ORIGINAL RESEARCH

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Initial Albumin-Bilirubin Grade as a Prognostic Indicator of Pancreatic Cancer with Liver Metastasis

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ABSTRACT Objective: Pancreatic cancer (PCa) is the fourth leading cause of cancer-related deaths. Thus, there is a need for prognostic indicators that can aid in disease classification and subsequent selection of appropriate treatment options. Albumin-bilirubin (ALBI) grade, which is calculated using a logarithmic formula, is indicative of liver function. The present study evaluated the prognostic performance of the initial ALBI grade for metastatic PCa in patients receiving first-line chemotherapy. **Material and Methods:** In this retrospective study, the medical records of 114 patients with de novo liver metastatic PCa and unresectable liver metastasis were evaluated. The ALBI grade was calculated using the formula (log10 bilirubin × 0.66) + (albumin × -0.085), and based on the grade, patients were divided into 3 groups, namely, ALBI Grade 1, ≤-2.60; ALBI Grade 2, between −2.60 and -1.39; and ALBI Grade 3, ≥-1.39. **Results:** Median progression-free survival (PFS) was 13 months [95% confidence interval (CI), 7.3-18.6]. The estimated PFS was 16 months for ALBI Grade 1 (95% CI, 13.0-20.4), 8 months for ALBI Grade 2 (95% CI, 7.5-9.9), and 5 months for ALBI Grade 3 (95% CI, 4.3-5.6). Median overall survival (OS) was 11 months (95% CI, 9.0-12.9). The estimated OS was 18 months for ALBI Grade 1 (95% CI, 14.4-21.5), 9 months for ALBI Grade 2 (95% CI, 7.8-10.1), and 6 months for ALBI Grade 3 (95% CI, 4.1-7.8; p<0.001). **Conclusion:** The initial ALBI grade demonstrated outstanding performance as an independent prognostic factor in PCa patients with liver metastasis.

Keywords: Pancreatic cancer; liver metastasis; albumin-bilirubin grade; prognostic indicator; progression-free survival; overall survival

Pancreatic cancer (PCa) is one of the most fatal types of cancer and is the fourth leading cause of cancer-related deaths in both males and females.[1] PCa is diagnosed mostly in the advanced stages. Although new treatment combinations are available, such as [FOLFIRINOX (FFX)] combination chemotherapy with fluorouracil, leucovorin, irinotecan, and oxaliplatin or gemcitabine and nab-paclitaxel (GNP), for metastasis in the clinical setting, the prognosis of PCa is not as high as desired.[2] Evidence for the benefit of targeted therapy is promising, although PCa has considerable tumor heterogeneity that restricts targeted therapies.[3] Prognostic indicators aid in classifying the disease and in subsequently selecting appropriate treatment options.

Metastasis is associated with poor prognosis; particularly, liver metastasis is associated with a low survival rate and poor quality of life. It is well known that liver function is critically important for treatment tolerance. Hence, determining prognostic indicators, especially indicators for liver functional capacity, has become vital. In advanced stages of PCa, clinical symptoms can affect decision making regarding treatment. Jaundice, cachexia, and fatigue are common symptoms in PCa, and their occurrence depends on the patient's hepatic function, which suggests that liver function may play a role in PCa prognosis.[4] The hepatic synthesis ability in chronic liver diseases can be assessed by measuring bilirubin and albumin levels. The level of bilirubin might affect the treatment strategy for PCa; for this reason, identification of jaundice is critically important, and its presence and severity should be followed up closely. Cachexy is associated with high morbidity and mortality in all

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cancers, including PCa. Albumin is one of the main indicators of cachexy. Both albumin and bilirubin levels can be affected by other clinical conditions such as ascites and encephalopathy. Therefore, an objective measurement model for liver dysfunction is needed.

