



Prognostic Value of Baseline ALBI Score Among Patients With Colorectal Liver Metastases: A Pooled Analysis of Two Randomized Trials

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Abstract

Albumin-bilirubin (ALBI) score has been shown to be a reliable prognostic indicator among hepatocellular carcinoma patients. A total of 1434 patients with colorectal liver metastases were included into this study. Higher ALBI score was associated with worse overall and progression-free survival among patients with colorectal liver metastases.

Background: Baseline albumin-bilirubin (ALBI) score has been shown to be a reliable prognostic predictor among patients with hepatocellular carcinoma. The current study aims at evaluating its prognostic impact among patients with colorectal liver metastases treated with first-line systemic therapy. **Materials and Methods:** Through the Project Data Sphere portal, de-identified clinical trial datasets of 2 clinical trials (NCT00115765; PACCE [Panitumumab Advanced Colorectal Cancer Evaluation Study] trial) and (NCT00364013; PRIME [Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy] trial) were downloaded. Baseline ALBI score was calculated for each included patient in this study. Kaplan-Meier curve/log-rank testing was used to evaluate overall and progression-free survival according to ALBI grades. Additional Cox regression models were run in order to evaluate factors affecting overall and progression-free survival. Factors with P -value $< .05$ in univariate analysis were included in multivariate analysis. **Results:** A total of 1434 patients with colorectal liver metastases were included in this study. Kaplan-Meier survival analysis was conducted to assess the impact of ALBI grade on overall and progression-free survival in the study cohort. For both endpoints, higher ALBI grade was associated with worse overall and progression-free survival ($P < .001$ for both endpoints). The following factors were significant for overall survival in univariate Cox regression analysis ($P < .05$): age, Eastern Cooperative Oncology Group (ECOG) score, lactate dehydrogenase (LDH), number of metastatic sites, body mass index, and ALBI score. When these factors were evaluated in multivariate Cox regression analysis, the following factors were predictive of worse overall survival: higher ALBI score ($P < .001$), higher number of metastatic sites ($P < .001$), higher LDH ($P < .001$), higher ECOG score ($P < .001$), and older age ($P < .001$). Similarly, the following factors were significant for progression-free survival in univariate Cox regression analysis ($P < .05$): age, race, ECOG score, LDH, number of metastatic sites, body mass index, type of chemotherapy, and ALBI score. When these factors were evaluated in multivariate Cox regression analysis, the following factors were predictive of worse progression-free survival: higher ECOG score ($P < .001$), higher LDH level ($P < .001$), higher number of metastatic sites ($P < .001$), and higher ALBI score ($P < .001$). **Conclusions:** Higher baseline ALBI score is associated with worse overall and progression-free survival among patients with colorectal liver metastases treated with first-line systemic therapy.

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Keywords: Albumin, Bilirubin, Prognosis, Scoring system, Survival

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Introduction

Colorectal cancer (CRC) represents one of the most common incident cancers as well as one of the most common causes of cancer deaths worldwide.¹ A considerable proportion of patients with CRC present with de novo metastatic disease. Moreover, many patients with initially localized CRC present later on with distant disease relapse.²

The liver is by far the most common and most prognostically relevant site of metastatic disease. Numerous studies were published to evaluate different prognostic indices/models among patients with colorectal liver metastases.³⁻⁵ However, the impact of baseline functional hepatic status on the outcomes of those patients was not adequately addressed. Moreover, the few studies that tackled the impact of hepatic functional status on the outcomes of those patients were based on retrospectively collected datasets with plenty of potential confounders.⁶

The albumin-bilirubin (ALBI) score is a simplified model that has shown prognostic relevance among patients with newly diagnosed hepatocellular carcinoma.⁷ Its prognostic relevance was proved among patients with early, intermediate, and advanced stages as well as among patients treated with surgery, locoregional treatment, or systemic treatment.⁸⁻¹² Moreover, its prognostic value was shown among patients with advanced liver cirrhosis without hepatocellular carcinoma.¹³ It remains to be seen and proven if this score (as a surrogate of the hepatic functional status of patients with colorectal liver metastases) could help predict the outcomes of those patients.

