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Prognostic Value of ALBI Score and Lymphocyte-Associated Inflammation Markers in Advanced Hepatocellular Carcinoma: A Single Centre Retrospective Cross-Sectional Study

ALBI Skoru ve Lenfosit İlişkili Enflamasyon Belirteçlerinin İleri Evre Hepatoselüler Karsinomda Prognostik Değeri: Tek Merkez Retrospektif Kesitsel Çalışma

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ABSTRACT

Aim: According to the information obtained from the World Health Organization database, the incidence of hepatocellular carcinoma (HCC) in Turkey increased by 17.78% between the years of 2018 and 2020. In this study, we investigated the prognostic value of albumin-bilirubin (ALBI) score and lymphocyte-associated inflammation markers on overall survival (OS) and progression-free survival (PFS) in advanced hepatocellular carcinoma.

Materials and Methods: Data of 141 patients with advanced HCC were included in this study. ALBI score and lymphocyte-associated inflammatory marker were calculated. As a result, the prognostic significance of these tests for survival were evaluated.

Results: The median age was 65 years (min: 26-max: 88). There were 58 (41.1%) hepatitis B virus (HBV) positive, 20 (14.2%) hepatitis C (HCV) positive and 63 (44.7%) patients with no history of hepatitis. Cut-off values of ALBI score and lymphocyte-associated inflammation markers were found by receiver operating characteristic analysis. ALBI (p<0.001), aspartate aminotransferase-to-lymphocyte ratio (ALRI) (p<0.001), prognostic nutritional index (PNI) (p=0.030), hemoglobin, albumin, lymphocyte, and platelet score (HALP) (p=0.003) scores were significantly associated with survival. In multivariate analysis, being ≥65 years old [hazard ratios (HR): 2.13; 95% confidence interval (CI): 1.44-3.17; p<0.001], ALRI≥30.79 (HR: 2.14; 95% CI: 1.20-3.82; p=0.009) predicted an increased risk of death and ALBI≥-2.54 (HR: 0.44, 95% CI: 0.29-0.69; p<0.001) predicted a decreased risk of death. Being ≥65 years old (HR: 174, 95% CI: 1.18-2.56; p=0.005) increased the risk of progression.

Conclusion: This study supports the statistically significant association of ALBI score and lymphocyte-associated inflammation markers (ALRI, PNI, HALP) with OS and PFS in advanced HCC patients. It is thought that this study will contribute to the literature and clinical practice.

Keywords: HCC, ALBI score, lymphocyte-associated inflammatory marker, ALRI, survival

ÖZ

Amaç: Dünya Sağlık Örgütü veri tabanından edinilen bilgiye göre, Türkiye'de hepatosellüler karsinom (HCC) insidansı 2018-2020 yılları arasında %17,78 artmıştır. Bu çalışmada, ilerlemiş hepatosellüler karsinomda albümin-bilirubin (ALBI) skoru ve lenfosit ilişkili enflamasyon belirteçlerinin genel sağkalım (GS) ve progresyonsuz sağkalım (PFS) üzerindeki prognostik değerini araştırdık.

Gereç ve Yöntem: Bu çalışmaya 141 ileri evre HCC hastasının verileri dahil edildi. Tanı anındaki laboratuvar verileri kullanılarak ALBI skor ve lenfosit ilişkili enflamasyon belirteçleri hesaplandı. Sonuç olarak bu testlerin sağkalım için prognostik önemi değerlendirildi.

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Bulgular: Medyan tanı yaşı 65'ti (min: 26-max: 88). Hepatitis B virüs (HBV) pozitif 58 (%41,1), hepatitis C virüs (HCV) pozitif 20 (%14,2) ve hepatit öyküsü olmayan 63 (%44,7) hasta vardı. ALBI skoru ve lenfosit ilişkili enflamasyon belirteçlerinin alıcı çalışma karakteristiği analizi analizi ile cut-off değerleri bulundu. ALBI (p<0,001), aspartat aminotransferaz-lenfosit oranı (ALRI) (p<0,001), prognostik nutrisyonel indeks (PNI) (p=0,030) ve hemoglobin, albümin, lenfosit, trombosit skoru (HALP) (p=0,003) skoru ile sağkalım arasında anlamlı ilişki bulundu. Multivariate analizde ≥65 yaş olanların [hazard oranı (HR): 2,13; %95 güven aralığı (GA): 1,44-3,17; p<0,001], ALRI≥30,79 olmanın (HR: 2,14; %95 GA: 1,20-3,82; p=0,009) artmış ölüm riskini; ALBI≥-2,54 olmasının ise (HR: 0,44; %95 GA: 0,29-0,69; p<0,001) azalmış ölüm riskini predikte ettiği belirlendi. Altmış beş yaş üstü olmanın (HR: 1,74, %95 GA: 1,18-2,56; p=0,005) progresyon riskini artırdığı belirlendi.

