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# Alpha 1-Antitrypsin Deficiency Carriers, Serum Alpha 1-Antitrypsin Concentration, and Non-Small-Cell Lung Cancer Survival

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## Abstract

**Introduction—**Although the association between alpha 1-antitrypsin deficiency ($\alpha_1$ATD) carriers and lung cancer risk has been found, the effects of $\alpha_1$ATD carriers and serum alpha 1-antitrypsin ($\alpha_1$AT) concentration on non-small-cell lung cancer (NSCLC) survival remained unclear.

**Methods—**Patients were selected from the Epidemiology and Genetics of Lung Cancer study at the Mayo Clinic with the criteria of 1) primary NSCLC diagnosis, and 2) available $\alpha_1$ATD carrier status tested by isoelectric focusing serum $\alpha_1$AT concentration by immunonephelometry. The effects of carrier status and serum $\alpha_1$AT concentration on survival were evaluated by Cox proportional hazards models with (1) a landmark approach where overall survival was defined from the time of blood draw to death from any cause, and (2) included only patients with blood draw time prior to initial treatment.

**Results—**1,321 patients were included in this study, with 179 $\alpha_1$ATD carriers and 1,142 non-carriers. No differences in overall survival by $\alpha_1$ATD carrier status were found [adjusted hazard ratio (AHR): 0.98; 95% CI: 0.82-1.18]. However, serum $\alpha_1$AT concentration was significantly associated with survival among all patients in the landmark model [AHR per 50 mg/dL increments: 1.15; 95% CI: 1.10-1.20] and among patients whose blood were drawn for serum $\alpha_1$AT level assessment before any treatment [AHR per 50 mg/dL increments: 1.44; 95% CI: 1.21-1.71].

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**Conclusions—**Being an $\alpha_1$ATD carrier had no significant effect on NSCLC survival. The increased serum $\alpha_1$AT concentration was a poor prognosis marker for NSCLC, regardless of carrier status.

### Keywords

alpha 1-antitrypsin; alpha 1-antitrypsin deficiency; non-small-cell lung cancer; survival

## INTRODUCTION

Lung cancer has been the leading cause of cancer death for both men and women in the United States and many regions of the world for approximately 40 years.[1] Substantial efforts have been made to identify prognostic factors that can be used for better disease management and improvement of survival. To date, only a few prognostic factors such as TNM stage have been established for determining patient management and predicting clinical outcome; however, they still cannot predict individuals' prognosis accurately within the same stage. Clinicians and researchers have been prompted by this issue to contemplate whether the aggressive nature of lung cancer is genetically predetermined and whether the differences in gene expressions could be identified as additional useful clinical outcome predictors.

Alpha 1-antitrypsin deficiency ($\alpha_1$ATD) is one of the most common genetic disorders affecting the Caucasian population, especially European descendants. It is an autosomal codominant disorder and characterized by a low serum concentration of alpha 1-antitrypsin ($\alpha_1$AT).[2] $\alpha_1$AT is the main blood-borne serine protease inhibitor of a broad range of proteases, the primary function of which is the inhibition of neutrophil elastase.[3-7] Our previous studies have shown that being an $\alpha_1$ATD carrier (i.e., heterozygous individuals who carry one deficient allele of the *SERPINA1* gene) is an independent risk factor for lung cancer.[8] The relationship between $\alpha_1$ATD carrier status and lung cancer prognosis is largely unknown. Several studies have reported that patients with $\alpha_1$AT expression in their tumor cells had worse prognosis than those without $\alpha_1$AT expression, suggesting that $\alpha_1$AT production in tumor cells may relate to more aggressive behavior in some cancers, including lung cancer.[9] Elevated serum $\alpha_1$AT concentration has been found in lung cancer patients compared to people without lung cancer.[10,11] However, the association of serum $\alpha_1$AT concentration with lung cancer prognosis has not been studied. The goals of this study were to investigate whether $\alpha_1$ATD carrier status and serum $\alpha_1$AT concentration could affect survival in non-small-cell lung cancer (NSCLC) patients.

