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Low Absolute Lymphocyte Count Correlates with Lymph Node Metastases and Worse Survival of Patients with Gastric Cancer

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ABSTRACT

Background. Several studies have found that the absolute lymphocyte (ALC) or neutrophil count predicts the survival of patients with solid tumors, and that the neutrophil-to-lymphocyte ratio and the prognostic nutritional index are useful markers of gastric cancer prognosis. However, it remains unclear whether the ALC is prognostic of lymph node (LN) metastasis in patients with gastric cancer. In this study, we aimed to explore the impact of ALC on prognosis and distinctive clinical characteristics in patients with gastric cancer.

Patients and Methods. The medical records of patients with gastric adenocarcinomas who underwent radical gastrectomy with curative intent at Seoul St. Mary's Hospital and Yeouido St. Mary's Hospital between January 2010 and December 2017 were reviewed. Of these, 4149 patients for whom preoperative white blood cell, neutrophil, and lymphocyte counts were available were enrolled.

Results. In all 4149 patients, ALC gradually decreased as the pN stage increased. Those with an ALC of less than 1360 cells/µL were defined as a low-ALC group, and advanced cT and cN stages were the strongest risk factors for LN metastasis in both univariate and multivariate analyses; undifferentiated tumor histology and a low ALC were also significant risk factors. Patients of all stages in the ALC-low group exhibited poorer prognoses. The ALC-low group also exhibited a higher recurrence rate in a greater proportion of LNs.

Conclusions. In patients with gastric cancer, as the preoperative ALC decreases, the incidence of LN metastasis increases. A low ALC is associated with a high recurrence rate, particularly in LNs.

The TNM stage strongly influences the initial curative and adjuvant treatments of patients with gastric cancer and their prognoses. However, even among patients of the same stage, the survival outcomes and recurrence incidences/ locations differ, and predictions are challenging. It is very important to predict lymph node (LN) metastasis, which greatly influences the extent of treatment.[1–4] In particular, in patients with early gastric cancer (EGC), a decision to perform endoscopic submucosal dissection (ESD) is greatly affected by LN metastasis status and thus the possibility of curative resection.[5,6]

Preoperative computed tomography (CT) is commonly used to predict LN metastasis. However, its predictive accuracy is only about 60%.[7–9] Endoscopic ultrasonography (EUS) can be used to evaluate perigastric LNs but the N-staging accuracy is only 50–90%.[10,11] Recent efforts have been made to increase imaging accuracy using artificial intelligence but such approaches have not yet been adequately verified.[12]

LNs are secondary lymphoid organs that contain lymphocytes such as white blood cells (WBCs) that include B and T cells. LNs filter the lymph and identify and contain infections. Thus, the absolute lymphocyte count (ALC) and lymphocyte functional status may directly influence LN metastasis and/or be predictive of it and thus be of prognostic

utility. Several studies have found that the ALC and absolute neutrophil count (ANC) are prognostic in patients with solid tumors, and more recent studies have reported that inflammatory markers including the neutrophil-to-lymphocyte ratio (NLR) and the platelet- to-lymphocyte ratio (PLR) predict the outcomes of patients with gastric cancer.[13,14] However, few studies have explored a possible association between the ALC and LN metastasis. That is our topic here: we investigated whether the ALC was prognostic of LN metastasis.