Sonuç: Bu çalışma, ileri evre HCC hastalarında ALBI skoru ve lenfosit ilişkili enflamasyon belirteçlerinin (ALRI, PNI, HALP) GS ve PFS ile istatistiksel olarak anlamlı ilişkisini desteklemektedir. Bu çalışmanın literatüre ve klinik pratiğe katkı sağlayacağı düşünülmektedir.

Anahtar Kelimeler: HCC, ALBI skor, lenfosit ilişkili enflamatuar belirteç, ALRI, sağkalım

INTRODUCTION

Liver cancer is the sixth most common type of cancer in the world. It is the fifth leading cause of death. Based on the World Health Organization (WHO) database GLOBOCAN, the incidence of hepatocellular carcinoma (HCC) in Turkey increased by 17.78% between the years of 2018 and 2020[1]. Differences in metabolic, endocrinological and behavioral factors in the etiology have been used to explain the frequency in men[2-4].

Risk factors for HCC, which is the most common histology in liver cancers, include alcohol, chronic viral hepatitis caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), aflatoxin, obesity, non-alcoholic steatohepatitis (NASH) caused by metabolic syndrome, haemochromatosis and other rare causes. Chronic inflammation due to alcohol, chronic viral hepatitis and NASH triggers unbalanced cytokine release and hepatocarcinogenesis. Poor differentiation of hepatocytes initiates the process progressing to dysplastic nodules and HCC[1,5,6]. Immune and inflammatory responses are important in the prognosis of tumor progression[7].

In advanced hepatocellular carcinoma, immunotherapy, tyrosine kinase inhibitors and locoregional therapies added to these therapies are the treatment options offered according to patient characteristics. Many prognostic features and markers used in this treatment selection have been defined. The prognostic properties of the scores calculated by biochemical and hematological parameters were evaluated before the treatment plan. Albümin-bilirubin (ALBI) score provides the evaluation of liver function with an evidence-based, objective and simple method[8]. Lymphocyte-associated inflammation scores [ALRI[9], PNI[10], Hemoglobin, albümin, lenfosit, trombosit score (HALP)[11], systemic immune inflammation score (SII)[12], neutrophil/lymphocyte ratio (NLR)[13], platelet-lymphocyte ratio (PLR)[14], lymphocyte-monocyte ratio (LMR)[15] and systemic inflammation response index (SIRI)[16]] have been shown to predict survival in clinical studies in different solid tumors.

In this study, we analyzed the prognostic value of ALBI score and lymphocyte-associated inflammation markers calculated before the treatment plan on survival in advanced HCC.

MATERIALS AND METHODS

This study included the data of 141 patients with advanced hepatocellular carcinoma who were followed up in Pamukkale University Faculty of Medicine, Department of Medical Oncology between July 2009 and March 2023. The approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Pamukkale University (approval number: E-60116787-020-476142, date: 15.01.2024). The entire clinic database was screened. Patients with missing clinicopathological data, severe infection, poor performance score (PS), second primary malignancy and chronic immunological disease were considered as exclusion criteria. Patients aged 18 years and older were included in the study. Age, chronic habits (smoking, alcohol), hepatitis markers and treatment history (systemic treatment, surgery, locoregional treatments) were recorded from patient files. Hematological and biochemical parameters measured before the treatment were retrospectively recorded from the hospital laboratory information system. Child, ALBI, ALRI, PNI, HALP, SII, NLR, PLR, LMR and SIRI scores were calculated using hematological and biochemical values. ALBI score=[log10 bilirubin (micromol/L) x 0.66]+[albumin (g/L)x-0.085] [ALBI grade 1 (score≤-2.60), grade 2 (score>-2.60 with≤-1.39) and grade 3 (>-1.39)], SII=platelet*neutrophil/lymphocyte, NLR=neutrophil/lymphocyte, PLR=platelet/lymphocyte, LMR=lymphocyte/monocyte, SIRI=neutrophil*monocyte/lymphocyte, ALRI=AST/lymphocyte, PNI=albumin(g/L)+5*lymphocyte(10^9/L) and HALP score=hemoglobin(g/L)*albumin(g/L)*lymphocyte (*10^9/L)/platelet(*10^9/L) were calculated.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as median ± standard deviation for continuous variables, and as n and % for categorical variables. Receiver operating characteristic (ROC) analysis was used to find the cut-off value of prognostic scoring (ALBI, ALRI, PNI, HALP, SII, NLR, PLR, LMR, SIRI). The Kaplan-Meier method was used for survival [overall survival (OS), PFS] analyses. Univariate analysis

was performed. Finally, multivariate Cox regression results were given for the evaluation of statistically significant parameters in survival analysis. P<0.05 was considered statistically significant.

