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ORIGINAL ARTICLE

Assessment of pretreatment albumin-bilirubin grade in pancreatic cancer patients with liver metastasis

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Summary

Purpose: *This study aimed to assess the effect of pretreatment albumin-bilirubin (ALBI) score on treatment outcomes in pancreatic cancer (PC) patients with liver metastasis at the time of diagnosis treated with chemotherapy (CT) in the first-line setting.*

Methods: *This was a retrospective study of 273 PC patients ≥18 years of age who had liver metastasis at the time of diagnosis and received CT in the first-line. ALBI score was calculated through the following formula; [(log10 bilirubin (μmol/L)×0.66)+[albumin(g/l)×−0.0852]. Patients were stratified into 3 categories based on the ALBI score as follows; grade I:ALBI ≤-2.60, grade II:-2.60<ALBI≤-1.39, and grade III:ALBI>-1.39.*

Results: *A total of 273 patients, [180 (65.9%) men and 93 (34.1%) women], were evaluated. The median age was 60 years. ALBI grade was I in 45 (16.4%) patients, II in 156 (57.1%) patients, and III in 72 (26.5%) patients. Based on the ALBI grade, median progression-free survival (mPFS) was 9 months in grade I patients, 6 months in grade II patients, and 4 months in grade III patients (p=0.002), with median overall survival (mOS) durations of 12 months vs. 8 months vs. 5 months, respectively (p<0.001). Multivariate analysis showed that ALBI grade II (HR,1.543) or III (HR,2.260) negatively affected survival.*

Conclusion: *A higher pretreatment ALBI grade is related to worse OS and PFS in PC patients with liver metastasis treated with a first-line CT, and therefore it can help predict the treatment outcomes in these patients.*

Key words: *pancreatic cancer, ALBI grade, albumin, bilirubin, survival, liver metastasis*

Introduction

Exocrine pancreatic cancer (PC) is an extremely lethal malignancy and the 8th leading cause of cancer-related deaths in both men and women. The incidence is higher in males than in females (rate, 1.3/1) and in blacks than in whites [1,2].

In PC, surgery is the sole potential curative treatment method. Unfortunately, only 15-20% of patients are candidates for curative surgery due to the delayed symptoms. Besides, the prognosis is poor even after R0 resection. Five-year survival following a surgical resection is about 30% for lymph node (LN)-negative patients and only 10% for LN-positive patients. In stage IV disease, 5-year survival is around 8%, with median overall survival (mOS) durations ranging between 3 and 6 months [3,4].

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Given the aggressive behavior and high mortality rates, patients diagnosed with PC need to be classified according to the disease severity. This classification can guide choosing the most appropriate treatment for patients. In addition, prognostic factors such as Tumor-Node-Metastasis (TNM) staging system, biomarkers such as carbohydrate antigen 19-9 (CA19-9), genomic analysis, and performance status have been proposed to this aim [5,6].

In clinical practice, it is important to utilize the markers that are easy to measure by non-invasive techniques. Serum tumor markers are quite easy to measure, as well as useful for diagnosis and prediction of survival. Many studies have demonstrated that CA19-9 is a predictor of survival in PC [7,8]. However, the level of CA19-9 can be found normal in a small subset of PC patients. Therefore, more sensitive markers are required to predict the prognosis of PC patients [9].

Recently, there is an increasing interest on the creation of predictive biomarkers for various cancers through hematological and serological tests. The albumin-bilirubin (ALBI) score was originally used to assess the severity of liver dysfunction in patients with hepatocellular carcinoma (HCC). The prognostic significance of the ALBI score has been proven in HCC patients with resectable or locally-advanced disease as well as in those with advanced