## MATERIALS AND METHODS

### Study population and design

This is a follow up study of our initial report on "Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk" in 2008.[8] Since 1997, patients with histologically confirmed primary NSCLC have been recruited prospectively into the Epidemiology and Genetics of Lung Cancer study at Mayo Clinic. All study subjects were enrolled following a procedure approved by the Mayo Clinic Institutional Review Board.[12, 13] Informed consent was obtained from each subject and blood samples for genotyping and serum measurement were collected after recruitment into study. Serum/plasma samples were separated and stored at −80°C. We limited our study samples to 1,321 patients whose $\alpha_1$ATD carrier status and serum $\alpha_1$AT concentration have been tested in our earlier study,[8] by isoelectric focusing[14] and immunonephelometry,[15] respectively. Of the 1,321 patients, 179 were $\alpha_1$ATD carriers and 1,142 were non-carriers.

### Patient follow up and data collection

After initial enrollment for study, all patients were actively followed with subsequent six month and annual follow-up by mailed questionnaires. Annual verification of patients' vital status was accomplished through the use of Mayo Clinic's electronic medical notes and registration database, next-of-kin reports, death certificates, and obituary documents filed in patient medical records, as well as the Mayo Clinic Tumor Registry and Social Security Death Index website. Full medical record abstraction was conducted to obtain the following variables for the 1,321 patients: age, gender, race, smoking history including smoking status and pack-years, histologic cell type, TNM stage[16], treatment modality, blood draw time for serum $\alpha_1$AT measurement, and other medical conditions.

### Statistical methods

Patient characteristics were compared between $\alpha_1$ATD carriers and non-carriers using a Pearson's $\chi 2$ test for categorical variables, and a Student's t test was used for continuous variables. Overall survival (OS) was defined as the time from NSCLC diagnosis to death. Patients who were alive at the last contact were censored. Univariate and multivariate Cox proportional hazards (PH) models were used to evaluate the prognostic impact on survival of all factors of interest. Factors were included in multivariate models if the *P* value was $< 0.05$ in the univariate analysis. Since blood draw times for $\alpha_1$AT serum concentration varied from baseline to months after diagnosis or treatment, two models were applied to investigate the effect of $\alpha_1$AT serum concentration on survival. First, a Cox PH model with a landmark approach was used with survival time defined as time from the date of blood draw to death. Patients who had a serum $\alpha_1$AT value were included in this analysis. In order to eliminate the potential confounding effect of treatment on serum $\alpha_1$AT concentration, a second model was performed only including those who had their blood draw before the initiation of any treatment. In this model, survival time was calculated as OS described above. HRs associated with a 50 mg/dL increase in serum $\alpha_1$AT are reported for a clinically useful interpretation. All analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, NC).

## RESULTS

### Patient characteristics and univariate analysis

Data for this analysis was frozen on August 19, 2010. Median follow-up time for the 326 patients who were alive at the time of analysis was 8.1 years with 90% patients had a follow-up time beyond 5 years. One hundred and thirty two (74%) patients in the carriers group and 863 (76%) in the non-carriers group have died at the time of analysis. The median OS was 2.9 years (95% CI: 2.3-4.0) in the carriers group and 2.7 years (95% CI: 2.4-3.0) in the non-carriers group. Among carriers, there were 106 (59%) MS (including subtypes MS, M1S, and M2S), 44 (25%) MZ (including subtypes MZ, M1Z, and M2Z), and 29 (16%) other uncommon $\alpha_1$ATD carriers (including M[null], MI, SZ, etc.). For further quality control, serum $\alpha_1$AT values for carriers whose $\alpha_1$AT concentration was >250 mg/dL (n=10) and non-carriers >500 mg/dL (n=18) were considered outliers (from Mayo Clinic normal value of 100-190mg/dL) and excluded from all analyses.

Demographic, tumor, and treatment characteristics are listed in Table 1 by carrier status. There were no significant differences in age, gender, race, stage, smoking status, pack years, cell type, and initial treatment between $\alpha_1$ATD carriers and non-carriers. The median serum $\alpha_1$AT concentration in carriers was 127 mg/dL (range: 56-249) compared to 178.0 mg/dL (range: 88-496) in non-carriers. There were a total of 135 patients (17 carriers and 118 non-carriers) with blood draw before the initiation of any treatment (10% of the total sample).

