

Albumin-to-alkaline phosphatase ratio at diagnosis predicts survival in patients with metastatic non-small-cell lung cancer

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Background: Previous studies have reported that the albumin-to-alkaline phosphatase ratio (AAPR), a novel blood biomarker-based index, is associated with clinical outcome in several cancers. However, data relating to lung cancer are rare. This study was performed to clarify the clinical significance of AAPR in patients with metastatic non-small-cell lung cancer (NSCLC).

Methods: In total, 290 stage IV NSCLC patients were enrolled in this retrospective study. Associations between serum enzyme levels and clinical characteristics were analyzed using the Mann–Whitney U-test or chi-squared test. Kaplan–Meier survival analysis and Cox's proportional hazard regression model were adopted to assess the prognostic value of AAPR for overall survival (OS).

Results: The optimal cut-off points for AAPR and lactate dehydrogenase (LDH) were 0.36 and 265.5 U/L, respectively. Patients with AAPR ≤ 0.36 had apparently longer survival than those with AAPR > 0.36 (13 vs 7 months, $P < 0.001$). Furthermore, AAPR was an independent predictor of OS in metastatic NSCLC in multivariate analysis (HR=0.657, 95% CI=0.504–0.856, $P < 0.01$). The prognostic impact of LDH for survival of NSCLC populations was also validated in this study (HR=1.462, 95% CI=1.070–1.999, $P < 0.05$).

Conclusion: Elevated AAPR can be an independent favorable prognostic indicator in metastatic NSCLC.

Keywords: AAPR, LDH, NSCLC, prognosis

Introduction

Lung cancer remains one of the most prevalent malignancies and the leading cause of cancer-related death worldwide.¹ Approximately 85% of primary lung cancers are non-small cell lung cancer (NSCLC), and more than half are metastatic NSCLC at the time of initial diagnosis, owing to a lack of typical symptoms in early disease.² Patients with metastatic NSCLC can be treated with chemotherapy, radiotherapy, or both. Thanks to advances in treatment, they can benefit from targeted therapy as well.³ However, the prognosis for metastatic NSCLC is extremely poor, with a 5-year survival rate of 3.9%.² Although the TNM classification system has the most marked discriminatory capacity for survival of cancers, it has reached its limits in metastatic NSCLC patients. Therefore, finding novel and efficient biomarkers to help predict clinical outcomes and guide clinical decision-making for metastatic NSCLC is of great importance.

Carcinogenesis and tumor progression always lead to abnormal serum enzyme synthesis, sometimes even before disease is clinically detectable.⁴ These enzymes

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can serve as useful indicators for tumor detection and monitoring. Alkaline phosphatase (ALP) is a hydrolase enzyme which is responsible for removing phosphate groups. Elevated serum ALP levels can be seen in liver, kidney, and bone diseases.⁵ ALP has been found to be associated with advanced cancer status.^{6,7} Lactate dehydrogenase (LDH) is another serum enzyme, which mainly participates in the conversion of pyruvate to lactate and is related to tumor metabolism. Numerous studies have found that LDH levels are elevated in various types of cancer, including NSCLC.^{8–11}

Albumin (ALB), one of the most commonly used methods to assess nutritional status, usually shows no or only slight changes in the early stages of cancer. But as the disease progresses, malnutrition and inflammation lead to ALB synthesis being suppressed and degradation increasing, which result in ALB levels dropping significantly.¹² The decreased ALB in cancer patients can result in shorter survival and increased cancer-related mortality.^{13,14} Besides ALB alone, several ALB-based markers, such as the Glasgow Prognostic Score,^{15,16} Advanced Lung Cancer Inflammation Index,¹⁷ and Prognostic Nutritional Index,^{18,19} have also been shown to correlate with survival in various cancers.

In the present study, we merge the parameters ALB and ALP to form a novel index called the albumin-to-alkaline phosphatase ratio (AAPR). The AAPR has been revealed as a prognostic indicator for hepatocellular carcinoma²⁰ and nasopharyngeal carcinoma.²¹ However, whether AAPR can predict survival in NSCLC patients has not yet been investigated. Thus, we performed this single-center retrospective study to explore for the first time the prognostic impact of AAPR and its relationship with clinical characteristics in patients with metastatic NSCLC. The correlation between LDH and prognosis of metastatic NSCLC was also demonstrated.

