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ORIGINAL PAPER

High percentage of α1-globulin in serum protein is associated with unfavorable prognosis in non-small cell lung cancer

Xiao Qu · Zhaofei Pang · Weiwei Yi · Ying Wang · Kai Wang · Qi Liu · Jiajun Du

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Abstract The association of the percentage composition of serum protein in patients undergoing lung resections for non-small cell lung cancer (NSCLC) with overall survival and recurrence-free survival has never been investigated. Patients were selected consecutively from the database of the Bio-Bank of Shandong Provincial Hospital. We retrospectively examined the impact of preoperative percentage composition of serum protein detected by serum protein electrophoresis on survival. Furthermore, we investigated the relationships between the potential prognostic biomarkers and clinicopathological factors. A total of 390 patients were evaluated. The higher percentage of α1-globulin in serum protein was significantly associated with histology type ($p < 0.001$), worse tumor status ($p < 0.001$) and higher pathological stage ($p = 0.004$). The α1-globulin percentage composition was an independent prognostic factor for overall survival (hazard ratio 1.52, 95 % CI 1.04–2.23, $p = 0.03$). High percentage of α1-globulin in serum protein was also related to short recurrence survival (hazard ratio 1.56, 95 % CI 1.14–2.13, $p = 0.005$). Our results showed that the percentage of α1-globulin in serum protein may be an independent prognostic factor in NSCLC.

Keywords Serum protein · α1-Globulin · Prognosis · Lung cancer · Survival

Introduction

Lung cancer is almost the leading cause of cancer-related deaths in the industrialized world [1]. Based on the latest global cancer statics, lung cancer accounts for 17 % of the total new cancer cases and 23 % of the total cancer deaths [2]. Researchers have spared no effort to find prognostic factors, which can be used to predict disease control or survival. Many prognostic factors, such as the lymph node status [3], histology [4], tumor size [5], performance status [6], fibrinogen [7] and age [8], have been well investigated in lung cancer. Although there are many well-established prognostic factors, it is still hard to predict the prognosis of individual patients accurately. Clinicians and researchers urgently need to identify economical and convenient predictors.

Recently, many scientists have noticed that the level of α1-antitrypsin (AAT) was elevated in the serum of lung cancer patients and can be used as a prognostic factor [9–11]. Li et al. [11] showed that the increased serum AAT concentration was a poor prognosis marker for non-small cell lung Cancer (NSCLC), regardless of carrier status. However, the concentration of AAT was detected by immunonephelometry in that study and was hard to be used in the clinical work, which restricts its clinical application.

Xiao Qu, Zhaofei Pang and Weiwei Yi have contributed equally to this work.

X. Qu · Z. Pang · Y. Wang · K. Wang · Q. Liu (✉) · J. Du
Institute of Oncology, Shandong Provincial Hospital Affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan 250021, People's Republic of China
e-mail: liuqi66@sdu.edu.cn

W. Yi
Department of Oncology, Shandong Provincial Hospital Affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan 250021, People's Republic of China

J. Du (✉)
Department of Thoracic Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Shandong University, 324 Jingwu Road, Jinan 250021, People's Republic of China
e-mail: dujiajun@sdu.edu.cn

It has been reported that AAT is the major component of α1-globulin electrophoresis bands, which can be easily detected by serum protein electrophoresis (SPE) [12]. SPE is commonly used to diagnose multiple myeloma or the disorders of serum protein. In this examination, serum proteins are separated into five fractions by size and electrical through placing serum on special paper treated with agarose gel and exposing to an electric current [13]. The proteins on the special paper are then stained, and their densities are measured to provide graphical data that can be easier to interpret [14]. The largest peak lies closest to the positive electrode is albumin. The next four components are labeled α1-, α2-, β- and γ-globulins.

