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ORIGINAL ARTICLE

The lactate dehydrogenase-to-albumin ratio is a prognostic biomarker in extensive-stage small-cell lung cancer

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ABSTRACT

Background: The lactate dehydrogenase-to-albumin ratio (LAR) is a promising prognostic marker in various malignancies. However, its clinical relevance in extensive-disease small-cell lung cancer (ED-SCLC) remains unclear.

Methods: We analyzed a total of 221 patients diagnosed with ED-SCLC between January 2008 and December 2021. Patients without treatment response data (n=8), those who did not receive systemic therapy (n=37), and those who lacked baseline LDH values (n=48) were excluded. The LAR was calculated by dividing baseline serum LDH (U/L) by albumin (g/L) and, using ROC analysis, the optimal cut-off level was determined to be 5.71 (sensitivity: 81.5%, specificity: 77.8%). Kaplan–Meier and Cox regression analyses were used to evaluate both progression-free (PFS) and overall survival (OS).

Results: A total of 128 patients diagnosed with ED-SCLC were included in our analysis. Patients with an LAR ≥5.71 had significantly shorter median OS (8.1 vs. 20.2 months, p<0.001) and PFS (5.9 vs. 9.4 months, p=0.003) compared to those with an LAR <5.71. In multivariate analysis, a high LAR was an independent predictor of a shorter OS (HR: 3.60; 95% CI: 1.35–9.60; p=0.010) and had a strong association with a shorter PFS (HR: 2.61; 95% CI: 0.95–7.14; p=0.063).

Conclusion: The LAR is a simple, cost-effective, and independent prognostic biomarker in patients with ED-SCLC. It could assist in risk stratification and guide treatment decisions in clinical practice.

Keywords: lactate dehydrogenase, albumin, LAR, small-cell lung cancer, prognosis, survival, biomarker

INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine tumor and has a poorer prognosis than non-small cell lung cancer (NSCLC) [1,2]. Unfortunately, two-thirds of patients are diagnosed with Extensive-disease SCLC (ED-SCLC) at the time of diagnosis and this is associated with a median overall survival (OS) of less than one year despite systemic therapy [3]. While immune checkpoint inhibitors have modestly improved outcomes in some patients [4], identifying reliable and inexpensive prognostic biomarkers is an unmet critical need in clinical practice.

Serum lactate dehydrogenase (LDH) is a marker of tumor burden and has been shown to correlate with adverse outcomes in SCLC [5]. Albumin reflects both nutritional and inflammatory status as well and hypoalbuminemia has been linked to poor survival in several malignancies [6]. Lactate dehydrogenase-albumin ratio (LAR) is created by the combination of these two biomarkers. Several studies have demonstrated that an elevated LAR is significantly associated with worse prognosis in gastrointestinal cancers [7-12], oral cancers [13], bladder [14], breast cancers [15] and hematological malignancies [16].

Despite its growing application, data on LAR in the context of SCLC are extremely limited. Although some studies have explored LDH or albumin separately or in composite prognostic models [5,6], no prior research has directly evaluated LAR as a unified biomarker in an ED-SCLC population receiving systemic chemotherapy.

The objective of this research was to determine if pretreatment LAR could predict outcomes in patients with ED-SCLC. We hypothesize that a higher LAR might point to both aggressive tumor behavior and tumor-related inflammatory response and support more informed treatment choices.

MATERIALS AND METHODS

Patients and data collection

This retrospective study included 128 patients diagnosed with extensive-disease ED-SCLC between January 2008 and December 2021 at our University Cancer Institute. The study inclusion criteria were as follows: a pathologically confirmed SCLC diagnosis, clinical-stage ED-SCLC, and having received at least 2 cycles of chemotherapy after diagnosis. Patients without available treatment response data, those who did not receive chemotherapy, and those with missing baseline LDH values were excluded from the analysis (Figure 1). Demographic data, comorbidities, Eastern Oncology Cooperative Group (ECOG) performance status, metastatic sites, treatment modalities, and baseline laboratory parameters were collected from medical records. Tumor response was evaluated using computed tomography (CT), with Response Evaluation Criteria in Solid Tumors criteria version 1.1 every three cycles until treatment discontinuation or disease progression. Progression-free survival (PFS) referred to the time from the initiation of first-line therapy to either documented disease progression or death. OS was measured from the time the start of first-line treatment to either death or the last known follow-up.