Table 1. Patient characteristics

Characteristics	*All patients (n=273) n (%)*	*Grade I (n=45) n (%)*	*Grade II (n=156) n (%)*	*Grade III (n=72) n (%)*	*p*
Gender					0.834
Men	180 (65.9)	28 (62.2)	104 (66.7)	48 (66.7)	
Women	93 (34.1)	17 (37.8)	52 (33.3)	24 (33.3)	
Age (year)					
Median (min-max)	60.0 (28-83)	60.0 (33-81)	60.5 (38-81)	60.0 (32-83)	0.566
ECOG PS					0.632
0-1	180 (65.9)	31 (68.9)	99 (63.5	50 (69.4)	
2	93 (34.1)	14 (31.1)	57 (36.5)	22 (60.6)	
Smoking	155 (56.8)	23 (51.1)	90 (57.7)	42 (58.3)	0.719
Alcohol use	11 (4.0)	1 (2.2)	6 (3.8)	4 (5.6)	0.652
Comorbidity					0.469
DM	94 (34.4)	12 (26.7)	55 (35.3)	27 (37.5)	0.981
HT	59 (21.6)	10 (22.2)	34 (21.8)	15 (20.8)	0.966
CIHD	19 (7.0)	3 (6.7)	11 (7.1)	5 (6.9)	
The site of metastasis at diagnosis					
Peritoneum	43 (15.8)	2 (4.4)	24 (15.4)	17 (23.6)	0.021
Lung	34 (12.5)	10 (22.2)	17 (10.9)	7 (9.7)	0.089
Distant LN	19 (7.0)	6 (13.3)	12 (7.7)	1 (1.4)	0.024
Bone	15 (5.5)	3 (6.7)	7 (4.5)	5 (6.9)	0.703
First-line regimen					0.745
Gemcitabine	79 (28.9)	10 (22.2)	44 (28.2)	25 (34.7)	
platine± gemcitabine	121 (44.3)	20 (44.4)	70 (44.9)	31 (43.1)	
nab-paclitaxel± gemcitabine	7 (2.6)	2 (4.4)	4 (2.6)	1 (1.4)	
FOLFIRINOX	66 (24.2)	13 (28.9)	38 (24.4)	15 (20.8)	
CEA, ng/mL	55.9±179.1	106.1±342.1	46.9±116.3	44.5±142.7	0.152
CA 19-9, U/mL	2291.0±9845.9	5260.2±22359.2	1704.4±3081.3	1726.9±6173.2	0.107
Hb, g/dL	12.5±1.8	12.7±1.9	12.6±1.6	12.1±1.9	0.635
ALBI score	-2.01±0.65	-2.87±0.19	-2.01±0.42	-0.92±0.36	<0.001
Final status					0.748
Dead	255 (93.4)	41 (91.1)	146 (93.6)	68 (94.4)	
Alive	18 (6.6)	4 (8.9)	10 (6.4)	4 (5.6)	

Abbreviations: ALBI, Albumin-bilirubin grade; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryogenic antigen; CIHD, Chronic ischemic heart disease; DM, Diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFIRINOX, Fluorouracil, leucovorin, irinotecan, and oxaliplatine; g/dL, Grams Per Deciliter; Hb, hemoglobin; HT, hypertension; LN, lymph node; ng/mL, Nano-gram/milliliter; OS, overall survival; PFS, Progression-free survival; U/mL, Units per milliliter.

HCC receiving local or systemic therapy [10-12]. In addition, recent studies have shown that it has prognostic value in a variety of cancers including colorectal cancer with liver metastasis, resectable gastric cancer, and resectable pancreatic cancer [13-15]. To the best of our knowledge, there is so far no study in the literature demonstrating the utility of ALBI score to predict the prognosis of PC patients with liver metastasis. Herein we intended to investigate the prognostic effect of pretreatment ALBI score on treatment outcomes in PC patients with liver metastases who received chemotherapy (CT) in the first-line.

Methods

Patients

This retrospective analysis was performed utilizing the medical data of 273 PC patients with liver metastasis at the time of diagnosis, who were treated and followed up from 2008 through 2018 at the department of medical oncology, Okmeydani Training and Research Hospital, Istanbul. The eligible patients were defined with the following inclusion criteria: ≥18 years, presence of liver metastasis at the time of diagnosis, receiving CT in the first-line, medical records with complete data, and adenocarcinoma histology. Patients with resectable disease, multiple primary tumors, non-adenocarcinoma histology, and missing data were excluded from the study.

Data collection

The data regarding the following clinical parameters were carefully obtained from the medical archive files: age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), history of smoking or alcohol use, presence of diabetes mellitus (DM), hypertension (HT) and chronic ischemic heart disease (CIHD), the site of metastasis at the time of diagnosis (liver, peritoneum, lung, distant lymph node [LN] and bone), CT regimen given in the first-line, basal values of carcinoembryogenic antigen (CEA), CA 19-9, and hemoglobin (Hb), and final status. ALBI score was calculated through the following formula: [(log10 bilirubin (μmol/l)×0.66)+[albumin (g/l) ×−0.0852]. Patients were then grouped into 3 categories based on the ALBI score as grade I: ALBI ≤ -2.60, grade II: -2.60 <ALBI ≤ - 1.39, and grade III: ALBI > -1.39.

Statistics

SPSS 22.0 for Windows software (IBM Corp. 2013) was used for all statistical analyses. Numerical variables between two independent groups were analyzed with Student's t-test in case of normal distribution, whereas Mann-Whitney U test was used otherwise. An overall 5% Type-I error level was used to infer statistical significance. The comparison of the rates between the groups was performed by chi-square analysis. Survival analyses were performed using Kaplan-Meier method and log-rank test. Determinant factors were examined with Cox univariate and multivariate analysis. Forward stepwise model was used with parameters having a p value below 0.150.

Results

Of the 273 patients, 180 (65.9%) were male and 93 (34.1%) female, with a median age of 60 years (range, 28-83). At the time of diagnosis, ECOG PS was 2 in 93 (34.1%) patients. ALBI grade was I in 45 (16.4%) patients, II in 156 (57.1%) patients, and III in 72 (26.5%) patients. History of smoking and alcohol consumption was present in 155 (56.8%) and 11 (4%) patients, respectively. Comorbidities such as DM, HT, and CIHD were present in 94 (34.4%), 59 (21.6%), and 19 (7%) patients, respectively. In addition to liver metastasis at the time of diag-

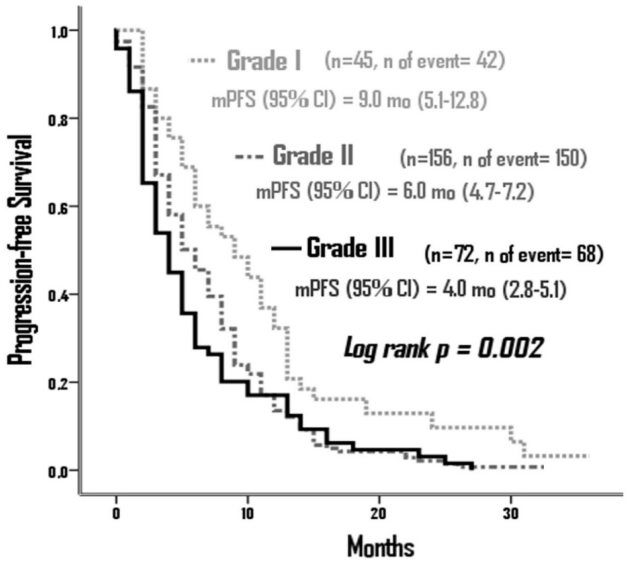

Figure 1. Progression-free survival according to ALBI grade.

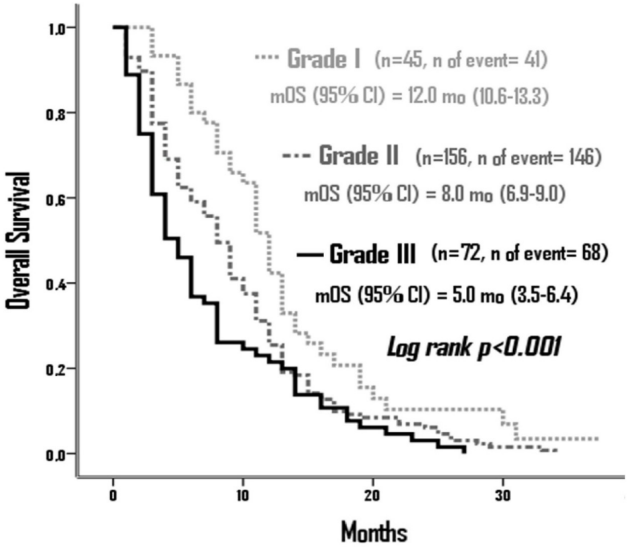

Figure 2. Overall survival according to ALBI grade.

Table 2. Univariate and multivariate analysis for OS

Characteristics	*Univariate Analysis for OS*			*Multivariate Analysis for OS*		
	HR	*95 % CI for HR*	*P*	*HR*	*95 % CI for HR*	*P*
Gender, Women vs. men	0.839	0.645±1.092	0.192			
Age, Year	0.997	0.985±1.009	0.622			
ECOG PS, 2 vs. 0-1	1.881	1.440±2.458	<0.001	2.227	1.678±2.953	<0.001
Smoking, Yes vs. No	1.014	0.790±1.301	0.915			
Alcohol, Yes vs. No	1.354	0.717±2.555	0.349			
DM, Yes vs. No	1.291	0.995±1.674	0.054			
HT, Yes vs. No	0.766	0.566±1.038	0.385			
CIHD, Yes vs. No	0.646	0.398±1.046	0.275			
Peritoneum met, Yes vs. No	0.963	0.689±1.343	0.823			
Lung met, Yes vs. No	1.198	0.825±1.738	0.342			
Distant LN met, Yes vs. No	0.926	0.556±1.541	0.767			
Bone met, Yes vs. No	0.815	0.473±1.402	0.460			
First-line therapy						
Gemcitabine	Ref.		0.032			0.002
Gemcitabine± Platine	1.036	0.774±1.385	0.813	1.091	0.955±1.744	0.096
Nub-paclitaxel ± gemcitabine	0.977	0.448±2.128	0.953	0.929	0.421±2.050	0.856
FOLFIRINOX	0.646	0.454±0.918	0.015	0.674	0.473±0.959	0.028
ALBI grade						
I	Ref.		0.001			<0.001
II	1.566	1.101±2.226	0.012	1.543	1.085±2.193	0.016
III	2.134	1.436±3.168	<0.001	2.260	1.515±3.373	<0.001
CEA, ng/mL	1.001	0.999	0.312			
CA 19-9, U/mL	1.004	1.001-1.005	0.037	1.009	1.004±1.017	0.041
Hb, g/dL	1.003	0.966-1.009	0.580			

Abbreviations: see Table-1

nosis, there were 43 (15.8%) patients with peritoneal metastasis, 24 (12.5) with lung metastasis, 19 (7%) with distant LN metastasis, and 15 (5.5%) with bone metastasis (Table 1).

The regimens given in the first-line setting were as follows: platinum (cisplatin or carboplatin) + gemcitabine in 121 (44.3%) patients, single-agent gemcitabine in 79 (28.9%), FOLFIRINOX in 66 (24.2%), and gemcitabine + nub-paclitaxel in 7 (2.6%) patients. Pretreatment values of CEA, CA 19-9, Hb, and ALBI grade were 55.9±179.1 ng/mL, 2291.0±9845.9 U/mL, 12.5±1.8 g/dL, and -2.01±0.65, respectively (Table 1).

Based on the ALBI grade, mPFS was 9 months (95 % confidence interval [CI], 5.1-12.8) in grade I patients, 6 months (95% CI, 4.7-7.2) in grade II patients, and 4 months (95% CI, 2.8-5.1) in grade III patients (Log rank p=0.002), with corresponding mOS durations of 12 months (95 % CI, 10.6-13.3), 8 months (95% CI, 6.9-9.0), and 5 (95% CI, 3.5-6.4) months (Log rank p<0.001) (Figures 1 and 2).

In univariate analysis, ECOG PS 2 (hazard ratio [HR], 1.881), increased CA 19-9 (HR,1.004), and ALBI grade II (HR,1.566) or III (HR,2.134) were found to be negative factors affecting survival, while administering FOLFIRINOX (HR,0.646) in the first-line was the factor associated with better survival. Similarly, multivariate analysis showed that ECOG PS 2 (HR,2.227), increased CA 19-9 (HR,1.009), and ALBI grade II (HR,1.543) or III (HR,2.260) negatively affected survival, whereas administering FOLFIRINOX (HR,0.674) in the first-line setting was found to be the factor positively affecting survival (Table 2).

Discussion

Albumin is synthesized in the liver and its decreased level is indicative of malnutrition and dysfunction of liver synthesis. In addition, increased serum bilirubin concentrations often suggest varying degree of liver dysfunction [16]. Calculation of the ALBI score requires the levels of serum bilirubin and albumin concentrations, which can only be measured through routine blood test. The effect of pretreatment functional status of the liver on

treatment outcomes in PC patients has not been adequately evaluated. In this study, we examined the effect of pretreatment ALBI grade on treatment outcomes in PC patients with liver metastasis receiving CT and observed a significant decrease in both PFS and OS as the ALBI grade increased.

After being shown in 2015 to offer prognostic benefit in resectable HCC patients, there has been a growing interest over the prognostic role of the ALBI grade [11,17,18]. Pinto et al designed a multicenter study including 2426 stage I to IV HCC patients and found that ALBI grade had prognostic value regardless of the stage and treatment modality, suggesting routine use of the ALBI grade to classify the functional reserve of liver in HCC patients [17]. Recently, in a multi-center study by Tsilimigras et al analyzing 706 resectable cholangiocarcinoma patients, the mortality rate was found to be 1.36 times higher in patients with grade III ALBI than in patients with grade I to II ALBI [19]. Similarly, in the study of 78 intrahepatic cholangiocarcinoma patients who underwent percutaneous microwave ablation, ALBI grade was found to be effective in predicting long-term results [20].

Kanda et al reported that ALBI grade was associated with DFS and OS after radical gastrectomy in 283 resectable gastric cancer patients [15]. In another recent study assessing colorectal cancer patients with liver metastases treated with first-line CT, higher pretreatment ALBI grade was found to be associated with worse OS and PFS [14]. In the literature, the only study regarding the prognostic value of ALBI in PC patients is the study by Yagyu et al who included 100 resectable PC patients. The authors found that ALBI grade II to III and high CA 19-9 negatively affected survival [13]. As observed in the studies mentioned above, DFS and OS in our study population were found to decrease as the ALBI grade increased, with ALBI grade II increasing the risk of mortality by 1.54 times and ALBI grade III increasing the risk by 2.26 times. In addition, similar to these studies, higher pretreatment CA 19-9 in our study negatively affected OS [7,8,13].

Many studies have demonstrated the superiority of CT over best supportive care in the first-line setting of metastatic pancreatic cancer [21-24]. In a phase 2 study, median OS was 5.6 months in patients receiving gemcitabine alone [23]. Later, PRODIGE study reported median OS of 11 months with FOLFIRINOX and 6.8 months with gemcitabine therapy [24]. In our study, all patients received CT and regimens were similar among ALBI groups. We observed that administration of FOLFIRINOX significantly reduced mortality compared to the gemcitabine regimen.

Our study was the first to demonstrate the prognostic role of ALBI grade on treatment outcomes in PC patients with liver metastasis, including a more homogeneous patient group treated with CT. In addition, unlike other studies, we divided the patient population into 3 groups according to the ALBI grade, with each group showing no difference in terms of CT regimens. However, this was a single-center and retrospective analysis, thus may have contained selection bias inherent in retrospective studies.

As a result, we showed that the pretreatment ALBI grade appears to be a promising prognostic biomarker associated with DFS and OS in PC patients with liver metastasis at diagnosis. The ALBI grade has the potential to be used as a routine test in clinical practice since it is an easy-to-measure and low-cost marker to predict treatment results in this patient group. However, our study results should be supported by larger studies.

Institutional review board statement

This study and all relevant procedures were implemented based on the declaration of Helsinki. The ethics committee approval was taken from the Ethics Committee Board of University of Health Sciences Okmeydani Training and Research Hospital (48670771-514.10).

Informed consent statement

The patients were not required to give informed consent for this study because the study utilized anonymous retrospective data obtained after each patient accepted the treatment by a written consent.

Author' contributions

Concept – AS, SC, SS; Design – NY, CG, SS; Supervision – SC, SS, CD, AbS; Resources – CG, SC, MMA, SA; Materials – AS, NY, MMA, CG; Data Collection and/or Processing – AS, NY, CD, AbS; Analysis and/or Interpretation – SC, MMA, AbS, SA; Literature Search – AS, CD, SS, AbS; Writing Manuscript – AS, SS, AbS; Critical Review – SC, CD, AbS, SA; Other – CG, MMA, SC, NY.

Conflict of interests

The authors declare no conflict of interests.

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