectal cancer. No association was found between LA index and postoperative quality markers. LA might be a new prognostic biomarker for colorectal carcinoma.*

Keywords: *Colorectal cancer, inflammation, biomarker.*

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Introduction

According to GLOBOCAN 2020 data published by the International Cancer Agency, Colorectal Cancer (CRC) ranks in third row among the most frequently diagnosed cancers worldwide (as second in women and third in men according to the frequency of diagnosis), and second among cancers that cause death. It is anticipated that 1,931,590 people were diagnosed with colorectal cancer in the said year, and 935,173 people (9.4%) died due to the same cancer[1]. Biomarkers that are guiding in diagnosis, treatment of diseases and their being classified in sub-types, can be determined more quickly with developing technology and new techniques. In recent years, the discovery of cancer biomarkers has become a main focus of cancer research. New biomarkers are needed, especially for CRC, which has an increasing incidence and still cannot achieve absolute success in early diagnosis/treatment. Cancer progression and metastasis do not only depend on the type of tumor cells, but nutrition and immunity also play an important role in these processes. Inflammatory cells and immune responses have consistently been seen as important factors in cancer prognosis. The immune or nutritional status of the host can be evaluated by hematological examination[2]. Lymphocytes has a role in both cytotoxic cell death and inhibition of tumor cell proliferation and metastasis by stimulating an immune response against the tumor

by means of activation of cytokines[3]. Cancer-related hypoalbuminemia is considered to be directly related to the patient's malnutrition. Other uncertain tumor-related factors are also likely involved. Cancer cells can produce cytokines such as interleukin-6 (IL-6), which regulate albumin production. In cancer patients, serum albumin remains clinically central to the assessment of nutritional status, disease severity, disease progression, and prognosis[4, 5].

Based on this evidence, a recent study reported that LA, being a new composite index calculating lymphocytes (/L) × albumin (g/L) (LA), is correlated with poor survival in rectal cancer[6]. In this study, it was aimed to evaluate the prognostic importance of LA combination in patients with colorectal cancer who underwent curative resection, as well as its relationship with postoperative complications.

Methods

After getting permission from the Ethics Committee of Çukurova University Faculty of Medicine, patients who underwent curative surgery for colorectal cancer between the dates of January 2015 and January 2019 were included in the study. Patients undergoing palliative surgery, those with chronic inflammatory/autoimmune disease, hematological disease and who were on immunosuppressive therapy and steroids were excluded from the study. Analyzes were made with the blood samples that were taken when the patients were hospitalized for operation. Cut-off value was specified by ROC curves and they were divided into two groups according to the cut-off value as Group 1 (LA low) and Group 2 (LA high). In these two groups, demographic characteristics, body mass index, ASA score, tumor marker level, type and nature of the operation, tumor localization, pathological stage of tumors, response to treatment in patients receiving neoadjuvant therapy, stoma status, conversion to open surgery, intraoperative complications, postoperative hospital stay, postoperative complications, unplanned hospital readmission, reoperation, long-term disease-free survival, and overall survival were compared.

Unplanned hospitalization within the first 30 days after discharge was considered as unplanned readmission to the hospital. Pathological stage of the disease was determined as per the 8th TNM Classification[7]. We considered unplanned reoperation as a surgical procedure under general, spinal or epidural anesthesia within 30 days of the index operative procedure for any reason, excluding follow-up procedures based on pathology results, in accordance with the ACS NSQIP definition[8].

Definition of coversion was the use of any incision made for anything other than sample extraction or port placement, as previously described. Extracorporeal anastomosis was not considered as conversion to open[9]. Anastomotic leakage was defined as a deterioration in the integrity of the anastomosis documented by a combination of clinical, radiological, and operative tools. Wound infection was defined as a superficial or deep incisional surgical site infection occurring in the surgical wound, according to the definition of the Centers for Disease Control (CDC)[10].

Sampling was calculated in g.power 3.1. In the sample calculation, it was found to be sufficient for more than 200 patients at the 0.5 effect level and the 0.05 Alpha significance level at 95% power.

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, while logistic regression was used for multivariance assessments. Patients were divided into two groups according to the survey, 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 CRC 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.