RESULTS

One hundred-forty one patients were included. The median age at the time of diagnosis was 65 years (min: 26-max: 88). Eastern Cooperative Oncology Group PS was '0-1' in 118 (83.7%) patients. The mean body mass index was 25.90±5.62. Of patients, 126 were male (89.9%) and male/female ratio was 9:1. HBV positive 58 (41.1%), HCV positive 20 (14.2%) and 63 (44.7%) patients had no history of chronic hepatitis. Forty eight (77%) of the patients without chronic hepatitis had a history of diabetes mellitus and steatohepatitis. They were thought to be HCC cases developing on the background of non-alcoholic steatohepatitis. One patient had haemochromatosis in the etiology, and received only locoregional treatment and no systemic treatment (mOS: 5 months). Alcohol use was present in 20 (14.2%) patients. Asymptomatic patients comprised 51 (36.2%) of the cohort. The presenting complaints were abdominal pain in 60 (42.6%), fatigue in 20 (14.2%), abdominal distension in 17 (12.1%) and jaundice and nausea and vomiting in 4 (2.8%) patients. The primary localization of the tumor was right lobe in 72 (51.1%), left lobe in 18 (12.8%) and multifocal in 51 (36.2%) patients. Tumor size was ≤50 mm in 74 (52.5%) patients. The number of tumors was single lesion in 67 patients (47.5%) and multiple in 62 patients (50.0%). First-line treatment included 41 patients (28.7%) who received no treatment, 6 patients (4.2%) who received single agent doxorubusin, 93 patients (65%) who received sorafenib and 1 patient (0.7%) who received immunotherapy. First-line treatment response was complete response in 11 (7.7%) patients, stable disease in 4 (2.8%) patients and progressed disease in 85 (59.4%) patients. Sixty one (42.7%) patients had no side effects. The most common side effects were skin rash, diarrhea, mucositis and hypertension, which were observed in 39 (27.3%) patients. Very few patients received second-line treatment. Four patients (2.8%) received sorafenib and 11 patients (7.7%) received regorafenib. Thirteen of these patients (86.7%) developed progression and died. In the third-line setting, 1 patient received nivolumab. No local treatment was given to 73 patients (51%). Ablative treatments included TAKE: 49 patients (34.3%), TARE: 6 patients (4.2%) and RF: 9 patients (6.3%). After all treatments, progression developed in 118 (83.7%) patients and 116 (82.3%) patients died. The mean follow-up period of the patients was 19.99±25.26 months. Cut-off values were found by ROC analysis and cut-offs based on the state of exitus (Table 1). To assess the presence of a significant association that could predict overall survival, univariate analysis was performed. ALBI (p<0.001), ALRI (p<0.001), PNI (p=0.030) and HALP (p=0.003) parameters were statistically significant in the prediction of survival. OS and PFS at two and five years for ALBI score and lymphocyte-associated inflammatory markers according to ROC analysis cut-offs were evaluated. In the whole group, mPFS was 4.36 (95% CI: 2.98-5.75) months and mOS was 9.10 (95% CI: 5.60-12.58) months. Two and five-year OS (27.4%: 13.9%) and PFS (11.7%: 1.7%) values were found. Age (p=0.003), ALBI (p<0.001), ALRI (p<0.001), PNI (p=0.032) and HALP (p=0.021) groups showed significant association with mOS. Age (p=0.005), ALBI (p=0.014) and ALRI (p=0.017) groups showed significant association with mPFS (Table 2). In univariate analysis, the variables age, ALBI, ALRI, PNI and HALP had significant relationships to predict overall survival (p<0.05) (Table 3). These variables, which were found to be significant as a result of the univariate analysis, were included in the multivariate Cox regression model. After multivariable cox regression, age of 65 years and older [hazard ratios (HR): 2.13; 95% confidence interval (CI): 1.44 to 3.17; p<0.001], ALRI≥30.79 (HR: 2.14; 95% CI: 1.20 to 3.82; p=0.009) predicted an increased risk of death, and ALBI≥2.54 (HR: 0.44; 95% CI: 0.29-0.69; p<0.001) predicted a decreased risk of death (p<0.001, -2loglikelihood=896.27) (Figure 1).

