

The prognostic significance of serum lactate dehydrogenase-to-albumin ratio in colorectal cancer

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Purpose: The purpose of our study was initially to explore the prognostic role of LDH-to-albumin ratio in patients with colorectal carcinoma (CRC) undergoing curative resection.

Methods: The retrospective study included 295 CRC patients that underwent curative resection. According to time-dependent receiver operating characteristics (ROC) analysis, the optimal cutoff value for pretreatment LDH-to-albumin ratio was 52.7. Cox regression univariate and multivariate analyses were utilized to analyze the prognostic factors for disease-free survival (DFS) and overall survival (OS).

Results: The 295 participants included 117 women (39.7%) and had an overall mean age of 55.8 ± 14.1 years. The median follow-up period was 31.8 ± 21 months (range, 6–78 months) and 53 patients (18.0%) died from cancer during the follow-up period. The 5-year DFS and OS rates were 65.4% and 68.5% in patients with LDH-to-albumin ratio <52.7 ($n = 152$), and were 55.2% and 55.4% in patients with LDH-to-albumin ratio ≥ 52.7 ($n = 143$), respectively. Kaplan-Meier curves showed that LDH-to-albumin ratio ≥ 52.7 was significantly associated with worse DFS and OS ($P = 0.003$ and $P < 0.001$, respectively). Multivariate analyses revealed that LDH-to-albumin ratio was an independent predictor of resectable CRC (odds ratio, 2.104; 95% confidence interval, 1.112–3.982; $P = 0.022$).

Conclusion: Our study revealed that high pretreatment LDH-to-albumin ratio level was an unfavorable prognosticator in patients with CRC undergoing curative resection. LDH-to-albumin ratio is a candidate to be a prognostic biomarker in clinical practice.

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Key Words: Colorectal neoplasms, Lactate dehydrogenase-to-albumin ratio, Survival

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and fourth leading cause of cancer-associated mortality worldwide. The global burden of CRC is expected to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 [1]. Despite the standardization of surgical procedures (total mesorectal excision and complete mesocolic excision) and the contributory effect of neoadjuvant and adjuvant therapies on

survival, recurrence occurs in 30%–50% of CRC cases [2]. There are numerous factors affecting survival in CRC that could be divided into 2 main groups: patient characteristics (performance status, age, and sex) and tumor characteristics (TNM stage, biomarkers, and gene mutations). However, it is well known that the survival time can differ even for patients with the same characteristics and the same disease stage at diagnosis. LDH and albumin are significant markers of systemic inflammation and have been shown to play a key role in promoting cancer

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progress and metastasis in many cancers including CRC [3-7].

The LDH assay is an inexpensive and practical analysis commonly used in clinical practice. LDH, which is a key enzyme in glycolysis, is required for the anaerobic conversion of pyruvate to lactate. LDH levels are regulated by the PI3K/AKT/mTOR pathway, the MYC oncogenic transcription factor, tumor hypoxia, and necrosis [8-10]. LDH levels are associated with tumor burden and may reflect tumor growth and invasive potential. Additionally, LDH levels have been shown to act as a significant prognostic marker of major malignancies including CRC and other gastrointestinal tract malignancies [11-16]. On the other hand, it has been reported that abnormal serum albumin is closely related to the progression of many diseases. Previous studies also indicated that low serum albumin levels are associated with poor prognosis in patients with esophageal, gastric, pancreatic cancers, and CRC [17-19]. Increased LDH value and low albumin value are indicators of poor survival. With a high LDH-to-albumin ratio, survival is expected to be poor. Although there is little or no documentation of the LDH-to-albumin ratio in the literature, LDH-to-albumin ratio has been shown to be associated with a poor prognosis in esophageal and hepatocellular cancers [20,21].

To our knowledge, there has been no study in the literature investigating the effect on LDH-to-albumin ratio on prognosis in CRC. The aim of this study was to assess the prognostic value of LDH-to-albumin ratio in patients with CRC after curative resection.