This retrospective observational study was approved by the Hacettepe University Ethics Committee (Protocol no: GO 22/1119, Date: 01.11.2022).

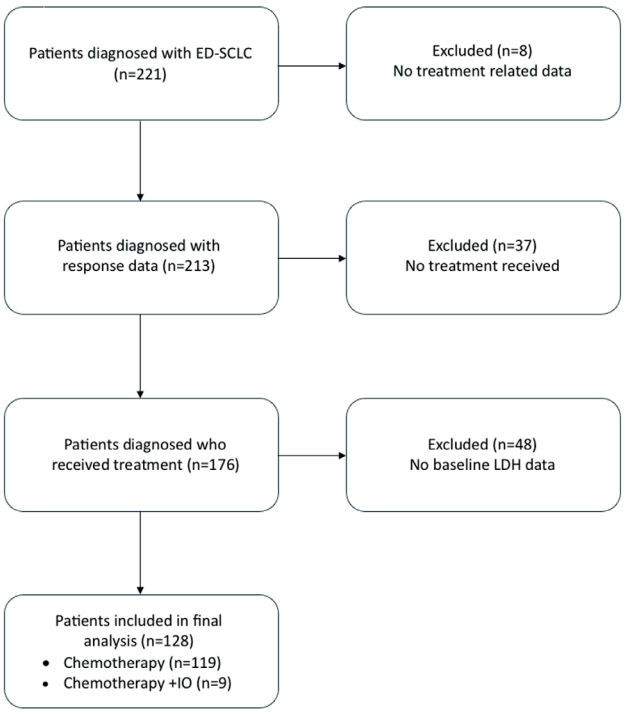

Figure 1. Flow chart of patient selection in ED-SCLC cohort.

ED-SCLC: extensive-disease small-cell lung cancer; IO: immunotherapy.

LAR and baseline laboratory parameters

Serum LDH and albumin levels were measured at the central biochemistry laboratory of our university hospital. LDH was measured using an enzymatic spectrophotometric method based on IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) standards. Albumin was measured using the bromocresol green method. Both tests were performed on routinely used automated analyzers. The LAR was calculated by dividing pretreatment serum LDH (U/L) by serum albumin (g/L). Baseline reference values were as follows: LDH = 240 U/L, albumin = 35-55 g/dL, and sodium = 135–145 mmol/L. Anemia was considered present if hemoglobin levels dropped below 13.5 g/dL in men or 12.0 g/dL in women.

Statistical analysis

Continuous variables are summarized as medians and interquartile ranges (IQRs), while categorical variables are mentioned as counts and percentages. Group comparisons for continuous variables based on LAR stratification were conducted using the Mann–Whitney U test for two groups and the Kruskal–Wallis H test for multiple groups. Categorical variables were compared using Fisher's exact test.

We used OS as the endpoint to calculate the LAR cut-off value and performed receiver operating characteristic (ROC) curve analysis. We calculated sensitivity and specificity using the area under the curve (AUC).

We conducted a bootstrapping analysis with 1000 resamples for validating the stability of the derived cut-off. In each repetition, a new sample was generated by using random sampling with replacement and the AUC was calculated again. Additionally, the mean AUC and 95% confidence interval were reported to evaluate the robustness of the model. The bootstrapping validation analysis was performed by using RStudio (version 2024.03.1+402) with the "pROC" package (version 1.18.5).

Furthermore, we assessed multicollinearity among LAR, LDH, and albumin using variance inflation factor (VIF) analysis. We calculated VIF values based on a linear regression model including these variables. A VIF value greater than 5 was considered indicative of significant collinearity. The VIF analysis was performed using RStudio (version 2024.03.1+402) with the "car" package.