Materials and methods

Participants

We retrospectively reviewed newly diagnosed stage IV NSCLC patients in West China Hospital from March 2007 to December 2013. The inclusion criteria included the following: 1) pathologically confirmed NSCLC; 2) clinically diagnosed metastasis; 3) serum ALB and ALP measured at diagnosis; and 4) follow-up data were available. Patients with a history of a second primary malignancy, detectable infections, and known liver or renal or bone diseases were

excluded from the study. In total, 290 NSCLC patients who met the inclusion criteria were eventually enrolled in the study. The West China Hospital Research Ethics Committee approved the study and signed informed consent from patients was waived because of the retrospective nature of the analysis. All patient data were treated with confidentiality, in accordance with the Declaration of Helsinki.

Clinical and follow-up data

We collected baseline and clinical characteristics of patients from the hospital medical system, including age, gender, smoking history, histology type, metastatic characteristics, and medication. Patients who had smoked fewer than 100 cigarettes in their lifetime were defined as non-smokers. Histology type was identified based on the WHO criteria established in 2004.²² Tumor stage was defined according to the seventh edition of the TNM classification.²³ Furthermore, pretreatment laboratory data covering ALB, ALP, and LDH were extracted. The AAPR was calculated by dividing the serum ALB by the serum ALP level.

The primary outcome of the study was patients dead of lung cancer. Time from diagnosis to death was measured as overall survival (OS). We obtained survival information by interviewing patients on the telephone or by checking medical records. The last follow-up was in October 2017.

Statistical analysis

The optimal cut-off values for the AAPR and LDH levels were determined using a biostatistical tool called Cutoff Finder (<http://molpath.charite.de/cutoff/>).²⁴ Statistical analyses were performed with SPSS software (version 22; IBM Corp., Armonk, NY, USA). Continuous variables were presented as medians and ranges, and later were transformed into dichotomous variables presented as frequencies and percentages. Comparison of clinicopathological characteristics between different groups was conducted by the Mann–Whitney U-test for continuous variables and chi-squared test for dichotomous variables. Associations between prognostic factors and OS were assessed by the Kaplan–Meier method and tested by the log-rank test, while Kaplan–Meier survival curves were drafted in Prism 5 (version 5.01; GraphPad Software, La Jolla, CA, USA). For univariate and multivariate survival analyses, Cox's proportional hazard regression model was adopted. Candidate variables with a *P*-value less than 0.2 in univariate analysis were included in the multivariate model. A two-sided *P*-value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of patients

Overall, 290 patients were involved in the study and their clinical characteristics are summarized in [Table 1](#). Among these, 170 (60.7%) were males, 128 (44.1%) were aged older than 60 years (mean: 55 years; range: 25–90 years), and 139 (47.9%) had a current/past history of smoking. According to the histology, 215 out of 290 patients (74.1%) had an adenocarcinoma, while 60 patients (20.7%) had a squamous cell carcinoma and 15 (5.2%) had other types. At the time of diagnosis, the majority of the patients (242; 83.4%) had developed two or fewer metastasis sites and nearly half of the patients (140; 48.3%) had liver/bone

metastasis. In addition, more than half of the patients (196; 67.6%) had received some form of systemic therapy, whereas the remaining patients (94; 32.4%) had not.

Using Cutoff Finder, an R-software engineered web-based system, we identified that the optimal cut-off values for AAPR and LDH were 0.36 and 265.5 U/L, respectively ([Figure 1](#)). Thus, 201 patients (69.3%) with AAPR >0.36 were categorized into the high AAPR group and the other 89 patients (30.7%) with AAPR ≤0.36 into the low AAPR group. When dividing the patients by level of LDH, 234 patients (80.7%) had LDH >265.5 U/L and 56 (19.3%) had LDH ≤265.5 U/L.

The distribution of clinical characteristics between the AAPR ≤0.36 and AAPR >0.36 groups is depicted in [Table 1](#).