METHODS

Study population and ethics statement

The retrospective study included 295 CRC patients that underwent curative resection that was performed by the same surgical team (UA, AB) in the gastrointestinal surgery clinics at Dicle University Medical School Hospital and Elazig City Hospital between January 2013 and June 2019. During the study, 371 patients were operated on. Seventy-six patients (35 with missing pretreatment laboratory data, 4 with hemolysis, 18 without curative resection, 7 with early mortality, and 12 with loss in follow-up) were excluded from the study. The study protocol was approved by Firat University Clinical Research Ethics Committee (No. 97132852/09), and the study was conducted in accordance with the Helsinki Declaration. Written consent was obtained from each patient. Inclusion criteria were as follows: (1) an endoscopic diagnosis of adenocarcinoma established prior to the treatment, (2) a complete laboratory workup including LDH and albumin levels conducted during diagnosis or within the last month, (3) an R0 resection, and (4) complete clinicopathologic characteristics and follow-up data. Exclusion criteria were as follows: (1) a prior history of cancer, (2) any form of acute or chronic inflammatory diseases

or infections, (3) any form of systemic diseases, (4) presence of hemolysis, and (5) surgical resection other than R0 resection. Laboratory values of the patients were recorded before taking neoadjuvant chemoradiotherapy or chemotherapy. Chemotherapy and radiotherapy cause tumor lysis and tumor size changes. Since this will cause misleading results in LDH value, laboratory values at the time of diagnosis were recorded. Long-term chemoradiotherapy was given before surgery in patients with locally advanced rectal carcinoma. The treatment decision (surgical or perioperative chemotherapy) in patients with liver metastasis was determined by the multidisciplinary team.

Data collection

The main clinical characteristics including age, sex, tumor location, differentiation, TNM stage, American Society of Anesthesiologists physical status classification, serum levels of LDH, albumin, CEA, and CA 19-9 were retrieved from retrospective medical records. Routine laboratory measurements including counts of WBC, neutrophils, lymphocytes, and platelets were performed before treatment. The LDH level was correlated with AST, ALT, and potassium levels, and was excluded from the study in the presence of hemolysis. Postoperative complications were classified based on the Clavien-Dindo classification [22]. Tumor staging was performed according to the Union for International Cancer Control-American Joint Committee on Cancer (UICC-AJCC) TNM Classification System 7th edition [23].

Follow-up

All the patients were followed up once a month within the first year, once every 6 months within the first 3 years,

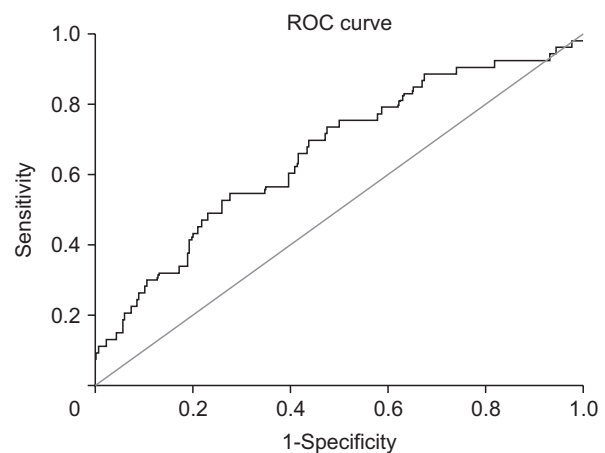


Fig. 1. The determination of the best cutoff of pretreatment LDH-to-albumin ratio. The cutoff value was 52.7. It resulted in a sensitivity of 69.8% and a specificity of 56.2% (area under the receiver operating characteristics (ROC) curve, 0.661; $P = 0.001$).

and once every year thereafter. Recurrence was identified based on radiological or biopsy (as needed) results, or surgical exploration. Disease-free survival (DFS) was defined as the

time interval between the date of operation and the time when recurrence was first identified. Overall survival (OS) was defined as the time interval from the date of surgery to the

Table 1. The relationship between LDH-to-albumin ratio and clinicopathological parameters in the present cohort

