Original Article

Clinical value of serum albumin level in patients with non-small cell lung cancer and anaplastic lymphoma kinase (ALK) rearrangement

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Background: There are few data on the clinical value of serum albumin (Alb) level as a prognostic indicator in advanced non-small cell lung cancer (NSCLC) patients with positive anaplastic lymphoma kinase (ALK) rearrangement. Thus, we retrospectively analyzed the clinicopathological features of advanced, ALK-positive NSCLC patients diagnosed and treated at our institution to investigate the effects of pretreatment serum Alb on outcome in this patient setting.

Methods: We selected 261 consecutive patients with newly diagnosed pathologically or cytologically confirmed NSCLC harboring ALK rearrangement between May 2016 and February 2018. The target-independent and dependent variables were Serum albumin level measured in patients before anticancer treatment and progression-free survival (PFS). Pre-treatment serum Alb levels and demographic, clinical, and histological characteristics, as well as outcome variables were recorded and analyzed. Serum albumin level was estimated before treatment and at every visit. The pretreatment and the lowest serum albumin level during treatment were recorded.

Results: The mean pretreatment Alb level was 42.185 g/L. Before the treatment initiation, low Alb level (<40 g/L) was measured in 74 (28.4%) patients and normal Alb (≥40 g/L) was measured in 187 (71.6%) participants. Low pretreatment Alb (<40 g/L) was more highly prevalent in those with pleural effusion (P=0.013). Pretreatment hypoalbuminemia was significantly associated with shorter progression-free survival (PFS) [8.0 months, 95% confidence interval (CI): 4.56–11.44 *vs.* 12.0 months, 95% CI: 9.85–14.15; P=0.046]. Crizotinib-treated participants had a significantly prolonged PFS compared to those treated with chemotherapy, regardless of Alb level [normal Alb level: 19.0 (95% CI: 12.72–25.28) *vs.* 8.0 (95% CI: 6.22–9.78), P<0.001; low Alb level: 12.0 months (95% CI: 10.13–13.87) *vs.* 6.0 months (95% CI: 2.95–9.05), P=0.006]. Multivariate analyses indicated that poor Eastern Cooperative Oncology Group performance status (ECOG PS) [hazard ratio (HR) =1.66; 95% CI: 1.16–2.38; P=0.005] and presence of pleural effusion (HR =2.43; 95% CI: 1.55–3.82; P<0.001) were significantly independent predictive factors for PFS in ALK-positive NSCLC.

Conclusions: Pretreatment hypoalbuminemia is associated with poor outcome of NSCLC patients harboring ALK rearrangement. However, the role of the pretreatment serum Alb level as predictive biomarker requires further investigation.

Keywords: Anaplastic lymphoma kinase (ALK); non-small cell lung cancer (NSCLC); serum albumin level; predictive factor; prognostic factor

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Introduction

According to US cancer statistics, 1,762,450 new cancer cases are diagnosed each year, of which 228,150 are lung cancers (1). Lung cancer is the most common cause of malignancy-related mortality worldwide, and responsible for 142,670 deaths annually (1). Non-small cell lung cancer (NSCLC) is the dominant histopathological type of lung cancer, which comprises 85% of all cases. Despite progress in diagnostic techniques and treatment, NSCLC still shows a poor 5-year survival rate (2). Several factors have been identified as predictors for patient survival, including gender, performance status (PS), disease extent, age, lactate dehydrogenase, CEA value, and neutrophil counts in NSCLC (3-8). However, their predictive power is reduced and barely transferrable to clinical use. Thus, it is important to recognize specific, sensitive, and easily-obtained biomarkers for NSCLC prognosis.

Anaplastic lymphoma kinase (ALK) gene rearrangements were firstly reported in 2007, and significant advances have been witnessed in their drug development for NSCLC (9,10). ALK rearrangement is fusion results from a small inversion within chromosome 2p, which leads to expression of a chimeric tyrosine kinase, in which the N-terminal half of echinoderm microtubule-associated protein-like 4 (EML4) is fused to the intracellular kinase domain of anaplastic lymphoma kinase (10). Present in 4–5% of NSCLC, ALK defines a molecular subset of NSCLC with distinct clinical characteristics, including never/light smoking history, adenocarcinoma histology, and younger age (11). The ALK-positive cancers are highly sensitive to small-molecule ALK kinase inhibitors, such as crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib (12-23). The discovery of ALK gene rearrangements and the development of anti-ALK agents have significantly changed the paradigm of treatment for NSCLC.