PATIENTS AND METHODS

Patients

The medical records of patients with gastric adenocarcinomas who underwent radical gastrectomy with curative intent in Seoul St. Mary's Hospital and Yeouido St. Mary's Hospital between January 2010 and December 2017 were reviewed. Of these, 4149 patients whose preoperative WBC and neutrophil and lymphocyte levels were measured were enrolled. In patients with early gastric cancer, EUS was performed to determine whether endoscopic submucosal dissection (ESD) was indicated. However, in cases beyond ESD indication based on endoscopic findings and surgery was deemed appropriate, EUS was not routinely performed. Therefore, preoperative staging employed CT scan. Nodal staging was based on the number of LNs of diameter greater than 0.8 cm evident in CT. All patients underwent conventional radical gastrectomy with curative intent, as dictated by the Korean Gastric Cancer Treatment Guidelines.[6] Patients with early gastric cancer underwent D1+ LN dissection and those with locally advanced cancer underwent D2 or D2+ LN dissection. The pathological stage was classified using the criteria of the 8th edition of the American Joint Committee on Cancer.[7] Postoperative complications were defined as any event occurring during surgery or within 30 days after surgery. The severities of complications and re-interventions were graded using the Clavien–Dindo (C–D) scale (grades I–V); serious complications were defined as those of grade III or higher.[15] The study was approved by the Institutional Review Board of the College of Medicine, Catholic University of Korea (approval no. SC22RISI0185). Patient records were anonymized (de-identified) prior to analysis.

Statistical Analysis

The chi-squared or Fisher's exact test was used to compare between-group differences in categorical variables and the Wilcoxon rank-sum test was used to compare continuous variables. All P-values were two-sided, and $P < 0.05$ was taken to indicate statistical significance. We drew receiver operating characteristic (ROC) curves to assess the correlation between ALCs and LN metastasis; the optimal ALC cutoff that predicted metastasis was derived as an area under the curve (AUC). Univariate and multivariate analyses were performed to identify independent risk factors for LN metastasis via binomial logistic analysis. Survival analysis was performed using the Kaplan–Meier method with the log-rank test for univariate analyses, while multivariate analysis of survival was performed using a Cox proportional hazards model. All statistical analyses were performed using SPSS version 22.0 software (SPSS, Chicago, IL, USA).

RESULTS

Clinicopathological and Operative Features

The baseline clinicopathological and operative characteristics of all patients are summarized in Table S1. Of the 4149 patients, 2696 (65.0%) were male and 1453 (35.0%) were female, with a mean age of 61.29 (± 12.01) years. Preoperatively, 2229 (53.7%) were diagnosed with EGC and 3123 (75.3%) were diagnosed with cN0-stage disease. The mean WBC was 6257.36 cells/µL (± 1822.24), the ANC was 3675.11 cells/µL (± 1519.50), and the ALC was 1935.89 cells/µL (± 637.90). Pathologically, 2822 (68.0%) patients had stage I cancer; 3226 (77.8%) underwent subtotal gastrectomy and 923 (22.2%) had total gastrectomy. Of all patients, 821 (22.0%) developed postoperative complications. Severe complications (C–D grades III–V) occurred in 226 (6.0%) (Table S1).

ALC and Pathological N Stages

Table 2 lists the differences in the WBC counts and ALC by pN stage. White blood cell count did not significantly differ between N0 and other stages, and no gradual changes were apparent. However, ALC significantly differed in those of stages pN2 and pN3 compared with N0. Although no statistical difference between patients of stages N0 and pN1 was apparent, ALC gradually decreased from stage N0 to pN3. For the 3123 patients deemed to have cN0 status in preoperative CT, WBC was not affected by N stage, but ALC gradually decreased as N stage increased (Table 1).

On the basis of the optimal lymphocyte number cutoff that predicted LN metastasis, patients with ALCs less than 1360 cells/µL were defined as an ALC-low group. When all patients were divided by ALC, the ALC-low group was older and of lower body mass index (Table S1). Notably, that group also had a higher WBC; ANC did not differ between the groups. Both the clinical and pathological stages were more advanced in the ALC-low than the ALC-high group. Although fewer LNs were retrieved, metastatic LNs were more common in the ALC-low group (Table S1).

