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Prognostic significance of albumin-to-alkaline phosphatase ratio for overall survival in metastatic lung adenocarcinoma patients

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ABSTRACT

Aims: This study aims to determine the prognostic significance of the pretreatment albumin/alkaline phosphatase ratio (AAPR) for overall survival in patients diagnosed with metastatic lung adenocarcinoma (MLA).

Methods: The medical records of 459 patients diagnosed with MLA between 2010 and 2021 were retrospectively reviewed. The AAPR was calculated using blood test results obtained at the time of diagnosis.

Results: The study identified the optimal threshold value for AAPR as 0.314. Patients with a high AAPR (AAPR>0.314) demonstrated significantly longer median survival and overall survival time compared to those with a low AAPR (AAPR ≤ 0.314) (p<0.001). Specifically, the median survival time for the low AAPR group was 2.13±0.29 (95% CI: 1.56-2.70) months, while the high AAPR group had a median survival time of 4.1±0.59 (95% CI: 2.90-5.23) months (p<0.001). The 1-year survival rates were 27.3% and 5.3% for the high and low AAPR groups, respectively (p<0.001). Additionally, an AAPR ≤ 0.314 increased the risk of death by 1.96 times at 1 year.

Conclusion: The AAPR was significantly reduced in MLA patients, making it a significant biomarker for forecasting prognosis and directing treatment options for these patients.

Keywords: Metastatic lung adenocarcinoma, albumin-to-alkaline phosphatase ratio, prognostic factor, survival

INTRODUCTION

Adenocarcinoma (ADC) accounts for approximately 40% of lung tumours and is often diagnosed at a late metastatic stage.[1] Survival rates for lung cancer are significantly affected by the presence of distant organ metastases. Detecting metastases at diagnosis remains a challenge and a reliable biomarker for this purpose has not yet been established. The process of carcinogenesis and tumour progression often results in abnormal serum enzyme synthesis before the clinical manifestation of the disease.[2] It is worth noting that inflammation and nutritional status are significant factors that influence the onset, development, treatment response, and clinical outcomes in cancer patients, as indicated by numerous recent studies.[3,4]

Assessing nutritional status often involves utilizing albumin (ALB), which also serves as a crucial indicator of the inflammatory response. Disease progression, malnutrition, and inflammation may hinder the synthesis of ALB, leading to a notable reduction in ALB levels.[5] Such a reduction in ALB levels has been associated with reduced survival and increased mortality in cancer patients.[6,7] Due to its association, albumin level has also been included in various scoring systems predicting the survival of patients with lung cancer.[8,9] Furthermore, elevated serum levels of alkaline phosphatase (ALP) are detected in liver, kidney, and bone diseases. Numerous studies have shown that elevated serum ALP levels are associated with a poorer prognosis in cancer patients.[10,11] The ratio of serum ALB to ALP level, known as the ALB/ALP ratio (AAPR), has gained popularity as a possible indicator of inflammatory and nutritional status in cancer patients. In 2015, Anthony et al.[12] reported on the prognostic value of AAPR and identified it as a significant predictor in hepatocellular carcinoma (HCC). Recent evidence further corroborates the observation that low pretreatment AAPR is linked to unfavorable outcomes in various malignancies, including non-small cell lung cancer.[13-15] A 20-year meta-analysis of 5951 patients with 10 different types of cancer in China found that those with a higher AAPR had a better OS than those with a

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lower AAPR. The integration of the AAPR-TNM system with the AAPR produced better results than the current TNM system.[16]

However, the prognostic significance of AAPR for survival in metastatic lung adenocarcinoma has not been extensively investigated. Therefore, this study aims to evaluate the impact of AAPR on the prognosis of patients with metastatic adenocarcinoma.

METHODS

The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.04.2023, Decision No: 2012-KAEK-15/2699). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was designed retrospectively, no written informed consent form was obtained from patients.

Patients

The study included MLA patients diagnosed and followed-up at Health Sciences University Ankara Atatürk Sanatorium Training and Research Hospital between January 2010 and January 2021.

The inclusion criteria were as follows: (I) Patients over 18 years old with histologically or cytologically confirmed metastatic lung adenocarcinoma diagnosed in the hospital's pulmonology departments, (II) patients with sufficient imaging data (such as computed tomography, magnetic resonance imaging, and PET-CT) for tumor staging, (III) patients who had not received any prior antitumor treatment (including radiotherapy, chemotherapy, immunotherapy, and targeted therapy), and (IV) patients with routine complete blood count and blood biochemistry results.