Table 1. ALBI score and lymphocyte-related inflammation markers cut-off values

Variables	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	p value
SII	0.571	0.444-0.697	≥452.38	57.6	56.5	0.284
ALBI	0.789	0.702-0.876	≥-2.54	69.5	69.6	**<0.001**
NLR	0.581	0.447-0.714	≥2.97	56.8	56.5	0.222
PLR	0.627	0.504-0.750	≥113.01	56.8	56.5	0.054
LMR	0.566	0.436-0.697	≤3.23	52.5	52.2	0.315
SIRI	0.544	0.413-0.675	≥1.42	52.5	52.2	0.507
ALRI	0.722	0.618-0.825	≥30.79	65.3	65.2	**<0.001**
PNI	0.644	0.527-0.760	≤10.68	60.2	60.9	**0.030**
HALP	0.696	0.586-0.805	≤43	65.3	65.2	**0.003**

AUC: Area under the curve, 95% CI: Confidence interval, ALBI: Albumin-bilirubin score, SII: Systemic immune inflammation score, NLR: Neutrophil/lymphocyte ratio, LMR: Lymphocyte-monocyte ratio and SIRI: Systemic inflammation response index, ALRI: Aspartate aminotransferase-to-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, PNI: Prognostic nutritional index, HALP: Hemoglobin, albumin, lymphocyte, and platelet score. p<0.05 was considered statistically significant

In the univariate analyses, age, ALBI, ALRI variables were significantly associated with PFS (p<0.05). These significant variables were included in the multivariate cox's regression model. According to multivariate Cox regression model results, it was determined that having over 65 years of age (HR: 1.74,95% CI: 1.18-2.56; p=0.005) increased the risk of progression (p=0.001,-2 loglikelihood=846.36) (Figure 2).

DISCUSSION

In this study, we analyzed the predictive value of ALBI score and lymphocyte-associated inflammation markers on prognosis in advanced HCC. There are studies in the literature calculating different prognostic scores in HCC using laboratory values before or after surgery. We found that ALBI score≥-2.54 (p<0.001), ALRI<30.79 (p<0.001), PNI≤10.68 (p=0.030) and HALP score>43 (p=0.003) were associated with longer overall survival. In the ROC analysis of the prognostic markers evaluated in the study, ALBI score (AUC=0.789) and ALRI score (AUC=0.722) had the largest AUC for mOS. Our findings suggest that ALBI score and lymphocyte-associated inflammation markers (ALRI, PNI and HALP) at the time of diagnosis may be prognostic indicators.

In addition to the immortality of cancer cells, genomic instability and inflammation are facilitating factors for cancer