Albumin-bilirubin (ALBI) grade, calculated using the logarithmic formula (log10 bilirubin×0.66)+(albumin×-0.085), is indicative of the hepatic function. The ALBI grade is considered the most effective tool for assessing liver function in hepatocellular carcinoma (HCC). Unlike the Child-Pugh score, the ALBI grade uses only objective parameters, namely, albumin and total bilirubin, and enables a better assessment. The Child-Pugh classification is widely used to assess hepatic function, but complications of hepatic disorders might affect the objective results. An alternative measurement tool such as ALBI grade has shown more objective results in HCC. ALBI grade has also shown predictive value for survival. Thus, the ALBI grade may be used as an alternative to the Child-Pugh score for assessing hepatic function.[5-7]

Because of the complications arising in cancers, serum bilirubin and albumin levels may be insufficient to evaluate liver function. The ALBI grade was first used to stratify HCC and showed better results than the Child-Pugh score. Next to HCC, the use of ALBI grade has been investigated in different cancers and hepatic disorders such as gastric cancer, colorectal cancer with liver metastasis, high-grade glioma, and PCa.[8-11] Currently, there is an urgent need for prognostic indicators that can aid in disease classification and the subsequent selection of appropriate treatment options.

The present study aimed to evaluate the performance of the initial ALBI grade as a prognostic index for metastatic PCa in patients receiving first-line chemotherapy.

MATERIAL AND METHODS

STUDY POPULATION

This study was a retrospective analysis of the medical records of PCa patients treated in the medical oncology departments of Medeniyet University, Marmara University, and Prof. Dr. Cemil Taşcıoğlu City Hospital from January 2010 to December 2020. Of the 285 patients diagnosed with pancreatic adenocarcinoma, 114 had de novo liver metastatic PCa and unresectable liver metastasis. Patients who had a diagnosis of adenocarcinoma histology and received first-line chemotherapy were included in the study. However, patients aged <18 years with a nonadenocarcinoma histology; with nonmetastatic or resectable tumors; who had received two or more lines of chemotherapy for metastatic disease; and who had a chronic hepatic disease such as autoimmune hepatitis or viral hepatitis, obstructive jaundice, or secondary malignancies were excluded from the study.

DATA COLLECTION

Data of age, sex, Eastern Performance Oncology Group Performance Score (ECOG PS), body mass index (BMI), and chemotherapeutic regimens were collected from the medical records of patients. Additionally, information on the levels of initial serum total bilirubin (μmol/L), albumin (g/L), C-reactive protein (mg/L), carbohydrate antigen (CA) 19-9 (U/mL) and carcinoembryonic antigen (CEA; ng/mL) was collected.

In line with previous studies, the ALBI grade was calculated using the formula (log10 bilirubin × 0.66)+(albumin×-0.085). According to the original study, patients were divided into 3 groups on the basis of the ALBI grade, wherein ALBI Grade 1 was defined as ≤-2.60, ALBI Grade 2 was between -2.60 and -1.39, and ALBI Grade 3 was ≥-1.39.[5]

The study protocol was approved by the İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Researchs Ethics Committee (date: March 10, 2021; no: 2021/0195), and the study was conducted in accordance with the Declaration of Helsinki.

STATISTICAL ANALYSIS

Quantitative variables were assessed using the Mann-Whitney U test, whereas qualitative variables were evaluated using the chi-square analysis. Survival analysis was conducted using the Kaplan-Meier method and compared using the log-rank test. Progression-free survival (PFS) was defined as the time between the start of first-line treatment and disease

recurrence. Overall survival (OS) was defined as the time from diagnosis until the date of death from PCa or the last follow-up, whichever occurred first. Univariate and multivariate Cox regression models were used to determine independent prognostic factors for both PFS and OS. For each prognostic factors, we calculated the hazard ratios (HRs) and corresponding 95% CIs. The confidence interval (CI) was accepted as 95% and statistical significance was indicated at a p value of ≤0.05. All statistical analyses were performed using IBM SPSS Statistics (version 24.0, Armonk, NY: IBM Corp.).