Albumin (Alb) is a plasma protein produced by the liver and is a commonly used biomarker for malnutrition, inflammation, and hepatic dysfunction. Malnutrition and inflammation are often seen in cancer patients. The progression of tumors, including lung cancer, is closely associated with cancer-related inflammation and malnutrition due to their suppression of Alb synthesis (24). Serum Alb level, alone or as a component of scoring systems [e.g., prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS)], has been assessed in multiple malignancies as a prognostic marker (24-28). There are a few studies have investigated the impact of serum Alb level on disease prognosis in NSCLC patients harboring ALK rearrangement. However, there still are many questions unsolved. Here, we conducted a retrospective analysis to determine whether serum Alb level is related to prognosis in NSCLC patients harboring positive ALK, and to clarify the relationships between serum Alb level and clinicoradiographic characteristics of NSCLC patients with ALK rearrangement. We also analyze the difference for hypoalbuminemia as a prognostic factor between different treatment (Crizotinib vs chemotherapy) for advanced NSCLC patients with ALK rearrangement. We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3379).

Methods

In this retrospective study, we analyzed the medical records of 261 consecutive patients with newly diagnosed, pathologically or cytologically confirmed NSCLC harboring ALK rearrangement between May 2016 and February 2018 at Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College.

Inclusion criteria were as follows: (I) patients with either histologically or cytologically confirmed diagnosis of ALK-positive advanced NSCLC; (II) sociodemographic, clinicopathological characteristics, and complete follow-up information of all patients were available; (III) patients were not receiving any anticancer therapies at the time of initial diagnosis; (IV) there was no concurrent malignancy or a history of a second primary malignancy. Patients with small cell lung cancer or staged with not advanced NSCLC or incomplete baseline information were excluded.

Clinical characteristics such as age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking status, histological classification, disease stage, and ALK status were investigated. The PS was recorded according to the ECOG PS scores. Tumor stage was determined according to the seventh edition of the tumor-node-metastasis (TNM) staging system by the

Table 1 Patient characteristics

Characteristics	Value
Age, median [range], years	51 [20–83]
Gender, n (%)	
Male	128 (49.0)
Female	133 (51.0)
Histology type, n (%)	
Adenocarcinoma	256 (98.1)
Adenosquamous carcinoma	1 (0.4)
Other	4 (1.5)
Presence of pleural effusion, n (%)	
Yes	52 (19.9)
No	209 (80.1)
Disease stage, n (%)	
IIIB	18 (6.9)
IV	243 (93.1)
ECOG status, n (%)	
0	158 (60.5)
1	90 (34.5)
≥2	13 (5.0)
First-line therapy, n (%)	
Chemotherapy	99 (37.9)
Crizotinib	154 (59.0)
Other	8 (3.1)

ECOG, Eastern Cooperative Oncology Group.

American Joint Committee on Cancer. The ALK status was determined by immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), polymerase chain reaction (PCR), or next generation sequencing (NGS). Response results, progression-free survival (PFS), and overall survival (OS) were investigated to evaluate outcomes. Tumor responses were assessed according to the response evaluation criteria in solid tumors (RECIST) v1.1 by computed tomography (CT) scan or magnetic resonance imaging (MRI) every 6–8 weeks. The PFS was defined as the time from the date of treatment to the date of disease progression or death.

Alb were tested on a beckman coulter AU680 automatic biochemical analyzer using the manufacturer's reagents. Quality control follows good laboratory practice (GLP). Serum Alb level was estimated before treatment and at every visit. The pretreatment and the lowest serum Alb level during treatment were recorded. The cut-off value for Alb was chosen according to the normal range in serum biochemistry testing, which was 4 g/dL corresponding to the normal limits given by the local laboratory at our institute. Participants with serum Alb levels under 4 g/dL were considered to be hypoalbuminemia. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College (No. 18-102/1680). Individual consent for this retrospective analysis was waived.