Univariate and multivariate analyses exploring the risk factors for LN metastasis revealed that advanced cT and cN

TABLE 1 Preoperative laboratory findings by pathological N stage (all patients and cN0 patients who underwent preoperative CT)

		WBC, cells/µL	P-value*	ALC, cells/µL	P value*
Total N = 4149		6257.36 (1 822.24)		1935.89 (637.90)	
	pN0 (n = 2 845)	6213.42 (1 756.10)		1968.53 (629.40)	
	pN1 (n = 483)	6385.98 (1 968.22)	0.071	1927.81 (640.65)	0.19
	pN2 (n = 367)	6386.07 (1 953.96)	0.08	1888.78 (669.82)	0.023
	pN3 (n = 454)	6291.87 (1 947.63)	0.42	1777.96 (637.34)	< 0.001
cN0 N = 3123		6190.00 (1 746.95)		1943.60 (632.91)	
	pN0 (n = 2504)	6164.66 (1 688.18)		1962.76 (2046.02)	
	pN1 (n = 309)	6285.85 (1 951.15)	0.297	1903.92 (636.41)	0.122
	pN2 (n = 175)	6186.85 (1875.93)	0.868	1841.79 (673.13)	0.015
	pN3 (n = 135)	6459.70 (2107.62)	0.112	1810.91 (604.08)	0.006

The data are means (± SDs). The chi-squared test was used to compare between-group differences in categorical variables and a P-value < 0.05 was deemed to indicate statistical significance

*Significantly different compared with the pN0 group

WBCs white blood cells, *ALC* absolute lymphocyte count

stages were the strongest such factors but ALC-low status [hazard ratio (HR) 1.375, *P* = 0.004] and the presence of an undifferentiated tumor (HR 1.400, *P* < 0.001) were also significant risk factors (Table 2).

ALC and Overall/Disease-Free Survivals

Univariate analysis revealed factors prognostic of the long-term oncological outcomes (Tables S2, 3); factors that significantly compromised prognosis were subjected to multivariate Cox's regression analysis (Table 3). In terms of overall survival, a high ECOG grade, lymphatic and neural invasion, an advanced pathological stage, and a low ALC (HR 1.347, *P* = 0.013) were the poorest prognostic factors. In terms of disease-free survival, lymphatic, vascular, and neural invasion and an advanced disease stage were the poorest prognostic factors. A low ALC was significant in univariate analysis (HR 2.264) but not significant in multivariate analysis (Tables S2, 3).

The Kaplan–Meier curves showed that all patients except those with stage IV of the ALC-low group experienced significantly poorer overall survival than others (Fig. 1); disease-free survival was also poorer but significantly so for only patients with stage II (Fig. 2). The recurrence rate by ALC status was significantly higher in the ALC-low than ALC-high group (6.4 versus 10.6%, *P* < 0.001; Table 4). In terms of recurrence site, the recurrence rate of the peritoneum and perigastric/distant LNs were significantly higher in the ALC-low than ALC-high group (1.4 versus 3.2%,

P = 0.014, and 1.6 versus 2.9%, *P* = 0.002, respectively, Table 4).

DISCUSSION

After radical gastrectomy, patients with gastric cancer always experience significant changes in life in terms of diet, nutritional status, and systemic immunity. Prediction of the precise cancer stage is very important when planning curative treatment. Life expectancy and quality of life after surgery must be thoroughly discussed with patients and their families, and treatment plans should be established. As mentioned above, preoperative staging relies solely on imaging, which is inaccurate.[8,9,11] The 8th edition of the AJCC guidelines states that cN staging is determined by counting the number of perigastric LNs that are round and/or of short axis diameter > 10 mm.[7] This is not reliable; pathologically metastatic LNs are not always that large. We found that a low ALC was a risk factor for LN metastasis and that the ALC gradually decreased from pathological stage N0 to N3 (thus as the stage increased). This was true of all 4149 patients, and also of the 3123 patients confirmed to be of stage cN0 via preoperative CT; the latter finding is particularly interesting.