Table 1 Distribution of baseline characteristics of 290 metastatic NSCLC patients according to AAPR level

Characteristics	Total, n (%)	AAPR ≤0.36, n (%)	AAPR >0.36, n (%)	P-value
Number of patients	290	89 (30.7)	201 (69.3)	
Age (years)				0.898
≤60	162 (55.9)	49 (55.1)	113 (56.2)	
>60	128 (44.1)	40 (44.9)	88 (43.8)	
Gender				0.696
Male	176 (60.7)	56 (62.9)	120 (59.7)	
Female	114 (39.3)	33 (37.1)	81 (40.3)	
Smoking status				1.000
Current/past	139 (47.9)	43 (48.3)	96 (47.8)	
Never	151 (52.1)	46 (51.7)	105 (52.2)	
Histology				0.502
SCC	60 (20.7)	15 (16.9)	45 (22.4)	
ADC	215 (74.1)	70 (78.7)	145 (72.1)	
Others	15 (5.2)	4 (4.5)	11 (5.5)	
Number of metastasis sites				0.001*
≤2	242 (83.4)	64 (71.9)	178 (88.6)	
>2	48 (16.6)	25 (28.1)	23 (11.4)	
Liver/bone metastasis				0.011*
Positive	140 (48.3)	53 (37.9)	87 (62.1)	
Negative	150 (51.7)	36 (24.0)	114 (76)	
Systemic therapy				0.007*
Yes	196 (67.6)	50 (56.2)	146 (72.6)	
No	94 (32.4)	39 (43.8)	55 (27.4)	
Albumin (g/L), median (range)	37.97 (23.5–64.8)	35.32 (23.5–45.9)	39.14 (28.2–64.8)	0.000*
ALP (U/L), median (range)	121.73 (1.46–2,170.0)	221.80 (79.0–2,170.0)	77.43 (1.46–119.0)	0.000*
LDH (U/L)				0.001*
≤265.5	234 (80.7)	61 (68.5)	173 (86.1)	
>265.5	56 (19.3)	28 (31.5)	28 (13.9)	

Note: *P<0.05.

Abbreviations: AAPR, albumin-to-alkaline phosphatase ratio; ADC, adenocarcinoma; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer; SCC, squamous cell carcinoma.

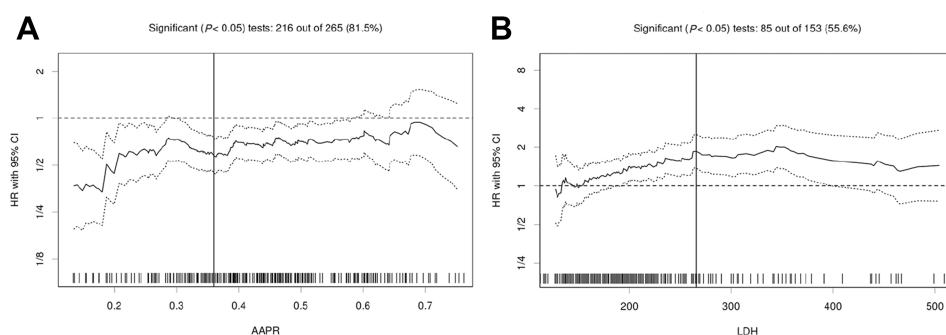


Figure 1 Hazard ratios for overall survival independent of cut-off point for (A) albumin-to-alkaline phosphatase ratio (AAPR) and (B) lactate dehydrogenase (LDH) in patients with metastatic non-small-cell lung cancer. The vertical line shows the optimal cut-off point with the most significant split (log-rank test). The plots were generated using Cutoff Finder.

Patients with elevated AAPR were more likely be those who harbored two or fewer metastasis sites, had undergone systemic therapy, had no liver/bone metastasis, and had LDH ≤ 265.5 U/L (all $P < 0.05$). However, no significant differences were found regarding age, gender, smoking status, and tumor histology type between the two groups (all $P > 0.05$).

A comparison of serum AAPR, ALP, LDH, and ALB levels in NSCLC patients with or without liver/bone metastasis is shown in Table 2. The results revealed that patients without liver/bone metastasis had higher AAPR and lower ALP than those with liver/bone metastasis (0.47 vs 0.40, $P < 0.001$; 80.17 vs 95.40 U/L, $P < 0.001$, respectively), while LDH and ALB levels in these two groups were not significantly different (both $P > 0.05$).