Statistical analysis

The categorical variables were analyzed by chi-square and Fisher's exact tests, and continuous variables were analyzed by Student's t test. Kaplan-Meier method was used to estimate the OS and PFS in all participants and in subgroups, and differences between each group were calculated using the log-rank test. Multivariate analysis was performed using Cox proportional hazard regression models. A P value <0.05 was taken to indicate statistical significance. Analyses were carried out using SPSS version 22.0 (IBM Corp., Chicago, IL, USA).

Results

Baseline population characteristics are presented in *Table 1*. The median age was 51 years (range, 20–83 years) with 51.0% being female. The study population included a vast majority of adenocarcinoma (98.1%), stage IV disease (93.1%) with 14.2% of patients having pleural effusion. Most participants showed a well-preserved physical condition at the time of evaluation, with 248 (95.0%) out of 261 participants having a PS of 0 or 1 (*Table 1*). A total of 99 participants received chemotherapy as first-line treatment, 154 received crizotinib, whereas 8 participants received other targeted treatment. Each patient's treatment was chosen by his/her doctor in charge. No difference was detected for the proportion of hypoalbuminemia among treatment groups (P=0.810).

The mean pretreatment Alb level was 42.185 g/L. *Table 2* shows that low Alb was (<40 g/L) measured in 74 (28.4%) participants and normal albumin (≥40 g/L) was measured

Table 2 Participant characteristics divided according to serum Alb <40 and ≥40 g/L

Characteristics	Pretreatment serum albumin level		P value
	<40 g/L	≥40 g/L	
Age			0.077
<60 years	50	146	
≥60 years	24	41	
Gender			0.238
Male	32	96	
Female	42	91	
ECOG score			0.833
0	42	116	
1	28	62	
2	3	7	
3	1	2	
Histology type			1.000
Adenocarcinoma	73	183	
Adenosquamous carcinoma	0	1	
Other	1	3	
Presence of pleural effusion			0.013
Yes	22	30	
No	52	157	
Disease stage			0.550
IIIB	4	14	
IV	70	173	
First-line therapy			0.810
Chemotherapy	27	72	
Crizotinib	44	110	
Other	3	5	

ECOG, Eastern Cooperative Oncology Group; Alb, albumin.

in 187 (71.6%) before the treatment initiation. Participants with pretreatment albumin <40 g/L had a higher prevalence of pleural effusion (P=0.013), and older participants (≥60 years) tended to have low-level Alb (P=0.077).

Clinical outcome

At data cut-off (June 2020), a total of 201 documented PFS events were observed (median follow-up, 16.1 months). The median PFS in participants with pre-treatment hypoalbuminemia was significantly shorter than that in those with a normal pre-treatment serum Alb level [8.0 months (95% CI: 4.56–11.44) *vs.* 12.0 months (95% CI: 9.85–14.15), P=0.046; *Figure 1*]. However, no difference was seen when stratified by treatment [crizotinib-treated patients (hypoalbuminemia *vs.* normal serum Alb): 12.0 months (95% CI: 10.13–13.87) *vs.* 19.0 months (95% CI: 12.72–25.28), P=0.072, *Figure 2A*; chemotherapy: 6.0 months (95% CI: 2.95–9.05) months *vs.* 8.0 (95% CI: 6.22–9.78), P=0.191, *Figure 2B*]. In addition, crizotinib yielded better PFS than chemotherapy regardless of pre-treatment serum Alb status, the P value was 0.006 and less than 0.001 for participants with pre-treatment hypoalbuminemia and normal serum Alb level, respectively (*Figure 2C,2D*). The Kaplan-Meier curves of PFS stratified by pretreatment Alb level and treatment are respectively shown in *Figure 2*. Response rate showed a similar trend when stratified by treatment and pretreatment serum Alb status (*Figure 3*).

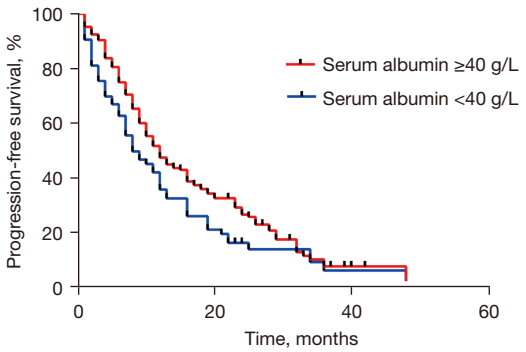

Figure 1 Progression-free survival (PFS) for the all population.