In univariate analysis, gender, stage, and cell type ($P<0.05$) were all significantly associated with OS. There was a significant association of serum $\alpha_1$AT with OS. Carrier status, age, race, smoking status and pack years were not significantly associated with OS (Table 2).

### Multivariate analysis

After adjusting for gender, stage and cell type, no survival differences by carrier status was found in NSCLC (HR: 0.98; 95% CI, 0.82-1.18; $P=0.83$). A significant association between serum $\alpha_1$AT concentration and OS was observed in the Cox PH model using the landmark approach (adjusted HR per 50 mg/dL increments: 1.15; 95% CI: 1.10-1.20; $P<0.0001$) in the presence of gender, stage, cell type, and carrier status. In the subgroup of patients who had their blood draw before treatment, the significant association remained, with an even bigger effect (adjusted HR per 50 mg/dL increments: 1.44; 95% CI: 1.21-1.71; $P<0.0001$). The results are shown in Table 3.

## DISCUSSION

To our best knowledge, this is the first study investigating the roles of $\alpha_1$ATD carriers and serum $\alpha_1$AT concentration on NSCLC survival. Although no difference on overall survival by carrier status was found, there were significant survival differences by $\alpha_1$AT serum concentration in patients with NSCLC, regardless of carrier status. Our study results revealed that potential prognostic role of $\alpha_1$AT concentration in NSCLC may be clinically useful to both carriers and non-carriers.

At least 10 million Americans and 120 million people worldwide are $\alpha_1$ATD carriers, who do not normally have severe $\alpha_1$ATD-related diseases, and most of them are not aware of their carrier status.[17] Although there have been multiple studies investigating the role of $\alpha_1$ATD carriers and risk of developing cancer, little is known about the potential prognostic impact of $\alpha_1$ATD carrier status on lung cancer survival. In our analysis of patients with lung cancer, no association between $\alpha_1$ATD carriers and survival was found. There are several potential explanations. First, the differences between $\alpha_1$ATD carriers and non-carriers may be too small to affect the overall course of NSCLC in the current study, thus the subtle difference can not be detected even though the sample size of our study was relatively large. Second, the malignancy may have developed mechanisms to act against the effect of carrying an $\alpha_1$ATD allele. Third, being an $\alpha_1$ATD carrier may have no impact on NSCLC survival.

$\alpha_1$AT is the major serine protease inhibitor in human plasma, which is synthesized primarily in the liver and, to a lesser extent, in peripheral blood monocytes, alveolar macrophages, and epithelial cells of the bronchial and gastrointestinal mucosa.[18-20] Researchers have been searching for a correlation between $\alpha_1$AT and the process of neoplasia, which may help in the diagnosis and the follow up of cancer patients. Various studies have been performed in different types of cancer, such as lung, liver, prostate, pancreases, cervix, and colorectal. Several studies reported an elevation of $\alpha_1$AT in cancer patients.[10, 11, 21-25] Additionally, multiple studies have shown some links between $\alpha_1$AT expression levels and cancer prognosis, but the conclusions were inconsistent.[24, 26-28] What we currently know about $\alpha_1$AT led us to believe that this protease inhibitor substance may play a role in NSCLC survival. A higher $\alpha_1$AT concentration was significantly associated with worse survival in patients with NSCLC in our study. There are several possible mechanisms to explain this finding. First, $\alpha_1$AT may have a function of modulating host-immunodefence mechanisms in favor of tumor cells, which may suppress the blastogenic or cytotoxic reactions of lymphocytes by inhibiting T cell-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and natural killer-cell activity.[9] Second, the participation of $\alpha_1$AT in tumoral invasiveness seems to be related to its degradation by matrix metalloproteinase, resulting in

the production of a COOH-terminal fragment that increases tumor growth in vivo.[29] Our findings suggest that $\alpha_1$AT serum concentration evaluation may be clinically useful in recognizing patients who are more likely to develop a worse outcome in NSCLC. Specifically, a higher serum $\alpha_1$AT concentration may indicate a tendency for a worse outcome.