Compared with other laboratory examination, SPE is very economical and can provide useful information. And the association of serum protein composition with the prognosis of NSCLC has never been investigated. The goal of the study is to investigate whether the serum protein composition could affect survival in patients with resected NSCLC. The primary outcome is overall survival (OS), and the secondary outcomes are recurrence-free survival (RFS) and the relationships of these factors to clinicopathological factors.

Patients and methods

Patients and treatments

The study was approved by the Ethical Committee of Shandong Provincial Hospital affiliated to Shandong University. We conducted a retrospective analysis of patients diagnosed with NSCLC who underwent radical surgery at Shandong Provincial Hospital affiliated to Shandong University between January 2006 and December 2008. Criteria for eligibility included Karnofsky performance score $\geq$70, weight loss <5 % in the prior 3 months, 18 $\leq$ age $\leq$ 75 and SPE examination performed at the second day after entering the hospital. SPE was examined with Sebia Hydrasys electrophoresis device (France) and the matched kit. The histological diagnosis was based on the classification criteria for lung cancers of the World Health Organization and International Association for the Study of Lung Cancer (WHO/IASLC) [15]. The extent of the disease was determined by TNM staging according to the new IASLC staging system [16].

Lobectomy, bilobectomy or pneumonectomy was performed on all enrolled patients according to the location or size of the lung neoplasm. Systematic mediastinum lymph node dissection was performed in all patients. All patients received standardized follow-up at a 3-month interval for the first 2 years after operation, a 6-month interval in the third year and yearly thereafter. Evaluation comprised a physical examination, complete blood count, chest computed tomography, brain magnetic resonance imaging and abdominal ultrasound.

To ensure reliable and consistent data collection, two independent trained physicians were assigned to review the relevant database of each case. Otherwise, all conflicts were discussed to obtain agreement.

Statistical analysis

The survival curves were estimated using Kaplan–Meier method and were compared using log-rank test. Overall survival was determined from the date of surgery to the date of death or last follow-up. Receiver operating characteristic (ROC) curves were used to identify the optimal cutoff points [17, 18]. To avoid the emergence of the bias, a running log-rank test was used at intervals between the 5th percentile and the 95th percentile of the percentage composition of serum proteins. The cutoff value was defined when the log-rank statistical value was maximum. To examine the association with clinicopathological factors, the Chi-squared test was used for categorical variables, and the*t* test for continuous variables. An internal cross-validation procedure was applied, splitting the whole sample in a training (67 %) and in a testing sample (33 %). The process was repeated 10 times; thus, we had 10 training samples and 10 corresponding testing samples. The best-fitting model was estimated for each training sample. Univariate analysis was performed using the Kaplan–Meier method, and statistical significances between survival curves were assessed by the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model to assay the independent predictive value of survival. The result was considered to be significant when the p value was less than 0.05, and all the p values were two-sided. The analyses were performed using the Statistical Package for Social Sciences (SPSS) program, version 20.0, in English.

Results

Patients characteristics

Patients and tumor characteristics are shown in Table 1. A total of 390 patients with stage I–III, 279 men and 111 women, were enrolled. The mean age at the time of operation was 59.2 (range from 23 to 74). The mean follow-up was 45 months (range from 1 to 80 months). The number of patients that presented with pathological stage I, II and III disease was 156 (39.9 %), 136 (35.0 %) and 98 (25.1 %), respectively.