Baseline clinical parameters were assessed together with serum Alb levels in univariate and multivariate analysis. In univariate analysis, older age, poor ECOG PS, and presence of pleural effusion were identified as adverse prognostic factors (*Table 3*). The multivariate Cox proportional hazards model revealed that ECOG PS (HR =1.66; 95% CI: 1.16–2.38; P=0.005) and presence of pleural effusion (HR =2.43; 95% CI: 1.55–3.82; P<0.001) were significantly independent predictive factors for PFS in ALK-positive NSCLC (*Table 3*).

Discussion

In this study, we examined the predictive value of pretreatment Alb status in a retrospective cohort of 261 locally advanced or metastatic NSCLC patients with

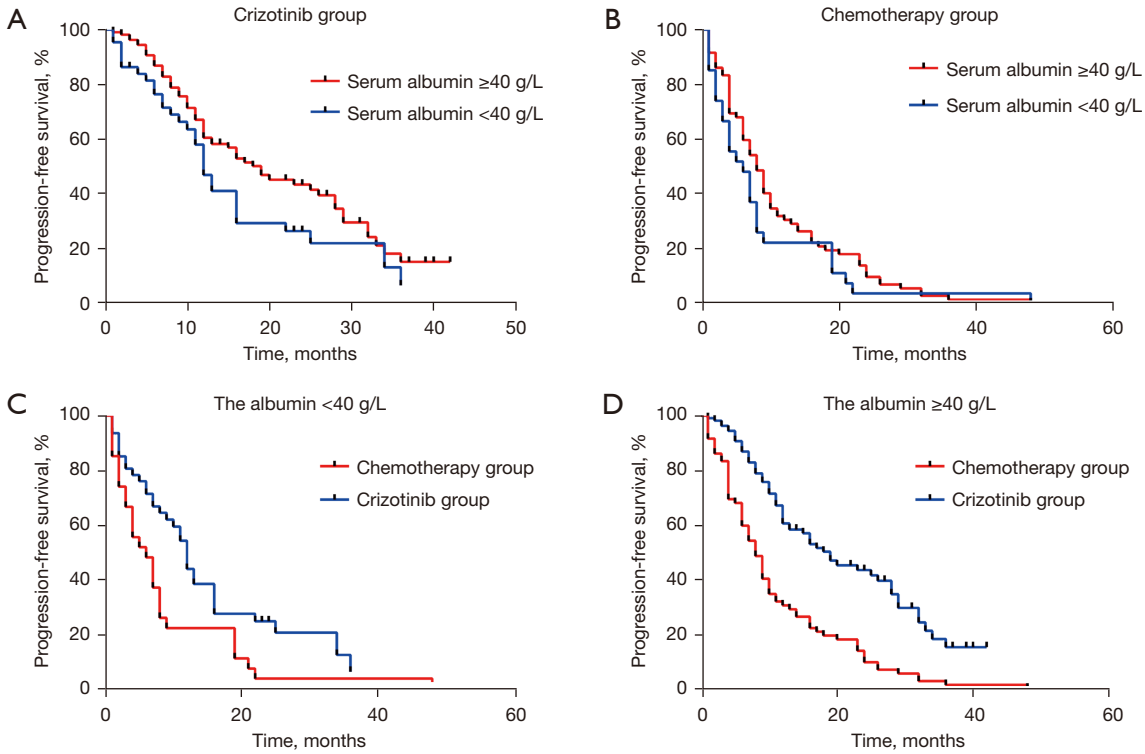

Figure 2 Progression-free survival (PFS) for crizotinib group (A), chemotherapy group (B), the albumin <40 g/L (C) and the albumin ≥40 g/L (D).