Kaplan–Meier survival analysis of AAPR for OS

The median follow-up time of the 290 NSCLC patients was 16 months (range: 1–84 months). Altogether, 277 patients died during the follow-up period. A difference in prognosis was apparent between patients in the high AAPR group and patients in the low AAPR group (13 months vs 7 months, $P < 0.001$) (Figure 2A). Later, stratified analyses were conducted. No significant difference was found in patients with

current/past smoking divided by level of AAPR ($P > 0.05$) (Figure 2B), while in patients without smoking history, those with high AAPR showed significantly better survival than those with low AAPR ($P < 0.001$) (Figure 2C). A similar survival trend was observed when patients were stratified into adenocarcinoma ($P < 0.001$) (Figure 2D), but not in non-adenocarcinoma ($P > 0.05$) (Figure 2E). Furthermore, we analyzed the relationship between AAPR and OS in patients with two or fewer metastasis sites and those with more than two, patients with and those without systemic therapy, and patients with and those without liver/bone metastasis, respectively. All of the results indicated that patients with elevated AAPR survived longer (all $P < 0.05$) (Figure S1).

Univariate and multivariate analyses for OS

AAPR level, LDH level, and systemic therapy were found to be significantly correlated with OS of metastatic NSCLC patients in univariate analysis (all $P < 0.001$), while age, gender, smoking status, and tumor histology type were not (all $P > 0.05$). In particular, the association between number of metastatic sites at diagnosis and OS was at the very edge of significance ($P = 0.053$). Four variables with a P -value less than 0.2 in univariate analysis were enrolled in multivariate analysis. The result revealed that AAPR was an independent

Table 2 Correlations between serum enzyme levels and liver/bone metastatic characteristics in NSCLC patients

Characteristics	Liver/bone metastasis		P-value
Median (range)	Positive	Negative	
AAPR	0.40 (0.02–0.74)	0.47 (0.02–44.38)	0.000*
ALP (U/L)	95.40 (47.00–1,573.00)	80.17 (1.46–2,170.00)	0.000*
LDH (U/L)	201.50 (117.00–966.00)	189.00 (46.00–691.00)	0.078
Albumin (g/L)	38.40 (26.60–51.30)	38.06 (23.50–64.80)	0.641

Note: * $P < 0.05$.

Abbreviations: AAPR, albumin-to-alkaline phosphatase ratio; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer.