Variable	Total	LDH-to-albumin ratio		P-value
		<52.7	≥52.7	
Patients	295 (100)	152 (51.5)	143 (48.5)	
Age (yr)				
<65	216 (73.2)	114 (75.0)	102 (71.3)	0.477
≥65	79 (26.8)	38 (25.0)	41 (28.7)	
Sex				
Female	117 (39.7)	100 (65.8)	78 (54.5)	0.048
Male	178 (60.3)	52 (34.2)	65 (45.5)	
Body mass index (kg/m ²)	27.7 ± 3.8	27.1 ± 3.3	28.4 ± 4.1	0.003
ASA PS classification				
I-II	213 (72.2)	115 (75.7)	98 (68.5)	0.172
≥III	82 (27.8)	37 (24.3)	45 (31.5)	
Tumor location				
Rectum	118 (40.0)	62 (40.8)	56 (39.2)	0.775
Colon	177 (60.0)	90 (59.2)	87 (60.8)	
Liver metastasis	25 (8.5)	6 (3.9)	19 (13.3)	0.008
Neoadjuvant therapy	94 (31.9)	47 (30.9)	47 (32.9)	0.720
LDH (U/L)	215 ± 68 (126–750)	182 ± 22 (126–236)	251 ± 81 (136–750)	<0.001
Albumin (g/dL)	3.81 ± 0.6 (2–5.1)	4.05 ± 0.4 (2.7–5.1)	3.53 ± 0.6 (2.0–5.0)	<0.001
PLR				
<141.8	136 (46.1)	76 (50.0)	74 (51.7)	0.523
≥141.8	159 (53.9)	76 (50.0)	69 (48.3)	
NLR				
<2.73	169 (57.3)	97 (63.8)	72 (50.3)	0.019
≥2.73	126 (42.7)	55 (36.2)	71 (49.7)	
CEA (ng/mL)				
<5	202 (68.5)	133 (87.5)	86 (60.1)	0.003
≥5	93 (31.5)	19 (12.5)	57 (39.9)	
CA 19-9 (ng/mL)				
<37	243 (82.4)	133 (87.5)	110 (76.9)	0.017
≥37	52 (17.6)	19 (12.5)	33 (23.1)	
Surgical approach				
Laparoscopic	177 (60.0)	106 (69.7)	71 (49.7)	<0.001
Open	118 (40.0)	46 (30.3)	72 (50.3)	
Anastomotic leak	15 (5.1)	3 (2.0)	12 (8.4)	0.001
Clavien-Dindo classification				
<III	270 (91.5)	145 (95.4)	125 (87.4)	0.024
≥III	25 (8.5)	7 (4.6)	18 (12.6)	
Postoperative stay (day)	9.6 ± 4.2	9.3 ± 3.7	9.9 ± 4.7	0.226
T category				
0–1–2	97 (32.9)	63 (41.4)	34 (23.8)	<0.001
3–4	198 (67.1)	89 (58.6)	109 (76.2)	
Lymph node status				
pN0	178 (60.3)	101 (66.4)	77 (53.8)	0.027
pN+	117 (39.7)	51 (33.6)	66 (46.2)	
Degree of differentiation				
Well	128 (43.4)	81 (53.3)	47 (32.9)	
Moderately	111 (37.6)	43 (28.3)	68 (47.6)	0.001
Poorly	56 (19.0)	28 (18.4)	28 (19.6)	

Table 1. Continued

Variable	Total	LDH-to-albumin ratio		P-value
		<52.7	≥52.7	
TNM stage				
0	14 (4.7)	10 (6.6)	4 (2.8)	
I	69 (23.4)	48 (31.6)	21 (14.7)	
II	85 (28.8)	39 (25.7)	46 (32.2)	<0.001
III	99 (33.6)	48 (31.6)	51 (35.7)	
IV	28 (9.5)	7 (4.6)	21 (14.7)	
Adjuvant therapy	195 (66.1)	91 (59.9)	104 (72.7)	
Follow-up time (mo)	31.8 ± 21.1	32.8 ± 22.7	30.8 ± 19.2	0.400
Recurrence	65 (22.0)	23 (15.1)	42 (29.4)	0.003
Disease-related death	53 (18.0)	16 (10.5)	37 (25.9)	0.001

Values are presented as number (%) or mean ± standard deviation (range).

ASA, American Society of Anesthesiologists; PS, physical status; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

date of death. For patients without any sign of an event, the last follow-up data constituted the terminal record.

Cutoff determination of LAR

According to the time-dependent receiver operating characteristic (ROC) curve analysis that was conducted for predicting patients that died before the median OS, the optimal cutoff value for pretreatment LDH-to-albumin ratio was 52.7, which resulted in a sensitivity of 69.8% and a specificity of 56.2% (area under the ROC curve, 0.661; $P = 0.001$) (Fig. 1). Based on this cutoff value, 152 patients (51.5%) had a lower and 143 patients (48.5%) had a higher LDH-to-albumin ratio value before treatment. On the other hand, the cutoff values determined for the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were 2.73 and 141.8, respectively ($P > 0.05$ for both).

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows ver. 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviations or median with ranges. Categorical variables were expressed as frequencies (number) and percentages (%). Continuous variables were compared using independent samples t-test and categorical variables were compared using chi-square test or Fisher exact test. The OS was estimated using the Kaplan-Meier method and the outcomes were compared using the log-rank test. A Cox regression model was used to analyze the independent prognostic risk factors. Significant factors identified in univariate analysis were subsequently enrolled in the multivariate Cox proportional hazard model. A 2-tailed P level of <0.05 was considered significant.

