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A Combination of Lymphocyte Count and Albumin Concentration as a New Prognostic Index for Hepatocellular Carcinoma

Hepatosellüler Karsinom için Yeni Bir Prognostik İndeks Olarak Lenfosit Sayısı ve Albümin Konsantrasyonunun Kombinasyonu

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Abstract

Aim: The presented study aims to evaluate the prognostic significance of the lymphocytes (/L) × albumin (g/L) (LA) score in patients with hepatocellular carcinoma.

Material and Method: The study included patients who underwent curative surgery for hepatocellular carcinoma between January 2004 and November 2020. The LA score was calculated using the formula lymphocytes (/L) ×albumin (g/L). The patients were subsequently divided into two groups based on a cut-off point of 4.620: Group 1 (Low LA) and Group 2 (High LA). The two groups were compared for clinical characteristics as well as oncological follow-up outcomes.

Results: The study included 36 patients, who were divided into Group 1 (n=21) and Group 2 (n=15). The MELD score was higher in Group 1 (12 vs. 9, p=0.022). The number of tumors, maximum tumor size and total tumor size were similar in both groups. At the last clinical follow-up, the mortality rate was 42.9% in Group 1 and 22.2% in Group 2. Recurrence rates were similar in both groups (42.9% vs. 33.3% p=0.467), and total survival (126 vs. 164 months p=0.1) and disease-free survival (26 vs. 29 months p=0.926) were also similar.

Conclusion: The use of the composite LA index – an indicator of immunonutritional status as a prognostic marker may not be significant in hepatocellular carcinoma patients undergoing curative resection.

Keywords: Hepatocellular carcinoma; Immunity; Lymphocytes; Nutritional status; Serum albumin.

Özet

Amaç: Bu çalışmanın amacı, lenfosit (/L) × albümin (g/L) (LA) skorunun prognostik önemini ve hepatosellüler karsinom ile olan ilişkisini araştırmaktır.

Gereç ve Yöntemler: Çalışma, Ocak 2004 ile Kasım 2020 arasında hepatosellüler karsinoma için küratif cerrahi yapılan hastaları kapsamaktadır. Lenfosit-Albumin (LA) skoru, lenfosit (/L) × albümin (g/L) formülü kullanılarak hesaplanmıştır. Hastalar daha sonra 4620 kesme değerine göre Düşük LA (Grup 1) ve Yüksek LA (Grup 2) olmak üzere iki gruba ayrılmıştır. İki grup, klinik özellikler ve onkolojik takip sonuçları açısından karşılaştırılmıştır.

Bulgular: Çalışma, 4620 LA kesme değerine göre Grup 1 (n=21) ve Grup 2 (n=15) olarak ayrılan 36 hastayı içermektedir. MELD skoru Grup 1'de daha yüksekti (12'ye karşı 9, p=0,022). Tümör sayısı, maksimum tümör boyutu ve toplam tümör boyutu her iki grupta benzerdi. Klinik takipte, Grup 1'deki mortalite oranı %42,9 iken, Grup 2'de %22,2 idi. Nüks oranları her iki grupta benzer bulunmuştur (%42,9'a karşı %33,3, p=0,467), toplam sağkalım (126'ya karşı 164 ay, p=0,1) ve hastalıksız sağkalım (26'ya karşı 29 ay, p=0,926) oranları da benzer bulunmuştur.

Sonuç: Küratif rezeksiyon geçiren HCC hastalarında, immünonütrisyonel durumun bir göstergesi olan bileşik LA indeksinin prognostik bir işaretçi olarak kullanımı anlamlı olmayabilir.

Anahtar Kelimeler: Hepatosellüler karsinom; İmmünite; Lenfosit; Nütrisyonel durum; Serum albumini.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is recognized as the seventh most prevalent cancer globally and ranks third in cancer-related deaths (Sung et al., 2021). Its incidence is particularly high in developing countries, primarily due to environmental influences, viral infections, dietary habits, and limited healthcare resources (Clancy, 2023; Villanueva et al., 2010). Despite advances in diagnostic accuracy, perioperative care, and surgical methods, the long-term outcomes post-hepatic resection are still suboptimal. Evidence indicates a recurrence rate as high as 70% within five years in several studies, with an overall survival rate under 15% over the same period (European Association, 2012; Jia et al., 2014). This underscores the critical need to identify patients with poor prognoses before undertaking major surgeries like hepatic resection. The factors affecting survival post-resection are under continuous investigation, with recent studies focusing on new immune-based treatments, especially for unresectable HCC (De Lorenzo et al., 2018; Rizzo & Brandi, 2021; Rizzo et al., 2022).