It has been hypothesized that LNs have anticancer effects by detecting cancerous cells, recruiting cytotoxic cells, inducing apoptosis, and maintaining immune surveillance via tumor antigen production, and the ALC reflects the numbers of peritumoral lymphocytes.[16–18] If low, such

TABLE 2 Univariate and multivariate analyses of preoperative factors associated with pathological LN metastasis

		Univariate				Multivariate			
		HR	95% CI		P value	HR	95% CI		P value
			Lower	Upper			Lower	Upper	
Age		1.015	1.010	1.021	< 0.001				
Sex	Male								
	Female	0.900	0.761	1.063	0.215				
ECOG score	0								
	1	1.120	0.921	1.363	0.256				
	2	1.273	0.872	1.857	0.211				
	3	0.875	0.318	2.410	0.796				
	4	3.607	0.147	88.567	0.432				
Smoking status	None								
	Past	1.159	0.944	1.423	0.160				
	Current	0.987	0.807	1.206	0.896				
Alcohol consumption	None								
	Social	0.858	0.724	1.017	0.078				
	Heavy	0.874	0.671	1.139	0.319				
Location	Upper								
	Middle	1.036	0.772	1.390	0.814				
	Lower	1.146	0.903	1.453	0.262				
Differentiation	D								
	UD	1.435	1.206	1.706	< 0.001	1.400	1.181	1.660	< 0.001
cT	cT1								
	cT2	3.852	3.117	4.759	< 0.001	3.821	3.096	4.715	< 0.001
	cT3	6.218	4.912	7.871	< 0.001	6.324	5.012	7.979	< 0.001
	cT4	7.340	5.450	9.884	< 0.001	7.451	5.554	9.996	< 0.001
cN	cN0								
	cN1	3.073	2.459	3.839	< 0.001	3.051	2.443	3.809	< 0.001
	cN2	6.718	4.841	9.323	< 0.001	6.750	4.870	9.356	< 0.001
	cN3	28.109	13.029	60.644	< 0.001	28.277	13.104	61.020	< 0.001
ALC	High								
	Low	1.369	1.101	1.701	0.005	1.375	1.107	1.707	0.004

HR hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *D* differentiated, *UD* undifferentiated, *ALC* absolute lymphocyte count

numbers are reduced, compromising cancer clearance from the gastric mucosa and LNs; these are the first defenses of the immune system. The recurrence rate, especially in the lymph nodes and peritoneum, was higher in the low ALC group than in the high ALC group (Table 4). This may be the result of direct metastasis due to failure of the primary defense mechanisms that lymphocytes must provide.

A decrease in ALC and reduced lymphocyte functionality compromise the activities of LNs; cancer metastasizes. In the ALC-low group, the number of retrieved LNs was smaller than in the other group, but the number of metastatic LNs was higher, in line with what is suggested above. In the ALC-low group, the preoperative CT stage was rather advanced. The extents of LN dissection did not differ between the groups; thus, the fewer LNs retrieved from the ALC-low group more likely reflects patient rather than surgical factors.

A few previous studies have found that ALC is associated with gastric cancer prognosis.[13,19–21] Our results are in line with Feng et al., who reported that a high monocyte count and a low ALC are independently prognostic of survival in patients with gastric cancer.[20] Many works have explored the prognostic utilities of NLR and PLR but these reflect inflammation and nutritional status rather than systemic immunity.[14,22,23] NLR and PLR may be affected by both long-term and recent conditions apparent at diagnosis; it is not easy to identify what might influence these markers. In addition, both are difficult to determine, and no correlation has been reported between either marker and LN metastasis or recurrence.

TABLE 3 Multivariate analysis of the poorest prognostic factors in terms of both overall survival and disease-free survival

		Overall survival				Disease-free survival			
		HR	95% CI		*P* value	HR	95% CI		*P* value
			Lower	Upper			Lower	Upper	
ECOG score	0								
	1	2.387	1.923	2.962	< 0.001				
	2	4.688	3.232	6.801	< 0.001				
	3	3.988	1.447	10.990	0.007				
	4	24.955	1.550	401.751	0.023				
Lymphatic invasion	No								
	1+	1.687	1.294	2.200	< 0.001	3.264	2.205	4.831	< 0.001
	2+	1.776	1.253	2.518	0.001	2.005	1.184	3.395	< 0.001
	3+	2.434	1.649	3.593	< 0.001	2.590	1.470	4.565	0.001
Vascular invasion	No								
	Yes					1.515	1.069	2.147	0.019
Neural invasion	No								
	Yes	1.980	1.544	2.540	< 0.001	1.816	1.308	2.523	< 0.001
pStage	I								
	II	1.513	1.121	2.042	0.007	1.499	0.976	2.302	0.065
	III	3.437	2.552	4.631	< 0.001	3.076	2.040	4.640	< 0.001
	IV	3.944	2.015	7.722	< 0.001	2.975	1.277	6.930	0.011
ALC	High								
	Low	1.347	1.064	1.704	0.013				