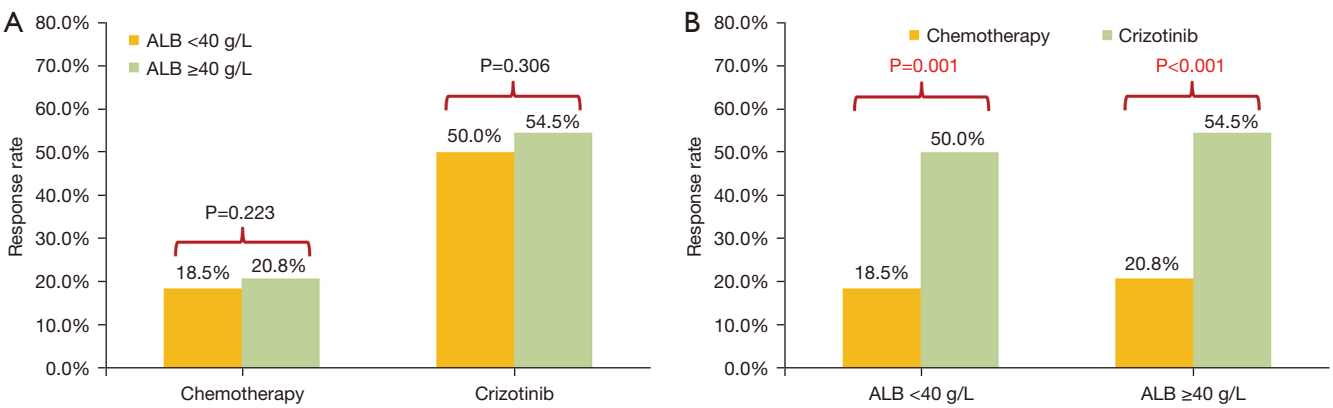

Figure 3 Response rate stratified by treatment and pretreatment serum albumin status.

positive ALK. To the best of our knowledge, the current study is the first to describe the correlation between pretreatment Alb status and clinical outcome in ALK-positive NSCLC patients. Participants with normal Alb level (≥40 g/L) had better PFS, and ECOG PS and presence of pleural effusion were independent prognostic factors in multivariable models.

Produced by the liver, Alb helps to maintain intravascular pressure and balance blood pH, as well as showing visceral protein function which represents the degree of malnutrition (29,30). Decreased serum Alb level is commonly seen in cancer patients due to cancer-related inflammation, cachexia, and malnutrition (cancer-related or treatment-related). Emerging data has demonstrated

Table 3 Univariate and multivariate Cox proportional hazards regression analyses

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (<60 *vs.* ≥60 years)	0.7273 (0.4741–1.116)	0.046	0.703 (0.454–1.089)	0.114
Gender (male *vs.* female)	0.9683 (0.6488–1.445)	0.694		
ECOG score (≤1 *vs.* >1)	3.000 (1.672–5.383)	0.001	0.803 (0.514–1.257	0.001
Smoking status (smoker *vs.* non-smoker)	0.8571 (0.5567–1.320)	0.776		
Primary site (left lung *vs.* right lung *vs.* bilateral lung)	1.295 (0.8750–1.963)	0.133		
Histological type (adenocarcinoma *vs.* adenosquamous carcinoma vs other)	0.7312 (0.1352–3.515)	0.780		
Pretreatment Alb level (<40 *vs.* ≥40 g/L)	1.016 (0.6600–1.565)	0.279		
Presence of pleural effusion (yes *vs.* no)	0.6349 (0.4069–0.9907)	0.014	0.603 (0.383–0.950)	0.029
First-line treatment (chemotherapy *vs.* crizotinib *vs.* other)	0.9374 (0.6225,1.403)	0.696		
Disease stage (IIIB *vs.* IV)	0.7643 (0.3225–1.899)	0.593		
Treatment lines (<2 *vs.* ≥2)	0.9669 (0.6469–1.440)	0.866		

HR, hazard ratio; CI, confidence interval; Alb, albumin.