Results

A total of 279 patients participated in our study. Mean age of the patient population was 61.4 +12.1 (20-107) and 36.2% of the patients were female. ROC analysis and ROC curve were created to establish a

cut-off value for the LA value. The ROC analysis yielded an area under the ROC curve of 65.7%. In other words, the cut-off point gives a correct answer with a rate of 65.7%. According to the cut off value we obtained, it is assumed that if the LA value 4413.2, it has an effect on survival with a sensitivity of 57% and with a specificity of 71 (Table 1). Graphic which is created to determine the diagnostic value of the LA score in predicting survival is shown in Figure 1.

	LA
AUC	0,657
95%-CI (%)	0,598-0,713
Cutoff	<4413,2
Specificity	71,43
95%-CI (%)	53,7-85,4
Sensitivity (%)	56,56
95%-CI (%)	50,1-62,9
PPV	19,1
95%-CI (%)	15,5-23,3
NPV	93,2
95%-CI (%)	89-95,9
+LR	0,61
-LR	1,98
p	**0,002**

Table 1: Proposed cut-off values for significant parameters associated with overall survival.

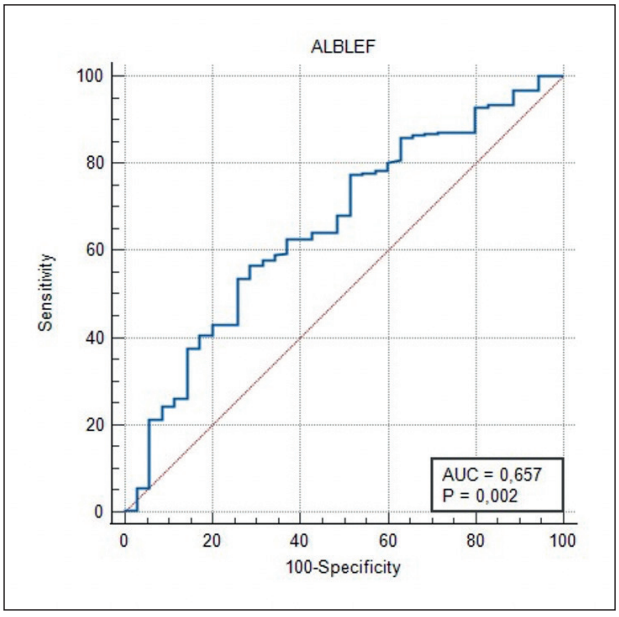

Figure 1: Receiver operating characteristic (ROC) curve analyses for the overall survival.

Patients are divided into two groups as per value of 4413:

- Group 1: low LA (score <4413);
- Group 2: high LA (score>4413).

There were 130 patients in group 1 and 149 patients in group 2. Mean age (61.7 vs 61.1, p: 0.702) of pation population, male gender rate (66.2% vs 61.7%,p: 0.445), ASA score distribution (p:0.454), BMI (26 vs 26.5 p:0.387) and tumor markers levels were similar between the groups. The rates of rectal tumor location (60% vs 32.9 p<0.001) and patients who received neoadjuvant therapy (45.4% vs 8.7% p<0.001) was higher in Group 1 (Table 2).

		Low LA n:130	High LA n:149	p*
Age (Mean+Std) (Min-max)		61,7±12,8 (20-107)	61,1±11,5 (27-91)	0,702
Gender	Male	86 (66,2)	92 (61,7)	0,445
	Female	44 (33,8)	57 (38,3)	
ASA score	1	67 (51,5)	68 (45,6)	0,454
	2	38 (29,2)	54 (36,2)	
	3	25 (19,2)	27 (18,1)	
Body mass index(Mean+Std) (Min-max)		26,0±4,8 25 (18-51)	26,5±4,4 26 (18-50)	0,387
CEA (Mean+Std) (Min-max)		6,82±1,63 (0-146)	4,77±8,4 (0-73)	0,182
Ca19.9 (Mean+Std) (Min-max)		42,5±160,8 (0-1760)	48,6±338,7 (0-4036)	0,851
Neoadjuvant therapy	No	59 (45,4)	13 (8,7)	**<0,001**
	Yes	71 (54,6)	136 (91,3)	
Tumor localization	Right-sided	31 (23,8)	52 (34,9)	<0,001
	Left-sided	21 (16,2)	48 (32,2)	
	Rectum	78 (60,0)	50 (32,9)	

Table 2: Demographic characteristics and preoperative findings of the patients.