RESULTS

The 295 participants included 117 women (39.7%) and had an overall mean age of 55.8 ± 14.1 years. Baseline characteristics of the cohort were shown in Table 1. The most common tumor localization was colon ($n = 177$, 60.0%) and resection of synchronous liver metastases was performed in 25 patients (8.5%). Before surgery, 86 patients received chemoradiotherapy (for locally advanced or metastatic rectal cancer), and 8 patients received chemotherapy only for metastatic colon cancer. LDH values in LDH-to-albumin ratio <52.7 and LDH-to-albumin ratio ≥ 52.7 groups were 182 ± 22 (range, 126–236) and 251 ± 81 (range, 136–750), respectively, and were significant ($P < 0.001$). The median LDH-to-albumin ratio value of the groups with LDH-to-albumin ratio <52.7 and LDH-to-albumin ratio ≥ 52.7 were 45.1 (range, 29.3–52.6) and 63.5 (range, 52.7–244.0), respectively, and were statistically significant ($P < 0.001$). Liver metastasis ($P = 0.008$), high serum LDH level ($P < 0.001$), CEA ≥ 5 ng/mL ($P = 0.003$), CA 19-9 ≥ 37 ng/mL ($P = 0.017$), low albumin level ($P < 0.001$), anastomotic leakage ($P = 0.001$), major complications (grade III–IV) ($P = 0.024$), lymph node positivity ($P = 0.027$), and advanced tumor stage ($P < 0.001$) were significantly higher in the group with higher LDH-to-albumin ratio compared to the group with lower LDH-to-albumin ratio (Table 1).

Median follow-up period was 31.8 months (interquartile range, 6–78 months). At the last follow-up, 53 patients (18%) died of cancer-related causes. Five-year OS and DFS rates were 68.5% and 65.4% in the group with lower LDH-to-albumin ratio and were 55.4% and 55.2% in the group with higher LDH-to-albumin ratio. Kaplan-Meier curves showed that LDH-to-albumin ratio ≥ 52.7 was significantly associated with worse OS and DFS ($P < 0.001$ and $P = 0.003$) (Fig. 2). When the effect of stage on survival is examined; survival was worse in stages

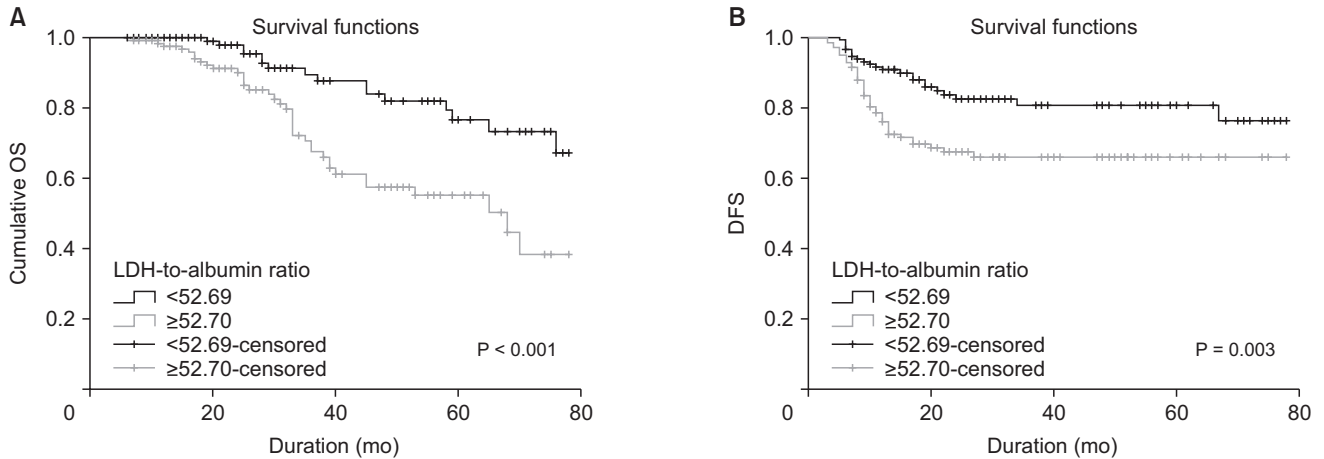


Fig. 2. Comparison of survival outcomes between patients with pretreatment LDH-to-albumin ratio ≥ 52.7 ($n = 143$) vs. pretreatment LDH-to-albumin ratio < 52.7 ($n = 152$). Kaplan-Meier survival analysis of (A) overall survival (OS) and (B) disease-free survival (DFS). Patients with LDH-to-albumin ratio < 52.7 had a significantly better 5-year OS rate than patients with LDH-to-albumin ratio ≥ 52.7 (68.5 % vs. 55.4 %; $P < 0.001$, log-rank test).