Table 1 Clinicopathological characteristics of patients

	Total = 390
Age (mean ± SD) (years)	59.2 ± 9.8
Sex (male/female)	279/111
Smoking index (mean ± SD)	510 ± 528
Comorbidity and past history	
Old pulmonary tuberculosis	16
Hypertension	59
Diabetes mellitus	18
Hepatitis	6
Coronary heart disease	20
Trachitis	31
Resected site (right/left)	175/215
Histological type (Ad/Sq/others)	182/155/53
Pathological staging (I/II/III)	156/136/98
Tumor status (T1/T2/T3/T4)	134/191/48/17
LN status (positive/negative)	181/209
Postoperative adjuvant chemotherapy	27
Albumin (mean ± SD) (g/L)	42.3 ± 4.0
Globulin (mean ± SD) (g/L)	27.6 ± 4.6
A/G (mean ± SD)	1.61 ± 0.28
Albumin electrophoresis bands, (mean ± SD) (%)	61.36 ± 4.24
α1-Globulin electrophoresis bands, (mean ± SD) (%)	2.82 ± 0.99
α2-Globulin electrophoresis bands, (mean ± SD) (%)	10.46 ± 2.13
β-Globulin electrophoresis bands, (mean ± SD) (%)	10.15 ± 1.40
γ-Globulin electrophoresis bands, (mean ± SD) (%)	15.19 ± 3.00

SD standard deviation, *Ad* adenocarcinoma, *Sq* squamous cell carcinoma, *large* large cell carcinoma, *small* small cell carcinoma

Cutoff value, univariate and multivariate analysis

As for the percentage of α1-globulin in serum protein, the maximum log-rank statistical value was 10.827 ($p = 0.001$) when the cutoff value was 2.4. Kaplan–Meier survival curves according to the optimal cutoff value are shown in Fig. 1. Higher percentage of α1-globulin was associated with worse overall survival. Furthermore, higher percentage of α1-globulin was also found to be associated with worse recurrence-free survival, and the result is shown in Fig. 2. The internal cross-validation was also conducted, and the cutoff value was proved to be stable (data not shown).

In univariate analysis, age, sex, stage, node status, tumor status and tumor differentiation, the absolute value of serum albumin, the percentage of serum albumin/α1-globulin/α2-globulin/γ-globulin and albumin/globulin ratio were all significantly associated with OS (Table 2).

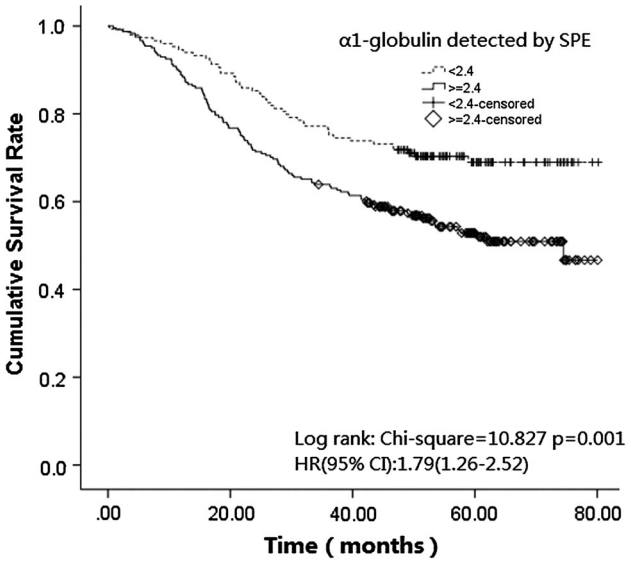

Fig. 1 Overall survival curves at the optimal cutoff value of the α1-globulin in serum protein in lung cancer patients; the overall 5-year survival rates were 70.3 % for the low ($n = 149$), which was significantly higher than 51.9 % for the high percentage of α1-globulin ($n = 241$)