Exclusion criteria from the study were as follows: (I) Patients younger than 18 years old, (II) patients with non-adenocarcinoma non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC), (III) patients with secondary cancer, (IV) patients with concomitant hepatitis, liver cirrhosis, cholecystitis, nephrotic syndrome, inflammatory diseases, and lymphoproliferative diseases, (V) patients with concomitant infections, (VI) patients with known bone fractures and bone disease, and (VII) patients whose information could not be accessed in the hospital records and computer database.

The study retrospectively included 459 patients with pathologically diagnosed adenocarcinoma and distant metastases. Overall survival was determined by assessing disease-free survival and time to death. AAPR at the time of diagnosis were calculated by obtaining the mean value. Patients were then categorized into low and high AAPR groups based on this value, and statistical analyses were performed to compare the two groups.

Clinical Data

The clinical data collected for this study included age, gender, smoking history, sites of metastasis, and pre-treatment AAPR values. The pretreatment AAPR was calculated as follows: AAPR=Serum ALB level (g/L) / Serum ALP level (IU/L).

Observation Indicators

Median overall survival (OS) was defined as the time interval between the initiation of therapy and the last follow-up and/or death.

Tumor Staging

Tumor staging was conducted based on the eighth edition of the staging criteria published by the International Association for the Study of Lung Cancer.[17]

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 software (Inc., Chicago, IL). The normality of the data was assessed using the Kolmogorov-Smirnov Test. Descriptive statistics were presented as median and min-max for normally distributed data. The relationship between AAPR level and categorical or continuous variables was analyzed using the chi-square test or Mann-Whitney U test, respectively. Prognosis based on overall survival (OS) was analyzed using Kaplan-Meier and log-rank tests. Univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors. Hazard ratios (HRs) along with bilateral p-values and corresponding 95% confidence intervals (CIs) were reported. All variables with a p-value <0.05 in the univariate analysis were included in the multivariate model. A p-value of <0.05 was considered statistically significant.

RESULTS

In our study, we included 459 patients who had pathological diagnoses of adenocarcinoma and distant metastasis (MLA), along with their pretreatment values. 80.2% (n=368) were male, 9.8% (n=91) were female, and the median age was 64 years (min 28-max 89). 353 (76.9%) patients had a smoking history. In terms of frequency, bone (59.9%, n=275) was the most commonly detected site of metastases, followed by the opposite lung (37.9%, n=174), pleura (36.4%, n=167), pleural effusion (29.9%, n=137), adrenal (28.8%, n=132), brain (18.8%, n=86), and liver metastases (15.3%, n=70).Spleen (n=11), skin (n=4), and vocal cord (n=1) metastases were classified as metastases in other sites.

The cut-off value for AALP was determined by analyzing ROC curves and the Youden index (Youden index=sensitivity + specificity-1). Among 459 MLA patients, an AALP value of 0.314 corresponded to the maximum Youden index value. Therefore, 0.314 was adopted as the proposed threshold for AALP. Of the patients, 308 had AALP >0.314, and 151 had AALP≤0.314.

Since ALP values were found to be higher in patients with liver and bone metastases, this particular group was analyzed separately. The analysis included a total of 283 patients with liver, bone, or both metastases, out of which 62 patients had both liver and bone metastases. The optimal subgroup cut-off for AAPR was found to be 0.335 when a separate cut-off was established for this group (with a sensitivity of 93.3%, specificity of 48.7%, AUC: 0.722; 95% CI 0.651-0.794; p<0.001). Both ROC curves are shown in Figure 1.

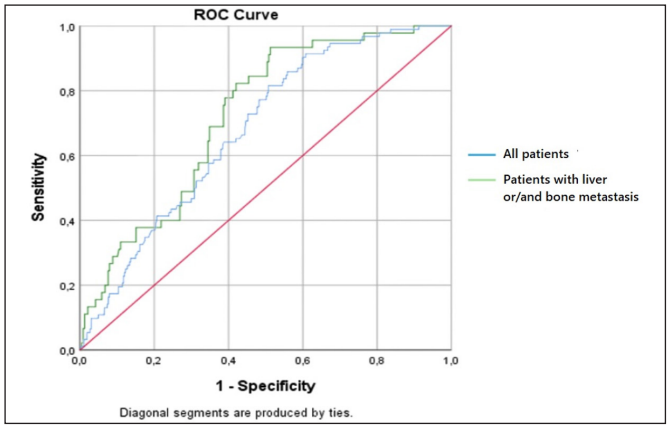

Figure 1. ROC analysis curves to predict 1-year survival in all ADC patients and only those withbone/kc mets.