HR hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *D* differentiated, *UD* undifferentiated, *LNs* lymph nodes, *ALC* absolute lymphocyte count

The strengths of our study are that it was the first to explore the relationships between ALC and LN metastasis/recurrence. We also found that ALC is both simpler to derive and more intuitively informative than numerical values such as NLR and PLR. Our findings have clearly demonstrated the significant risk associated with low ALC, suggesting a promising direction for future investigations. Currently, tumor, nodes, metastasis (TNM) stage remains the most robust prognostic factor in gastric cancer. Further research is needed to explore whether ALC status could be incorporated as an additional component in staging. In terms of clinical application, for patients with low ALC it is important to recognize that LN metastasis may be more prevalent than indicated by preoperative CT staging results when making decisions about the extent of surgery or planning postoperative surveillance intervals and examination scopes. Additionally, further studies are required to evaluate the impact on prognosis when ALC is restored through immune augmentation in patients with gastric cancer. However, given the growing evidence of improved patient outcomes with the combination of immune checkpoint inhibitors or Chimeric Antigen Receptor T cell (CART) with conventional anticancer agents, and their increasing clinical use, it is reasonable to anticipate that ALC could serve as a promising target for novel therapies.

One of the limitations of our work was that it was retrospective. However, we enrolled a relatively large number of patients treated at two centers; our data will aid the design of future prospective studies on the prognostic utility of ALC in terms of both LN metastasis and survival. However, the numerical and functional declines of lymphocytes that trigger metastasis remain unclear; it is important to explore whether lymphocyte restoration might improve survival. In addition, the clinical differences such as age, BMI, and smoking/alcohol status between patient groups according to ALC status cannot be completely ruled out as potential influences on patient prognosis. In our results, only high ECOG status was identified as a risk factor related to overall survival. Therefore, additional analysis adjusting for these factors using a large cohort will be needed for a detailed review in the future. Lastly, the cutoff for ALC used in our study was determined using AUC, but considering the limitations of a single study, it should be further validated through various research efforts.

In conclusion, assessment of ALC not only increased the accuracy of preoperative N staging, but was also prognostic. ALC may be immunologically prognostic because it influences LN metastasis, patient survival, and recurrence. Further studies should explore the mechanism in play and whether ALC might serve as a therapeutic target.
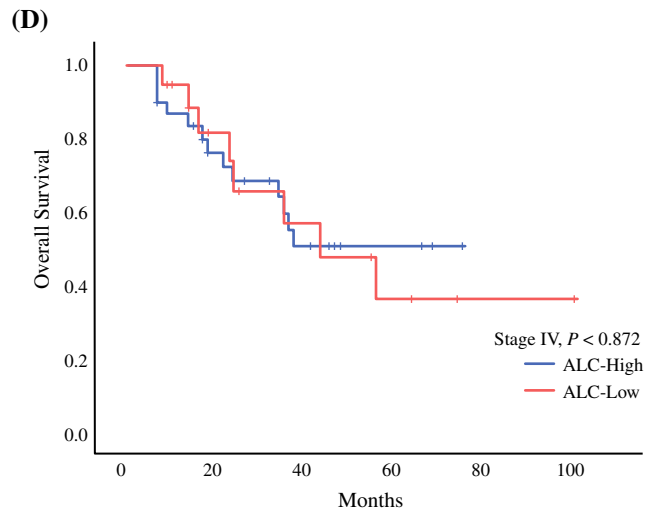
(A)
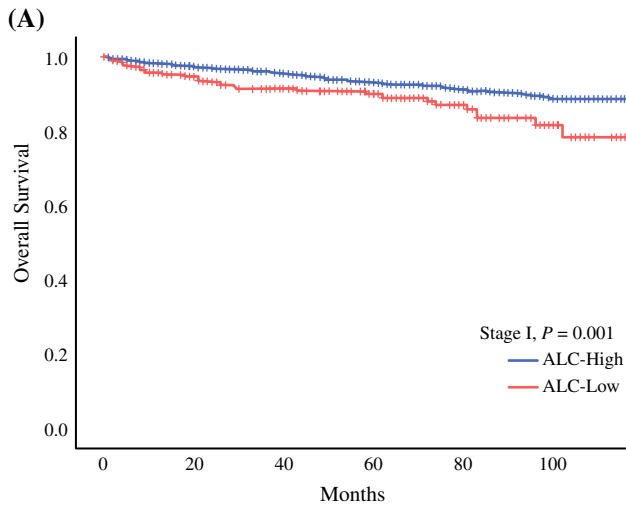
Months	0	20	40	60	80	100
ALC High	2341	1877	1501	974	493	167
ALC Low	398	306	240	158	81	29

