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The albumin-bilirubin (ALBI) grade as a significant prognostic factor in colorectal cancer patients with liver metastases

Karaciğere metastatik kolorektal kanserde önemli bir prognostik faktör olarak albumin-bilirubin (ALBI) gradı

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Abstract

Aim: Colorectal cancer is one of the most common cancers and liver metastases are frequent during its course. Albumin-bilirubin (ALBI) score/grade was shown to predict survival in hepatocellular carcinoma. We aimed to assess the prognostic value of the ALBI score/grade in colorectal cancer patients with liver metastases.

Methods: Medical records of patients with colorectal cancer and synchronous or metachronous liver metastases were reviewed. Serum albumin, total bilirubin, lactate dehydrogenase, carcinoembryogenic antigen and neutrophil-to-lymphocyte ratio at the time of first liver metastasis were determined. ALBI score was calculated from serum albumin and bilirubin and was graded. Multivariate regression models were used to evaluate prognostic factors.

Results: The study included 223 patients. Median overall survival was 23.9, 16.0 and 4.0 months for ALBI grades 1, 2 and 3, respectively (P<0.001). In the first multivariate model, serum albumin was an independent prognostic factor (Hazard ratio=1.97, P=0.001) but total bilirubin was not (Hazard ratio=1.43, P=0.17). In the second multivariate analysis, ALBI grade was a significant predictor of overall survival (Hazard ratio=1.54, P=0.02 for ALBI grade 2 and Hazard ratio=3.85, P<0.001 for ALBI grade 3).

Conclusion: ALBI grade may be a valuable prognostic method to estimate the mortality of patients with colorectal cancer and liver metastases.

Keywords: Albumin-bilirubin grade, Colorectal cancer, Liver metastasis, Prognostic factor

Öz

Amaç: Kolorektal kanser en sık görülen kanserlerden biridir ve hastalık sürecinde karaciğer metastazı sık olarak gelişmektedir. Albumin-bilirubin (ALBI) skoru/gradının hepatoselüler kanserde sağkalımı predikte ettiği gösterilmiştir. Bu çalışmada ALBI skoru/gradının karaciğer metastatik kolon kanserindeki prognostik değerinin araştırılması amaçlanmıştır.

Yöntemler: Kolorektal kanser tanılı ve senkron ya da metakron karaciğer metastazı olan hastaların tıbbi kayıtları incelenmiştir. Karaciğer metastazının saptandığı andaki serum albumin, total bilirubin, laktat dehidrojenaz, karsinoembryonik antijen and nötrofil-lenfosit oranı belirlenmiştir. Albumin ve bilirubin kullanılarak ALBI skoru hesaplanmış ve derecelendirilmiştir. Prognostik faktörler çok değişkenli regresyon modelleri ile değerlendirilmiştir.

Bulgular: Çalışmaya 223 hasta dahil edildi. Medyan genel sağkalım ALBI grad 1, 2 ve 3 için sırasıyla 23.9, 16.0 ve 4.0 ay olarak saptandı (P<0.001). İlk çok değişkenli modelde serum albumin bağımsız bir prognostik faktörken (Tehlike oranı=1.97, P=0.001) total bilirubin değildi (Tehlike oranı=1.43, P=0.17). İkinci çok değişkenli analizde ALBI gradın genel sağkalımı bağımsız olarak predikte edebildiği görüldü (ALBI grad 2 için tehlike oranı=1.54, P=0.02 ve grad 3 için tehlike oranı=3.85, P<0.001).

Sonuç: ALBI gradı karaciğer metastazı olan kolorektal kanser hastalarında mortaliteyi tahmin etmek için değerli bir prognostik metod olabilir.