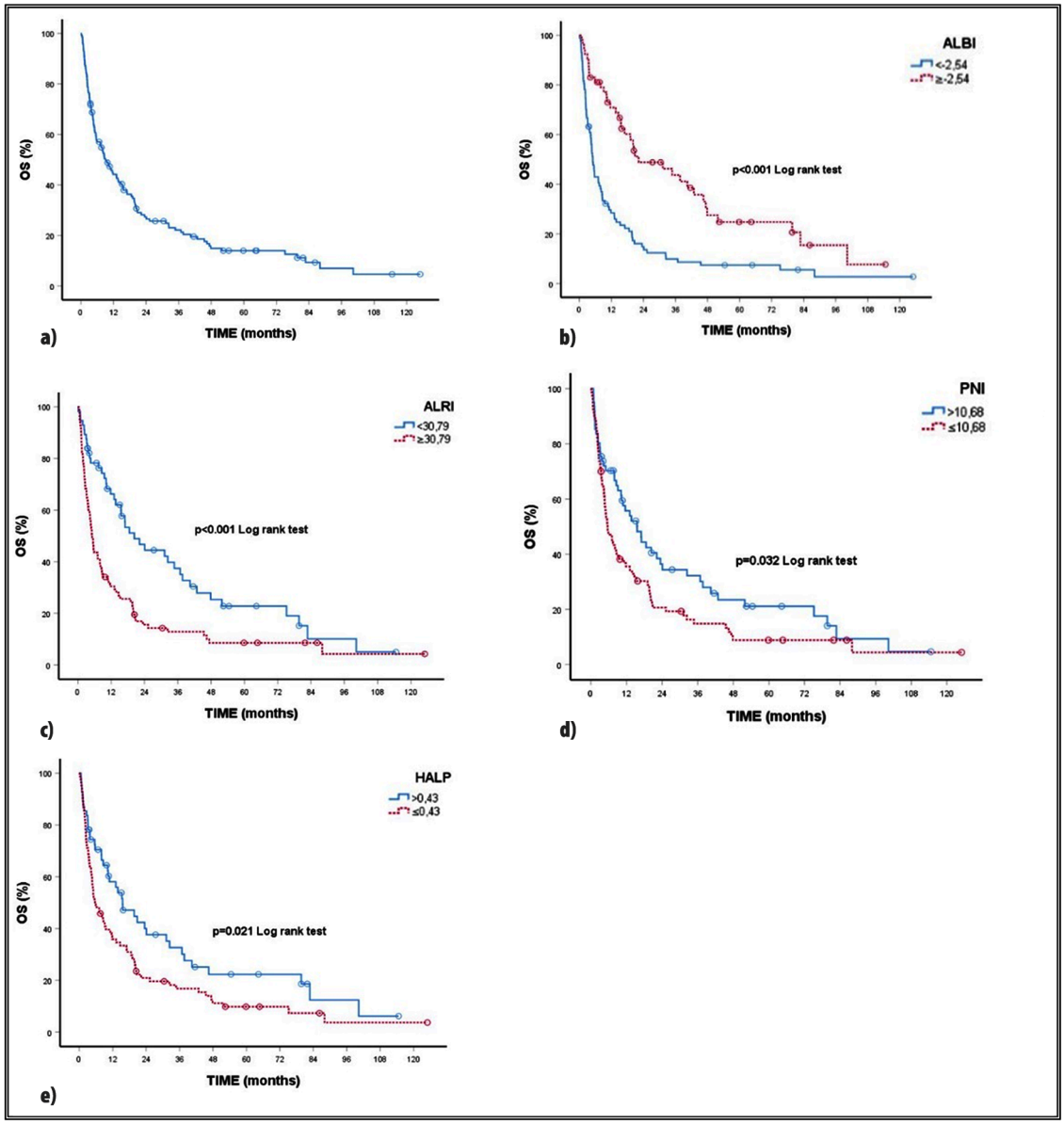

Figure 1. Graphical representation of multivariate Cox regression results on the effect of ALBI Score and Lymphocyte Related Prognostic Markers on survival

ALBI: Albumin-bilirubin, OS: Overall survival, ALRI: Aspartate aminotransferase-to-lymphocyte ratio

formation. The tumor microenvironment, which results from the interaction of cancer stem cells, cancer cells and stromal cells, is involved in tumor formation and progression[17].

Salazar-Onfray et al.[18] reported direct and indirect effects of cytokines. Cytokines may have direct effects by inhibiting and stimulating growth and indirect effects by triggering angiogenesis and causing inflammatory cell migration. Previously published studies have described that chronic inflammation is important in all processes of tumor formation, malignant transformation, invasion and metastasis. The inflammatory response in the tumor microenvironment provides escape from the immune response by causing neutrophilia, thrombocytosis, lymphopenia and lymphocyte dysfunction. It has been the subject of a large number of clinical studies that hematological and biochemical results of inflammatory reaction significantly predict the prognosis of solid tumors[17].

A systemic review about ALBI score has revealed that ALBI score better discriminates the prognosis in HCC patients compared to child-pugh, which is most frequently used by clinicians. This study suggests that the ALBI score alone is not sufficient to predict prognosis and that the predictive ability of ALBI should be improved. New algorithms are needed for prognosis prediction in HCC[8].

Zhao et al.[9] conducted a clinical study on 598 patients with HCC, who were receiving palliative care only, and the ALRI score was shown to be an independent prognostic factor in predicting OS (HR: 3.166, 95% CI: 1.411-7.103; p=0.005). In this study, two year survival was 20.0% in patients with ALRI<30.79 and 7.2% in patients with ALRI≥30.79 (HR: 2.14, 95% CI: 1.20-3.82; p=0.009). After multivariable analysis with patient age, ALBI, ALRI, HALP and PNI, survival was 7.0% for patients over 65 years old (HR: 2.13, 95% CI: 1.44-3.17; p<0.001) and ALRI≥30.79 (HR: 2.14, 95% CI: 1.20-3.82; p=0.009), while the risk of death increased in patients with ALBI≥-2.54 (HR: 0.44, 95% CI: 0.29-0.69; p<0.001). Multivariate analysis identified patient age, ALBI, and ALRI as independent prognostic factors for survival.