(B)
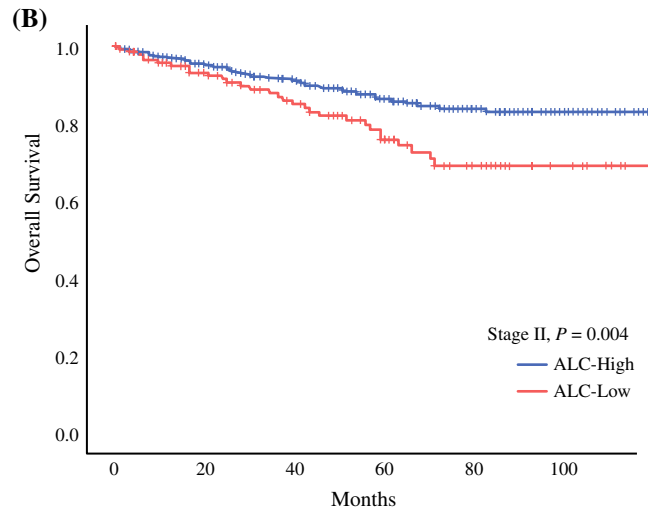
Months	0	20	40	60	80	100
ALC High	337	257	199	131	67	26
ALC Low	79	58	44	29	19	9

(C)
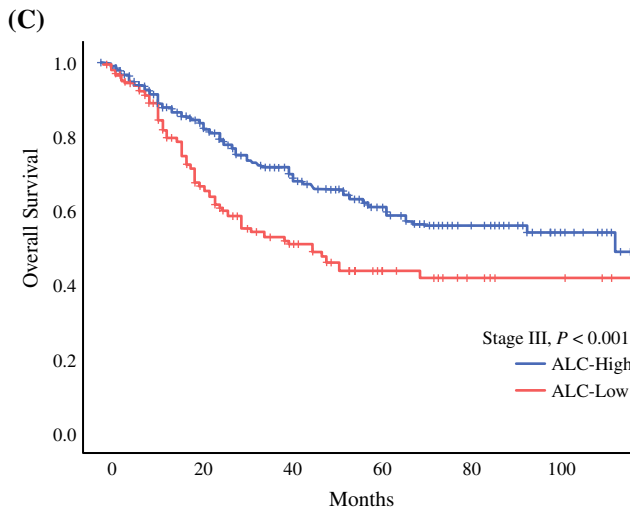
Months	0	20	40	60	80	100
ALC High	384	298	223	138	68	30
ALC Low	90	68	49	28	12	3

(D)