There is a growing consensus on several prognostic indicators in predicting long-term outcomes for HCC patients. Emerging evidence links systemic inflammation and the immune status of HCC patients to cancer progression (Harimoto et al., 2013; Uchinaka et al., 2018; Voron et al., 2015). Based on these findings, numerous recent studies have highlighted a significant correlation between systemic inflammatory responses (SIRs) and HCC prognosis, considering its classification as an inflammation-driven cancer (Howell et al., 2017; Yang et al., 2017). Moreover, serum albumin levels, indicative of liver function, are recognized as crucial prognostic factors in HCC cases (Johnson et al., 2015).

A study introduced the lymphocyte-to-albumin ratio (LA) as a new composite index, linking it to lower survival rates in colorectal cancer (Yamamoto et al., 2021). It also highlights the use of the Barcelona Clinic Liver Cancer (BCLC) and Albumin-Bilirubin (ALBI) systems for prognosis in liver cancer, focusing on tumor characteristics, liver function, and metabolic markers (Nault et al., 2018). This research specifically investigates the LA ratio's prognostic value in liver cancer patients, an area previously underexplored (Yang et al., 2020). This study investigates the potential of the LA ratio as an additional prognostic biomarker in HCC, where research is currently lacking.

MATERIAL AND METHOD

Following authorization from the local ethics committee at Çukurova University (Approval Date: 03.12.2021, Reference No: 117/17), this study identified individuals who underwent

curative surgery for hepatocellular carcinoma between January 2004 and November 2020. Eligible participants excluded those under 18, those who had palliative resection, or whose medical records were incomplete. An analysis was conducted on the eligible patients' medical records, utilizing a database incorporating pathology and clinical follow-up data.

The formula for calculating the LA ratio is derived from multiplying the lymphocyte count (/L) by the albumin level (g/L), using blood samples taken at the time of patient admission for surgical procedures. The cut-off value for the LA score was determined using Receiver Operating Characteristic (ROC) curves, leading to the classification of patients into two groups: Group 1 (Low LA) and Group 2 (High LA), according to the established cut-off. Comparative analyses between these cohorts included an array of variables: demographic and clinical characteristics, confirmed ascites, history of encephalopathy, Child-Pugh classification, etiological factors, laboratory parameters, Alpha-Fetoprotein (AFP) levels, Model for End-Stage Liver Disease (MELD) scores, tumor location, number and total size of tumors, multicentricity, surgical procedures, postoperative complications, perioperative mortality, recurrence during follow-up, current clinical status, and measurements of overall and disease-free survival.

Overall survival was characterized as the time span from the initial diagnosis to the patient's death, while disease-free survival was the interval from the liver resection to the radiologically verified recurrence of the tumor.

The types of liver resections were classified as segmentectomy, lobectomy, or transplantation, following the Milan Criteria for determining transplant suitability (Mazzaferro et al., 1996). The Milan Criteria stipulate either a solitary tumor no larger than 5 cm, up to three tumors with none exceeding 3 cm in size, and no significant vascular invasion or metastatic presence.

Statistical Assessment

The statistical analysis of the data was performed using IBM SPSS Statistics (Version 23.0. Armonk, NY: IBM Corp.). Categorical measurements were summarized based on numbers and percentages, and continuous measurements based on means, standard deviations and minimum-maximum. The normality of the data was analyzed with a Shapiro-Wilk test; categorical variables were compared with Chi-square and Fisher’s tests; an Independent Samples (Student's) t-test was used for normally distributed groups, and a Mann-Whitney U test for non-normally distributed groups. The sensitivity and specificity of the LA score were calculated based on the mortality of the study patients, and a cut-off point was established from an

examination of the area under the ROC curve. Kaplan-Meier and Log-rank tests were used to analyze the survival and disease-free survival findings of the patients. The statistical significance level was set at 0.05 for all tests.