Anahtar kelimeler: Albumin-bilirubin gradı, Karaciğer metastazı, Kolorektal kanser, Prognostik faktör

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Introduction

Colorectal cancer (CRC) stands out as one of the most important causes of cancer-related deaths globally. Liver is the leading site of CRC dissemination, with 15-25% of patients having hepatic metastasis at initial presentation and up to 70% of patients will develop liver metastasis during the disease course [1,2]. Five-year survival of CRC with liver metastasis remains below 10% without curative treatment [1]. Various clinicopathological (e.g. performance status, tumor histology, tumor location) and biochemical (e.g. lactate dehydrogenase, carcinoembryogenic antigen, albumin) factors were identified to indicate prognosis of patients with metastatic CRC [3]. Nevertheless, there is no general consensus on their reliability and validated prognostic markers are still required for these patients.

The albumin-bilirubin (ALBI) score/grade is a novel method based on serum albumin and bilirubin levels that was demonstrated to predict mortality of acute-on-chronic liver failure and acute upper gastrointestinal bleeding in liver cirrhosis before [4,5]. From the oncological perspective, the first assessment of ALBI score/grade was in patients with hepatocellular carcinoma (HCC) and showed that it was an accurate prognostic model to indicate the severity of liver damage and to estimate the long-term survival of these patients [6]. Subsequent studies demonstrated the prognostic value of ALBI score/grade in HCC patients who were treated with different modalities like chemoembolization, radiofrequency ablation, radiotherapy or targeted agents [7-10].

Considering the fact that the prognostic value of ALBI score/grade in cancers except HCC is not elucidated sufficiently yet, we designed this study based on the hypothesis that it could predict survival in CRC patients with established liver metastases as an objective method.

Materials and methods

Study design

This study had a cross-sectional design. Medical files of colon and rectal cancer patients who were evaluated between February 2007 and September 2018 in our clinic were examined. Patients with histologically proven colorectal adenocarcinoma who had liver metastases at the time of diagnosis or developed them later were included. Synchronous or metachronous dissemination to other sites than liver did not preclude from enrollment to the study. Gender, age, primary tumor location and date of first liver metastasis and date of exitus or last visit were acquired from the files. Date of first liver metastasis was accepted as the date of computed tomography, magnetic resonance imaging or positron emission tomography in which liver metastasis was first documented. Having access to the registry system of our institute, we recorded serum albumin, total bilirubin, carcinoembryogenic antigen (CEA), lactate dehydrogenase (LDH) levels and complete blood counts at the time of first liver metastasis (these parameters were routinely tested at baseline and then periodically in our clinic). An approval for this study was granted by Trakya University Faculty of Medicine Clinical Trials Ethics Committee on 14 January 2019 (Protocol code: 2018/334).

Calculation of ALBI scores and categorization of prognostic factors

ALBI score was calculated using the formula of linear prediction model in its original study: ($\log_{10}$ bilirubin x 0.66) + (albumin x -0.085) [2]. Bilirubin and albumin in this equation are measured in μmol/L and g/L, respectively. According to the original research again, patients were assigned into three prognostic groups: ≤-2.60 as ALBI grade 1, >-2.60 and ≤-1.39 as ALBI grade 2 and >-1.39 as ALBI grade 3.

Upper limits of normal for serum total bilirubin, LDH, CEA and lower limit of normal for serum albumin in the institutional laboratory of biochemistry were set as cut-off values. Consequently, patients were categorized into two groups (below and above the cut-off value) for these variables. Neutrophil-to-lymphocyte ratio (NLR) of each patient was calculated using complete blood counts. A receiver operating characteristic (ROC) curve was constructed to determine a cut-off value for NLR and the most sensitive value for prediction of survival was accepted in the case of a statistically significant area under curve (AUC). Simultaneously, distribution of NLR was tested with Kolmogorov-Smirnov method for normality. Patients were also categorized into two groups of primary tumor side for prognostication: Left colon (from rectum to splenic flexure) and right colon (from caecum to hepatic flexure) or transverse colon. Age at the time of liver metastasis was included in the analyses with a cut-off of 65 years.