Months	0	20	40	60	80	100
ALC High	366	258	163	71	30	15
ALC Low	152	81	50	23	9	3

FIG. 1 Overall survival by ALC status; **A** pathological stage I ($P = 0.001$), **B** stage II ($P = 0.004$), **C** stage III ($P < 0.001$), **D** stage IV ($P = 0.872$)
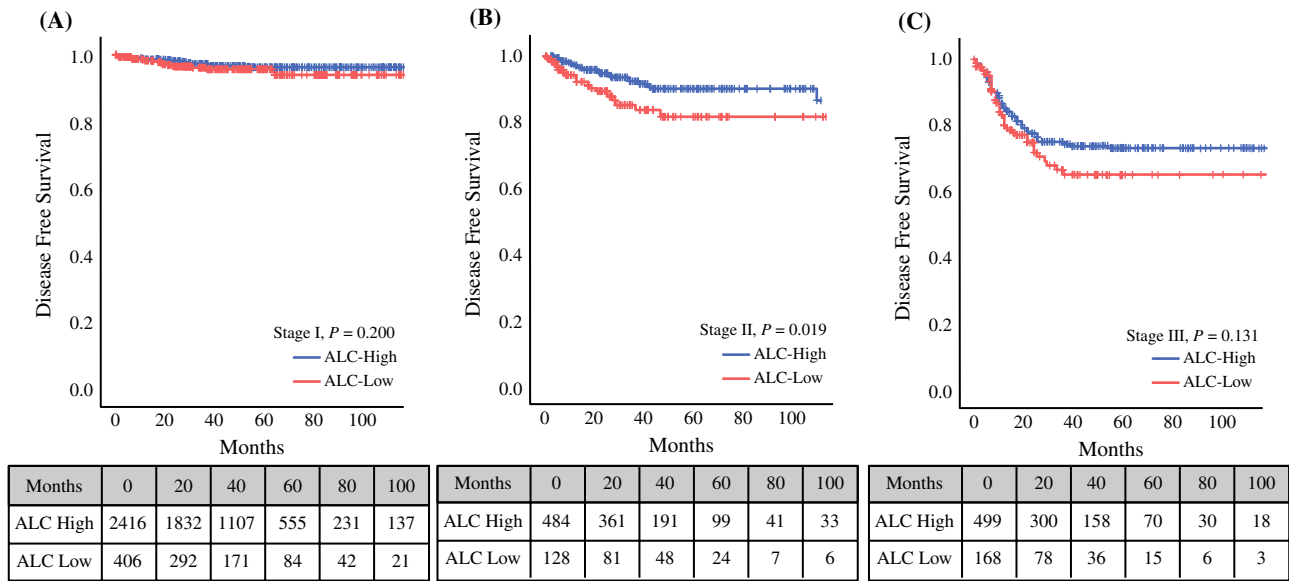
FIG. 2 Disease-free survival by ALC status; **A** pathological stage I (*P* = 0.200), **B** stage II (*P* = 0.019), **C** stage III (*P* = 0.131)

TABLE 4 Recurrence rate and pattern of the patients according to ALC status

		Total (*N* = 4149)	ALC-high (*n* = 3429)	ALC-low (*n* = 720)	*P* value*
Recurrence	Yes	296 (7.1%)	220 (6.4%)	76 (10.6%)	< 0.001
	Peritoneum	72 (1.7%)	49 (1.4%)	23 (3.2%)	0.002
	LNs	75 (1.8%)	54 (1.6%)	21 (2.9%)	0.014
	Distant organ	139 (3.4%)	110 (3.2%)	29 (4.0%)	0.256
	Unknown	10 (0.2%)	7 (0.2%)	3 (0.4%)	

Data given as percentage (%). Chi-squared test was used to evaluate between-group differences in categorical variables and a *P* value < 0.05 was deemed to indicate statistical significance. *LNs* lymph nodes

DATA AVAILABILITY All data and materials are available upon reasonable request to Y.J.J.

DISCLOSURE The authors declare that they have no conflicts of interest to report.

ETHICAL APPROVAL This study was approved by the Institutional Review Board of the College of Medicine, Catholic University of Korea (approval no. KC20RISI0344) and adhered to the Declaration of Helsinki and the dictates of Good Clinical Practice. All procedures met the ethical standards of the responsible committees on human experimentation (institutional and national) and those of the Declaration of Helsinki of 1964 and later versions.

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