a correlation between hypoalbuminemia and survival outcome in cancer patients, including those with lung cancer (25-28,31). Espinosa *et al.* reported that Alb level was predictive for survival in non-operable NSCLC which consisted of a heterogeneous population (31). For early-stage disease, pre-operative hypoalbuminemia was found to be significantly correlated with larger tumor size and visceral pleural invasion, and hypoalbuminemia has been reported as a negative prognostic factor for tumor recurrence and survival in patients with resected NSCLC (32,33). In other cohort studies, investigators have reported relationships between Alb-contained models such as albumin-to-alkaline phosphatase ratio (AAPR), PNI, or GPS and the prognosis of lung cancer (34-38). Significant unfavorable OS and disease-free survival (DFS) was seen in resected NSCLC patients with low AAPR (36). High pretreatment albumin and neutrophil combined prognostic grade (ANPG), high fibrinogen and serum Alb levels (FA score), and low PNI has been reported as a negative prognostic factor for survival (35,36,39,40). The GPS is calculated with C-reactive protein and Alb values, and high GPS predicts poor prognosis for operable-stage lung cancer patients (38). For patients with NSCLC harboring driver mutation, Fiala *et al.* reported that hypoalbuminemia was the strongest factor predicting OS among those treated with erlotinib, even stronger than epidermal growth factor receptor (EGFR) mutation (41). These findings suggest that serum Alb is an objective, simple, and effective marker that predicts survival outcomes even in the targeted therapy era.

Since its discovery, it has been well-established that ALK rearrangements predict favorable response to the treatment with ALK inhibitors in patients with advanced-stage NSCLC. With respect to Alb level, most previous studies were performed on patients treated with chemotherapy; in the present study, we focused on the impact of pretreatment serum Alb in a large cohort of patients with ALK-positive NSCLC. In this study, hypoalbuminemia was more common in participants with pleural effusion (P=0.013) and those older than 60 years (P=0.077), while clinical characteristics such as gender, histology, and disease stage did not affect the prevalence of hypoalbuminemia. We observed significantly shorter PFS for patients with hypoalbuminemia compared to those with normal-level serum Alb (8.0 *vs.* 12.0 months, P=0.046). A previous study demonstrated that Alb level identifies a group of NSCLC patients with hypoalbuminemia who are more likely to respond poorly to chemotherapy, which may be explained by the fact that malnourished patients tolerate chemotherapy poorly (31). In contrast to previous studies, despite a numerical difference, the difference was not statistically significant in chemotherapy-treated patients, the median PFS was 8.0 and 6.0 months according to pre-treatment serum Alb level (P=0.191). A possible explanation

was the limited sample size, only 27 chemotherapy-treated patients with hypoalbuminemia were included in this analysis. Additionally, the chemotherapy regimen was pemetrexed plus cisplatin, which had better safety profile and less drug-related discontinuation than other regimens (42). For crizotinib-treated patients, pre-treatment hypoalbuminemia seemed to be associated with shorter PFS (12.0 *vs.* 19.0 months) with a borderline P value of 0.072, suggesting relatively lower efficacy of ALK inhibitors in this population. Moreover, crizotinib yield better PFS benefit when compared with chemotherapy regardless of Alb status, indicating that crizotinib is still a preferable option for in ALK-positive patients with hypoalbuminemia.

The multivariate Cox proportional hazards model confirmed that poor ECOG PS and presence of pleural effusion were independently associated with shorter survival. Previous studies have demonstrated that Alb level can predict the prognosis of NSCLC patients (31-33). However, the prognostic value of Alb level was inconsistent in this study. We speculated that this difference may be attributed to the different populations enrolled in previous studies which mostly consisted of early-stage patients (32,33). Moreover, the level of Alb is related to many factors, such as inflammation, hepatic insufficiency, and changes in the volume of body fluids.

This research was limited by the retrospective single-center cohort and small sample size. Since other ALK inhibitors (ceritinib, alectinib) were approved in 2018 in China, we only analyzed data from crizotinib-treated patients, and failed to collect treatment information after progression on first-line treatment. In addition, the Alb levels were influenced by many factors including disease stage, inflammation, hepatic insufficiency, and changes in the volume of body fluids. Future studies should take these factors into account.

In conclusion, the results of this retrospective study indicate that pretreatment hypoalbuminemia is associated with poor outcome of NSCLC patients harboring ALK rearrangement. Crizotinib provided a better option than chemotherapy in patients with low pretreatment Alb level. However, Alb level alone seems to be insufficient to predict the survival in ALK-positive NSCLC patients, better prognostic markers integrating Alb levels and other factors need to be investigated in future studies.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3379

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-3379

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3379). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College (No. 18-102/1680). Individual consent for this retrospective analysis was waived.

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