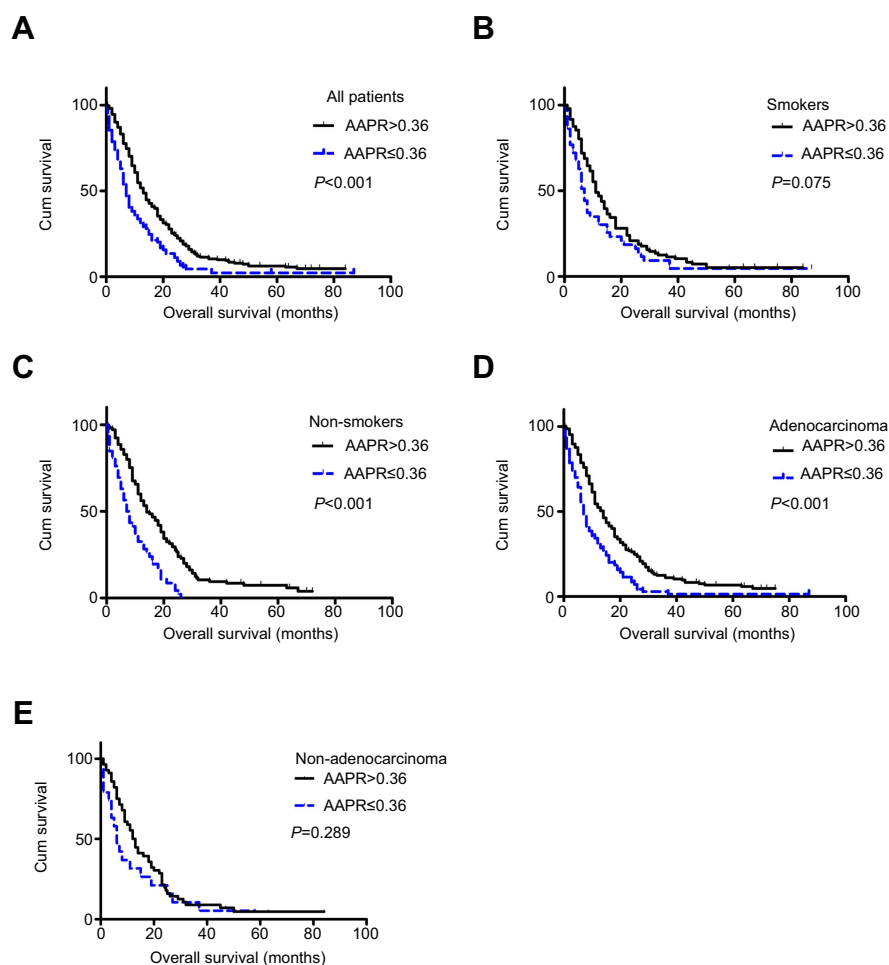


Figure 2 Kaplan–Meier curves of overall survival according to albumin-to-alkaline phosphatase ratio (AAPR) level in (A) all patients, (B) current/past smokers, (C) non-smokers, (D) adenocarcinoma, and (E) non-adenocarcinoma.

prognosis predictor for metastatic NSCLC patients (HR=0.657, 95% CI=0.504–0.856, $P<0.05$). The number of metastatic sites (HR=1.418, 95% CI=1.026–1.960, $P<0.05$), systemic therapy (HR=0.441, 95% CI=0.338–0.577,

$P<0.001$), and LDH level (HR=1.462, 95% CI=1.070–1.999, $P<0.05$) were also significantly related to OS in multivariate analysis (Table 3), and their Kaplan–Meier survival curves are shown in Figure 3.

Table 3 Prognostic factors for overall survival of metastatic NSCLC patients in univariate and multivariate Cox regression analyses

Variables	Univariable	P-value	Multivariable	P-value
	HR (95% CI)		HR (95% CI)	
Age (years) (>60/≤60)	1.199 (0.945–1.520)	0.143	1.107 (0.868–1.411)	0.413
Gender (female/male)	1.059 (0.831–1.350)	0.643		
Smoking status (current or past/never)	1.037 (0.819–1.314)	0.763		
Histology (ADC/non-ADC)	1.006 (0.768–1.317)	0.996		
Number of metastasis sites (>2/≤2)	1.362 (0.995–1.864)	0.053	1.418 (1.026–1.960)	0.034*
Systemic therapy (yes/no)	0.426 (0.329–0.551)	0.000*	0.441 (0.338–0.577)	0.000*
LDH (>265.5/≤265.5 U/L)	1.829 (1.354–2.470)	0.000*	1.462 (1.070–1.999)	0.017*
AAPR (>0.36/≤0.36)	0.587 (0.454–0.758)	0.000*	0.657 (0.504–0.856)	0.002*

Note: * $P<0.05$.

Abbreviations: AAPR, albumin-to-alkaline phosphatase ratio; ADC, adenocarcinoma; non-ADC, non-adenocarcinoma; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer.