RESULTS

The data of 114 patients who had a PCa diagnosis of liver metastasis between January 2010 and December 2020 were reviewed retrospectively. Among all patients, 63 (55.3%) were male, and 51 (44.7%) were female, with a median age of 60 years (35-79) and a median BMI of 23.6 kg/m^2 (14.5-40.4). As for the ECOG PS, 101 (88.6%) patients had ECOG PS 0, and 13 (11.4%) had ECOG PS 1. All patients had de novo liver metastatic PCa: 64 were treated with FOLFIRINOX, and 50 with GNP. The CEA and CA 19-9 levels assessed at the time of diagnosis were 12.6 ng/mL (1.1-1995) and 352.5 U/mL (0.8-24728), respectively. Based on the ALBI grades, 35 (30.7%), 49 (43%), and 30 (26.3%) patients were assigned to the Grade 1, 2, and 3 groups, respectively. The baseline clinicopathological characteristics of the patients are summarized in Table 1.

The results of the univariate analysis revealed that first-line treatment option, initial CA 19-9 levels, and initial ALBI grade were significant prognostic factors for PFS, and the results of the multivariate analysis revealed that only the initial ALBI grade was an independent risk factor for PFS (Table 2, Table 3). The median PFS of all patients was 13 months (95% CI, 7.3-18.6). The estimated PFS was 16 months for ALBI Grade 1 (95% CI, 13.0-20.4), 8 months for ALBI Grade 2 (95% CI, 7.5-9.9), and 5 months for ALBI Grade 3 (95% CI, 4.3-5.6). The Kaplan-Meier curves showed that ALBI Grade 1 demonstrated a better PFS than ALBI Grades 2 and 3, and the difference was significant with a p value of <0.001 (Figure 1).

TABLE 1: Patients' baseline clinicopathological characteristics.

Male	63 (55.3%)
Female	51 (44.7%)
Median age	60 (35-79)
BMI	23.6 (14.5-40.4)
ECOG	
0	101 (88.6%)
1	13 (11.4%)
First-line regimen	
FOLFIRINOX	64 (56.1%)
GNP	50 (43.9%)
Cycles of treatment (n)	6 (2-12)
CEA, ng/mL	12.6 (1.1-1995)
CA19-9, U/mL	352.5 (0.8-24728)
ALBI	Grade 1 n:35 (30.7%)
	Grade 2 n:49 (43%)
	Grade 3 n:30 (26.3%)

BMI: Body mass index; ECOG: Eastern Performance Oncology Group; GNP: Gemcitabine and nab-paclitaxel; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen; ALBI: Albumin-bilirubin;

The univariate analysis also showed that first-line treatment regimen and ALBI grade were prognostic factors for OS, and multivariate analysis identified both these parameters as independent risk factors with significant differences (Table 2, Table 3). The median OS of all patients was 11 months (95% CI, 9.0-12.9). Patients treated with FOLFIRINOX had a better OS than those treated with GNP. The choice of first-line treatment regimen seem to be effective in PCa (HR: 0.274, 95% CI, 0.142-0.527; p<0.001). The estimated OS was 18 months for ALBI Grade 1 (95% CI, 14.4-21.5), 9 months for ALBI Grade 2 (95% CI, 7.8-10.1), and 6 months for ALBI Grade 3 (95% CI, 4.1-7.8). The Kaplan-Meier curves revealed that the OS differed based on the ALBI grade, and this difference was significant (p<0.001; Figure 2).

DISCUSSION

The liver is the most frequent site of metastasis in PCa, and the hepatic function determines patient survival and quality of life.[12] As PCa is associated with a high mortality rate, and so the definition of prognostic biomarkers for PCa should be considered very important. In the present study, we stratified patients according to their ALBI grade and identified significant differences in survival rates.

TABLE 2: Results of the univariate analysis for PFS and OS.

	PFS			OS		
	HR	95% CI	p value	HR	95% CI	p value
Sex Male Female	1.425	0.672-3.018	0.337	1.911	1.010-3.617	0.253
Age at diagnosis	0.055	0.050-0.076	0.048	0.973	0.935-1.013	0.882
BMI	0.980	0.092-1.077	0.502	0.992	0.929-1.058	0.429
ECOG 0 1	0.396	0.075-2.102	0.138	0.098	0.077-0104	0.064
First-line regimen FOLFIRINOX GNP	0.009	0.002-0.045	<0.001	0.072	0.022-0.43	<0.001
CEA (ng/mL)	0.999	0.997-1.002	0.149	0.711	0.634-1.002	0.308
CA19-9 U/mL	0.041	0.037-0.075	0.034	0.975	0.886-1.056	0.577
ALBI GRADE Grade 1 Grade 2 Grade 3	0.009	0.002-0.045	0.019	0.010	0.002-0.040.	0.050

PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; ECOG: Eastern Performance Oncology Group; GNP: Gemcitabine and nab-paclitaxel; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen; ALBI: Albumin-bilirubin.

TABLE 3: Results of multivariate analysis of PFS ann OS.

	PFS			OS		
	HR	95% CI	p value	HR	95% CI	p value
Age at diagnosis	0.980	0.947-1.013	0.229			
First-Line regimen FOLFIRINOX GNP	2.149	0.857-5.390	0.103	0.274	0.142-0.527	<0.001
CA19-9 U/mL	1.000	1.000-1.000	0.761			
ALBI GRADE						
Grade 1	0.012	0.003-0.055	<0.001	0.016	0.004-0.059	<0.001
Grade 2	0.086	0.054-0.237	<0.001	0.086	0.028-0.270	<0.001
Grade 3	0.192	0.082-0.450	<0.001	0.055	0.017-0.114	<0.001

PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; GNP: Gemcitabine and nab-paclitaxel; CA: Carbohydrate antigen; ALBI: Albumin-bilirubin.

Albumin is synthesized in the liver, and a decrease in serum albumin levels leads to hepatic dysfunction or protein malnutrition.[13,14] In PCa, hepatic metastases cause a decrease in liver function, resulting in a fall in serum albumin levels. Bilirubin is produced in hepatocytes and modified by cholangiocytes before entering circulation. Hepatic diseases increase the production and secretion of bilirubin, thus, resulting in increased levels of bilirubin.[15,16] The ALBI grade, calculated based on the albumin and bilirubin levels, has been assessed in many cancers including HCC. The ALBI grade was first assessed by Johnson et al. in 1,313 patients with HCC who were stratified according to their ALBI grade, and the authors suggested that ALBI grade may be a promising prognostic marker and a simple, effective tool for the assessment of hepatic function in HCC.[5] The need for the application of ALBI grading in HCC is because complications result from liver diseases (such as ascites, encephalopathy, or variceal bleeding that result in hypotension and hypoalbuminemia) prevent access to objective parameters such as serum bilirubin and

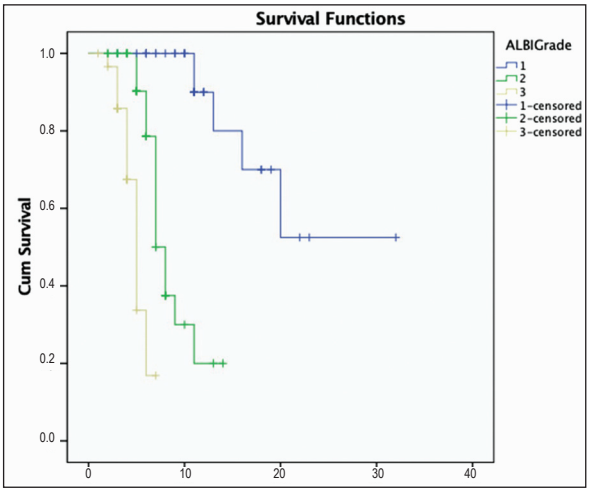

FIGURE 1: Kaplan-Meier curve of progression-free survival based on the initial ALBI grade.
ALBI: Albumin-bilirubin.

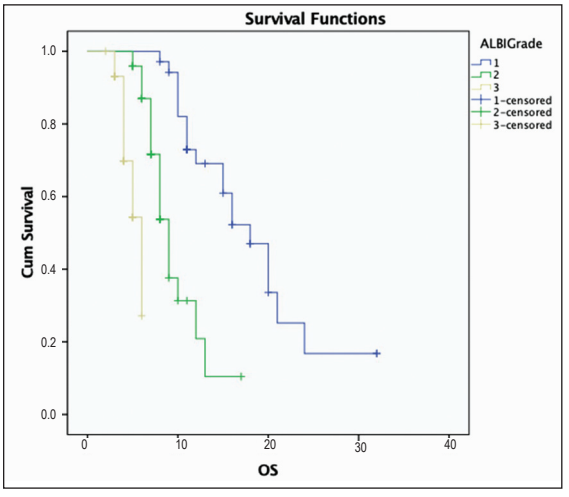

FIGURE 2: Kaplan-Meier curve of overall survival based on the initial ALBI grade.
ALBI: Albumin-bilirubin; OS: Overall survival.

albumin levels and prevent them from being evaluated clearly. Hiraoka et al. assessed the clinical value of ALBI grade for staging and predicting prognosis in a study of 46,681 HCC patients, wherein they compared ALBI grade with the Japan Integrated Staging approach, which combines the Child-Pugh classification and tumor, node, metastasis staging.[17] The authors found ALBI grade to be a useful prognostic marker, particularly in patients planned for curative treatments such as ablative therapy or resection. They also identified ALBI grade as a valuable parameter in revealing hepatic function. The inadequate use of the Child-Pugh classification in HCC classification is that it involves direct calculations based on the serum bilirubin and albumin levels; the ALBI logarithmic measurement parameter was tried as an alternative and showed better results. In the present study, we evaluated the initial ALBI grade, calculated using a logarithmic formula based on total bilirubin and albumin levels in liver metastatic PCa patients, and this grade could be used to stratify patients into 3 different risk categories in PCa. Among the 3 groups, a significant difference was observed in both PFS and OS. Additionally, in the present study, the increase in liver failure and the decrease in the survival rate of patients were parallel to each other. ALBI grading may help clinicians to stratify patients into different risk groups and choose appropriate treatment options.

Inflammation is an important event in every stage of tumor development, that is, from transformation of malignant cells to metastatic cells.[18,19] Albumin is a negative inflammatory parameter; hence, cancer patients are expected to have decreased albumin levels. Particularly in PCa, the coexistence of malnutrition is often both the cause and the consequence of symptoms. Tumor progression induces malnutrition and further decreases albumin levels, thus coinciding with a decrease in the ALBI grade. However, an objective observation of a decrease in the ALBI grade may preclude a prognostic assessment of the disease. For this reason, a more objective evaluation can be made using methods such as ALBI grading. The results of the present study confirm that both PFS and OS were decreased in patients with ALBI Grade 3.

After HCC, many trials have assessed the relationship between ALBI grade and patient survival in various cancers. Zhu et al. investigated the potentially predictive value of ALBI grade for postoperative complications and OS in curative gastric cancer patients and found better survival rates and less complication risks in the low-grade ALBI group.[20] Furthermore, Küçükarda et al. reported that the ALBI grade was a prognostic marker in gastric cancer patients involving liver metastases, wherein 203 patients were assigned into 3 groups based on the ALBI grade.[21] The authors found that ALBI Grade 1 patients had better survival than patients in the other groups, and the present study obtained similar results, that is, increased PFS and OS in ALBI Grade 1 pa-

tients. Confirming patient grouping using a more objective algorithm may yield more reliable results.

Zhang et al. assessed ALBI grade in 149 patients with PCa and assigned them into 2 groups based on high- and low-grade ALBI, different from that in original HCC studies.[22] ALBI grade was found to be a useful prognostic marker for PCa with liver metastasis. Additionally, ALBI grade had predictive value in the selection of treatment options, especially for combination therapies. Patients with an ALBI grade of <2.6 had better survival results when they received combination therapies than those in the other groups. This result suggests that patients with ALBI Grade 1 could tolerate more intensive treatment and side effects and could benefit from combination therapies. In the present study, patients who received FFX recorded longer OS, whereas no such result could be seen for PFS. Combination therapies seemed to be more effective in PCa.

ALBI grade was also studied as a prognostic marker in curative options. Imamura et al., investigated the initial ALBI grade in patients with PCa who underwent operation.[23] Overall, 1,006 patients were included, but 877 were eligible for resection. The patients were divided into 2 groups, namely, low ALBI grade (ALBI Grade 1) and high ALBI grade (ALBI Grades 2 and 3). After the operation, patients with low ALBI grade had better OS than those with high ALBI grade. Yagyu et al. evaluated pretreatment prognostic markers in 100 patients who were diagnosed with PCa and underwent pancreatectomy.[11] The patients were divided into groups based on high and low CA 19-9 levels (cutoff ≥35 U/mL) and ALBI grade (2 and 3 vs. 1). The authors found better 5-year OS rates in patients with low CA 19-9 levels and ALBI Grade 1. The combination of CA 19-9 levels and ALBI grade was an independent prognostic marker in PCa patients who underwent resection.

Sakin et al. evaluated ALBI grade in 273 PCa patients with liver metastasis, in line with the present study.[24] The authors stratified patients according to pretreatment ALBI grades and investigated the potential of the prognostic indicator. Initial ALBI grade was an important prognostic indicator. Patients with ALBI Grade 1 had better survival rates, whereas those with ALBI Grade 3 had worse PFS and OS. The present study demonstrated similar results in terms of the difference in both PFS and OS according to the 3 ALBI grades. The initial ALBI grade was found to be a useful prognostic marker in PCa with liver metastasis, and patients with ALBI Grade 1 recorded increased survival parameters in both PFS and OS when compared with those with ALBI Grades 2 and 3.

Contrary to the findings of many studies, only one study has shown that albumin and bilirubin values are not related to patient survival. A retrospective study of 201 patients with advanced PCa performed in China showed that baseline bilirubin and serum protein levels were not associated with prognosis.[25] However, as a limitation of that study, the authors highlighted that all the enrolled patients in their hospital had PCa and received minimally invasive treatment combined with systemic therapy. Thus, all patients had normal levels of nutritional status, which might have introduced a bias. Albumin, in particular, is one of the main nutritional parameters.

The present study has a few limitations. The number of liver metastatic sites differed among the patients; the medical records were analyzed only for the presence of liver metastasis. Future studies should distinguish patients based on the number of liver metastatic sites. Next, this study had a retrospective design, with a small sample size; further prospective studies involving a larger number of patients are needed to verify the importance of ALBI grade in PCa with liver metastasis.

CONCLUSION

The initial ALBI grade was confirmed to be an independent prognostic factor in PCa patients with liver metastasis. Serum albumin and bilirubin levels are easily accessible and measurable parameters. The ALBI grade, calculated using the logarithmic formula of these parameters, may be used to identify de novo PCa involving liver metastasis at the time of initial diagnosis and stratify patients objectively for selecting treatment strategies.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-

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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: *Seval Ay, Özgecan Dülgar, Deniz Tataroğlu Özyükseler;* ***Design:*** *Seval Ay, Rukiye Arıkan, Muhammed Mustafa Atcı;* ***Control/Supervision:*** *Mahmut Gümüş;* ***Data Collection and/or Processing:*** *Seval Ay, Rukiye Arıkan, Muhammed Mustafa Atcı;* ***Analysis and/or Interpretation:*** *Seval Ay;* ***Writing the Article:*** *Seval Ay;* ***Critical Review:*** *Mahmut Gümüş;* ***References and Fundings:*** *Rukiye Arıkan;* ***Materials:*** *Muhammed Mustafa Atcı.*

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