Our study has several significant strengths. First, the sample size is reasonably large. Second, the disease phenotype (tumor characteristics) was properly defined. Detailed epidemiological and clinical information were carefully and completely collected, with thorough quality control procedures. Third, the long follow-up time increased the statistical power to detect the effect on survival. However, our study does have limitations. First, although we tried our best to get the patients' blood samples as soon as possible, still the majority of blood samples could not be drawn before treatment. Therefore when the association between serum $\alpha_1$AT concentration and NSCLC survival was evaluated, the date of blood draw was used as baseline instead of NSCLC diagnosis to measure survival. We further examined a subgroup of patients with blood draw before treatment, where NSCLC diagnosis date was used at starting point to assess survival. The effect of serum $\alpha_1$AT on survival became even bigger in these patients (adjusted HR per 50 mg/dL increments: 1.44; 95% CI: 1.21-1.71). In this way, the association between serum $\alpha_1$AT concentration and NSCLC survival was further demonstrated with a higher $\alpha_1$AT levels corresponding to worse survival outcome. Second, no data was available on some other potential prognostic factors for survival in the database (e.g., ECOG Performance Status and comorbidity information). Finally, there may be multiple other genes and modulators involved in the *SERPINA1* gene mutation, expression, and serum $\alpha_1$AT concentration, which should be incorporated into the future studies, as well.

In conclusion, we did not find a significant association between $\alpha_1$ATD carriers and overall survival in NSCLC patients. However, our results indicate that the $\alpha_1$AT serum concentration may be a biological marker of potential prognostic significance in NSCLC, regardless of carrier status. Our findings will add constructively to the existing body of knowledge about the promising serum biomarkers on NSCLC prognosis. Future studies are warranted to confirm these findings and their clinical application values.

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## REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2009. CA Cancer J Clin. 2009; 59:225–249. [PubMed: 19474385]
2. Krowka MJ. Recent pulmonary observations in alpha 1-antitrypsin deficiency, primary biliary cirrhosis, chronic hepatitis C, and other hepatic problems. Clin Chest Med. 1996; 17:67–82. [PubMed: 8665791]
3. Khan H, Salman KA, Ahmed S. Alpha-1 antitrypsin deficiency in emphysema. J Assoc Physicians India. 2002; 50:579–582. [PubMed: 12164415]
4. Luft FC. Alpha-1-antitrypsin and its relevance to human disease. J Mol Med. 1999; 77:359–360. [PubMed: 10353439]
5. Perlmutter DH. Liver injury in alpha1-antitrypsin deficiency: an aggregated protein induces mitochondrial injury. J Clin Invest. 2002; 110:1579–1583. [PubMed: 12464659]