Survival outcomes, including OS and PFS, were estimated using the Kaplan–Meier method. Differences between survival curves were evaluated via the log-rank test. The Cox proportional hazards regression model was employed for uni- and multivariate analyses to verify the independent predictive value of the pretreatment LAR in OS and PFS. Variables that showed a p-value below 0.10 in the univariate analyses were used for inclusion in the multivariate Cox regression models. Results are presented as hazard ratios (HRs) along with 95% confidence intervals (CIs). A two-sided p-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using SPSS software, version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 128 patients diagnosed with ED-SCLC were included in the final analysis. We excluded patients with missing LDH, outcome, or treatment data. These missing values were not imputed, as they were considered clinically meaningful and non-random (Figure 1). The median age was 64 years (IQR: 58–69), and the majority were male (90.6%). Almost 73% of patients had an ECOG performance status of <2. In addition, approximately 70% (n=89) of patients had at least one comorbidity. One hundred and nineteen received platinum-etoposide-based chemotherapy, and nine patients (7%) received platinum-etoposide combined with immunotherapy as first-line treatment. No statistically significant differences were observed between the two groups regarding age, sex, ECOG performance status, metastatic involvement (including adrenal metastases, p=0.38), or administration of prophylactic cranial irradiation (PCI). The baseline characteristics of patients stratified by LAR levels are shown in Table 1.

Table 1. Baseline characteristics stratified by lactate dehydrogenase-to-albumin ratio (LAR) cut-off

Characteristic	Total N=128 (%100)	LAR<5.71 N=29 (22.7%)	LAR≥5.71 N=99 (77.3%)	p value
Age median (IQR), years	64 (58, 69)			
Age groups (years)				0.10
<65	70 (54.7)	12 (17.1%)	58 (82.9%)	
≥65	58 (45.3)	17 (29.3%)	41 (70.7%)	
Gender				0.21
Female	12 (9.4)	1 (8.3%)	11 (91.7%)	
Male	116 (90.6)	28 (24.1%)	88 (75.9%)	
Comorbidity				0.59
No	39 (30.5)	10 (25.6%)	29 (74.4%)	
Yes	89 (69.5)	19 (21.3%)	70 (78.7%)	
Cardiac Diseases	34 (26.6)	3 (8.8%)	31 (91.2%)	
Diabetes	24 (18.7)	7 (29.2%)	17 (70.8%)	
Hypertension	58 (45.3)	12 (20.7%)	46 (79.3%)	
Second Malignancy	13 (10.2)	7 (53.8%)	6 (46.2%)	
COPD	14 (10.9)	4 (30.8%)	9 (69.2%)	
ECOG				0.97
<2	93 (72.7)	21 (22.6%)	72 (77.4%)	
≥2	35 (27.3)	8 (22.9%)	27 (77.1%)	
Liver metastasis				0.13
Yes	46 (35.9)	7 (15.2%)	39 (84.8%)	
No	82 (64.1)	22 (26.8%)	60 (73.2%)	
Adrenal metastasis				0.38
Yes	25 (19.5)	4 (16.0%)	21 (84.0%)	
No	103 (80.5)	25 (24.3%)	78 (75.7%)	
Brain metastasis				0.43
Yes	14 (10.9)	2 (14.3%)	12 (85.7%)	
No	114 (89.1)	27 (23.7%)	87 (76.3%)	
Bone metastasis				0.41
Yes	66 (51.6)	13 (19.7%)	53 (80.3%)	
No	62 (48.4)	16 (25.8%)	46 (74.2%)	
1st-line chemotherapy				0.67
Cisplatin/etoposide	82 (64.2)	19 (23.2%)	63 (76.8%)	
Carboplatin/etoposide	39 (30.5)	10 (25.6%)	29 (74.4%)	
Oral etoposide	2 (1.5)	0 (0%)	2 (100%)	
Weekly carboplatin	2 (1.5)	0 (0%)	2 (100%)	
Carboplatin after cisplatin/etoposide	3 (2.3)	0 (0%)	3 (100%)	
Immunotherapy				**0.015**
Yes	9 (7)	5 (55.6%)	4 (44.4%)	
No	119 (93)	24 (20.2%)	95 (79.8%)	
PCI				0.20
Yes	21 (16.4)	7 (33.3%)	14 (66.7%)	
No	107 (83.6)	22 (20.6%)	85 (79.4%)	
Hemoglobin (g/dL)				0.85
Low	46 (35.9)	10 (21.7%)	36 (78.3%)	
Normal	82 (64.1)	19 (23.2%)	63 (76.8%)	
Na (mmol/L)				0.49
Low	28 (21.9)	5 (17.9%)	23 (82.1%)	
Normal	100 (78.1)	24 (24.0%)	76 (76.0%)	
LDH (U/L)				**<0.001**
Low	34	28 (82.4%)	6 (17.6%)	
High	94	1 (1.1%)	93 (98.9%)	
Albumin (g/L)				**0.017**
Low	24 (18.7)	1 (4.2%)	23 (95.8%)	
Normal	104 (81.3)	28 (26.9%)	76 (73.1%)	