In order to avoid the potential confounding effect of retrospectively collected datasets, the current analysis was based on a number of prospectively collected datasets downloaded from the Project Data Sphere (PDS). The aim of the current study is thus to evaluate the prognostic impact of baseline ALBI score on the outcomes of patients with colorectal liver metastases treated with first-line systemic chemotherapy. The primary hypothesis of this study is that ALBI score — as a measure of liver function — might predict the outcomes of patients with colorectal liver metastases.

Materials and Methods

About the Project Data Sphere (PDS)

PDS is an international initiative based on a number of stakeholders including governmental agencies and drug companies who work as sponsors for a number of landmark clinical trials.¹⁴ This initiative aims at facilitating the access of interested researchers to de-identified raw data of multiple clinical trials. Such an initiative

should hopefully allow making the best use out of previously published clinical trials by asking new research questions on the existing clinical trial datasets.

Clinical Trial Datasets

The current study is based on a pooled analysis of the raw data of 2 previously completed phase III trials (NCT00115765; PACCE [Panitumumab Advanced Colorectal Cancer Evaluation Study] trial) and (NCT00364013; PRIME [Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy] trial) evaluating a number of chemotherapy regimens in the first-line treatment of metastatic CRC. The clinical trial datasets were downloaded from the PDS portal after obtaining necessary approvals. Characteristics of each of the 2 included trials are detailed in Table 1. Detailed methodology and primary results of each of the included trials were published elsewhere.^{15,16} Among 1777 patients from both clinical trials, only 1485 patients had liver metastases before study entry. After excluding 51 patients with unknown ALBI score, 1434 patients were finally included in the current study (Figure 1).

ALBI Score

The ALBI score was calculated based on baseline albumin and total bilirubin measurement. It is calculated according to the following equation (ALBI score = $-0.085 \times [\text{albumin g/L}] + 0.66 \lg_{10} [\text{Tbil } \mu\text{mol/L}]$).¹⁷ The resultant ALBI grades were defined as follows: (grade 1, ≤ -2.60 ; grade 2, > -2.60 to ≤ -1.39 ; and grade 3, > -1.39).

Data Collection

The following baseline data were collected from each included patient in the current study: age at diagnosis, gender, race, primary tumor location (colon vs. rectum), body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) score, baseline ALBI grade and score, number of organs with distant metastases, lactate dehydrogenase (LDH), months from initial diagnosis to start of treatment, prior oncologic surgery to the primary, prior adjuvant treatment, chemotherapy regimen, and treatment duration. It has to be noted that sidedness within the colon (right- vs. left-sided) was not reported in the available clinical trial datasets. KRAS testing was available only in the PACCE clinical trial dataset but not in the PRIME clinical trial dataset.