Statistical analysis

Overall survival (OS) was accepted as the time interval between the detection of liver metastasis and date of exitus or last visit (final update on September 27th, 2018). Probability of survival was tested with Kaplan-Meier method and comparison of survival for each factor was done using a stratified log-rank test. Factors with a *P*-value of <0.05 were selected for multivariate analysis. Cox regression model was utilized to determine independent predictors of survival and their hazard ratios (HRs), these were analyzed in a backward stepwise method. Since ALBI score results from an equation including albumin and bilirubin which are potential prognostic indicators themselves, two separate multivariate models were conducted: Model 1 that included serum albumin and bilirubin without ALBI grade and Model 2 that included ALBI grade without these two variables. Confidence interval (CI) was set as 95% and a 2-sided *P*-value as <0.05 for statistical significance. SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics For Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for all statistical analyses.

Results

Patient characteristics

A total of 223 patients were included in the study. Median age of the patients at the time of documented liver metastasis was 63 (55-70) years. Patients who were 65 years old or older made up 42.2% of the study population. The proportion of male patients was 67.7%. Primary tumor was located in left colon in 79.4% of patients. LDH was above the cut-off value (246 U/L) in 117 patients (52.5%). For CEA, upper limit of normal was 5 ng/mL in our institute and 156 patients (70%) were above this threshold. ROC curve analysis for NLR resulted in a

statistically insignificant AUC (0.567; 95% CI, 0.465-0.668; P=0.20). Therefore, a normality test was done and a median NLR of 2.9 was accepted as the cut-off value considering the distribution was not normal (P<0.001). Percent of patients with a NLR of 2.9 or more was 50.2 in our study.

Fifty-one patients (22.9%) had a serum albumin level lower than 3.5 g/dL and 29 patients (13%) had a serum bilirubin level more than 1.2 mg/dL. ALBI scores of all patients ranged between -0.14 and -3.61 (median: -2.69). ALBI grade was 1 in 126 of the patients (56.5%), 2 in 81 patients (36.3%) and 3 in 16 patients (7.2%). Table 1 summarizes the baseline characteristics of the patients.

Survival outcomes

Median follow-up time in the study was 19.7 months (95% CI, 17.3-22.3). At the final update, death has occurred in 187 patients (83.9%). In patients with ALBI grade 1, 1- and 2-year survival rates were 80% and 50% respectively. For ALBI grade 2, these rates were 62% and 29%, respectively. Patients who had an ALBI grade of 3 had a 1-year survival rate of 25% and 2-year survival rate of only 8%. Median OS in ALBI grade 1, 2 and 3 groups were 23.9, 16.0 and 4.0 months, respectively (P<0.001) (Figure 1).

Univariate analyses of all prognostic factors are shown in Table 2. Besides ALBI grade, advanced age (≥65 years), primary tumor location, higher baseline serum LDH, CEA and total bilirubin levels, a lower baseline serum albumin level and a higher baseline NLR were all found to affect OS significantly. In the multivariate Model 1 including serum albumin and total bilirubin and excluding ALBI grade (displayed in Table 3), age ≥65 years, higher LDH and CEA levels, a higher NLR and a lower albumin level (HR=1.97, P=0.001) were detected as independent prognostic factors while higher total bilirubin was not (HR=1.43, P=0.17). In the multivariate Model 2 excluding serum albumin and total bilirubin, ALBI grade 2 (HR=1.54, P=0.02) and grade 3 (HR=3.85, P<0.001) were both independent predictors of survival after adjusting for other factors (Table 3).

Table 1: Baseline demographical and clinical characteristics of the patients

Variable	Number of patients (%)
Gender	
Male	151 (67.7)
Female	72 (32.3)
Age (years)	
<65	129 (57.8)
≥65	94 (42.2)
Primary tumor location	
Left colon	177 (79.4)
Right or transverse colon	44 (19.7)
Unknown	2 (0.9)
LDH (U/L)	
≤246	95 (42.6)
>246	117 (52.5)
Unknown	11 (4.9)
CEA (ng/mL)	
≤5	37 (16.6)
>5	156 (70)
Unknown	30 (13.4)
NLR	
<2.9	111 (49.8)
≥2.9	112 (50.2)
Albumin (g/dL)	
<3.5	51 (22.9)
≥3.5	172 (77.1)
Total bilirubin (mg/dL)	
≤1.2	194 (87)
>1.2	29 (13)
ALBI grade	
1	126 (56.5)
2	81 (36.3)
3	16 (7.2)