LAR: lactate dehydrogenase-to-albumin ratio; IQR: interquartile range; COPD: chronic obstructive pulmonary disease; ECOG: Eastern Cooperative Oncology Group; PCI: prophylactic cranial irradiation; LDH: lactate dehydrogenase; Na: sodium.

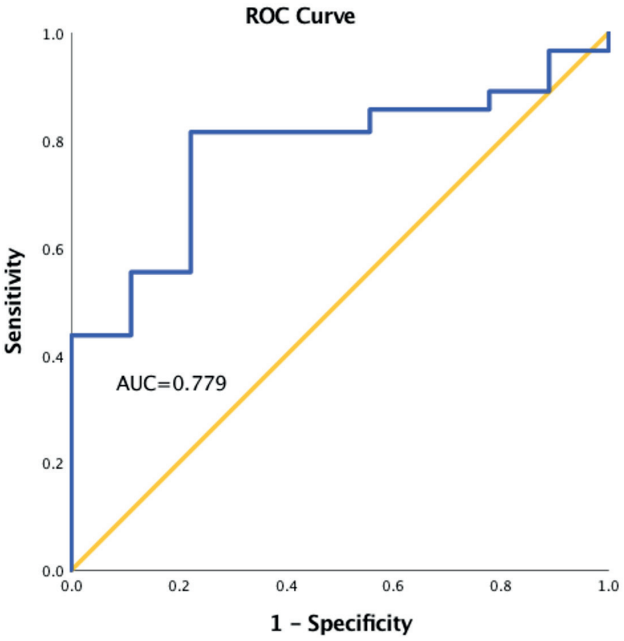

Figure 2. Receiver operating characteristic (ROC) curve of the lactate dehydrogenase-to-albumin ratio (LAR) for predicting overall survival. The area under the curve (AUC) was 0.779, indicating good discriminatory performance.

LAR cut-off value determination

The ROC analysis identified an optimal LAR threshold of 5.71 for predicting OS, with an AUC of 0.779. This cut-off provided a sensitivity of 81.5% and specificity of 77.8% for distinguishing between favorable and unfavorable survival outcomes (Figure 2).

We validated the stability of the cut-off value using the bootstrapping analysis. The mean AUC was 0.775 and the 95% CI ranged from 0.647 to 0.889. These results confirmed that the internal consistency of the LAR threshold (Supplementary Figure 1).

Survival outcomes

At the time of analysis, 123 patients (96.1%) had experienced progression, and 119 patients (92.9%) had died. A total of nine patients were censored in the survival analysis: two were lost to follow-up, and seven were alive at last follow-up. The median PFS in the low LAR group (<5.71) was 9.4 months (95% CI: 7.3–11.5), compared to 5.9 months (95% CI: 4.9–6.8) in the high LAR group (p=0.003) (Figure 3). The median OS was 20.2 months (95% CI: 11.7–28.7) in the low LAR group, markedly higher than the 8.1 months (95% CI: 6.9–9.3) in the high LAR group (p<0.001) (Figure 4). Furthermore, a low albumin level was associated with poor OS (5.6 months (95% CI, 2.96–8.24) vs. 10.4 months (95% CI, 7.85–12.94), p<0.001) and patients with high LDH values were found to have a shorter OS (15 (95% CI, 11.98–18.02) vs 8.3 (95% CI, 6.92–9.68) months, p=0.001).