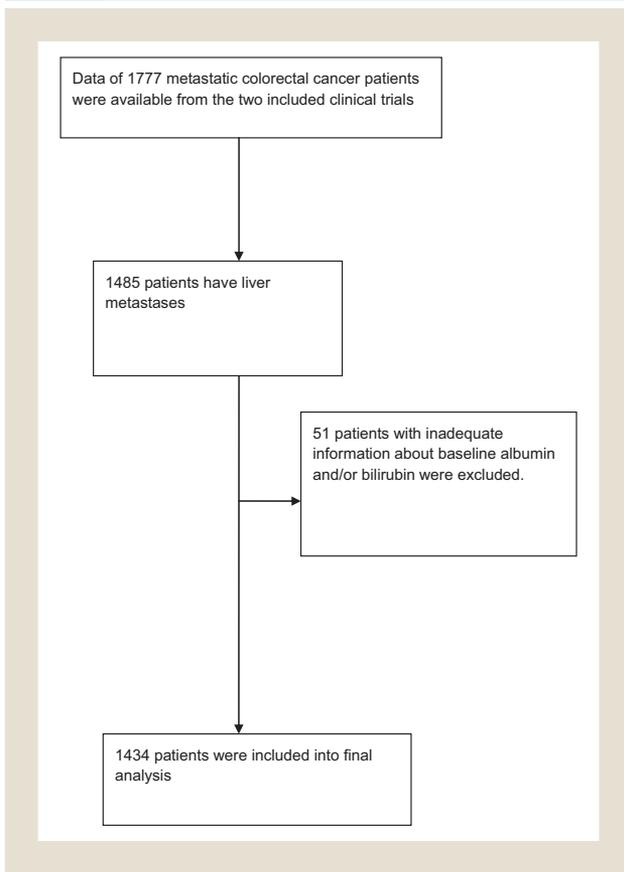
According to clinical trials, protocols, and primary reports, all included patients have acceptable performance status and adequate

Table 1 Clinical Trial Cohorts Included in the Current Study

Study	Treatment Regimen	Percentage of Patients in the Pooled Analysis	Start Date	Completion Date
NCT00115765 (PACCE)	Experimental arm: chemotherapy and bevacizumab with panitumumab. Active comparator: chemotherapy and bevacizumab.	46%	June 2005	December 2009
NCT00364013 (PRIME)	Experimental arm: panitumumab plus FOLFOX Active comparator: FOLFOX alone	54%	August 2006	March 2013

Abbreviations: FOLFOX = leucovorin, fluorouracil, and oxaliplatin; PACCE = Panitumumab Advanced Colorectal Cancer Evaluation Study; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.

Figure 1 Flow Chart of the Selection Process of the Study Cohort



baseline organ function (including liver and renal functions). Primary endpoints of the current study include overall survival (defined as the time from randomization until the death of any cause) and progression-free survival (defined as the time from randomization until disease progression or death).

Statistical Considerations

Descriptive statistics were used to explore frequencies as well as central tendency statistics of different baseline clinicopathologic variables. Kaplan-Meier analysis/log-rank testing was used to evaluate overall and progression-free survival according to ALBI grades.

Additional Cox regression models were run in order to evaluate factors affecting overall and progression-free survival. The following factors were evaluated in univariate analyses: age, race, gender, ECOG score, LDH level, chemotherapy regimen, number of metastatic sites, site of the primary tumor, prior adjuvant treatment, BMI, and ALBI score. Factors with *P*-value < .05 in univariate analysis were included in multivariate analysis. Statistical calculations were conducted through SPSS program version 20 (IBM).

Results

Patients' Characteristics

A total of 1434 patients were included in this study. The median age was 61 years (range, 22-88 years), the median BMI

Table 2 Baseline Characteristics of Included Patients in the Study (1434 Patients)

Parameter	N (%)
Age, y	
Median (range)	61 (22-88)
Missing	0
Gender	
Male	863 (60.2)
Female	571 (39.8)
Race	
Caucasian	1304 (90.9)
Others	130 (9.1)
Body mass index	
Median (range)	25.9 (15.7-58)
Missing	0
ECOG	
0	806 (56.2)
1	593 (41.4)
2	35 (2.4)
Primary tumor site	
Colon	1063 (74.1)
Rectum	371 (25.9)
Number of organs with distant metastases	
1	471 (32.8)
2	476 (33.2)
≥3	487 (34)
LDH ≥ 1.5 upper limit of normal	
Yes	421 (29.4)
No	966 (67.4)
Unknown	47 (3.3)
Prior oncologic surgery to the primary	
No	942 (65.7)
Yes	492 (34.3)
Prior adjuvant treatment	
No	1293 (90.2)
Yes	141 (9.8)
Chemotherapy regimen	
Panitumumab + FOLFOX	387 (27)
Bevacizumab + FOLFOX	263 (18.3)
Bevacizumab + FOLFIRI	60 (4.2)
Panitumumab + bevacizumab + FOLFOX	277 (19.3)
Panitumumab + bevacizumab + FOLFIRI	61 (4.3)
FOLFOX	386 (26.9)
Months since primary diagnosis	
Median (range)	2 (0-144)
Missing	27
Treatment duration, mo	
Median (range)	5.6 (0.1-43.7)
Missing	0
ALBI grade	
ALBI 1	786 (54.8)
ALBI 2	616 (43)

ALBI Score for mCRC

Table 2 Continued

Parameter	N (%)
ALBI 3	32 (2.2)
ALBI score	
Mean (range)	-2.66 (-3.79 to -0.21)
Missing	0

Abbreviations: ALBI = albumin-bilirubin; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = leucovorin, fluorouracil, and irinotecan; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; LDH = lactate dehydrogenase.

was 25.9 (range, 15.7-58), and the median ALBI score was -2.66 (range, -3.79 to -0.21). Patients with male gender represent 60.2% of the study cohort, patients with white race represent 90.9%, patients with ECOG score of 0 represent 56.2%, and patients with colon as the primary tumor site represent 74.1%. Of the included patients, 32.8% have a single site of metastasis (liver-only distant metastasis), 29.4% have LDH \geq 1.5 upper limit of normal, and 54.8% of the patients have ALBI grade 1. Of the included patients, 65.7% underwent prior oncologic resection of the primary, and 9.8% received prior adjuvant treatment following resection. Patients treated with

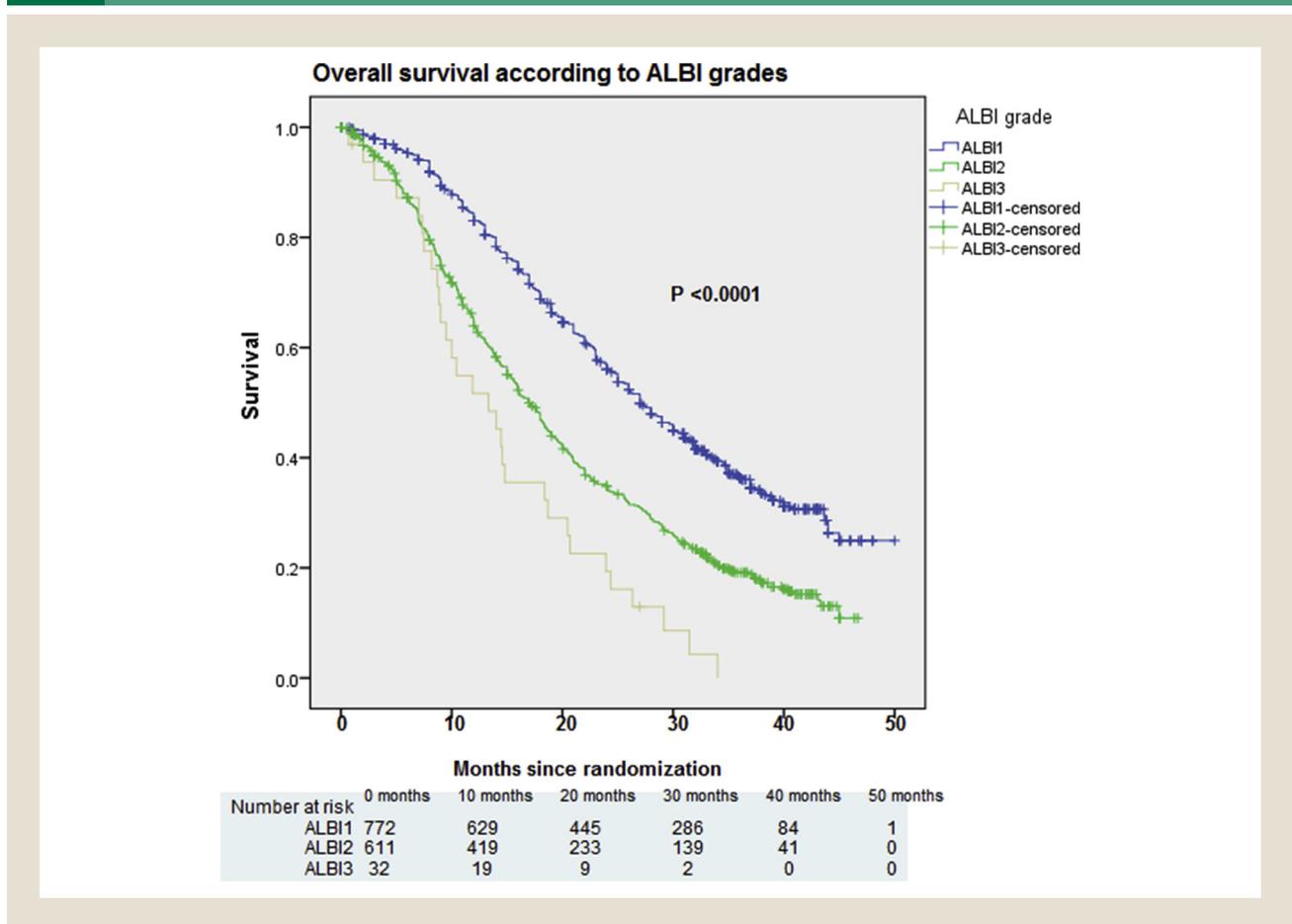
FOLFOX (leucovorin, fluorouracil, and oxaliplatin) chemotherapy alone as first-line metastatic regimen represent 26.9%, the median months from initial diagnosis until treatment was 2 months (range, 0-144 months), and the median treatment duration was 5.6 months (range, 0.1-43.7 months) (Table 2). The median follow-up duration for the entire cohort was 19 months (range, 0.1-50 months).

Survival Outcomes

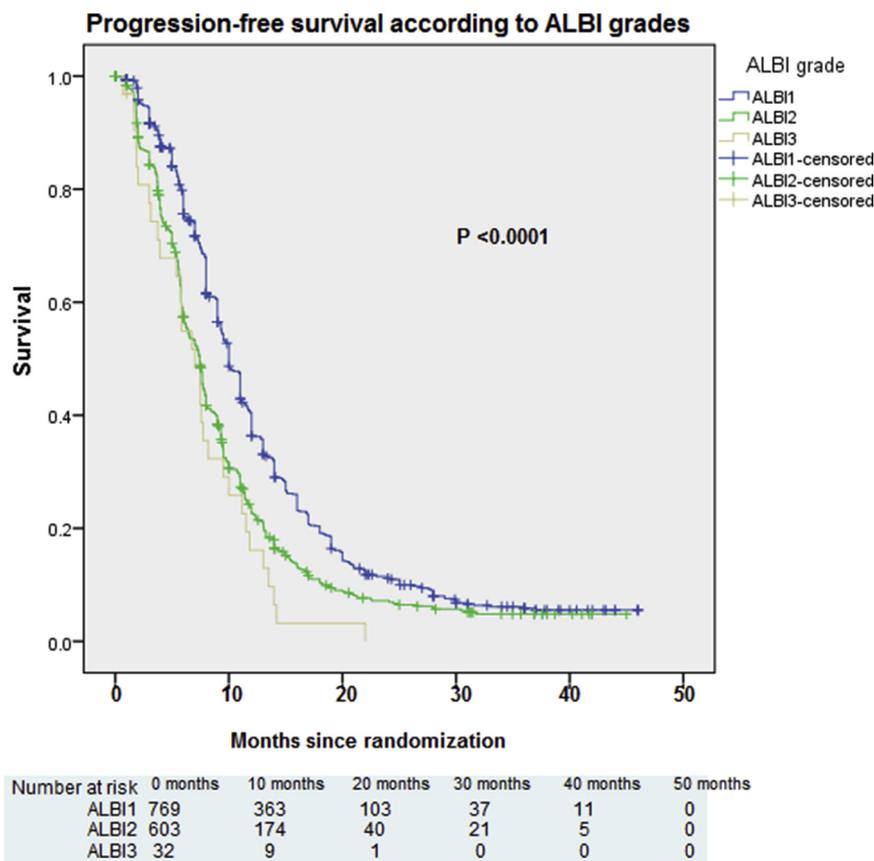
Kaplan-Meier survival analysis was conducted to assess the impact of ALBI grade on overall and progression-free survival in the study cohort. For both endpoints, higher ALBI grade was associated with worse overall and progression-free survival ($P < .001$ for both endpoints) (Figures 2 and 3).

Univariate Cox-regression analyses were then conducted to evaluate the impact of the following factors on overall survival (age, race, gender, ECOG score, LDH level, chemotherapy regimen, number of metastatic sites, site of the primary, prior adjuvant treatment, BMI, and ALBI score). The following factors were significant for overall survival in univariate analysis ($P < .05$): age, ECOG score, LDH, number of metastatic sites, BMI, and ALBI score. When these factors were evaluated in multivariate analysis, the following factors were predictive of worse overall survival:

Figure 2 Kaplan-Meier Survival Curve for the Impact of Baseline ALBI Score on the Overall Survival of Included Patients



Abbreviation: ALBI = albumin-bilirubin.

Figure 3 Kaplan-Meier Survival Curve for the Impact of Baseline ALBI Score on the Progression-free Survival of Included Patients

Abbreviation: ALBI = albumin-bilirubin.

higher ALBI score ($P < .001$), higher number of metastatic sites ($P < .001$), higher LDH ($P < .001$), higher ECOG score ($P < .001$), and older age ($P < .001$) (Table 3).

Similarly, univariate Cox regression analysis was conducted to evaluate factors affecting progression-free survival using the same factors evaluated above. The following factors were significant for progression-free survival in univariate analysis ($P < .05$): age, race, ECOG score, LDH, number of metastatic sites, BMI, type of chemotherapy, and ALBI score. When these factors were evaluated in multivariate analysis, the following factors were predictive of worse progression-free survival: higher ECOG score ($P < .001$), higher LDH level ($P < .001$), higher number of metastatic sites ($P < .001$), and higher ALBI score ($P < .001$) (Table 4).

Through univariate analysis, an additional assessment of the prognostic value of each of serum albumin and serum bilirubin individually was conducted. Both lower serum albumin and higher serum bilirubin were associated with worse overall and progression-free survival ($P < .001$ for each parameter and for each endpoint).

An additional univariate analysis was conducted to evaluate the prognostic value of ALBI score among the entire clinical trial

population (including those with or without liver metastases). ALBI score remains prognostic in the overall population ($P < .001$ for both overall and progression-free survival). However, it has to be remembered that, among this entire population, 83% have liver metastases. So, the results of the entire population are likely to be affected by the majority of patients with liver metastases.

Discussion

To the best of our knowledge, this is the first study to evaluate the prognostic impact of baseline ALBI score on the outcomes of patients with colorectal liver metastases treated with first-line systemic chemotherapy. This study shows that higher baseline ALBI score is associated with worse overall and progression-free survival outcomes. This prognostic value is independent of other established prognostic factors among patients with metastatic CRC. These findings, coupled with the simplicity and easy-to-use nature of this scoring system, endorse its routine use in clinical practice.

A number of weaknesses have to be acknowledged in this analysis; foremost, in spite of the fact that the current study is based on prospectively collected clinical trial datasets, the prognostic impact

Table 3 Univariate and Multivariate Cox Regression Analysis for Factors Affecting Overall Survival

Parameters	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (continuous)	1.017 (1.010-1.023)	<.001	1.014 (1.007-1.021)	<.001
Race				
White/Caucasian	Reference			
Other categories	0.919 (0.719-1.174)	.498	—	
Gender				
Male	Reference			
Female	1.003 (0.940-1.071)	.953	—	
ECOG score				
2	Reference		Reference	
0	0.209 (0.147-0.296)	<.001	0.470 (0.317-0.696)	<.001
1	0.369 (0.260-0.524)	<.001	0.721 (0.491-1.058)	.094
LDH \geq 1.5				
Yes	Reference		Reference	
No	0.743 (0.641-0.862)	<.001	0.655 (0.566-0.759)	<.001
Chemotherapy				
Panitumumab + FOLFOX	Reference		—	
Bevacizumab + FOLFIRI	0.924 (0.642-1.330)	.671		
Bevacizumab + FOLFOX	0.853 (0.683-1.066)	.162		
FOLFOX	1.166 (0.965-1.409)	.112		
Number of metastatic sites				
\geq 3	Reference		Reference	
1	0.519 (0.443-0.608)	<.001	0.601 (0.511-0.707)	<.001
2	0.684 (0.588-0.796)	<.001	0.761 (0.653-0.887)	<.001
Site of the primary				
Rectum	Reference			
Colon	1.011 (0.941-1.087)	.758	—	
Prior adjuvant treatment				
Yes	Reference			
No	1.120 (0.997-1.259)	.056	—	
BMI (continuous)	0.979 (0.966-0.991)	.001	0.989 (0.977-1.002)	.109
ALBI score (continuous)	1.988 (1.776-2.227)	<.001	1.416 (1.239-1.620)	<.001

Abbreviations: ALBI = albumin-bilirubin; BMI = body mass index; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = leucovorin, fluorouracil, and irinotecan; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; HR = hazard ratio; LDH = lactate dehydrogenase.

of ALBI score was not the primary research question of these clinical trials. Thus, the current study is still considered a retrospective analysis of the prospectively collected dataset. This indicates that the current study might have the potential confounders and biases included in any retrospective study. Moreover, RAS and BRAF statuses were not clearly reported in the available datasets from PDS. This might have particularly confounded the assessment of chemotherapy efficacy among study participants.

On the other hand, the above weaknesses have to be seen through the lens of the clear strengths of this study, including the higher credibility associated with prospectively collected clinical trial datasets (compared with comparable retrospectively collected institutional cohorts) and the novelty associated with testing ALBI score in the setting of colorectal liver metastases.

The findings of the current study point out to an important perspective in managing patients with colorectal liver metastases

compared with patients with hepatocellular carcinoma. For patients with hepatocellular carcinoma, assessment of baseline liver function is a very fundamental part of the prognostic stratification and therapeutic decision-making process (eg, within Barcelona Clinic Liver Cancer classification).¹⁸ On the other hand, specific and detailed assessment of baseline liver function does not occupy the same importance level among patients with colorectal liver metastases. The current study suggests that baseline liver functional status might predict oncologic outcomes of patients with colorectal liver metastases and suggests that detailed assessment of baseline liver function should occupy a better position in the decision-making process.

Additional research questions that need to be answered in future studies would include possible impact of baseline ALBI score on the oncologic/hepatologic outcomes of patients with colorectal liver metastases undergoing specific locoregional

Table 4 Univariate and Multivariate Cox Regression Analysis for Factors Affecting Progression-free Survival

Parameters	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (continuous)	1.008 (1.002-1.013)	.007	1.005 (0.999-1.010)	.118
Race				
White/Caucasian	Reference		Reference	
Other categories	0.856 (0.770-0.952)	.004	0.860 (0.691-1.072)	.180
Gender				
Male	Reference			
Female	1.021 (0.910-1.145)	.729	—	
ECOG score				
2	Reference		Reference	
0	0.324 (0.230-0.457)	<.001	0.556 (0.384-0.807)	.002
1	0.463 (0.328-0.653)	<.001	0.722 (0.501-1.040)	.088
LDH \geq 1.5				
Yes	Reference		Reference	
No	0.692 (0.612-0.782)	<.001	0.788 (0.691-0.899)	<.001
Chemotherapy				
Panitumumab + FOLFOX	Reference		Reference	
Bevacizumab + FOLFIRI	0.843 (0.614-1.157)	.290	0.870 (0.718-1.055)	.157
Bevacizumab + FOLFOX	0.887 (0.735-1.071)	.214	0.967 (0.832-1.125)	.668
FOLFOX	1.338 (1.131-1.581)	.001	2.670 (0.361-19.776)	.336
Number of metastatic sites				
\geq 3	Reference		Reference	
1	0.572 (0.497-0.658)	<.001	0.654 (0.563-0.760)	<.001
2	0.790 (0.690-0.904)	.001	0.847 (0.738-0.973)	.019
Site of the primary				
Rectum	Reference			
Colon	0.953 (0.894-1.016)	.140	—	
Prior adjuvant treatment				
Yes	Reference			
No	1.064 (0.964-1.174)	.216	—	
BMI (continuous)	0.980 (0.969-0.991)	<.001	0.989 (0.978-1.000)	.058
ALBI score (continuous)	1.620 (1.463-1.795)	<.001	1.264 (1.110-1.439)	.001

Abbreviations: ALBI = albumin-bilirubin; BMI = body mass index; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = leucovorin, fluorouracil, and irinotecan; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; HR = hazard ratio; LDH = lactate dehydrogenase.

therapies (eg, surgery or locoregional ablation/embolization). This might also help predict the risk of decompensation following resection of colorectal liver metastases. For patient with hepatocellular carcinoma, it has been shown that ALBI score predicts mortality and hepatic decompensation following these procedures.⁸⁻¹² Likewise, the impact of baseline ALBI score on the outcomes of liver metastases from other solid tumors needs to be evaluated in future studies.

The current study has shown a prognostic relevance for baseline ALBI score even among patients with more than one site of metastases (ie, extra-hepatic metastatic disease in addition to hepatic metastatic disease). This might indicate that in patients with hepatic and extra-hepatic metastatic disease, the functional impact of the hepatic disease still carries an important role in the overall prognosis of the disease.

It has also to be noted that, although ALBI score/grade has been established as an evaluation tool for hepatic reserve function, it might also play a role as an evaluation tool for nutritional status (because of the observed correlation between serum albumin and nutritional status). However, one has to note that — in the present study — when the prognostic value of each of serum albumin and serum bilirubin was evaluated separately, both of them were prognostic for overall and progression-free survival. This probably indicates that the prognostic value of ALBI score in the current study goes beyond simple nutritional indicator of serum albumin.

In conclusion, higher baseline ALBI score is associated with worse overall and progression-free survival among patients with colorectal liver metastases treated with first-line systemic therapy. Future studies might aim at clarifying the impact of baseline ALBI

ALBI Score for mCRC

score on the outcomes of patients with colorectal liver metastases treated with surgical/locoregional therapies.

Clinical Practice Points

- ALBI score has been shown as a reliable prognostic marker among patients with hepatocellular carcinoma.
- Through the PDS portal, de-identified datasets from 2 clinical trials (PRIME and PACCE) were downloaded.
- Kaplan-Meier analysis and Cox regression analysis were used to determine the prognostic relevance of ALBI score among patients with colorectal liver metastases.
- A total of 1434 patients with colorectal liver metastases were included into this analysis.
- Higher ALBI score is associated with worse OS and PFS among patients with colorectal liver metastases treated with first-line chemotherapy.

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Disclosure

The author has stated that he has no conflicts of interest.

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