Results showed that patients with a high AAPR greater than 0.314 had significantly longer median survival and overall survival than patients with a low AAPR of 0.314 or less (p<0.001). Specifically, median survival was 2.13±0.29 (95% CI: 1.56-2.70) months for the low AAPR group and 4.1±0.59 (95% CI: 2.90-5.23) months for the high AAPR group (p<0.001). The one-year survival rates were 27.3% for the high AAPR group and 5.3% for the low AAPR group (p<0.001; Figure 2). An AAPR of ≤0.314 increased the risk of death by 1.96 times within one year.

According to ROC analysis anticipating 1-year mortality, 283 patients diagnosed with ADC and liver and/or bone metastases were grouped into high (AALP >0.335; n=164) and low (AALP≤0.335; n=119) categories using an optimal cut-off value of 0.335. The low AALP group had a median survival of 1.97±3.67 (95% CI 1.47-2.53) months, which was statistically significantly lower (p<0.001) compared to the high AALP group of 3.48±10.31 (95% CI 2.0-4.97) months. In this cohort, the 1-year survival rate was 2.5% and 25.6% in the lower and higher categories, respectively (p<0.001).

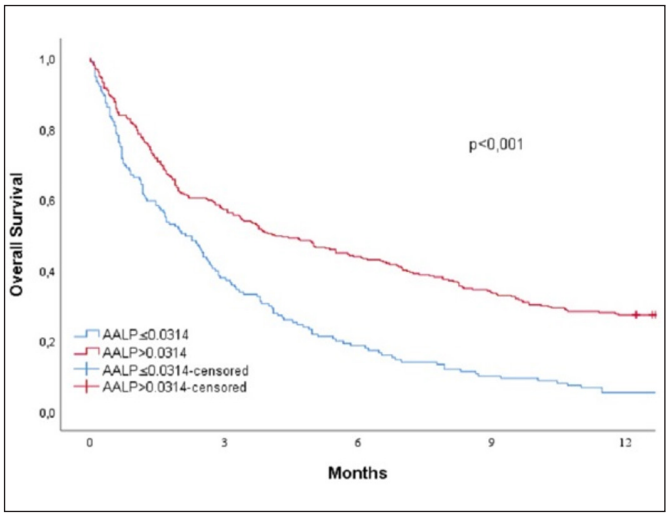

Figure 2. Kaplan-Meier curve illustrating the relationship between AALP and overall survival in patients diagnosed with ADC. The p-value was calculated using the log-rank test.

Table 1. The relationship between clinical characteristics and distant metastasis regions with AALP

		AALP≤ 0,314 (n=151)	AALP> 0,314 (n=308)	p
Gender	Male Female	124 (33.7%) 27 (29.7%)	244 (66.3%) 64 (70.3%)	0.464
Smoking Status	No Yes	30 (28.3%) 121 (34.3%)	76 (71.7%) 232 (65.7%)	0.251
Contralateral Lung	No Yes	91 (31.9%) 60 (34.48%)	194 (68.1%) 114 (65.52%)	0.572
Bone	No Yes	46 (25%) 105 (38.18%)	138 (75%) 170 (61.82%)	0.003
Liver	No Yes	115 (29.56%) 36 (51.43%)	274 (70.44%) 34 (48.57%)	<0.001
Brain	No Yes	121 (32.44%) 30 (34.88%)	252 (67.56%) 56 (65.11%)	0.664
Pleura	No Yes	97 (33.22%) 54 (32.34%)	195 (66.78%) 113 (67.66%)	0.846
Malignant pleural effusion	No Yes	103 (31.99%) 48 (35.04%)	219 (68.01%) 89 (64.96%)	0.525
Adrenal	No Yes	99 (30.28%) 52 (39.4%)	228 (69.72 80 (60.6%)	0.06
Other	No Yes	111 (29.9%) 40 (45.5%)	260 (70.1%) 48 (54.5%)	0.005

Mann Whitney-U test, AALP: Albumin/Alkalen fosfataz

ALB and ALP levels were not included in the multivariate model in the univariate and multivariate Cox regression analyses predicting 1-year survival, as they influenced AAPR. However, in the univariable analysis, ALB and ALP levels were also identified as significant factors affecting one-year survival (p<0.001). According to the results of the multivariate analysis, an AAPR of 0.314 or less, male gender, smoking history, bone metastases and cranial metastases all had a significant effect on survival at one year. (Table 2).