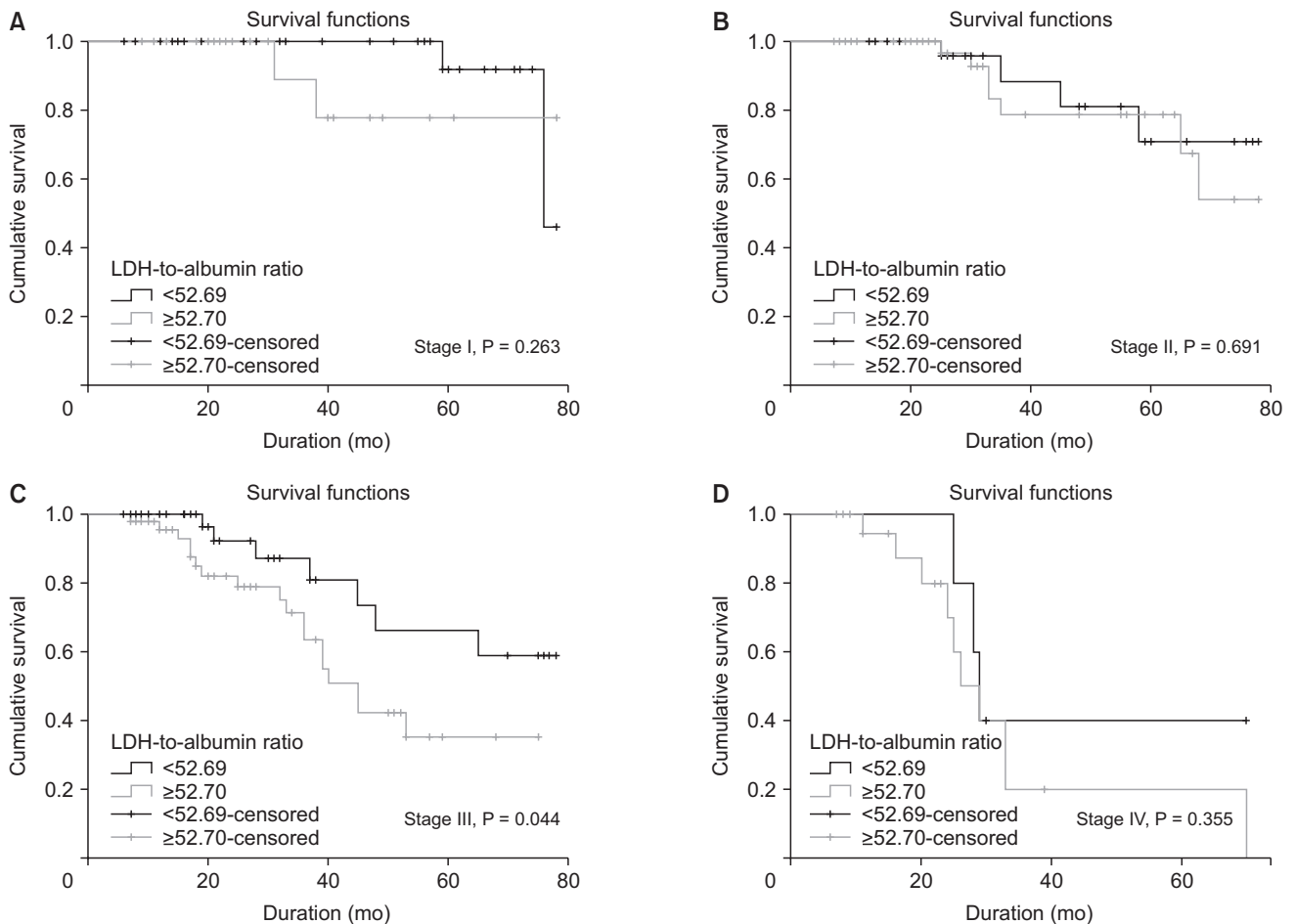


Fig. 3. Distribution of Kaplan-Meier survival curves by stages. In stages II, III, and IV, survival was worse in the group with LDH-to-albumin ratio ≥ 52.7 , but only in stage III was significant ($P = 0.044$).