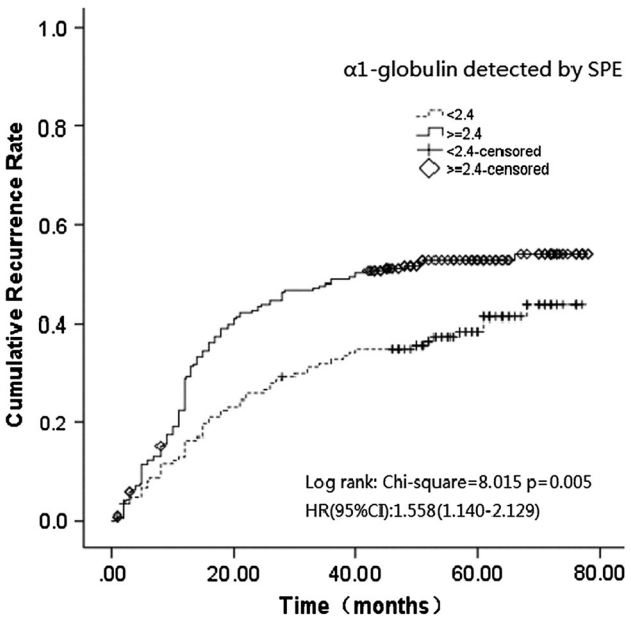

Fig. 2 Recurrence-free survival curves at the cutoff value of the α1-globulin in serum protein in lung cancer patients

Histology type, absolute value of serum globin, total serum protein and the percentage of β-globulin were not significantly associated with OS (Table 2).

Multivariate analysis results are shown in Table 3. The percentage of α1-globulin was an independent prognostic factors for overall survival (hazard ratio 1.52, 95 % CI 1.04–2.23, $p = 0.03$). The absolute value of albumin, the

Table 2 Univariate analyses of prognostic factors for NSCLC

Variables	Unadjusted HR (95 % CI)	*p* value
Age		
<67	Reference	
≥67	1.55(1.11–2.17)	0.010
Sex		
Female	Reference	
Male	1.68(1.14–2.46)	0.008
Stage		
I	Reference	
II	3.13(2.03–4.82)	<0.001
III	4.74(3.06–7.36)	<0.001
LN status		
Negative	Reference	
Positive	3.11(2.23–4.34)	<0.001
Tumor status		
1	Reference	
2	1.41(0.97–2.03)	0.070
3–4	1.91(1.22–2.99)	0.005
Histology type		
Other	Reference	
Sq	0.73(0.46–1.15)	0.180
Ad	0.69(0.44–1.09)	0.108
Tumor differentiation		
Well	Reference	
Moderately	3.53(1.12–11.13)	0.032
Poorly	4.01(1.23–13.05)	0.021
Albumin		
<42.6	Reference	
≥42.6	0.71(0.52–0.97)	0.032
Globin		
<27.95	Reference	
≥27.95	1.32(0.96–1.8)	0.080
Total protein		
<70.55	Reference	
≥70.55	0.76(0.55–1.04)	0.085
A/G		
<1.57	Reference	
≥1.57	0.69(0.50–0.94)	0.018
Albumin detected by SPE		
<61.1		
≥61.1	0.71(0.52–0.97)	0.034
α-1 Globulin detected by SPE		
<2.4	Reference	
≥2.4	1.79(1.26–2.52)	0.001
α-2 Globulin detected by SPE		
<8.2	Reference	
≥8.2	2.66(1.25–5.68)	0.008
β-Globulin detected by SPE		
<8.6	Reference	
≥8.6	0.69(0.43–1.13)	0.145
γ-Globulin detected by SPE		
<13.0	Reference	
≥13.0	1.78(1.12–2.81)	0.014

Survival time was calculated from the date of surgery

SPE serum protein electrophoresis, *HR* hazard ratio, *CI* confidence interval

Table 3 Multivariate analysis

	Adjusted HR (95 % CI)	*p* value
Albumin		
<42.6	Reference	
≥42.6	0.86(0.60–1.24)	0.413
A/G		
<1.57	Reference	
≥1.57	0.85(0.59–1.21)	0.365
Albumin detected by SPE		
<61.1	Reference	
≥61.1	0.88(0.62–1.26)	0.489
α-1 Globulin detected by SPE		
<2.4	Reference	
≥2.4	1.52(1.04–2.23)	0.030
γ-Globulin detected by SPE		
<13.0	Reference	
≥13.0	1.44(0.86–2.42)	0.169

Survival time was calculated from the date of surgery

SPE serum protein electrophoresis, *HR* hazard ratio, *CI* confidence interval

percentage of serum albumin/γ-globulin in serum protein and albumin/globulin ratio had predictive values only in univariate analysis, but not in multivariate analysis.