RESULTS

The research encompassed 36 patients, divided into two cohorts based on their LA scores: Group 1 was defined as low LA group with 21 patients and group 2 was defined as high LA group with 15 patients. Mortality was used as the criterion in a Receiver Operating Characteristic (ROC) analysis to establish a cut-off point for the LA score, which showed an area under the curve of 70.8%, indicating a 70.8% accuracy in mortality prediction. LA scores below 4620 were associated with increased mortality at follow-up, with a sensitivity of 75% and a specificity 75% (Figure 1 and Table 1).

Table 1. Proposed cut-off values for significant parameters in overall survival**.**

	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)	p
Lymphocytes x Albumin	<4620	75 (42.8–94.5)	75 (53.3–90.2)	60 (41.1–76.3)	85.7 (68.7–94.3)	0.708 (0.533–0.847)	**0.032**

CI: Confidence Interval, **PPV:** Positive Predictive Value, **NPV:** Negative Predictive Value, **AUC:** Area Under Curve

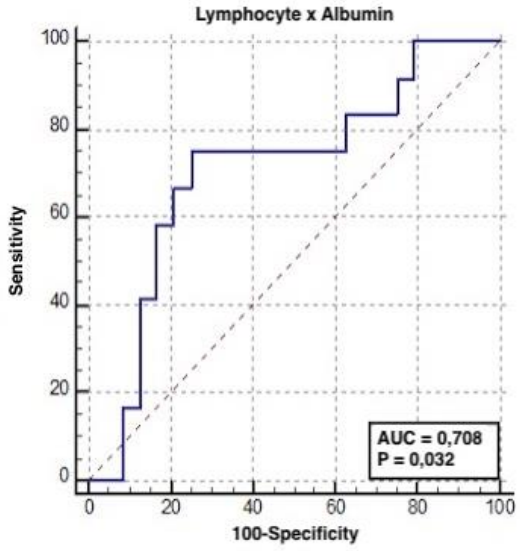

Figure 1. Receiver Operating Characteristic (ROC) curve analyses for mortality

In terms of demographics, a majority of participants in both groups were male (76.2% in Group 1 and 86.7% in Group 2, with p = 0.434), and the average ages were comparable (65 years for Group 1 and 64 years for Group 2, with p = 0.872) (Table 2). A larger percentage of patients in Group 2 were classified as Child-Pugh class A compared to Group 1 (81.5% vs. 50%, p = 0.049).

The most common cause identified in both groups was Hepatitis B virus (HBV) infection (53.6% in Group 1 vs. 66.7% in Group 2, p = 0.547).

Table 2. Demographic and clinical data

	Low n (%)	**High n (%)**	**p**
Gender			
Male	16 (76.2)	13 (86.7)	0.434
Female	5 (23.8)	2 (13.3)	
Age	65 (45–85)	64 (28–74)	0.872
ASA			
1	3 (14.3)	4 (26.7)	
2	11 (52.4)	9 (60)	0.336
3	7 (33.3)	2 (13.3)	
Abdominal pain	13 (61.9)	8 (53.3)	0.607
Jaundice	10 (47.6)	8 (53.3)	0.735
Preoperative biopsy	1 (4.8)	2 (13.3)	0.359
Preoperative percutaneous biliary drainage	11 (52.4)	5 (33.3)	0.257
Preoperative ERCP stent	11 (52.4)	5 (33.3)	0.320
Neoadjuvant therapy	1 (4.8)	-	NA

Clinical parameters showed that Group 1 had higher International Normalized Ratio (INR) values (1.2 vs. 1.1, p = 0.022), Child-Pugh scores (6.5 vs. 6, p = 0.015), Model for End-Stage Liver Disease (MELD) scores (12 vs. 9, p = 0.022), and Neutrophil-to-Lymphocyte Ratio (NLR) values (5.02 vs. 2.58, p < 0.001) than Group 2.