LDH: Lactate dehydrogenase, CEA: Carcinoembryogenic antigen, NLR: Neutrophil-to-lymphocyte ratio

Table 2: Univariate analysis of prognostic factors for overall survival

Factor	OS in months (95% CI)	1-year survival (%)	2-year survival (%)	P-value for OS
Gender				
Male	20.1 (16.9-23.4)	68	42	0.17
Female	18.3 (13.1-23.4)	72	35	
Age (years)				
<65	22.4 (17.5-27.2)	76	48	0.01
≥65	14.1 (10.5-17.8)	61	28	
Primary tumor location				
Left colon	20.4 (17.9-22.9)	75	42	0.006
Right or transverse colon	11.6 (9.5-13.7)	49	28	
LDH (U/L)				
≤246	23.3 (21.0-25.7)	79	48	<0.001
>246	15.8 (12.3-19.3)	62	33	
CEA (ng/mL)				
≤5	24.0 (11.7-36.3)	89	54	0.001
>5	18.8 (16.0-21.6)	68	39	
NLR				
<2.9	23.9 (19.7-28.1)	77	50	<0.001
≥2.9	16.1 (12.4-19.8)	62	29	
Albumin (g/dL)				
<3.5	9.1 (1.6-16.6)	45	18	<0.001
≥3.5	22.0 (19.0-25.0)	77	46	
Total bilirubin (mg/dL)				
≤1.2	21.4 (18.8-24.0)	73	43	<0.001
>1.2	8.5 (0.0-18.5)	45	16	
ALBI grade				
1	23.9 (19.6-28.1)	80	50	<0.001
2	16.0 (11.9-20.1)	62	29	
3	4.0 (3.2-4.9)	25	8	

OS: Overall survival, CI: Confidence interval, LDH: Lactate dehydrogenase, CEA: Carcinoembryogenic antigen, NLR: Neutrophil-to-lymphocyte ratio

Table 3. Multivariate Models 1 and 2 evaluating prognostic factors for overall survival

Factor	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	2.30 (1.60-3.30)	<0.001	2.28 (1.57-3.31)	<0.001
Primary tumor location	1.40 (0.92-2.12)	0.12	1.25 (0.81-1.93)	0.31
LDH	1.47 (1.03-2.11)	0.03	1.47 (1.03-2.10)	0.03
CEA	1.88 (1.19-2.98)	0.007	1.93 (1.22-3.05)	0.005
NLR	1.99 (1.39-2.86)	<0.001	2.09 (1.46-2.99)	<0.001
Albumin	1.97 (1.32-2.95)	0.001		
Total bilirubin	1.43 (0.86-2.37)	0.17		
ALBI grade				
Grade 1			Reference	
Grade 2			1.54 (1.08-2.20)	0.02
Grade 3			3.85 (1.85-8.00)	<0.001

HR: Hazard ratio, CI: Confidence interval, LDH: Lactate dehydrogenase, CEA: Carcinoembryogenic antigen, NLR: Neutrophil-to-lymphocyte ratio

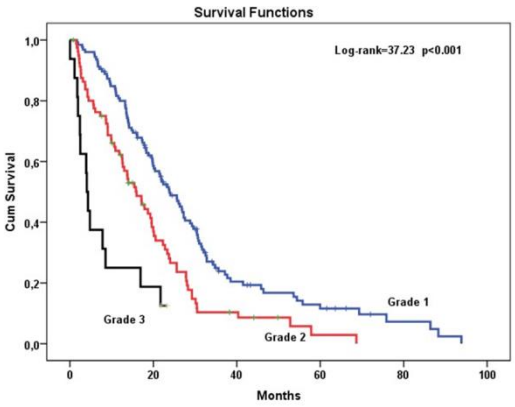

Figure 1: Kaplan-Meier plots stratified by ALBI grade (The horizontal and vertical axes show overall survival and cumulative survival rate, respectively)

Discussion

In our study, we revealed that ALBI grade may be a valuable prognostic tool for CRC patients with liver metastases and can remarkably predict their survival. In addition, advanced age, serum albumin, LDH and CEA levels and NLR were significantly associated with mortality of these subjects. The importance of ALBI grade is related to its potential to identify patients with liver-metastatic CRC who will have unfavorable outcomes at initial presentation.