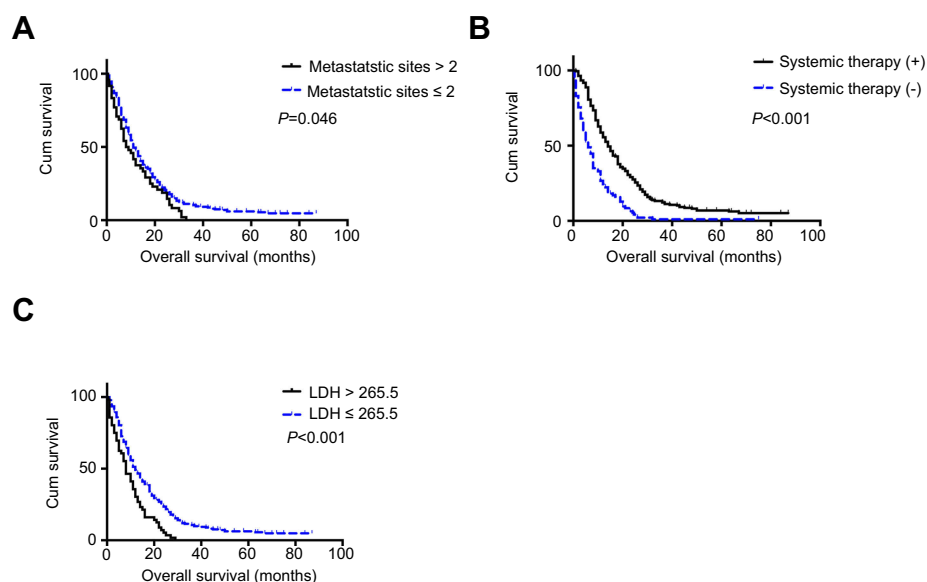


Figure 3 Kaplan-Meier curves of overall survival according to (A) metastatic sites, (B) systemic therapy, and (C) lactate dehydrogenase (LDH).

Discussion

The main aim of the present retrospective study was to elucidate the associations between the AAPR and survival in patients with metastatic NSCLC. We found that elevated AAPR was correlated with longer survival in metastatic NSCLC patients, especially for patients who were non-smokers and had confirmed adenocarcinoma. Later, we identified AAPR as an independent favorable prognostic indicator for metastatic NSCLC in multivariate analysis. We also proved that LDH had a prognostic effect in metastatic NSCLC patients.

By multivariate analysis, the high AAPR group was found to be independently related to better survival in metastatic NSCLC. The novel APPR index, calculated from two routine blood parameters, namely ALB and ALP, was first derived in a cohort of hepatocellular carcinoma patients receiving curative surgery, where Chan et al identified that a lower AAPR level increased the risk of early death 3.3-fold and the risk of tumor relapse 2.3-fold.²⁰ A later study retrospectively reviewed 209 metastatic nasopharyngeal carcinoma patients treated with cisplatin-based regimens, and found that higher AAPR indicated longer OS and progression-free survival compared with lower AAPR (24.3 months vs 17.3 months, 8.4 months vs 5.9 months, respectively).²¹ All of these results were consistent with our findings.

We also conducted subanalyses stratified by clinical characteristics, considering that some of the baseline characteristics were uneven between the AAPR >0.36 and AAPR ≤0.36 groups. When it comes to subanalyses divided by smoking status and tumor histology types, the discriminatory

power of AAPR for OS stayed strong in patients who were non-smokers and had adenocarcinomas, while, in contrast, it became insignificant in those who were smokers and non-adenocarcinoma patients. This result may be explained by the fact that adenocarcinoma was a predominant histological type among lung cancer in non-smokers, while distant metastases such as bone or liver metastases developed earlier and were more prevalent among adenocarcinomas compared to non-adenocarcinomas.²⁵ During subanalyses among patients with two or fewer metastasis sites and those with more than two, patients with or without systemic therapy, and those with absent or existing liver/bone metastasis, we found that the tendency remained unchanged, which demonstrates that the AAPR predicted prognosis independently of therapies, number of metastatic sites, and liver/bone metastatic status at diagnosis.

Moreover, in multivariate analysis, we found that having two or fewer metastatic sites, the presence of systemic therapy, and low LDH level were significant related to better survival. Although it is generally acknowledged that the first two conditions predict longer survival than those harboring more than metastatic sites and without systemic therapy, they are not as cheap and convenient as AAPR in predicting prognosis. Regarding LDH, we validated its prognostic value for survival, as indicated in previous studies.^{10,11} AAPR and LDH could supplement each other in clinical application.

There are several shortcomings of our study. First, as this was a retrospective and single-center study, multicenter and well-designed prospective studies are needed to validate our

findings. Second, although we excluded patients with known liver, renal, and bone diseases to restrict confounding factors, patients with undiscovered liver, renal, or bone diseases could have been mistakenly enrolled in the study. Third, there should be little difference between AAPRs of 0.35 and 0.37, but they fell on the side of high risk and low risk, respectively, based on the current study, owing to our transforming AAPR into a dichotomous variable when it was actually a continuous one. Moreover, the optimal cut-off value for AAPR requires external validation. Fourth, the mutation status of genes, eg, *EGFR*, *KROS*, and *EML4-ALK*, and performance status of patients were unknown owing to information loss or unavailable data. Further studies are required to assess correlations between AAPR level and specific gene mutations, and to explore the prognostic impact of the AAPR in NSCLC treated with targeted therapy. Finally, whether dynamic changes in AAPR could be applied to monitor cancer progression and response to therapy in NSCLC remains to be solved in future research.