6. Yang P, Tremaine WJ, Meyer RL, et al. Alpha1-antitrypsin deficiency and inflammatory bowel diseases. Mayo Clin Proc. 2000; 75:450–455. [PubMed: 10807072]
7. Coakley RJ, Taggart C, O'Neill S, et al. Alpha1-antitrypsin deficiency: biological answers to clinical questions. Am J Med Sci. 2001; 321:33–41. [PubMed: 11202478]
8. Yang P, Sun Z, Krowka MJ, et al. Alpha1-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. Arch Intern Med. 2008; 168
9. Higashiyama M, Doi O, Kodama K, et al. An evaluation of the prognostic significance of alpha-1-antitrypsin expression in adenocarcinomas of the lung: an immunohistochemical analysis. Br J Cancer. 1992; 65
10. Harris CC, Cohen MH, Connor R, et al. Serum alpha1-antitrypsin in patients with lung cancer or abnormal sputum cytology. Cancer. 1976; 38:1655–1657. [PubMed: 1086707]
11. Daddi G, Mancini PA, Parola D, et al. Alfa-antitrypsin increase in lung cancer. Boll Ist Sieroter Milan. 1976; 55:510–512. [PubMed: 1088073]
12. Yang P, Allen MS, Aubry MC, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. Chest. 2005; 128:452–462. [PubMed: 16002972]
13. Yang P, Wentzlaff KA, Katzmann JA, et al. Alpha1-antitrypsin deficiency allele carriers among lung cancer patients. Cancer Epidemiol Biomarkers Prev. 1999; 8:461–465. [PubMed: 10350443]
14. Tietz, NW. Clinical Guide to Laboratory Tests. 2nd ed.. WB Saunders Co.; Philadelphia, PA: 1990.
15. Beckman Instructions 015-247517-E. Beckman Instruments, Inc.; Brea, CA: 1994.
16. Greene, FL.; Page, DL.; Fleming, ID., et al. AJCC Cancer Staging Manual. Springer; New York, NY: 2002. p. 91-98.
17. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. Lancet. 2005; 365:2225–2236. [PubMed: 15978931]
18. Haviland DL, McCoy RL, Whitehead WT, et al. Cellular expression of the C5a anaphylatoxin receptor (C5aR): demonstration of C5aR on nonmyeloid cells of the liver and lung. J Immunol. 1995; 154:1861–1869. [PubMed: 7836770]
19. Faust D, Raschke K, Hormann S, et al. Regulation of alpha1-proteinase inhibitor release by proinflammatory cytokines in human intestinal epithelial cells. Clin Exp Immunol. 2002; 128:279–284. [PubMed: 11985518]
20. Cichy J, Potempa J, Travis J. Biosynthesis of alpha1-proteinase inhibitor by human lung-derived epithelial cells. J Biol Chem. 1997; 272:8250–8255. [PubMed: 9079644]
21. Dabrowska M, Mantur M, Panasiuk A, et al. Does the concentration of alpha 1-proteinase inhibitor reflect the transformation of liver cirrhosis to liver carcinoma? Neoplasma. 1997; 44:305–307. [PubMed: 9473790]
22. Tountas Y, Sparos L, Theodoropoulos C, et al. Alpha 1-antitrypsin and cancer of the pancreas. Digestion. 1985; 31:37–40. [PubMed: 3872237]
23. Ward AM, Cooper EH, Turner R, et al. Acute-phase reactant protein profiles: an aid to monitoring large bowel cancer by CEA and serum enzymes. Br J Cancer. 1977; 35:170–178. [PubMed: 13805]
24. Ward AM, Cooper EH, Houghton AL. Acute phase reactant proteins in prostatic cancer. Br J Urol. 1977; 49:411–418. [PubMed: 73395]
25. Latner AL, Turner GA, Lamin MM. Plasma alpha-1-antitrypsin levels in early and late carcinoma of the cervix. Oncology. 1976; 33:12–14. [PubMed: 1086450]
26. Huang H, Campbell SC, Nelius T, et al. Alpha1-antitrypsin inhibits angiogenesis and tumor growth. Int J Cancer. 2004; 112:1042–1048. [PubMed: 15316942]
27. Tahara E, Ito H, Taniyama K, et al. Alpha 1-antitrypsin, alpha 1-antichymotrypsin, and alpha 2-macroglobulin in human gastric carcinomas: a retrospective immunohistochemical study. Hum Pathol. 1984; 15:957–964. [PubMed: 6207098]
28. Simpson WG, Heys SD, Whiting PH, et al. Acute phase proteins and recombinant IL-2 therapy: prediction of response and survival in patients with colorectal cancer. Clin Exp Immunol. 1995; 99:143–147. [PubMed: 7531626]

29. Kataoka H, Uchino H, Iwamura T, et al. Enhanced tumor growth and invasiveness in vivo by a carboxyl-terminal fragment of alpha1-proteinase inhibitor generated by matrix metalloproteinases: a possible modulatory role in natural killer cytotoxicity. Am J Pathol. 1999; 154:457–468. [PubMed: 10027404]