With regards to the operative features, emergency surgery rates (12.3% vs 12.1%) were similar in the groups. However, stoma creation rate was higher in group 1 (55.4% vs 28.9% p<0.001). Operattive characteristics are shown in Table 3. Tumor stage, mucinous tumor histology rate (20.8 % vs 15.4%) p:0.369, and well differentiated tumor rate (50% vs 47%,p:0.499) were similar in the groups. Poor response to neoadjuvant therapy was more frequent in group 1 (35.6% vs 14.3% p<0.001). (Table 4).

		Low LA n:130	High LA n:149	p*
Surgical	Emergency	16 (12,3)	18 (12,1)	NA
	Elective	114 (87,7)	131 (87,9)	
Operative technique	Open	73 (56,2)	93 (62,4)	0,328
	Laparoscopic	57 (43,8)	56 (37,6)	
Stoma creation	No	58 (44,6)	106 (71,1)	**<0,001**
	Yes	72 (55,4)	43 (28,9)	
Conversion	No	9 (6,9)	4 (2,7)	0,151
	Yes	121 (93,1)	145 (97,3)	
Intraoperative complication	No	124 (95,4)	145 (97,3)	0,627
	Yes	6 (4,6)	4 (2,7)	

Table 3: Operative data.

		Low LA n:130	High LA n:149	p*
Histological type	Mucinous	28 (20,8)	23 (15,4)	0,369
	NOS	100 (76,9)	125 (83,9)	
	Signet ring cell	2 (1,5)	1 (0,7)	
Pato grade	Low differentiated	27 (20,8)	26 (17,4)	0,499
	Medium differentiated	38 (29,2)	53 (35,6)	
	Well-differentiated	65 (50)	70 (47)	
Pato stage	0	2 (1,5)	1 (0,7)	0,285
	1	32 (24,6)	22 (14,8)	
	2	1 (0,8)	0 (0)	
	2A	7 (5,4)	16 (10,7)	
	2B	38 (29,2)	38 (25,5)	
	2C	1 (0,8)	1 (0,7)	
	3A	6 (4,6)	8 (5,4)	
	3B	24 (18,5)	38 (25,5)	
	3C	72 (55,4)	43 (28,9)	
Tumor regression (only rectum)	Poor response	16 (35,6)	1 (14,3)	**<0,001**
	Minimal response	16 (35,6)	5 (71,4)	
	Medium response	8 (17,7)	1 (14,3)	
	Complete response	5 (11,1)	0 (0)	

Table 4: Pathological features based on LA level.

Postoperative complications, length of stay, unplanned readmission to the hospital, and reoperation rates were similar in the groups. In the follow-up, distant organ metastases developed more frequently in Group 1 (10% vs 4% p:0.048) (Table 5).

	Low LA n:130	High LA n:149	p*
Postop period stay hospital	9,74±7,92	9,23±6,54	0,556
(Mean+Std) (Min-max)	(2-75)	(1-49)	
Wound place infection	23 (17,7)	16 (10,7)	0,119
Anastomotic leak	2 (1,5)	5 (3,4)	0,333
Reoperation	7 (5,4)	8 (5,4)	NA
Unplanned readmission to hospital	22 (16,9)	15 (10,1)	0,112
Local recurrence	8 (6,2)	3 (2,0)	0,076
Distant organ metastasis	13 (10)	6 (4,0)	**0,048**

Table 5: Perioperative and postoperative clinical and oncological outcomes.

After accounting all patient and tumor characteristics including tumor location, and stage, low LA was found to be an independent risk factor in relation to the decreased survival in multivariate analysis. (HR (95%-Cl) 2,840 (1.332-6.057) p:0.007). Overall survival (44.2 vs 51.02 p:0.005) and disease free survival (47.1 vs 52.18 p:0.025) rates was lower in Group 1 compared to Group 2 (Figure 2 and 3). Subgroup analysis was performed for colon and rectal cancer patients. Overall survival rate of colon (43.4 vs 50.7 p:0.033) and rectal cancer (43.4 vs 50.7 p:0.033) was lower in Group 1 compared to Group 2 (Table 6 and Figure 4).