II, III, and IV, but only stage III was statistically significant ($P = 0.044$) (Fig. 3).

Univariate analysis was performed to determine the

prognostic value of LDH-to-albumin ratio and other clinical variables for OS (Table 2). The analysis indicated that the presence of liver metastasis ($P < 0.001$), LDH-to-albumin ratio

Table 2. Univariate Cox regression analyses of survival outcomes in patients with colorectal carcinoma

Variable	All stage (n = 295)			Expect stage IV (n = 267)		
	No. (%)	OR (95% CI)	P-value	No. (%)	OR (95% CI)	P-value
Age, ≥65 yr	79 (26.8)	0.667 (0.325–1.370)	0.270	73 (27.3)	0.558 (0.234–1.332)	0.189
Female sex	117 (39.7)	1.625 (0.946–2.791)	0.078	106 (39.7)	1.596 (0.857–2.974)	0.141
ASA PS classification, ≥III	82 (27.8)	1.032 (0.541–1.969)	0.923	72 (27.0)	0.840 (0.370–1.906)	0.676
Liver metastasis	25 (8.5)	5.433 (2.608–11.318)	<0.001	-	-	-
Neo-adjuvant therapy	94 (31.9)	1.192 (0.647–2.198)	0.573	80 (30.0)	0.601 (0.277–1.305)	0.198
LDH	215 ± 68	1.003 (1.001–1.005)	0.001	212 ± 64	1.003 (1.001–1.005)	<0.010
Albumin	3.81 ± 0.60	0.604 (0.388–0.942)	0.026	3.82 ± 0.59	0.572 (0.343–0.953)	0.032
LDH-to-albumin ratio, ≥52.7	143 (48.5)	2.802 (1.551–5.062)	0.001	122 (45.7)	2.672 (1.372–5.205)	<0.010
PLR, ≥141.8	159 (53.9)	1.260 (0.722–2.200)	0.417	144 (53.9)	1.327 (0.698–2.521)	0.388
NLR, ≥2.73	126 (42.7)	1.329 (0.775–2.280)	0.301	115 (43.1)	1.484 (0.797–2.762)	0.213
CEA, ≥5 ng/mL	93 (31.5)	3.792 (2.183–6.587)	<0.001	75 (28.1)	3.392 (1.809–6.362)	<0.001
CA 19-9, ≥37 ng/mL	52 (17.6)	3.156 (1.783–5.584)	<0.001	42 (15.7)	2.708 (1.375–5.334)	<0.010
Anastomotic leak	15 (5.1)	2.728 (1.082–6.876)	0.033	12 (4.5)	2.944 (1.044–8.307)	0.041
CD classification, ≥III	25 (8.5)	2.359 (1.058–5.259)	0.036	22 (8.2)	2.542 (1.058–6.107)	0.037
T category, ≥3–4	198 (67.1)	5.596 (2.226–14.065)	<0.001	174 (65.2)	4.386 (1.717–11.201)	<0.010
Lymph node status, pN+	117 (39.7)	3.354 (1.922–5.851)	<0.001	99 (37.1)	3.566 (1.878–6.774)	<0.001
Poorly differentiation	56 (19.0)	1.603 (0.899–2.859)	0.110	45 (16.9)	1.316 (0.656–2.640)	0.440
TNM stage, ≥III–IV	127 (43.1)	4.572 (2.512–8.323)	<0.001	99 (37.1)	3.582 (1.886–6.803)	<0.001
Adjuvant therapy	195 (66.1)	4.487 (1.918–10.497)	0.001	171 (64.0)	3.352 (1.407–7.988)	<0.010

OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; PS, physical status; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; CD, Clavien-Dindo.

≥52.7 (P = 0.001), CEA ≥5 ng/mL (P < 0.001), CA 19-9 ≥37 ng/mL (P < 0.001), anastomotic leakage (P = 0.033), grade III–IV complications (P = 0.036), pT3–4 (P < 0.001), lymph node positivity (P < 0.001), and TNM stage III–IV (P < 0.001) were associated with OS. On multivariate analysis, however, only LDH-to-albumin ratio ≥52.7 (odds ratio [OR], 2.104; 95% confidence interval [CI], 1.112–3.982; P = 0.022) and liver metastasis (OR, 3.520; 95% CI, 1.100–11.257; P = 0.034) were found to be independent predictors of OS (Table 3).