The validation study of ALBI score/grade in HCC has placed Child-Pugh score, which is a standardized predictive and prognostic model in patients with liver cirrhosis and HCC, as a comparator [6]. Unfortunately, there are no such standard

prognostic models established in CRC yet. Köhne's model including performance status, white blood cell count, serum alkaline phosphatase level and number of metastatic sites was evaluated in two metastatic CRC studies and was shown to be applicable in these patients [11,12]. However, its prognostic value may be controversial because it does not contain serum LDH level which was addressed as an important prognostic factor by many studies regarding metastatic CRC [13-15]. Another simplified model consisting of serum LDH and performance status was shown to discriminate better than Köhne's model but it has not found general use either [13]. In our study, we evaluated other objective prognostic parameters concurrently and observed that ALBI grade was an independent predictor of survival.

Albumin is a nutritional and inflammatory marker produced by the liver, it was first reported as a prognostic factor in CRC by Heys et al. [16]. Subsequent studies highlighted its value in predicting long-term outcomes of CRC patients [17,18]. On the other hand, bilirubin has no known physiologic role but along albumin, it is a major determinant of the hepatic functional status in chronic liver disease and HCC. Limited data exists about the prognostic value of serum bilirubin in CRC. Zhang et al. [19] associated higher serum bilirubin levels with reduced OS in resected stage II and III CRC, while Yang et al. [20] demonstrated its prognostic impact in stage IV disease. After adjusting for other factors in our study, serum albumin independently predicted overall survival whereas total bilirubin did not. In contrast, ALBI grade was an independent negative prognostic factor in a second multivariate analysis, with a 1.5- and 3.9-fold increased risk of death for ALBI grades 2 and 3, respectively. Especially, baseline ALBI grade 3 could predict shorter survival prior to treatment. It is controversial which cut-off value of serum albumin should be used to determine worse prognosis. Therefore, we suggest that ALBI score/grade may be a reliable and universally applicable objective model for estimating outcomes of CRC patients with liver metastases.

LDH is considered as a major prognostic indicator in many published CRC studies. Likewise, CEA is obviously a marker affecting long-term survival of stage IV CRC patients [21]. Our analyses show that higher LDH and CEA are associated with an approximately 1.5- and 1.9-fold increased risk for death in liver-metastatic CRC, respectively. Additionally, A NLR of ≥3 was confirmed to correlate with worse survival in metastatic CRC treated with first-line systemic therapy by Dell'Aquila et al. [22] before. Having used a close cut-off (≥2.9), we have shown that NLR is a markedly significant predictor of overall survival in metastatic CRC with liver metastases as well. On the other hand, impact of age on CRC prognosis has been more arguable than the above-mentioned parameters. Jiang et al. [23] showed in a large study population that younger CRC patients had longer OS in all stages despite presenting with more adverse features. Contrarily, Fu et al. [24] stated that young adults with advanced CRC had worse survival compared to their older counterparts and age was not an independent prognostic factor. Patients who were 65 years old or older had worse OS in our study and advanced age was independently associated with over 2-fold higher risk of death compared to patients younger than 65 years. Although aging is a heterogeneous process, our result may be in part explained by increasing comorbidities and declining of performance status that could contribute to the impact of advanced age on the outcomes of the patients.

Limitations

There were some limitations in this study. We could not evaluate performance status, which is an established prognostic factor in many cancers, because of largely missing data in patient files. Another issue that could be addressed by future studies is how ALBI score/grade would perform in CRC patients with only extrahepatic metastases.

Conclusion

Our study shows that a higher baseline ALBI grade is associated independently with poor overall survival in CRC patients with liver metastases. It may be an useful method in metastatic CRC, for which a generally acceptable prognostic model has to emerge yet.

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