Relationships between α1-globulin percentage composition in serum protein and clinicopathological factors

The relationships between α1-protein fraction and clinicopathological factors are shown in Table 4. The high percentage composition of α1-globulin in serum protein was significantly associated with sex ($p < 0.001$), histology type ($p < 0.001$), tumor status ($p < 0.001$) and pathological stage ($p = 0.004$), which were all certain prognostic factors for the lung cancer. Furthermore, the high percentage composition of α1-globulin significantly associated with the absolute value of albumin ($p = 0.004$) or the percentage of albumin in serum protein ($p < 0.001$).

Table 4 Relationships between preoperative α1-globulin percentage composition in serum protein and clinicopathological factors

Clinicopathological factors	Percentage of α1-globulin		*p* value
	<2.4 $n = 149$	≥2.4 $n = 241$	
Age (mean ± SD) (years)	58.2 ± 9.2	59.6 ± 10.8	0.190
Sex (male/female)	89/60	190/51	<0.001
Comorbidity and past history			
Old pulmonary tuberculosis	7	9	0.794
Hypertension	22	37	0.996
Diabetes mellitus	7	11	1.000
Hepatitis	3	3	0.679
Coronary heart disease	8	12	1.000
Trachitis	11	20	0.848
Histology type (Sq/Ad/others)	40/93/16	115/89/37	<0.001
Tumor status (T1/T2/T3)	73/61/15	61/130/50	<0.001
Node status (positive/negative)	61/88	120/121	0.096
Pathological stage (1/2/3)	75/44/30	81/92/68	0.004
Albumin (mean ± SD) (g/L)	43.1 ± 4.0	41.9 ± 4.0	0.004
Globulin (mean ± SD) (g/L)	27.5 ± 4.2	27.7 ± 4.8	0.797
Total protein (mean ± SD) (g/L)	70.6 ± 5.3	69.5 ± 5.5	0.069
Albumin detected by SPE (%)	63.6 ± 3.0	60.0 ± 4.3	<0.001
β-Globulin detected by SPE (%)	9.9 ± 1.4	10.3 ± 1.4	0.016
γ-Globulin detected by SPE (%)	15.0 ± 2.9	15.3 ± 3.1	0.304
Albumin/globulin ratio	1.76 ± 0.24	1.52 ± 0.27	<0.001

As for age, node status, globulin, total protein, γ-globulin percentage composition in serum protein, no significant differences were detected.

Discussion

To our best knowledge, it is the first time to investigate percentage composition of serum protein on survival of NSCLC patients and their relationships with clinicopathological factors. The results of this study suggested that the percentage of α1-globulin in serum protein maybe an independent prognostic factor of patients with NSCLC. Till now, we could not focus any researches which investigate the relationship of α1-globulin percentage compositions in serum protein with lung cancer survival.

SPE is widely available in hospitals and clinics by virtue of its common use to diagnosis multiple myeloma. Our study provided the prospect that SPE may be used to as the prognostic factor for the survival of NSCLC.