When stage IV patients were excluded, 5-year survival was 70% in the group with LDH-to-albumin ratio <52.7 and 58.9% in the group with LDH-to-albumin ratio ≥52.7 (P = 0.003, Fig. 4). In the univariate and multivariate analyses performed by excluding stage IV, the LDH-to-albumin ratio ≥52.7 was again an independent risk factor associated with poor prognosis (OR, 2.166; 95% CI, 1.059 to 4.429; P = 0.034) (Tables 2, 3).

DISCUSSION

This study investigated the effect of LDH-to-albumin ratio on prognosis in CRC, based on the high LDH and low albumin levels associated with poor prognosis in many cancers. The results indicated that high LDH-to-albumin ratio had an adverse effect on the prognosis in CRC patients undergoing curative resection. To our knowledge, this is the first study in the literature investigating the relationship between LDH-to-albumin ratio and prognosis in CRC patients. The oxidoreductase LDH, which converts pyruvate to lactate when oxygen is absent or in short supply, plays a crucial role in the metabolism of cancer cells. LDH-A is overexpressed in hypoxic carcinomas as well as metastatic cancer cells, and its levels correlate with tumor viability. In numerous tumor types, serum LDH levels are indirect markers of tumor hypoxia, neo-angiogenesis, and poor prognosis [12,24]. Additionally,

Table 3. Multivariable Cox regression analyses of survival outcomes in patients with colorectal carcinoma

Variable	All stage			Except stage IV		
	β	OR (95% CI)	P-value	β	OR (95% CI)	P-value
Liver metastasis	1.258	3.520 (1.100–11.257)	0.034	-	-	-
LDH-to-albumin ratio, ≥52.7	0.744	2.104 (1.112–3.982)	0.022	0.773	2.166 (1.059–4.429)	0.034
CEA, ≥5 ng/mL	0.653	1,921 (0.968–3.811)		0.720	2.055 (0.957–4.412)	
CA 19-9, ≥37 ng/mL	0.206	1.229 (0.641–2.356)		-0.025	0.975 (0.438–2.173)	
Anastomotic leak	0.825	2.282 (0.547–9.518)		0.760	2.138 (0.537–8.510)	
CD classification, ≥III	-0.079	0.924 (0.286–2.987)		0.028	1.028 (0.320–3.297)	
T category, ≥3–4	0.834	2.302 (0.844–6.279)		0.545	1.724 (0.573–5.190)	
Lymph node status, pN+	0.312	3.354 (0.345–5.407)		-4.274	0.014 (0.000–3.646)	
TNM stage, ≥III–IV	0.194	1.214 (0.258–5.720)		4.812	122.966 (0.000–3.299)	
Adjuvant therapy	0.643	1.902 (0.695–5.209)		0.364	1.439 (0.452–4.577)	

OR, odds ratio; CI, confidence interval.

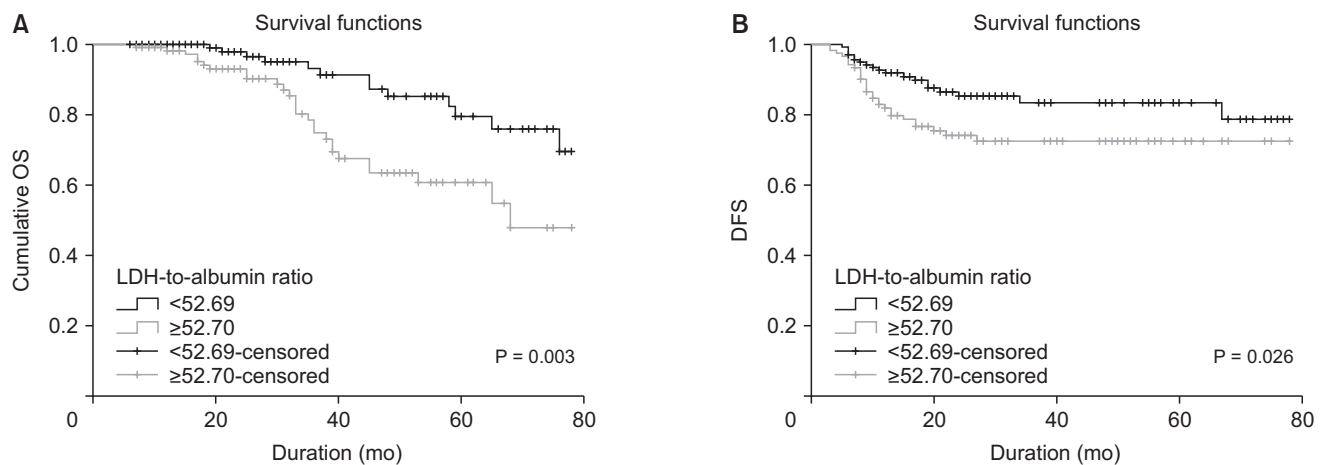


Fig. 4. Kaplan-Meier survival analysis of (A) overall survival (OS) and (B) disease-free survival (DFS), excluding stage IV patients. Patients with LDH-to-albumin ratio <52.7 had a significantly better 5-year OS rate than patients with LDH-to-albumin ratio ≥52.7 (70% vs. 58.9%; P = 0.003, log-rank test).

high LDH is closely associated with increased tumor vascular intensity, increased tumor burden, and tumor progression [25]. Serum albumin level is a significant marker of nutritional status. Tumor-related systemic inflammatory response may contribute to the progressive loss of albumin. In addition, hypoalbuminemia significantly influences the length of hospital stay and complication rates, specifically surgical site infection, enterocutaneous fistula, and deep vein thrombosis formation. For this reason, low albumin level may be a valuable prognostic factor for poor survival in CRC patients [11,26-28].

Studies reporting on the prognostic effect of LDH-to-albumin ratio are highly limited and are relatively recent. Feng et al. [20] evaluated 346 patients with esophageal squamous-cell carcinoma and reported that LDH-to-albumin ratio, TNM stage, and weight loss were effective on survival. The authors determined a cutoff value of 5.5 for LDH-to-albumin ratio and suggested that LDH and albumin alone had no effect on the prognosis of the disease [20]. In another study, Gan et al. [21] found that high LDH-to-albumin ratio was associated with poor prognosis in patients with hepatocellular cancer. The drawback of that study is that both LDH and albumin levels could be affected by the presence of the underlying chronic liver disease regardless of the tumor. In the present study, the cutoff value of albumin level was determined as 52.7 and was expressed as g/dL; however, it would have been determined as 5.27 if it had been expressed as g/L. Determining the LDH-to-albumin ratio level before treatment in patients with CRC may be useful in predicting the prognosis. More aggressive and combined therapies may be recommended to improve prognosis in patients with LDH-to-albumin ratio ≥ 52.7 . Especially in metastatic CRC, high LDH level affects prognosis more negatively. Therefore, the use of chemotherapy protocols with bevacizumab is recommended in patients with high LDH and metastases [29,30].

In our study, resection of synchronous liver metastases was performed in 25 patients (8.5%) to achieve an R0 resection. However, recurrence occurred in 72.0% of patients (18 out of 25) within a period of 2 years. On the other hand, both liver metastasis and LDH-to-albumin ratio were found to be independent risk factors for prognosis (OR, 3.520; 95% CI, 1.100–11.257; $P = 0.034$). Liver metastasis was present in 89.3% of patients (25/28) in stage IV group. The reason for the TNM stage not being statistically significant is that it can be analyzed together with stage III. Namely TNM stage IV (liver metastasis) is an independent predictor associated with poor prognosis, such as LDH-to-albumin ratio. Liver metastasis is the most common site of distant spread and approximately 15%–25% of CRC patients will have distant metastases at the time of primary diagnosis while another 18%–25% patients will develop distant metastases within 5 years from the first diagnosis. Over the last several decades, there has been an increase in surgical

resection of liver metastasis, and this procedure has been shown to have a positive contribution to OS. However, it has also been shown that recurrence occurs in 40%–75% of patients after liver resection [31-33].

There are several limitations associated with the present study: (1) the study had a relatively small number of patients; (2) the study had a retrospective design; (3) the groups of patients in the study were heterogeneous since the study evaluated patients with colon and rectal cancers in a single study; (4) the results could not be verified by long-term follow-up; and (5) the optimum cutoff value for the preoperative LDH-to-albumin ratio was unknown although 52.7 was set as the cutoff value using the results of an ROC analysis. Despite these limitations, it is the first study to examine the effect of LDH-to-albumin ratio on prognosis in CRC, and we believe it is important.

In conclusion, high LDH-to-albumin ratio is an independent risk factor for OS in CRC patients undergoing curative resection. Although further prospective studies with large patient series and longer follow-up periods are needed to substantiate the effect of LDH-to-albumin ratio on the prognosis of CRC, we consider that LDH-to-albumin ratio is a practical and inexpensive marker that can be used in predicting the prognosis of many cancers.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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