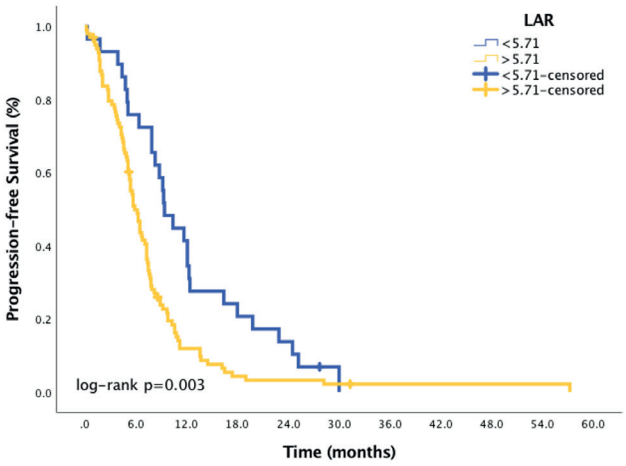

Figure 3. Kaplan–Meier curve for progression-free survival (PFS) stratified by lactate dehydrogenase-to-albumin ratio (LAR).

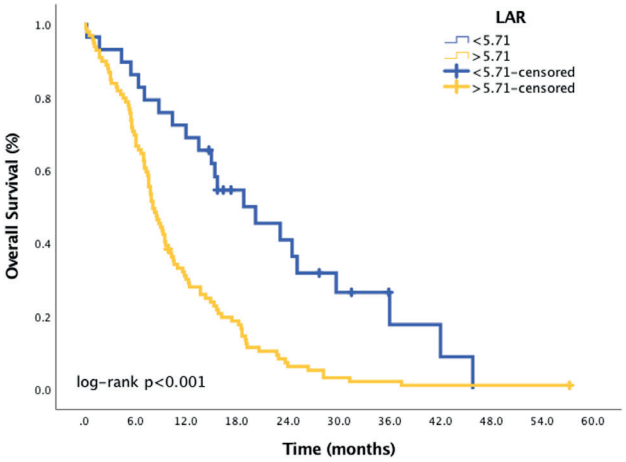

Figure 4. Kaplan–Meier curve for overall survival (OS) stratified by lactate dehydrogenase-to-albumin ratio (LAR).

Cox regression analysis

In univariate Cox regression analysis (Table 2), a high LAR was significantly associated with a shorter PFS (HR: 1.89; 95% CI: 1.23–2.90; p=0.004) and OS (HR: 3.36; 95% CI: 2.01–5.63; p<0.001); however, it did not remain significant in multivariate model for PFS (p=0.13). Other factors associated with a shorter PFS included liver (HR: 2.21; p<0.001) and brain metastases (HR: 2.24; p=0.007), low albumin (HR: 1.99; p=0.004), and an absence of PCI (HR: 0.39; p<0.001). Notably, liver (HR: 3.10; p<0.001) and brain metastases (HR: 3.80; p<0.001), elevated LDH

Table 2. Univariate and multivariate cox regression analysis for progression-free survival

Characteristics	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age groups (years)				
<65	Reference			
≥65	1.05 (0.73-1.50)	0.79		
Gender				
Female	Reference			
Male	1.45 (0.77-2.73)	0.25		
Comorbidity				
Yes	1.08 (0.73-1.60)	0.69		
No	Reference			
ECOG				
0-1	Reference			
≥2	1.19 (0.79-1.79)	0.40		
Liver metastasis				
Yes	2.21 (1.49-3.26)	**<0.001**	1.53 (0.98-2.39)	0.06
No	Reference			
Adrenal metastasis				
Yes	0.88 (0.56-1.38)	0.57		
No	Reference			
Brain metastasis				
Yes	2.24 (1.25-4.01)	**0.007**	1.69 (0.89-3.17)	0.10
No	Reference			
Bone metastasis				
Yes	1.06 (0.74-1.5)	0.73		
No	Reference			
Immunotherapy				
Yes	1.22 (0.59-2.51)	0.59		
No	Reference			
PCI				
Yes	0.39 (0.24-0.66)	**<0.001**	0.47 (0.28-0.80)	**0.005**
No	Reference			
Hemoglobin				
Low	1.03 (0.71-1.49)	0.89		
Normal	Reference			
Na				
Low	1.25 (0.81-1.93)	0.20		
Normal	Reference			
LDH				
Normal	Reference			
High	1.67 (1.11-2.50)	**0.014**	0.76 (0.31-1.87)	0.55
Albumin				
Low	1.99 (1.25-3.16)	**0.004**	1.39 (0.82-2.38)	0.22
Normal	Reference			
LAR				
<5.71	Reference			
≥5.71	1.89 (1.23-2.92)	**0.004**	2.11 (0.81-5.50)	0.13