The α1-protein fraction is comprised of α1-glycoprotein, thyroid-binding globulin, transcortin and α1-antitrypsin (AAT) [14]. Our result showed that high percentage of α1-globulin in serum protein was associated with unfavorable prognosis for resected NSCLC. There are many possible mechanisms to explain the finding. The most important mechanism may be that AAT, the major component of α1-protein fraction, actually influences the survival of NSCLC patients. Previously, many studies have investigated the correlation between AAT serum concentration and the process of neoplasia. The results showed that AAT serum level was elevated in different types of malignancies such as hepatocarcinoma [9], multiple myeloma [10], lung cancer [19], laryngeal carcinoma [20] and colorectal carcinoma [21]. It is known to us that AAT is the main serine protease inhibitor and can inhibit neutrophil elastase [22–24]. It is synthesized in the liver primarily and also appeared in peripheral blood monocytes, alveolar macrophages and epithelial cells of the bronchial and gastrointestinal mucosa [25, 26]. AAT may have the ability to suppress the blastogenic or cytotoxic reactions of lymphocytes by inhibiting T cell-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity and natural killer-cell activity [27]. These biological behaviors regulate host immunodefence mechanisms and make it in favor of tumor cells [28]. It also can be degraded by matrix metalloproteinase and produce a COOH-terminal fragment, which increases the ability of tumor growth and invasion in vivo [29]. In our study, the fact that the high percentage of α1-globulin had a significant correlation with tumor status and pathological stage would support the hypothesis. Li et al. [11] showed that the increased serum AAT concentration was a poor prognosis marker for NSCLC, regardless of carrier status. Our finding suggested that a higher percentage of α1-globulin may indicate a tendency for a worse outcome. The percentage of α1-globulin in serum protein should be a potent prognostic factor in the present study.

Interestingly, a high percentage of γ-globulin in serum protein was a poor prognostic factor in lung cancer only in the univariate analysis (univariate analysis, $p = 0.014$; multivariate analysis, $p = 0.169$). This finding was also seen in the absolute value of globulin with marginal p value ($p = 0.080$). Some researchers have confirmed that intravenous injection of IgG treatment in murine melanoma reduced the number of lung metastases and prolonged survival time of mice [30]. In this study, the high percentage of γ-globulin was significantly associated with tumor status (data not shown). The high concentration of γ-globulin may be useless to the tumor because of high frequency of tumor antigen modulation. This made the tumor escape from the immune system and promote infiltration. The repeated stimulation from the antigen increased the

concentration of γ-globulin. However, this view cannot be confirmed at this moment. The exact mechanism and the association of γ-globulin with clinicopathologic factors need more clinical data and experiments.

Albumin has also been shown to be an independent prognostic factor in lung cancer in other study [31]. In the present study, albumin was a significant prognostic factor in univariate analysis, but not in multivariate analysis. The result was the same with Kobayashi et al. [32]. The absolute value of albumin was significantly associated with tumor status, histology type and tumor differentiation (data not shown). Furthermore, albumin also reflects the nutrition status, which is highly associated with sex, age and many other factors. Since these factors were adjusted in the multivariate analysis, albumin was not a statically significant prognostic factor.

Our study had several significant strengths. Firstly, the sample size was reasonably large. Secondly, the histology type and tumor characteristics were properly defined. Detailed clinical information was extracted from the professional and well-established Bio-Bank. The information was carefully and completely collected, with high quality control procedures. Thirdly, the long follow-up time increased the statistical power to detect the effect on survival. Fourthly, we focused on the questions that have never been investigated, and the results can be easily applied for clinical. Nevertheless, our study did have limitations. The principal methodological limitation was the retrospective use of medical records for data collection. The serum of the patients enrolled in the study was impossible to be collected. So it was difficult to conduct Western blot or ELISA to detect the serum concentration of AAT in a subset of high and low α1-globulin samples with short and long survival. The association of these serum proteins with lung cancer-specific biomarkers was not studied since the clinical data were not sufficient. It has been reported that AAT could be used as a serological biomarker for predicting the utility of EGFR-TKI treatment for advanced NSCLC [33]. The future study should concentrate on the impact of α1-protein fraction on the response of specific therapy. A prospective study is required to determine the prognostic and treatment value of α1-protein.

Conclusion

In conclusion, our results showed that the percentage of α1-globulin in serum protein was an independent prognostic factor in lung cancer. Our findings will add constructively to the existing knowledge about the promising serum biomarkers on lung cancer prognosis. The subject for future investigation is to confirm the finding and figure out the mechanisms.

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Conflict of interest The authors have no conflicts of interest to declare.

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