Table 2. Univariate and multivariate analysis results for 1-year survival in ADC patients.

	Univariate Analysis Results			Multivariate Analysis Results		
	HR	CI	p	HR	CI	p
AALP (≤0,314, >0,314)	0.672	1.58 - 2.42	<0.001	0.584	1.44-2.23	<0.001
Age	0.009	0.99-1.02	0.78	-	-	-
Gender(male, female)	0.476	1.22-2.12	0.001	0.327	1.08-1.91	0.045
Smoking History(no, yes)	0.477	1.24-2.09	<0.001	0.301	1.004-1.82	0.047
Contralateral metastasis	0.192	0.98-1.49	0.072	-	-	-
Bone metastasis	0.402	1.21-1.85	<0.001	0.308	1.087-1.70	0.007
Liver metastasis	0.426	1.16-2.01	0.002	0.099	0.82-1.48	0.517
Cranial metastasis	0.344	1.09-1.82	0.008	0.285	1.03-1.72	0.032
Pleural metastasis	0.095	0.89-1.35	0.378	-	-	-
Malignant pleural effusion	0.113	0.89-1.39	0.317	-	-	-
Adrenal metastasis	0.267	1.05-1.62	0.018	0.101	0.88-1.39	0.39
Metastasis in other regions	0.441	1.21-1.99	0.001	0.239	0.97-1.67	0.086

HR: Hazard ratio, CI: confidence interval, AALP: Albumin/alkalen fosfataz.

DISCUSSION

Serum levels of ALB and ALP are two key liver function test parameters that can reflect biochemical and pathological changes in a number of medical conditions and are used as a cost-effective and readily available laboratory test. However, the use of the AAPR for prognosis in malignant disease is limited. Compared to traditionally used biomarkers such as tumor stage, the AAPR appeared to provide additional information, including tumor burden, inflammation, and nutritional status.[18]

This may clarify the prognostic influence of AAPR across different cancers, different stages of the same tumour, and different treatments for cancer patients. It is therefore possible that AAPR could be an independent indicator for many different types of cancer. In NSCLC, it is critical to perform the necessary assessments in newly diagnosed patients to select the most appropriate treatment plan that will improve survival. In planning the optimal treatment for a patient with metastatic NSCLC, patient and tumour characteristics are critical. This is particularly true for adenocarcinoma, where targeted therapies are being developed and prognostic markers are needed to guide treatment decisions.

In the present study, it has been shown that AALPR may serve as a promising prognostic indicator in clinical applications and that a decreased level of AALPR is associated with a poor OS in patients with MLA.

In a 20-year meta-analysis of a total of 5951 patients with 10 different types of cancer in China, cut-off values in the studies ranged from 0.35 to 0.68. Patients with higher AAPR had better OS when divided into two categories according to the median value of 0.44 (HR: 0,50; %95 GA: 0,43-0,58; p <0,001). In a subgroup analysis by tumour type, a higher AAPR was associated with a better OS in NSCLC (HR: 0.45; 95% CI: 0.26-0.78; p<0.001), SCLC (HR: 0.60; 95% CI: 0.44-0.82; p<0. 001), HCC (HR: 0.49; 95% CI: 0.34-0.69; p<0.001), pancreatic ductal adenocarcinoma (PDC) (HR: 0.47; 95% CI: 0.31-0.71; p<0.001) and nasopharyngeal carcinoma (NPC) (HR: 0.42; 95% CI: 0.21-0.85; p=0.016). In a subgroup analysis by tumour type in this meta-analysis, a higher AAPR was associated with a better OS in NSCLC (HR: 0.45; 95% CI: 0.26-0.78; p<0.001), SCLC (HR: 0.60; 95% CI: 0.44-0. 82; p<0.001), HCC (HR: 0.49; 95% CI: 0.34-0.69; p<0.001), PDC (HR: 0.47; 95% CI: 0.31-0.71; p<0.001) and NPC (HR: 0.42; 95% CI: 0.21-0.85; p=0.016). They showed that pre-treatment AAPR can be used as a prognostic indicator in NSCLCs, SCLCs, HCCs, PDACs, and NPCs. They have also shown that correlating the AAPR-TNM system with the AAPR gives better results than the current TNM system.[16]