LAR: lactate dehydrogenase-to-albumin ratio; ECOG: Eastern Cooperative Oncology Group; PCI: prophylactic cranial irradiation; LDH: lactate dehydrogenase.

Table 3. Univariate and multivariate cox regression analysis for overall survival

Characteristics	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
Age groups (years)				
<65	Reference			
≥65	0.99 (0.69-1.43)	0.97		
Gender				
Female	Reference			
Male	1.67 (0.88-3.17)	0.11		
Comorbidity				
Yes	1.17 (0.78-1.74)	0.44		
No	Reference			
ECOG				
0-1	Reference			
≥2	1.38 (0.91-2.09)	0.13		
Liver metastasis				
Yes	3.1 (2.03-4.78)	**<0.001**	1.93 (1.20-3.11)	**0.007**
No	Reference			
Adrenal metastasis				
Yes	0.90 (0.57-1.43)	0.67		
No	Reference			
Brain metastasis				
Yes	3.80 (2.07-6.99)	**<0.001**	2.84 (1.48-5.48)	**0.002**
No	Reference			
Bone metastasis				
Yes	1.35 (0.93-1.94)	0.11		
No	Reference			
Immunotherapy				
Yes	0.81 (0.35-1.83)	0.61		
No	Reference			
PCI				
Yes	0.34 (0.19-0.58)	**<0.001**	0.41 (0.23-0.73)	**0.002**
No	Reference			
Hemoglobin				
Low	0.93 (0.64-1.36)	0.72		
Normal	Reference			
Na				
Low	1.19 (0.78-1.84)	0.42		
Normal	Reference			
LDH				
Normal	Reference			
High	2.03 (1.31-3.14)	**0.001**	0.63 (0.28-1.42)	0.27
Albumin				
Low	2.47 (1.55-3.92)	**<0.001**	1.66 (0.99-2.79)	0.056
Normal	Reference			
LAR				
<5.71	Reference			
≥5.71	3.36 (1.38-8.14)	**<0.001**	3.2 (1.31-7.81)	**0.011**

LAR: lactate dehydrogenase-to-albumin ratio; ECOG: Eastern Cooperative Oncology Group; PCI: prophylactic cranial irradiation; LDH: lactate dehydrogenase.

(HR: 2.03; p=0.001), low albumin (HR: 2.47; p<0.001), and an absence of PCI (HR: 0.34; p<0.001) were also significant predictors for OS (Table 3). No significant association was found between sodium levels and either OS or PFS in both univariate and multivariate analyses (p=0.42 and p=0.20, respectively).

A high LAR remained an independent prognostic factor for OS (HR: 3.36; 95% CI: 1.38–8.14; p=0.007), along with liver and brain metastases, low albumin, and a lack of PCI in multivariate Cox analysis (Table 3). It's worth mentioning that the LAR did not reach statistical significance in the adjusted model (p=0.135), but liver and adrenal metastases and an absence of PCI remained significant for PFS (Table 2).

DISCUSSION

SCLC is a highly invasive malignancy with rapid growth, early spread and high recurrence rates. It represents approximately 13–15% of all lung cancers and is usually diagnosed at an extended stage of disease [17]. ED-SCLC treatment has recently been improved with the addition of first-line immune checkpoint inhibitors (ICIs) [18]. Despite improved treatment options, most patients still face a poor prognosis [19], and this makes it important to find simple, affordable biomarkers that can guide treatment decisions. Several inflammatory and nutritional biomarkers, such as the prognostic nutritional index and systemic immune–inflammation, have shown prognostic significance in SCLC treated with both chemotherapy and immunotherapy [6,13].