It was determined that those with low lymphocyteXAlbumin value had a 0.375 times higher risk of mortality than those with high levels (Exp (B) 0.375 95% CI (0.184-0.766) p=0.007).

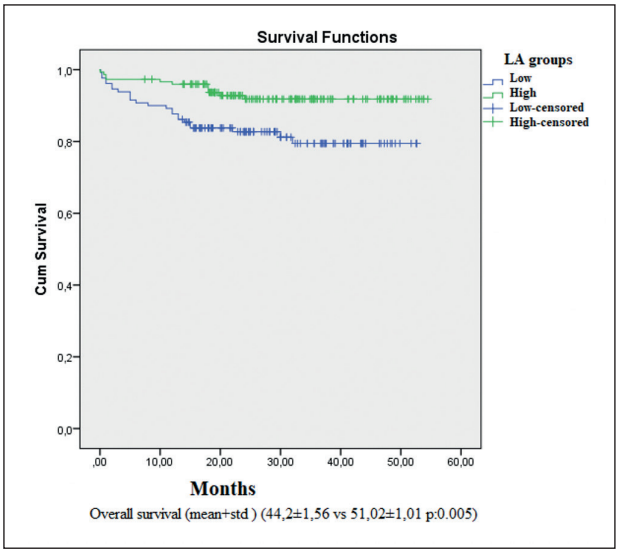

Figure 2: Overall survival as per LA groups.

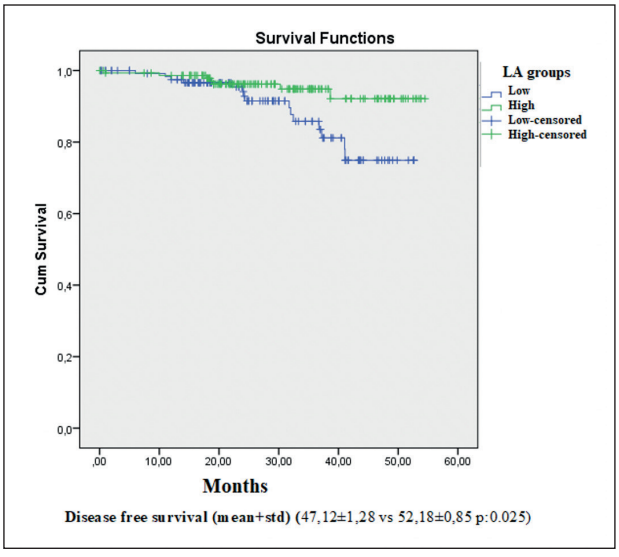

Figure 3: Disease free survival as per LA groups.

Survival subgroup	LA	Mean				p
		Estimate	Std. Error	95% Confidence Interval		
				Lower Bound	Upper Bound	
Colon	Low	43,467	2,594	38,383	48,550	0,033
	High	50,799	1,265	48,319	53,279	
Rectum	Low	44,705	1,935	40,912	48,497	0,033
	High	50,894	1,626	47,707	54,082	

Table 6: Overall survival in colon and rectal cancer subgroups as per LA groups.

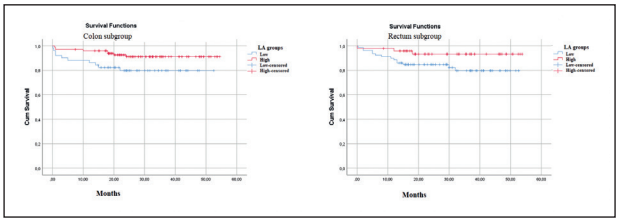

Figure 4: Overall survival in colon and rectal cancer subgroups as per LA groups.

Discussion

In this study, the prognostic significance of LA index was examined in patients who underwent radical surgery for nonmetastatic colorectal cancer in a single center. Apart from the recognized prognostic factors in the TNM stage, the contribution of LA ratio, being a parameter that reflects the inflammatory and nutritional status, to prognosis and its relationship with postoperative complications were evaluated. In the analysis realized by considering all the differences related to patient characteristics and disease stage, LA index was determined to be an independent risk factor for OS ve DFS in patients who underwent curative resection for CRC.