Table 3. Laboratory parameters

	Low (n=21)	**High (n=15)**	**p**
WBC mm3 /L	10.5 (5.3–30)	10.6 (6.1–31)	0.700
Neutrophil count mm3 /L	8.8 (3.3–27.2)	6.8 (3.4–27.8)	0.553
Lymphocyte count mm3 /L	1.4 (0.8–2.5)	2.56 (1.3–8.8)	**<0.001**
Platelet count mm3 /L	304.5 ± 22.1	272.4 ± 20.6	0.314
CRP	10.3 (0.3–170)	5.52 (0.2–61)	0.748
Preop Hgb gr/dl	11.7 ± 0.4	13.7 ± 0.4	**0.001**
Preop albumin gr/dl	2.67 ± 0.1	3.45 ± 0.1	**0.002**
Total bilirubin mg/dL	7 (0.4–25.4)	2.29 (0.4–18.8)	0.078
Direct bilirubin mg/dL	3.84 (0.1–12.1)	0.82 (0.1–15.9)	0.095
Ast	71 (18–465)	115 (24–537)	0.178
Alt	80 (13–648)	137 (14–623)	0.248
Alp	284 (58–1769)	319 (47–670)	0.700
Ggt	194 (30–1155)	327 (42–1739)	0.312
Cea	3.5 (0.9–137)	2.1 (0.6–6)	0.095
Ca19.9	310 (0.8–20270)	71 (1.6–1631.5)	**0.013**

WBC: White Blood Cell, **CRP:** C-reactive protein, **Hgb:** Hemoglobin, **AST:** Aspartate Aminotransferase, **ALT:** Alanine Aminotransferase, **ALP:** Alkaline Phosphatase, **CEA:** Carcinoembryonic Antigen

Rates of preoperative Radiofrequency Ablation or Transarterial Chemoembolization were comparable between the groups (35.7% in Group 1 vs. 22.1% in Group 2, p = 0.271). The majority of lesions were located in the right lobe of the liver in both groups (71.4% in Group 1 vs. 66.7% in Group 2, p = 0.702). The number of tumors, maximum tumor size, and total tumor size were similar in both groups, as were the types of operations and postoperative complications. Notably, there were two deaths from postoperative sepsis and one from pneumonia and liver failure in the perioperative period (Table 4).

Table 4. Operational details

	Low n (%)	**High n (%)**	**p**
Surgery			
Biliary	13 (61.9)	10 (66.7)	
Hepatic	2 (9.5)	3 (20)	0.441
Hepatic + biliary	6 (28.6)	2 (13.3)	
Tumor localization			
Intrahepatic	4 (19)	6 (40)	
Perihilar	9 (42.9)	2 (13.3)	0.133
Distal	8 (38.1)	7 (46.7)	
Intraoperative complications	-	1 (6.7)	0.230
Vascular invasion	1 (4.8)	4 (26.7)	0.061
Duration of operation	280.2 ± 31.5	268.2 ± 21.1	0.773
Length of postoperative hospital stay	16.5 ± 1.4	14.9 ± 1.7	0.497
Postoperative complications according to Clavien-Dindo			
1	19 (90.5)	13 (86.7)	
2	2 (9.5)	1 (6.7)	0.472
3B	-	1 (6.7)	
Postoperative mortality	-	2 (13.3)	0.085
Reoperation	-	1 (6.7)	0.230
90-day unplanned readmission	9 (42.9)	2 (13.3)	0.058

At the most recent clinical follow-up, mortality rates were 42.9% in Group 1 and 22.2% in Group 2. Recurrence rates were also comparable (42.9% in Group 1 vs. 33.3% in Group 2, p = 0.467).

Table 5. Pathological Characteristics

	Low n (%)	**High n (%)**	**p**
Tumor size	2.8 (0.7–10)	3.13 (0.5–6.2)	0.683
Number of lymph nodes	7 (1–18)	8 (3–47)	0.392
Number of metastatic lymph nodes	4.5 (2–10)	4.5 (4–5)	NA
Pathological grade			
1	-	1 (6.7)	
2	11 (52.4)	9 (60)	
3A	3 (14.3)	3 (20)	0.210
3C	7 (33.3)	1 (6.7)	
4	-	1 (6.7)	

There was no significant difference in overall survival (126 months in Group 1 vs. 164 months in Group 2, p = 0.1) and disease-free survival (26 months in Group 1 vs. 29 months in Group 2, p = 0.926) between the groups.

DISCUSSION

This study investigates the prognostic relevance of the LA index and its correlation with clinical outcomes in HCC patients who have undergone curative resection. It was found that a low LA score correlates with elevated Child-Pugh scores and more advanced Child-Pugh classes, and that patients with lower LA scores also tended to have higher MELD scores. No association between LA score and overall and disease-free survival were identified, nor any association with the postoperative period or long-term oncological follow-up.