Chronic inflammation in the liver parenchyma due to different etiological causes triggers unbalanced cytokine release and hepatocarcinogenesis. The increase in AST seen in liver parenchymal damage is accompanied by loss of lymphocyte function in response to inflammation. The ALRI score obtained by formulating these variables is a prognostic marker. The ALBI score provides an evidence-based, objective and simple method for the evaluation of liver function. With its applicability to clinical practice, this result is considered a contribution to the literature.

Feng et al.[10] showed that PNI, GGT/ALT and tumor number evaluated before hepatectomy in 283 HCC patients were

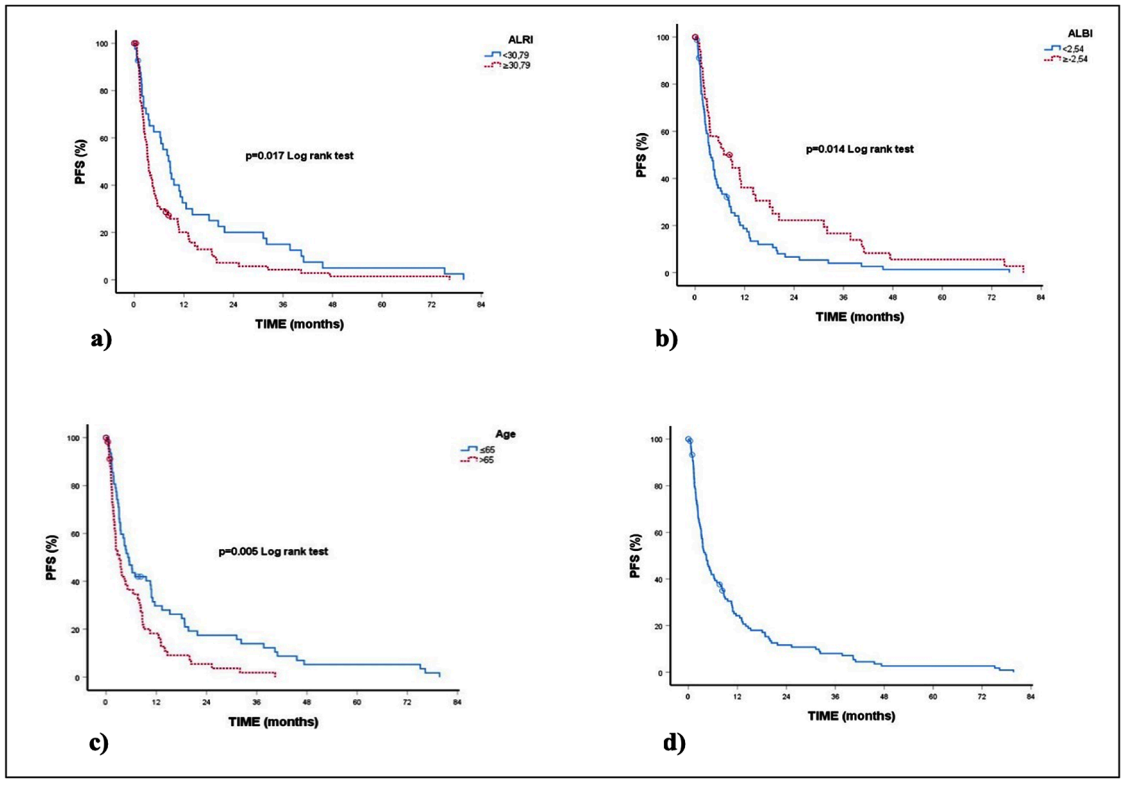

Figure 2. Multivariable Cox regression results of (a) ALRI, (b) ALBI, and (c) age variables and (d) progression-free survival curve in the entire patient group

ALBI: Albumin-bilirubin, PFS: Progression-free survival, ALRI: Aspartate aminotransferase-to-lymphocyte ratio

prognostic for OS in multivariate Cox regression analysis; PNI<48.48 (p=0.029) and gamma-glutamyl transferase (GGT)/alanine aminotransferase (ALT)≥1.65 (p=0.005) were associated with increasing OS and DFS. In this study, consistent results were obtained as reported in the literature. Two-year survival was 36.4% when PNI>10.68 and 20.6% when PNI≤10.68. Although a PNI≤10.68 was found to be significantly associated with increased survival in univariate analysis (HR: 5.63, 95% CI: 9.36-21.75; p=0.032); it was not found to be significant in multivariate analysis (HR: 0.65, 95% CI: 0.37-1.14; p=0.138). This marker, which assesses nutritional status and inflammation together, may be prognostic for survival.

HALP consists of hemoglobin, albumin, lymphocyte and platelet values. It provides evaluation of nutritional and inflammatory responses. In a clinical study with 273 HCC patients, Zhou and Yang[11] found that a preoperative HALP score below the cut-off value was significantly associated with a worse prognostic outcome (HR: 1.708, 95% CI: 1.192-2.448, p=0.004). In this study, the two-year survival rate in patients with a HALP score≤43 was 20.9% in a univariate analysis. In patients with HALP score >43, it was 40% (HR: 1.708, 95% CI: 7.30-23.76, p=0.021) and a significant relationship was found in accordance with the literature. The reason why HALP score >43 is associated with longer OS is based on the parameters in the formula. The absence of hypoxia due to anemia, adequate remaining liver parenchyma and absence of inflammation are associated with increased survival.

Katayama et al.[12] in a multi-center study on 1117 patients, a higher preoperative SII score was significantly associated with worse PFS in non-invasive bladder cancer (HR: 1.84, 95% CI: 1.23-2.77; p=0.003). In this study, high SII score was not significantly associated with survival prediction in HCC (95% CI: 0.444-0.697; p=0.222).

In another clinical study, in 166 non-small cell lung cancer patients with cranial metastases, survival was better in patients with NLR<5 calculated before radiosurgery (p=0.040). The increase in NLR value resulted in an increased risk of death (HR: 1.054, 95% CI: 1.024-1.085; p<0.001). However, it was reported that lymphocyte-based prognostic scoring (PLR, LMR) does not predict survival[13]. In this study, NLR rate did not predict OS (95% CI: 0.447-0.714, p=0.222), whereas lymphocyte-related inflammatory scores were significantly associated with survival (HR: 2.14, 95% CI: 1.20-3.82, p<0.001).

In a meta-analysis of 22 studies on PLR, the association between PLR and response to neoadjuvant chemotherapy was significant in 5533 breast cancer patients. It was found to be statistically significant (HR: 0.77, 95% CI: 0.67-0.88, p=<0.001) that high PLR value predicted low pathological complete response (PCR) and poor prognosis[14]. In this study, no significant association was found between high PLR score and survival in HCC (95% CI: 0.504-0.750, p=0.054). Negative results were thought to be due to the small patient numbers.

Neumann et al.[15] investigated prognostic scoring in 1294 pancreatic cancer patients using univariate and multivariate analyses. LMR≥1.6 (HR: 0.60; 95% CI: 0.61-0.79, p<0.001) and NLR<4 (HR: 1.5; 95% CI: 1.2-1.6; p=0.001) were found to significantly predict OS. In this study, no significant association was found with LMR and NLR cut-offs in survival analysis (95% CI: 0.436-0.697, p=0.315).

Another clinical study included 680 American prostate cancer patients of African and European descent. The median follow-up was 5.9 years and 194 deaths occurred. NLR>2.9 (HR: 1.23, 95% CI: 1.03-1.48; p=0.01), SII>430.8 (HR: 1.66, 95% CI: 1.06-2.60, p=0.01) and SIRI>0.9 (HR: 1.22, 95% CI: 1.02-1.46; p=0.01) were significantly associated with worse OS and DFS (prostate cancer-related mortality)[16]. In this study, NLR≥2.97 (95% CI: 0.447-0.714, p=0.222), SIRI≥1.42 (95% CI: 0.413-0.675, p=0.507) and SII≥452.38 (95% CI: 0.444-0.697, p=0.222) were not significantly associated with survival in HCC.

Study Limitations

This study had some limitations that may have affected the results. Firstly, it included single center data and low number of patients. Moreover, since the data were collected retrospectively, all data that would increase inflammation may not have been recorded.

Unfortunately, these limitations were also present in the studies evaluating the effect of inflammation scores on survival in cancer patients in the literature. Although the data were collected retrospectively, inflammation scores were found to be statistically significantly associated with survival depending on cancer pathogenesis.

CONCLUSION

In conclusion, there are studies on HCC and inflammation in preclinical, clinical and surgical areas with a large number of patients. In this study, we examined the predictive value of ALBI score calculated before the treatment plan and lymphocyte-associated inflammation markers (ALRI, PNI, HALP, SII, NLR, PLR, LMR and SIRI) on prognosis in advanced HCC. We found that ALBI score≥-2.54 and lymphocyte-associated inflammation markers ALRI<30.79, PNI≤10.68 and HALP>43 may be good prognostic indicators. In our clinical practice, the evaluation of patient age, ALBI score and ALRI score together will enable us to predict the survival in HCC patients. Multicenter prospective studies planned with a high number of patients may be recommended in the future.