LDH levels often increase due to changes in tumor metabolism. Even when oxygen is present, cancer cells prefer glycolysis to produce energy which is known as the Warburg effect. This metabolic shift promotes lactate production and supports rapid tumor growth. LDH elevation may also reflect tumor-related necrosis and hypoxia. Therefore, serum LDH can act as an indirect indicator of tumor burden and aggressive biological behavior [20]. It has been associated with tumor burden, hypoxia, and poor outcomes in various malignancies, including SCLC [21]. In addition, Zhou et al. found a 1.92-fold increased risk of death in patients with abnormally elevated baseline LDH values compared to patients with normal LDH values [5]. Also, elevated LDH levels have been consistently associated with poor prognosis in SCLC patients in previous studies [22,23]. These findings align with our results and reinforce the clinical relevance of LDH as a readily accessible biomarker in the management of extensive-stage SCLC.

Albumin is an important biomarker that reflects systemic inflammation, nutritional status, and overall physiological reserve [24-26]. Low albumin levels, often reflecting malnutrition, have been associated with unfavorable outcomes in individuals with cancer [27]. Many studies have linked hypoalbuminemia to adverse outcomes in many conditions, including cardiovascular, surgical, and infectious diseases [28-31]. Similar to these studies, we observed that lower albumin levels were clearly associated with shorter OS in ED-SCLC [32].

As mentioned above, LAR combines tumor-related (LDH) and host-related (albumin) features in a single metric. This integration may better capture the interplay between tumor aggressiveness and the patient's systemic condition. In our study, LAR remained independently associated with survival, even after adjusting for LDH and albumin separately. These results suggest that LAR may offer more comprehensive prognostic value than either marker alone. Our results are also compatible with previous studies in other malignancies such as hepatocellular carcinoma [7], Hodgkin's lymphoma [33], nasopharyngeal carcinoma [34], and esophageal squamous cell carcinoma [35]. These findings underline the broad applicability of the LAR as a prognostic indicator.

Although CRP values were not available in our study cohort, inflammation-based prognostic tools such as the Glasgow Prognostic Score (GPS) may still be relevant. GPS incorporates serum CRP and albumin levels and reflects both nutritional and inflammatory status. Previous studies have shown that GPS has prognostic value in patients with extensive-stage small-cell lung cancer [36]. Including GPS or similar CRP-based indices alongside LAR in future studies could help provide a more comprehensive evaluation of systemic inflammation and survival outcomes.

In order to assess the robustness of the LAR cut-off value, we performed a bootstrapping analysis with 1000 iterations. The consistent AUC values

observed across samples indicate strong internal validity. Nonetheless, external validation remains essential to confirm generalizability.

The LAR cut-off value varies among studies, and values of, for example, 5.5 [7], 4.04 [37] and 3.8 [14] have been suggested. Differences in tumor type, sample size, geographical region and laboratory equipment may explain this variation. In our cohort, an LAR cut-off of 5.71 effectively distinguished patients with significantly different survival outcomes. While the LAR was independently associated with OS, it did not reach statistical significance for PFS (p=0.13). This may be due to the modest sample size or potential confounding factors. Therefore, conclusions regarding the predictive role of LAR for PFS should be interpreted cautiously and confirmed in larger cohorts.

LDH and albumin values, which showed a significant difference in survival in univariate analysis (p=0.014 and 0.004 for PFS; p=0.001 and <0.001 for OS, respectively), did not show this difference in multivariate analysis (p=0.55 and 0.22 for PFS; p=0.27 and 0.056 for OS, respectively). For this reason, we assessed multicollinearity using VIF analysis. Clearly, LAR and LDH showed very high VIF values (89.0 and 85.4, respectively) which reflecting strong collinearity due to the mathematical relationship between the variables. This likely explains why LDH lost statistical significance in multivariate analysis when LAR was included. Albumin showed a moderate VIF (2.98), suggesting acceptable collinearity. Eventually, these results support the idea that LAR captures the combined prognostic effect of LDH and albumin more effectively than when they are analyzed separately.