The Prognostic Nutritional Index (PNI), formulated as PNI = (10 × Albumin [g/dL]) + (0.005 × total lymphocyte count/mm3), serves as a measure of patients' nutritional health and was originally devised for evaluating both immunological and nutritional states in individuals undergoing surgery in the gastrointestinal area (Onodera et al., 1984). Given the crucial role of nutrition in shaping immune responses, a connection is often drawn between low albumin levels (hypoalbuminemia) and weakened immune functions. The total lymphocyte count, another key element of the PNI, assumes a significant role in the prognostic evaluation of cancer patients, as it is frequently included in various inflammatory prognostic indices due to its importance in predicting patient outcomes. Lymphocytes are essential in cell-mediated immunity, especially in combating cancer cells through cytotoxic activities (Chen et al., 2023; Mantovani et al., 2008; Roxburgh & McMillan, 2010). In a study of 717 patients undergoing curative resection for

HCC, Imai et al. found the PNI to be superior to the Controlling Nutritional Status (CONUT) score, the neutrophil/lymphocyte ratio, the platelet / lymphocyte ratio or the Glasgow Prognostic Score, as an indicator of overall and disease-free survival in patients with HCC undergoing curative liver resection (Imai et al., 2020).

The CONUT score is another widely used metric for assessing nutritional and immunological health, utilizing a straightforward calculation based on three parameters: serum total cholesterol levels, total lymphocyte count, and albumin concentration in peripheral blood (Tanio et al., 2019). Numerous studies have linked a high preoperative CONUT (PreCONUT) score with both long-term survival outcomes and post-operative complications in HCC patients undergoing liver surgery (Harimoto et al., 2018; Takagi et al., 2017). In 2017, Takagi K et al. found that a PreCONUT score of 3 or higher was a dependable, independent indicator of decreased survival following liver resection in HCC patients (Takagi et al., 2017). Additionally, subsequent research indicated that a heightened PreCONUT score could be a predictive marker for survival among HCC patients (Harimoto et al., 2017).

In a pioneering study by Yamamoto T et al., which was the first to establish the LA score, 448 stage II/III rectal cancer patients who underwent curative resection were included. The study discovered an association between a low LA score and decreased overall and relapse-free survival rates. The researchers concluded that the LA score could help identify patients with a high risk of recurrence and proposed that it might also be beneficial in guiding postoperative treatment choices to prevent recurrence (Yamamoto et al., 2021). Chen and et al. also investigated the LA value in 216 newly diagnosed lung cancer patients and demonstrated that the LA value is statistically significantly correlated with invasion depth, lymph node metastasis, and clinical stage. They found that the LA value was lower as the disease progressed in their study (Chen et al., 2023). Based on the available evidence, the present study investigated the relationship between LA levels and HCC, and found LA to have no association with the clinical characteristics of tumors and survival, but to be associated with Child-Pugh and MELD scores, indicating liver function, and with the NLR value. These findings suggest that the LA score reflects liver function or inflammatory and immunological status rather than tumor status.

Evaluation of the prognosis at the diagnosis stage in HCC has an important place in the treatment management. It can be difficult to determine the prognosis in HCC due to factors such as the presence of an underlying cirrhotic background, different factors in the etiology of cirrhosis, and differences in the bio behavior of the tumor. In addition to the parameters used as prognostic factors such as portal vein thrombosis, tumor size, Child-Pugh class, AFP level,

extrahepatic metastasis, lymph node metastasis, different markers will be revealed; it will be determined which of a wide range of treatment methods such as resection, liver transplantation, ablation, systemic therapy will be used. In addition to conventional prognostic factors, LA score and similar scoring systems can be expected to take place more in clinical practice due to their easy and cheap use.

The primary constraints of this study include its retrospective nature and the relatively small patient cohort, which introduces certain statistical limitations. Nonetheless, we contend that this research makes a significant contribution to existing knowledge as it is the first to explore the prognostic implications of the LA score in patients with HCC.

CONCLUSION

In conclusion, the LA index, representing immunonutritional status in HCC patients undergoing curative resection, fails to reliably predict prognosis or postoperative outcomes. This highlights the need for extensive, multicenter research to clarify its prognostic value and establish a definitive LA index cut-off, crucial for understanding its role in HCC treatment outcomes.

Data Availability statement The data that support the findings of this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interests.

Ethics Approval: The study protocol was approved by the ethics committee of the University of Çukurova (Date: 03.12.2021 No:117/17)

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