Table 2. Two-year and five-year OS and PFS values of ALBI score and lymphocyte-related inflammation markers				
OS (overall-survival) (months)	**2 years %**	**5 years %**	**Median (95% CI)**	**p value**
General	27.4	13.9	9.10 (5.60-12.58)	
Age (years)				
≤65	36.3	20.0	16.93 (9.04-24.82)	**0.003**
>65	17.8	6.8	5.86 (1.63-10.09)	
Gender				
Male	28.4	14.4	9.10 (5.45-12.75)	0.786
Female	16.7	-	8.66 (2.87-14.46)	
ALBI				
<-2.54	14.9	7.4	5.00 (3.93-6.06)	**<0.001**
≥-2.54	48.8	24.8	22.20 (4.84-39.55)	
ALRI				
<30.79	46.7	22.8	20.33 (11.29-29.36)	**<0.001**
≥30.79	15.6	8.6	5.13 (4.09-6.17)	
PNI				
>10.68	36.4	21.1	15.56 (9.36-21.75)	**0.032**
≤10.68	20.6	8.9	5.63 (3.42-7.84)	
HALP				
>43	40.0	22.3	15.53 (7.30-23.76)	**0.021**
≤43	20.9	9.8	5.63 (2.33-8.93)	
PFS (months)	**2 years %**	**5 years %**	**Median (95% CI)**	**p**
General	11.7	2.7	4.36 (2.98-5.75)	
Age				
≤65	17.5	5.2	5.26 (3.43-7.09)	**0.005**
>65	5.5	-	5.63 (1.78-4.61)	
Gender				
Male	12.8	2.9	4.13 (2.67-5.59)	0.925
Female	-	-	4.36 (0.00-12.44)	
ALBI				
<-2.54	6.7	1.3	3.80 (2.43-5.16)	**0.014**
≥-2.54	22.2	5.6	6.93 (1.93-11.93)	
ALRI				
<30.79	20.0	5.0	8.66 (6.11-11.22)	**0.017**
≥30.79	7.2	1.4	3.43 (2.76-4.10)	
PNI				
>10.68	13.1	4.4	6.26 (1.73-10.79)	0.474
≤10.68	23.1	1.5	3.80 (2.75-4.84)	
HALP				
>43	12.9	5.1	8.66 (5.57-11.75)	0.135
≤43	11.7	1.5	3.43 (2.64-4.21)	

OS: Overall survival, PFS: Progression-free survival, 95% CI: Confidence interval, ALBI: Albumin-bilirubin score, ALRI: Aspartate aminotransferase-to-lymphocyte ratio, PNI: Prognostic nutritional index, HALP: Hemoglobin, albumin, lymphocyte, and platelet score. p<0.05 was considered statistically significant

Table 3. Multivariate Cox regression results for various clinical variables

	OS		PFS	
	Multivariate		Multivariate	
Variables	HR (95% CI)	p value	HR (95% CI)	p value
Age (Ref:≤65)	2.13 (1.44-3.17)	**<0.001**	1.74 (1.18-2.56)	**0.005**
ALBI (Ref:<-2.54)	0.44 (0.29-0.69)	**<0.001**	0.71 (0.46-1.12)	0.145
ALRI (Ref:<30.79)	2.14 (1.20-3.82)	**0.009**	1.47 (0.95-2.29)	0.080
PNI (Ref:>10.68)	0.65 (0.37-1.14)	0.138	-	
HALP (Ref:>43)	1.25 (0.80-1.94)	0.312	-	
	p<0.001; -2Log likelihood=896.27		p=0.001;-2Log Likelihood=846.36	

OS: Overall survival, PFS: Progression-free survival, 95% CI: Confidence interval, ALBI: Albumin-bilirubin score, ALRI: Aspartate aminotransferase-to-lymphocyte ratio, HALP: Haemoglobin, albumin, lymphocyte, and platelet score, PNI: Prognostic nutritional index, p<0.05 was considered statistically significant

Ethics

Ethics Committee Approval: The approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Pamukkale University. (approval number: E-60116787-020-476142, date: 15.01.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Concept: M.Ö., G.G.D., Design: M.Ö., Data Collection or Processing: M.Ö., Analysis or Interpretation: M.Ö., G.G.D., B.Y.T., A.G.D., B.Ç.D., T.D., T.G.K., A.Y., S.D., S.T., B.A.Y., G.S.Ö., Literature Search: M.Ö., Writing: M.Ö.

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