Multivariate Cox analysis further identified liver and brain metastases, low albumin, and an absence of PCI as independent predictors of OS. A high LAR remained significant after adjusting for these variables (HR: 3.36; 95% CI: 1.38–8.14; p=0.007). For PFS, liver and adrenal metastases were significantly associated with worse outcomes. These results emphasize the negative prognostic impact of visceral metastases [38,39]. Furthermore, an absence of PCI emerged as an independent adverse prognostic factor for both OS and PFS, in our study. This finding correlates with previous research indicating that PCI can reduce the occurrence of brain metastases in ED-SCLC while also enhancing disease management. According to recent meta-analyses PCI had significant reductions in brain metastasis risk and prolonged PFS, even when compared to MRI-based surveillance strategies [40,41]. Moreover, Chen et al. and Yılmaz et al. reported improved clinical outcomes in patients who received PCI following a good response to initial therapy [42,43].

In our cohort, hyponatremia was not significantly associated with survival outcomes. Although hyponatremia has been reported as a poor prognostic factor in SCLC in previous studies [44-46], its lack of significance in our analysis may be related to the limited number of patients with low sodium levels.

This study has several limitations. First, it is a retrospective, single-center analysis, which may affect the generalizability of the results and may introduce institutional bias related to patient management and data recording practices. Second, we excluded patients without baseline LDH or albumin values and those not receiving systemic therapy to ensure data completeness and consistency in prognostic analysis. We acknowledge that this may have introduced selection bias, possibly favoring patients with better overall performance status and more complete records. Third, although a minority of patients (n=9) received immunotherapy, this group was too small for subgroup analysis, and it had limited the applicability of our findings to current treatment standards. Additionally, the optimal LAR cut-off value may vary depending on population characteristics, laboratory methods, and therapeutic context. Therefore, albeit bootstrap analysis supported the internal consistency of our findings, our results require validation in larger, prospective cohorts.

In conclusion, pretreatment LAR can be used in clinical practice as an accessible, simple and promising prognostic tool in ED-SCLC and can reflect tumor burden and systemic status. Since LDH and albumin levels are routinely used in our daily oncology practice, clinicians can easily calculate LAR at the time of diagnosis. High LAR values may help to identify patients with a poor prognosis. These patients might benefit from closer follow-up, early supportive care, or more intensive treatment when appropriate. However, we should

also know that further prospective studies are needed to confirm its clinical usefulness, especially in the immunotherapy era.

Author contribution

Study conception and design: FY, SY, ÖDT, HÇY, DCG, HT, ZA and ME; data collection: FY, SY, ÖDT, HÇY, DCG, HT, ZA and ME; analysis and interpretation of results: FY, SY, HÇY, HT and ME; draft manuscript preparation: FY, SY, ÖDT, HÇY, DCG, HT, ZA and ME. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Ethics Committee (Protocol no: GO 22/1119, Date: 01.11.2022).

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Conflict of interest

The authors declare that there is no conflict of interest.

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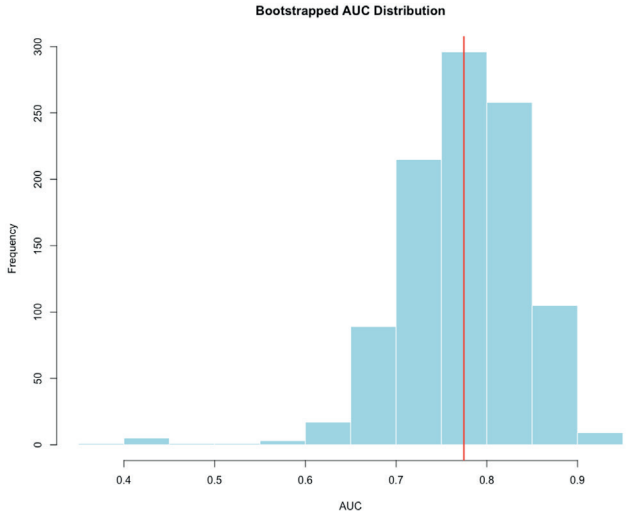

Supplementary Figure 1. Bootstrapped distribution of AUC values for the LAR cut-off.

The histogram illustrates the distribution of AUC values obtained from 1000 bootstrap iterations. The red vertical line indicates the mean AUC. This analysis was conducted to assess the internal validity and robustness of the LAR cut-off in predicting overall survival. AUC: area under curve; LAR: lactate dehydrogenase-albumin ratio.