## Table 1
## Characteristics of 1,321 non-small-cell lung cancer patients

| Patient Characteristics | $\alpha_1$ATD Carriers (179) No. (%) | $\alpha_1$ATD Non-carriers (1142) No. (%) | *P* value |
|---|---|---|---|
| **Age** | | | 0.88 |
| Mean (SD) | 65.7 (10.2) | 65.4 (11.1) | |
| Median (range) | 67.0(37.0-86.0) | 67.0 (18.0-92.0) | |
| **Gender** | | | 0.74 |
| Female | 78 (43.6) | 513 (44.9) | |
| Male | 101 (56.4) | 629 (55.1) | |
| **Race** | | | 0.13 |
| Caucasian | 162 (90.5) | 1067 (93.6) | |
| Non-Caucasian | 17 (9.5) | 73 (6.4) | |
| Missing | 0 | 2 | |
| **Stage** | | | 0.79 |
| I | 75 (41.9) | 440 (38.5) | |
| II | 18 (10.1) | 109 (9.5) | |
| III | 47 (26.3) | 314 (27.5) | |
| IV | 39 (21.8) | 279 (24.4) | |
| **Smoking status** | | | 0.69 |
| Never | 27 (15.2) | 169 (15.2) | |
| Former | 96 (53.9) | 633 (56.9) | |
| Current | 55 (30.9) | 310 (27.9) | |
| Missing | 1 | 30 | |
| **Pack years** | | | 0.77 |
| Never smokers | 27 (15.1) | 168 (14.7) | |
| ≤40 | 65 (36.3) | 405 (35.5) | |
| >40 and <60 | 34 (19.0) | 255 (22.4) | |
| ≥60 | 53 (29.6) | 312 (27.4) | |
| Missing | 0 | 2 | |
| **Histologic cell type** | | | 0.36 |
| Adenocarcinoma | 99 (55.3) | 682 (59.7) | |
| Squamous | 57 (31.8) | 305 (26.7) | |
| Others[†] | 23 (12.8) | 155 (13.6) | |
| **Initial treatment** | | | 0.33 |
| Surgery | 93 (54.7) | 650 (60.0) | |
| Radiation or chemotherapy, or both | 60 (35.3) | 322 (30.7) | |
| Other or none | 17 (10.0) | 111 (10.3) | |
| Missing | 9 | 59 | |
| **Serum $\alpha_1$AT concentration, mg/dL** | | | <0.0001 |
| Mean (SD) | 138.6 (42.09) | 199.3 (70.99) | |
| Median (range) | 127.0 (56.0-249.0) | 178.0 (88.0-496.0) | |

| Patient Characteristics | $\alpha_1$ATD Carriers (179) No. (%) | $\alpha_1$ATD Non-carriers (1142) No. (%) | *P* value |
|---|---|---|---|
| Missing or outliers | 10 | 8 | |

Abbreviations: $\alpha_1$ATD, alpha 1-antitrypsin deficiency; $\alpha_1$AT, alpha 1-antitrypsin; $\alpha_1$AT, alpha-1 antitrypsin; SD, standard deviation.

† Includes large cell, not specified non-small-cell lung cancer, adenosquamous carcinoma, sarcomatoid, and other mixed cell types.

## Table 2

### Univariate analysis

| Patient characteristics | Unadjusted HR (95% CI) | *P* value |
|---|---|---|
| **Age** (10 years increase) | 1.02 (0.96, 1.09) | 0.47 |
| **Gender** | | |
| Female | Reference | |
| Male | 1.19 (1.05, 1.35) | 0.01 |
| **Race** | | |
| Non-Caucasian | Reference | |
| Caucasian | 1.27 (0.98, 1.65) | 0.07 |
| **Stage** | | |
| I | Reference | |
| II | 1.94 (1.55, 2.44) | <.0001 |
| III | 3.15 (2.67, 3.71) | <.0001 |
| IV | 5.04 (4.25, 5.96) | <.0001 |
| **Smoking status** | | |
| Never | Reference | |
| Former | 0.98 (0.82, 1.18) | 0.85 |
| Current | 0.90 (0.74, 1.10) | 0.32 |
| **Pack years** | | |
| Never smokers | Reference | |
| ≤40 | 0.91 (0.75, 1.10) | 0.33 |
| >40 and <60 | 1.01 (0.82, 1.24) | 0.93 |
| ≥60 | 1.03 (0.84, 1.26) | 0.77 |
| **Histologic cell type** | | |
| Other cell type | Reference | |
| Adenocarcinoma | 0.67 (0.56, 0.81) | <0.0001 |
| Squamous | 0.77 (0.63, 0.94) | 0.01 |
| **$\alpha_1$ATD carrier status**[¶] | | |
| