ORIGINAL RESEARCH

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The Relationship of Albumin-Bilirubin Grade with Right and Left Colon in Patients with Colon Cancer Treated with Regorafenib

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ABSTRACT Objective: The purpose of this study is to evaluate the association between albumin-bilirubin (ALBI) grade and right and left colon in colon cancer (CC) patients with liver metastases who received regorafenib treatment. **Material and Methods:** This retrospective study included 126 patients treated with regorafenib and was divided into normal-ALBI (ALBI Grade 1) and high-ALBI groups (ALBI Grades 2 and 3). The optimal cut-off values of neutrophil-lymphocyte ratio and prognostic nutritional index (PNI), evaluated by receiver operating characteristic curve analysis, were 4.41 and 40.85, respectively. The associations between parameters with survival were analyzed using Kaplan-Meier curves and compared by the log-rank test. Cox proportional hazards regression analyzes were used to evaluate the prognostic significance of the parameters for progression-free survival (PFS) and overall survival (OS). **Results:** The ALBI group for OS (p=0.043) in the right CC (RCC) and the number of metastatic organs for PFS (p=0.048) were found to be independent prognostic variables. The overall response rate (ORR) was significantly higher in the group with low ALBI for RCC. In RCC, adverse events (AE) were higher in the group with high ALBI than in the normal group (p=0.028). The number of metastatic organs in left CC (LCC) (p=0.008, p<0.001, p=0.042) was found to be independent prognostic for both PFS and OS. Both ORR and disease control rate were significantly higher in the LCC group with high PNI. **Conclusion:** In RCC cases with liver metastases treated with regorafenib, the ALBI group was significantly associated with prognosis, survival, response rates, and AE. ALBI grade should be considered in RCC patients receiving regorafenib therapy.

Keywords: Albumin-bilirubin grade; colon cancer; liver; metastasis; regorafenib

Colon cancer (CC) ranks third among all cancers and is the second leading cause of cancer-related deaths worldwide.[1] More than 50% of CC patients subsequently develop systemic metastases, with 60% of metastases to the liver.[2]

Although the albumin-bilirubin (ALBI) score, by combining the serum albumin and bilirubin, is an evaluation method for liver function, it is considered a significant prognostic indicator in patients with hepatocellular carcinoma (HCC).[3,4] Regorafenib, is used as a later-line standard therapy in metastatic CC (mCC) and is an oral agent that inhibits vascular endothelial growth factor (VEGF) 1-3 receptors, platelet-derived growth factor receptor, fibroblast growth factor receptor, and multiple tyrosine kinase inhibitors.[5] Regorafenib is mainly metabolized in the liver by cytochrome P450 3A4 and UDP-glucuronosyltransferase 1A9 and excreted along with its active metabolites.[6] ALBI score might affect regorafenib efficacy and associated adverse events (AE) and can serve as a predictive factor in patients with liver metastasis of mCC as well as HCC.[7]

Recent evidence indicates that right CC (RCC) and left CC (LCC) behave differently in terms of clinicopathological features and embryological development and prognosis.[8] Although some studies have reported that RCC has a worse prognosis than LCC, these findings did not show a significant difference in the 5-year mortality rate.[9,10]

Inflammation is involved in the pathogenesis and progression of various cancers, including CC.[11,12] The prognostic importance of prognostic nutritional index (PNI) and neutrophil-lymphocyte ratio (NLR), has been demonstrated in CC.[13,14]

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In this study, we aimed to examine the associations of NLR, PNI, and ALBI grade with survival parameters, response rates, and AE in RCC and LCC patients with liver metastases treated with regorafenib.

MATERIAL AND METHODS

In this study, 126 patients with liver mCC who received regorafenib treatment between January 2011 and July 2021 in the Medical Oncology Department of Adnan Menderes University were retrospectively analyzed. While the patients received regorafenib treatment once daily for 21 days, the initial dose was determined at the physician's discretion, according to the general condition of the patient. All patients received first-and second-line fluoropyrimidine, irinotecan, oxaliplatin, anti-epidermal growth factor receptor, and anti-VEGF therapy. The inclusion criteria were: a) Patients with a histologically confirmed diagnosis of colon adenocarcinoma; b) Patients diagnosed with Stage IV CC according to the 8th edition of the American Joint Committee on Cancer; c) Patients with liver metastases and d) Patients with full clinicopathological and follow-up data records. The exclusion criteria were: a) Patients with other solid organ malignancies; b) Patients without liver metastases; c) Patients with inflammatory, hematological, as well as immunological diseases and; d) Patients < 18 years of age.

ETHİCAL DECLARATİON

The study had been approved by the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (date: September 23, no: E-53043469-050.04.04-81997) and followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

DATA COLLECTİON AND DEFİNİTİON

Baseline clinical variables such as Eastern Cooperative Oncology Group performance status, gender, age, tumor characteristics as well as laboratory investigations, including neutrophil, lymphocyte, and platelet counts at the time of diagnosis, were obtained from the electronic database of our hospital. NLR was calculated by dividing the neutrophil count by the lymphocyte count. PNI values were calculated with the formula [(10×albumin (g/L))+(0.005×total lymphocyte count)] while the ALBI score was calculated with the formula (0.085×[albumin g/L]+0.66 Log10 [total bilirubin μmol/L]).

The ALBI scores were defined as Grades 1 (score ≤-2.60), Grade 2 (-2.60 to ≤-1.39), and Grade 3 (score >-1.39), respectively.[15] In this study, RCC was defined as the part localized from the cecum to the proximal splenic flexure, whereas the LCC was the tumor area distal to the splenic flexure.[16]

DETERMİNATİON OF OPTİMAL CUT-OFF VALUES OF ALBI GRADE AND OTHER PARAMETERS

The patients with ALBI Grade 1 were categorized into the normal-ALBI group, and those with ALBI Grade 2 or 3 into the high-ALBI group. As per the receiver operating characteristic (ROC) curve analysis, the optimal cut-off values for NLR, and PNI were 4.41, and 40.85, whereas the AUC values for NLR and PNI were 0.57 and 0.64, respectively.

STUDY ENDPOİNTS

Progression-free survival (PFS) was defined as the time interval between regorafenib initiation and disease progression and/or death, while the overall survival (OS) was defined as the time interval between treatment initiation and last follow-up and/or death.

EFFİCACY OUTCOME

Tumor response was determined according to the Response Evaluation Criteria in Solid Tumors manual version 1.1.[17] Overall response rate (ORR) was defined as complete response (CR)+partial response (PR), and disease control rate (DCR) was described as CR+PR+stable disease (SD).

EVALUATİON OF ADVERSE EVENTS

It included AE like liver dysfunction, diarrhea, hand-foot skin reactions, nausea, and fatigue. Liver dysfunction was defined according to the CORRECT trial and Common Terminology Criteria for Adverse Events version 4.0.[18]

STATİSTİCAL ANALYSİS

The ROC curve analysis determined the cut-off values for relevant variables. Shapiro-Wilk test was used

for normally distributed variables. Fisher's exact test or chi-square (c^2) test was used to examine the association between RCC and LCC with clinic-pathological parameters. Kaplan-Meier curves were plotted to analyze the associations between potential prognostic variables and survival outcomes, while the log-rank test was used for comparing survival distributions among prognostic sub-groups. The prognostic importance of NLR, PNI, ALBI-Grade, and other parameters on survival outcomes were evaluated using univariate and multivariate Cox proportional hazards regression analyses. SPSS (Version 21 SPSS, Inc., Chicago, IL, USA) was used for all the statistical analyses, and a p-value<0.05 was considered for statistical significance.

RESULTS

BASELİNE CHARACTERİSTİCS

The median age of the 126 study patients was 65 (38-87) years. Of all the patients, 59 (46.8%) and 67 (53.2%) were RCC and LCC cases, respectively. The clinic-demographic characteristics of our cohort are presented in Table 1.

ASSOCİATİON OF ALBI GRADE AND OTHER INFLAMMATORY PARAMETERS WİTH SURVİVAL OUTCOMES

At a median follow-up of 6 (1-50) months, the median PFS and OS were 4 and 7 months, respectively. Although both PFS (6.24, 10.9, p=0.663) and OS (11.6, 18.5, p=0.58) were shorter in RCC than in LCC, the difference was not statistically significant.

According to Kaplan-Meier analysis, PFS (4.4, 9.1 months, p=0.025; 7.6, 11.6 months, p=0.027) and OS (7.3, 18 months, p=0.003; 12.4, 19.1 months, p=0.011) in both RCC and LCC patients with high ALBI grade, were shorter and statistically significant (Figure 1).

Although both PFS and OS were reduced in the group of patients with NLR≥4.41 in RCC, the difference was not statistically significant (4.1 vs. 7.1 months, p=0.129; 9.1 vs. 12.2 months, p=0.542). In LCC, the patients with NLR≥4.41 had shorter PFS and OS, and the difference was significant for both PFS and OS (7.7 vs. 10 months, p=0.038; 11.4 vs. 17.0 months, p=0.030).

In RCC with PNI<40.85, both OS (5.6 vs. 14.5 months, p=0.006) and PFS (4.4 vs. 7.1 months, p=0.141) were shorter and the difference was significant only for OS. In LCC patients with PNI<40.85, OS (8.0 vs. 23.1 months, p=0.054) and PFS were shorter (4.8 vs. 14.8 months, p=0.290) in duration, and the difference was not significant.

PROGNOSTİC SİGNİFİCANCE OF INFLAMMATORY BİOMARKERS

In the univariate analysis for PFS, the ALBI group [hazard ratio (HR): 1.893, p=0.048] and the number of metastatic organs (HR: 2.663, p=0.015) were significant parameters in RCC cases (Table 2). In LCC, the ALBI group (HR: 1.714, p=0.049) and the number of metastatic organs (HR: 0.347, p=0.003) were significant parameters for PFS in LCC (Table 3).

In the univariate analysis for OS, the ALBI group (HR: 2.759, p=0.006) and PNI (HR: 0.429, p=0.011) were significant parameters in RCC patients, whereas in LCC cases, the ALBI group (HR: 2.061, p=0.018), NLR (HR: 1.878, p=0.043), number of metastatic organs (HR: 0.172, p<0.001, HR: 0.351, p=0.011) were significant parameters.

In multivariate analysis, the number of metastatic organs (HR: 2.296, p=0.048; HR: 0.388, p=0.008) was an independent prognostic variable for PFS in both RCC and LCC (Table 2, Table 3). In multivariate analysis, an independent prognostic variable was found for OS in the ALBI group (HR: 2.264, p=0.043) in RCC, and the number of metastatic organs (HR: 0.220, p<0.001, HR: 0.418, p=0.042) in LCC (Table 4).

EFFİCACY OUTCOME

While the ORR was 18.6% and 11.9% in RCC and LCC, respectively, the difference was not significant. The DCR was 42.3% and 17.9% in RCC and LCC cases; the difference was significant (p=0.294, p=0.003). ORR was significantly higher in the group with low ALBI for RCC and high PNI for LCC. DCR was significantly higher in the group with high PNI in LCC (Table 5).

TABLE 1: Clinicopathological characteristics of RCC and LCC patients.

	All patients (n=126) (100%)	RCC (n=59) (46.8%)	LCC (n=67) (53.2%)	p value
Age				0.56
<65	67 (53.2)	33 (55.9)	34 (50.7)	
≥65	59 (46.8)	26 (44.1)	33 (49.3)	
Gender				0.91
Female	57 (45.2)	27 (45.8)	30 (44.8)	
Male	69 (54.8)	32 (54.2)	37 (55.2)	
Smoking				0.05
No	81 (64.3)	43 (72.9)	38 (56.7)	
Yes	45 (35.7)	16 (27.1)	29 (43.3)	
ECOG				0.24
0	40 (31.7)	19 (32.2)	21 (31.3)	
1	34 (27.0)	12 (20.3)	22 (32.8)	
2	52 (41.3)	28 (47.5)	24 (35.8)	
Number of metastatic organs				0.89
1	71 (54.0)	32 (54.2)	39 (58.2)	
2	31 (24.6)	15 (25.4)	16 (23.9)	
≥3	24 (21.4)	12 (20.3)	12 (17.9)	
RAS				<0.001
Wild	73 (57.9)	17 (28.8)	56 (83.6)	
Mutant	53 (42.1)	42 (71.2)	11 (16.4)	
BRAF				0.09
Wild	96 (76.2)	49 (83.1)	47 (70.1)	
Mutant	30 (23.8)	10 (16.9)	20 (29.9)	
Adverse events				0.65
Liver dysfunction	22 (17.5)	14 (23.7)	8 (11.9)	
Diarrhea	28 (22.2)	12 (20.3)	16 (23.9)	
Hand-foot skin reaction	16 (12.7)	7 (11.9)	9 (13.4)	
Nausea	11 (8.7)	5 (8.5)	6 (9.0)	
Fatigue	11 (8.7)	4(6.8)	7 (10.4)	
None	38 (30.2)	17 (28.8)	21 (31.3)	
NLR				0.36
<4.41	82 (65.1)	36 (61)	46 (68.7)	
≥4.41	44 (34.9)	23 (39)	21 (31.3)	
PNI				0.74
<40.85	51 (40.5)	23 (39)	28 (41.8)	
≥40.85	75 (59.5)	36 (61)	39 (58.2)	
ALBI-group				0.05
Normal	52 (41.3)	19 (32.2)	33 (49.3)	
High	74 (58.7)	40 (67.9)	34 (50.7)	
ALBI-score	-2.39 (-0.37 to -3.33)	-2.35 (-0.56 to -3.18)	-2.42 (-0.37 to -3.33)	0.85

RCC: Right colon cancer; LCC: Left colon cancer; ECOG: Eastern Cooperative Oncology Group performance status; NLR: Neutrophil-lymphocyte ratio; PNI: Prognostic nutritional index; ALBI: Albumin-bilirubin.

AE RELATİON WİTH ALBI GROUP

In RCC, AE was higher in the ALBI group than in the normal group (p=0.028), while in LCC cases, there was no difference in AE in the ALBI high group compared with the normal group (p=0.211).

DISCUSSION

A large number of studies have asserted the differences between the histopathological and clinicopathological characteristics of RCC and LCC in

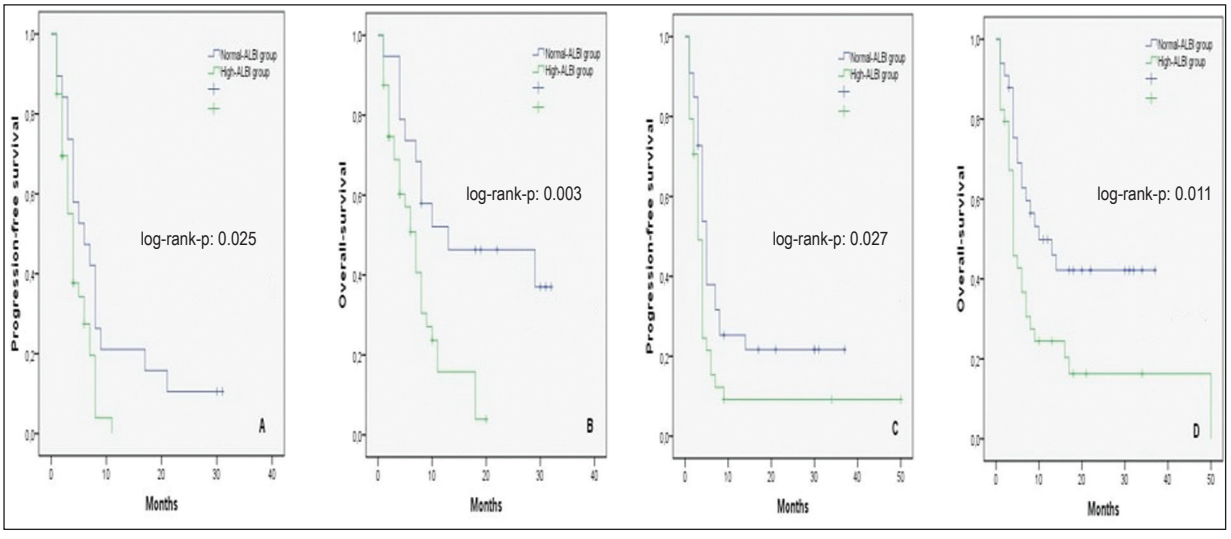

FIGURE 1: Kaplan-Meier curves for progression-free survival for RCC (A) and overall survival (B), progression-free survival for LCC (C), and overall survival (D) according to the ALBI groups.
ALBI: Albumin-bilirubin; RCC: Right colon cancer; LCC: Left colon cancer.

terms of prognostic variables and treatment strategies.[19,20] The relationship between ALBI-grade and prognosis has been investigated in many cancers, including pancreatic cancer, gastric cancer (GC), and HCC.[21-23] This study investigated the association between RCC, LCC, and ALBI grade in CC patients with liver metastases receiving regorafenib therapy and found that the ALBI grade was significantly associated with prognosis, survival, response rates, and AE in RCC patients. Our results showed that both PFS and OS were significantly shorter in the LCC group with high NLR, whereas ORR and DCR were significantly higher in the high PNI group. Our study is the first study to investigate the differences and response rates of ALBI grade in RCC and LCC patients with liver mCC, treated with regorafenib.

In a study conducted on 871 RCC and 748 LCC patients, no difference was found in terms of OS times for both regions.[24] Another study conducted on 135 mCC patients treated with regorafenib compared the response rates in RCC and LCC cases and stated that PFS was found to be significantly longer in LCC than in RCC, while no difference was observed in ORR and DCR for both sites. In the same study, the number of metastatic sites was an independent prognostic parameter for PFS.[25] In our study, the number of metastatic sites was an important factor for PFS in both RCC and LCC patients. Similar to previous studies, both PFS and OS times were longer in LCC than in RCC patients, but the difference was not significant. In contrast, our study depicted that while ORR was higher in RCC than in LCC patients, the difference was not significant, whereas a higher value of DCC in RCC than in LCC patients depicted statistical significance. Due to the differences in results between multiple scientific studies, it would be imperative to confirm our results with a larger patient population.

NLR is considered a prognostic variable in some cancers such as pancreatic cancer, breast cancer (BC), and lung cancer.[26] In a study conducted by Nogueira-Costa et al. in 102 patients with mCC, NLR (cut-off: 2.35) was found to be an independent prognostic factor for OS.[27] In another study by Mazaki et al., in which 375 patients with Stage II-III CC who underwent surgery were examined, 5-year OS and recurrence-free survival were significantly lower in LCC cases in the high NLR (cut-off: 3) group; however, this difference was not significant in RCC patients.[28] In another study conducted by Cha et al. in Stage III CC patients, there was no difference in NLR levels according to tumor localization, and NLR (cut-off: 3) was not found to be a prognostic factor.[29] Guo et al., in their study on patients with Stage I-III RCC and LCC, suggested that NLR (cut-off: 2.3) was depicted as an independent predictor of both OS and disease-

TABLE 2: Univariate and multivariate analyses for prognostic factors of PFS for RCC.

	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
RCC				
Age				
<65	Ref			
≥65	1.157 (0.647-2.067)	0.623		
Gender				
Female	Ref			
Male	1.629 (0.914-2.903)	0.098		
Smoking				
No	Ref			
Yes	0.902 (0.492-1.655)	0.740		
ECOG				
0	Ref			
1	0.965 (0.522-1.784)	0.911		
2	1.071 (0.475-2.414)	0.869		
Number of metastatic organs				
1	Ref		Ref	
2	2.663 (1.211-5.854)	0.015	2.296 (1.008-5.230)	0.048
≥3	2.175 (0.902-5.243)	0.083	1.757 (0.689-4.478)	0.238
RAS				
Wild	0.601 (0.326-1.107)	0.102		
Mutant	Ref			
BRAF				
Wild	1.006 (0.491-2.104)	0.965		
Mutant	Ref			
NLR				
<4.41	Ref			
≥4.41	1.508 (0.830-2.740)	0.177		
PNI				
<40.85	0.671 (0.371-1.212)	0.186		
≥40.85	Ref			
ALBI-group				
Normal	Ref		Ref	
High	1.893 (1.007-3.559)	0.048	1.539 (0.782-3.026)	0.212

PFS: Progression-free survival; RCC: Right colon cancer; HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group performance status; NLR: Neutrophil-lymphocyte ratio; PNI: Prognostic nutritional index; ALBI-group: Albumin-bilirubin group.

free survival in RCC cases.[20] Similar to Mazaki et al., in our study, although the PFS & OS were of shorter duration in RCC patients with NLR ≥4.41, the difference was not significant, whereas the difference was significant in LCC cases.[28] Our study was in accordance with Cha et al. and did not find any significant difference in NLR levels in both RCC and LCC patients.[29] The resultant differences between several studies on these parameters might be due to the clinical stages of the patients, cut-off values, and the time of NLR examination. Integrating our results with other clinical studies might provide crucial inputs for better patient outcomes.

PNI, another inflammatory marker, is now considered a prognostic factor in many cancers such as HCC and BC.[30,31] The prognostic significance of PNI (cut-off: 46) for OS has been demonstrated in a study conducted on 308 patients with mCC.[14] The prog-

TABLE 3: Univariate and multivariate analyses for prognostic factors of PFS for LCC.

LCC				
Age				
<65	Ref			
≥65	1.238 (0.729-2.104)	0.429		
Gender				
Female	Ref			
Male	1.246 (0.727-2.135)	0.424		
Smoke				
No	Ref			
Yes	0.897 (0.524-1.536)	0.693		
ECOG				
0	Ref			
1	0.653 (0.345-1.236)	0.190		
2	0.561 (0.293-1.075)	0.082		
Number of metastatic organs				
1	Ref		Ref	
2	0.347 (0.174-0.691)	0.003	0.388 (0.193-0.782)	0.008
≥3	0.716 (0.333-1.543)	0.394	0.899 (0.404-1.997)	0.793
RAS				
Wild	0.850 (0.427-1.694)	0.645		
Mutant	Ref			
BRAF				
Wild	1.217 (0.687-2.158)	0.501		
Mutant	Ref			
NLR				
<4.41	Ref			
≥4.41	1.713 (0.969-3.031)	0.064		
PNI				
<40.85	0.773 (0.454-1.317)	0.344		
≥40.85	Ref			
ALBI-group				
Normaly	Ref		Ref	
High	1.714 (1.002-2.934)	0.049	1.729 (0.982-3.046)	0.058

PFS: Progression-free survival; LCC: Left colon cancer; ECOG: Eastern Cooperative Oncology Group performance status; NLR: Neutrophil-lymphocyte ratio; PNI: Prognostic nutritional index; ALBI-group: Albumin-bilirubin group.

nostic importance of PNI for OS has also been demonstrated in another study on 3,301 patients with CRC.[32] A similar reported study on 355 patients with CC, PNI (cut-off: 47.5) was found to be a clinically significant variable in the TNM staging and metastasis prediction.[33] In our study, unlike other studies, the evaluation of survival times by tumor regions suggested that although PFS and OS were shorter in RCC patients with PNI<40.85, the difference was significant only for OS value. In LCC, those with PNI<40.85 had shorter OS with PFS, and the difference was not significant for either of them. Besides, in our study, ORR and DCR were significantly higher in the group with high PNI in LCC. In patients treated with regorafenib, low PNI, especially in LCC, may be considered to be positively predictive for ORR and DCR.

TABLE 4: Univariate and multivariate analyses for prognostic factors of OS for RCC and LCC.

	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
RCC					**LCC**			
Age								
<65	Ref				Ref			
≥65	1.560 (0.831-2.926)	0.166			1.183 (0.658-2.126)	0.575		
Gender								
Female	Ref				Ref			
Male	1.404 (0.748-2.636)	0.291			1.380 (0.758-2.511)	0.292		
Smoke								
No	Ref				Ref			
Yes	0.842 (0.435-1.629)	0.610			0.919 (0.510-1.655)	0.777		
ECOG								
0	Ref				Ref			
1	0.815 (0.414-1.602)	0.553			0.511 (0.249-1.048)	0.067		
2	0.721 (0.292-1.783)	0.479			0.509 (0.252-1.028)	0.060		
Number of metastatic organs								
1	Ref				Ref			
2	1.939 (0.877-4.286)	0.102			0.172 (0.081-0.365)	<0.001	0.189 (0.087-0.408)	<0.001
RAS								
Wild	1.076 (0.540-2.147)	0.834			0.965 (0.448-2.075)	0.926		
Mutant	Ref				Ref			
BRAF								
Wild	1.307 (0.603-2.832)	0.497			1.328 (0.714-2.472)	0.371		
Mutant	Ref				Ref			
NLR								
<4.41	Ref				Ref			
≥4.41	1.204 (0.641-2.262)	0.563			1.878 (1.020-3.457)	0.043	1.545 (0.780-3.060)	0.212
PNI								
<40.85	0.429 (0.223-0.826)	0.011	0.607 (0.299-1.231)	0.166	0.580 (0.322-1.046)	0.070		
≥40.85	Ref		Ref		Ref			
ALBI-group								
Normaly	Ref		Ref		Ref			
High	2.759 (1.335-5.705)	0.006	2.264 (1.024-5.002)	0.043	2.061 (1.130-3.757)	0.018	1.435 (0.719-2.865)	0.306

OS: Overall survival; RCC: Right colon cancer; LCC: Left colon cancer; HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group performance status; NLR: Neutrophil-lymphocyte ratio; PNI: Prognostic nutritional index; ALBI-group: Albumin-bilirubin group.

ALBI grade is a marker that is of prognostic importance in various malignancies such as HCC, pancreatic cancer, and GC.[34-36] It was shown that tumor necrosis factor-alpha and interleukin-6 mediate the down-regulation of albumin levels in many malignancies.[1,37,38] Besides, due to decreased albumin levels and increased bilirubin levels in many liver diseases such as liver metastases and HCC, the ALBI score, which is calculated by the combined use of serum albumin and bilirubin values, is now being used to evaluate liver's functional capacity more objectively.[4,15] In a pooled analysis of 1,434 patients with liver metastases receiving first-line therapy, high ALBI grade was associated with poor survival for

TABLE 5: Comparison of tumor response rate as a prognostic parameter for RCC and LCC.

	ORR (ORR=CR+PR) %	p value	DCR (DCR=CR+PR+SD) %	p value
RCC				
NLR		0.377		0.89
<4.41	22.2 (8/36)		41.6 (15/36)	
≥4.41	13.0 (3/23)		43.4(10/23)	
PNI		0.117		0.687
<40.85	8.6 (2/23)		39.1 (9/23)	
≥40.85	25.0 (9/36)		44.4 (16/36)	
ALBI group		0.001		0.593
Normal	42.1 (8/19)		47.3 (9/19)	
High	7.5 (3/40)		40.0 (16/40)	
LCC				
NLR		0.680		0.601
<4.41	13.0 (6/46)		19.5 (9/46)	
≥4.41	9.5 (2/21)		14.2 (3/21)	
PNI		0.011		0.009
<40.85	0 (0/28)		3.5 (1/28)	
≥40.85	20.5 (8/39)		28.2 (11/39)	
ALBI group		0.121		0.183
Normal	18.1 (6/33)		24.2 (8/33)	
High	5.8 (2/34)		11.7 (4/34)	

Data were statistically analyzed using a chi-square test; RCC: Right colon cancer; LCC: Left colon cancer; CR: Complete response; PR: Partial response; DCR: Disease control rate; SD: Stable disease; NLR: Neutrophil-lymphocyte ratio; PNI: Prognostic nutritional index; ALBI-group: Albumin-bilirubin group; ORR: Overall response rate

both PFS and OS, while high ALBI grade and the number of metastases were shown as independent prognostic factors.[4] There has been only one study examining the relationship between mCC cases treated with regorafenib and ALBI score to date.[6] In this study, OS and time to treatment failure were significantly shorter in the high-ALBI group than in the normal-ALBI group, and the ALBI score was independently prognostic for OS.[6] Moreover, DCR was found to be significantly reduced in the high-ALBI group, when compared with the normal-ALBI group, along with substantial liver dysfunction.[6] In contrast, our study evaluated the ALBI group separately for RCC and LCC cases, and the normal ALBI group displayed longer durations for PFS and OS in both regions. Although the difference was significant for both parameters, the independent prognosis was not indicated. Besides, the number of metastatic organs for PFS in RCC and the ALBI group for OS was found as an independent prognostic parameter in our study. This finding might be associated with a poor prognosis with an ALBI score, possibly because RCC metastasizes to the liver in a larger volume and impairs liver functions due to the higher tumor burden. It was evident that AE was higher in the group with high ALBI grades in RCC than in the normal group, which may be important in terms of predictability of AE and toxicity management by evaluating ALBI score according to tumor location in liver mCC patients planning for treatment with regorafenib. ORR was higher in the normal ALBI group for RCC cases. Additionally, our study excluded patients without liver metastases, unlike other studies, which is important for the homogeneity of the groups. However, since the data view significance of ALBI grade in patients receiving regorafenib with CC is limited, it is

imperative to integrate our results with future studies having a larger sample size.

Although our study was the first to show that ALBI grade is an independent prognostic factor for OS in RCC patients receiving regorafenib, the limitation of our study was that it was retrospective along with small sample size. Hence, prospective and multicenter studies should be conducted to assess the prognosis of CC patients receiving regorafenib therapy.

CONCLUSION

ALBI grade can be considered as a new parameter predicting the survival times and response rates in CC patients receiving regorafenib. ALBI grade is an advantageous parameter because it is easy to check, sensitive and inexpensive. In conclusion, ALBI grade can be considered an important parameter that should be carefully evaluated in RCC patients receiving regorafenib therapy for a better prognosis.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hatice Yılmaz;* ***Design:*** *Esin Oktay;* ***Control/Supervision:*** *Hatice Yılmaz;* ***Data Collection and/or Processing:*** *Hatice Yılmaz;* ***Analysis and/or Interpretation:*** *Esin Oktay;* ***Literature Review:*** *Esin Oktay;* ***Writing the Article:*** *Hatice Yılmaz;* ***Critical Review:*** *Hatice Yılmaz;* ***References and Fundings:*** *Esin Oktay;* ***Materials:****Hatice Yılmaz.*

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