Conclusion

AAPR, a simple, inexpensive, and easily gained biomarker-based index, can be an independent predictor for OS in metastatic NSCLC. Further large-scale prospective studies are needed to validate and expand our findings.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

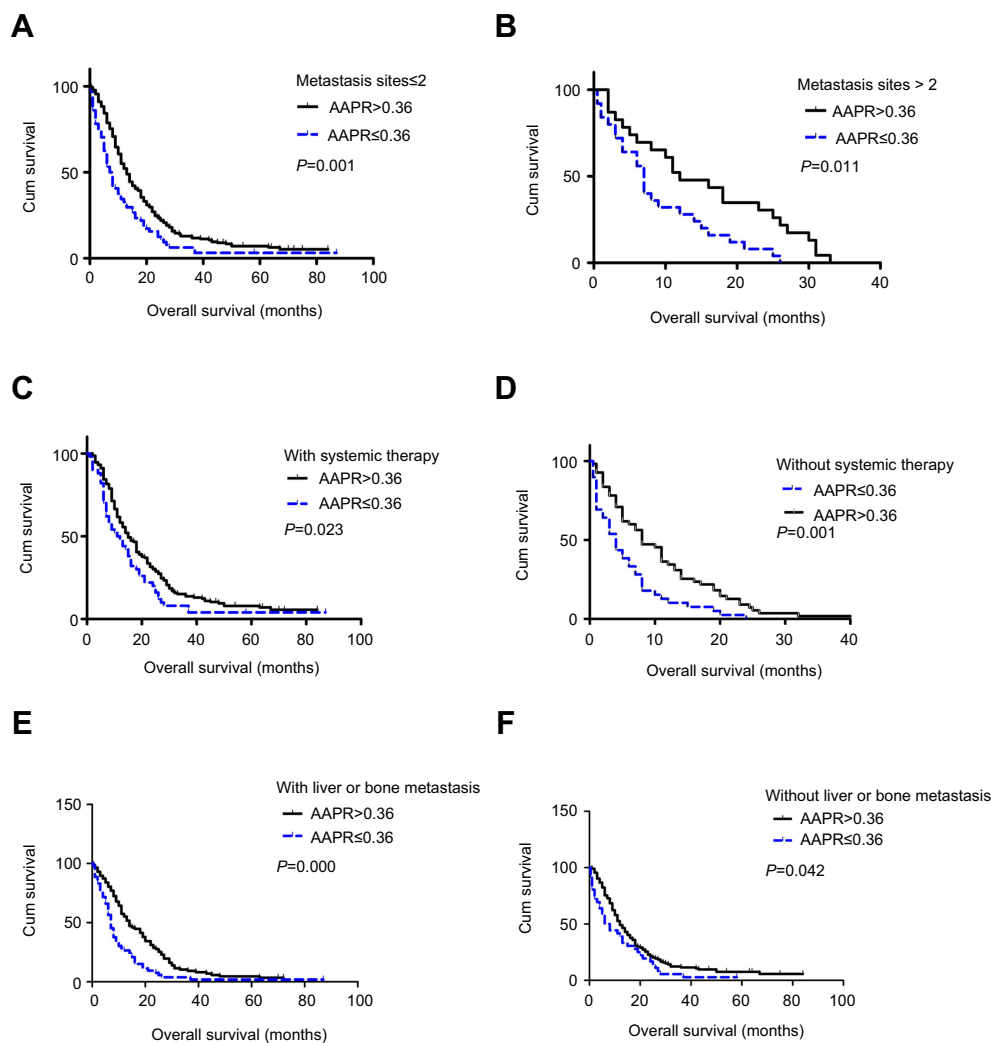


Figure S1 Kaplan-Meier curves of overall survival according to albumin-to-alkaline phosphatase ratio (AAPR) level in patients (A) with two or fewer metastasis sites, (B) with more than two metastasis sites, (C) with systemic therapy, (D) without systemic therapy, (E) with liver/bone metastasis, and (F) without liver/bone metastasis.

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