Most important prognostic factors correlated with colorectal cancer in the literature are stage, histological grade, local tumor spread, presence of distant metastases, blood or lymphatic vessel invasion, residual tumor after curative surgery, and preoperative CEA elevation[11] . In addition to TNM staging, there is increasing evidence that immune response can be a significant prognostic indicator, and many prognostic scoring systems were defined based on the existence of systemic inflammatory response[12-14]. Besides, nutritional status was shown to be a prognostic factor in colorectal cancer, and the correlation between impaired nutritional status and increased risk of postoperative complications was shown in various studies[15-19].

In a cohort of 30,676 colorectal cancer patients by Hu.W.H, 5230 had mild hypoalbuminemia (<35 and >=30 g/L) and 21,310 had normal albumin levels (>=35/g/L). There were significant correlations between mild hypoalbuminemia and 11 postoperative morbidities, including deep vein thrombosis, pulmonary embolism, superficial and deep surgical site infection, pneumonia, septic shock, ventilator >48 hours, blood transfusion, return to the operating room, stroke, and reintubation. Mild hypoalbuminemia was also correlated with overall complication (B=0.064, p<0.001) and total hospital stay (B=2.236, p<0.001)[20]. In a similar way, in the Haskins IN study, preoperative hypoalbuminemia increased the risk of 30-day mortality significantly (p<0.0001). Correlation of hypoalbuminemia with 30-day results was more significant in patients who underwent open surgery and underwent intra-abdominal anastomosis. It was seen that the risk of negative events increased at ≤3.1 g/dL albumin level[21]. Haga, Y et al considered low preoperative serum albumin level as a risk factor for decreased survival in EPOS-CC score study they conducted[22]. Predictive impact of albumin on survival is observed in cancers of the gastrointestinal tract. In their systematic review, Gupta et al found that in 26 of 29 studies, high albumin levels were associated with better survival in patients with gastrointestinal cancer. Level of lymphocyte count was shown to be one of the important prognostic factors affecting survival in various malignancies[23] Oh, S. Y et al. demonstrated that the level of lymphocyte count is an independent prognostic factor in patients with rectal adenocarcinoma treated with preoperative chemoradiotherapy[24].

Similarly, Tanio A et al found that low lymphocyte count was associated with decreased survival time in colorectal cancer[25] Chiarelli, M et al determined that preoperative lymphocytopenia was associated with 30-day mortality, serious complications, and anastomotic leakage in patients who underwent intestinal resection for various reasons[26]. Lymphocytes include $CD4^+$ and $CD8^+$ T cells, NK cells, NKT cells, gamma-delta T cells and B cells, which are closely associated with tumor immunity. Hence, an association between fewer lymphocytes and impaired tumor immunity leading to tumor progression seems logical. Based on this evidence, Yamamoto, T et al included 448 patients with stage II/III rectal cancer who were undergoing curative resection in their study. They found that a low LA score was associated with reduced overall survival and relapse-free survival, and they concluded that it could be used to identify a high-risk subgroup for recurrence. it can also help on decision of postoperative treatment to prevent recurrence[6].

In our current study, we determined a correlation between LA index and tumor location in patients who underwent curative resection in relation to colorectal cancer, such that tumors located in the rectum had a lower LA index. Rectal cancers with a low LA index were less responsive to neoadjuvant therapy. A low LA was correlated with distant organ metastases developed during follow-up, and a low LA index shortened the survival time. When we

conducted subgroup analysis, we found that the role of colon tumors was more effective in decreased survival. LA index did not influence reoperation and readmission rates, which are among the postoperative quality indicators, in our study. There are many studies in the literature comparing the immunonutritional composite indices, but there is no study comparing the LA index with other indices. As new studies are carried out on this subject, it is possible to say something scientifically clear. This study has some limitations. The number of patients receiving neojuvant therapy was also different in the groups, which may lead to a decrease in LA value. This was a retrospective study having a relatively small population and hence, it may be affected by selection bias. As our study is one of the pioneering studies in relation to this subject in the literature, we believe that it contributes to the literature.

In conclusion, this study indicated a correlation between low LA index and decreased overall and DFS in patients with curative therapy for colorectal cancer. LA index, which is an independent risk factor for decreased survival, can be used to predict the prognosis for CRC patients. Further prospective studies with larger cohort are needed to confirm these findings.

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