Li D et al, in a study of 290 metastatic NSCLC patients, of whom 215 (74.1%) had adenocarcinoma, found that patients with AAPR >0.36 had longer survival than those with AAPR ≤0.36 (13 vs 7 months, p<0.001). Patients without liver/bone metastases had higher AAPR and lower ALP than those with liver/bone metastases (0.47 vs. 0.40, p<0.001; 80.17 vs. 95.40 U/L, p<0.001, respectively). LDH and ALB levels were not significantly different in these two groups (both p>0.05).[18]

Our study group was comprised solely of patients with adenocarcinoma within the NSCLC category. All patients were metastatic and had not undergone any previous treatment. In our study, similar to the meta-analysis by Tian et al.[16] and the research by Li et al.[18] the high AALP group had a significantly longer median survival time than the low AALP group, reflecting a positive disease prognosisAgain, as in the study by Li et al.[18] we looked at 283 patients with ADC and bone metastases separately and found that the median survival of the high AALP group (>0.335; n=164) was significantly higher than that of the low AALP group. The 1-year survival rates

in the low and high AALP groups were 2.5% and 25.6%, respectively.

In their study, Zhou et al.[19] examined 224 patients with advanced NSCLC and established the threshold value for AAPR as 0.35. Kaplan-Meier analysis revealed a median OS of 9.73 months (95% CI=8.6-12.33) for AAPR <0.35 and 13.7 months (95% CI=11.43-16.37) for AAPR ≥0.35 (log-rank p <0.0001). The Cox regression analysis further demonstrated that AAPR <0.35 increased the risk of death (HR=1.65, 95% CI=1.11-2.46). They also found that the risk of dying was 71% higher when comparing those with bone metastases to those without.

Furthermore, another study conducted by Zhou et al.[20] focused on 808 patients with advanced NSCLC. They classified the patients into three groups based on their AAPR levels: low (AAPR<0.34, n=266), moderate (AAPR=0.34-0.47, n=259), and high (AAPR>0.47, n=283). The results showed that moderate and high AAPR levels were associated with better outcomes, with hazard ratios (HR) of 0.77 (95% CI=0.58-1.03) and 0.59 (95% CI=0.45-0.78), respectively. The median OS for low, moderate, and high AAPR groups was 9.3, 11.8, and 16.9 months, respectively (p<0.001). Similar results were seen in subgroup analyses in almost all subgroups.

A study of AAPR in patients with advanced NSCLC was conducted by Liu et al.[21] their results showed a noteworthy decrease in AAPR levels. Patients with elevated AAPR had a median progression-free survival (PFS) and OS of 17 months and 23 months, respectively, whilst those with diminished AAPR had a median PFS and OS of 8 months and 13 months, respectively. The area under the curve (AUC) of AAPR for both PFS and OS was higher than that of ALB and ALP (p<0.05). Low AAPR was associated with significantly shorter PFS and OS compared to high AAPR, with a median PFS of 8 months vs. 25 months and a median OS of 12 months vs. 36 months.

In our study, similar to the results of the aforementioned articles, we found that the high AAPR group (AAPR>0.314) had a significantly longer median survival and overall survival than the low AAPR group (AAPR ≤ 0.314), indicating a better disease prognosis. In the present sturdy, we also found that an AAPR ≤ 0.314 was associated with a 1.96-fold increase in the risk of death within one year.

CONCLUSION

Our study represents the initial evaluation of AAPR in patients diagnosed with the adenocarcinoma subtype, in contrast to other studies in the relevant literature that concentrate on advanced-stage NSCLC.

The findings demonstrate a considerable reduction in AAPR levels amongst patients diagnosed with metastatic lung adenocarcinoma (MLA) and therefore, indicate its utility as a valuable biomarker that can aid in predicting prognosis as well as guiding treatment decisions among these patients.

However, it is important to note that the study has some limitations. The study was conducted retrospectively at a single centre. In order to establish the independent prognostic potential of the AAPR value and to gain a deeper understanding of its relationship with median survival, prospective studies are needed which encompass all factors that could influence the AAPR value.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.04.2023, Decision No: 2012-KAEK-15/2699).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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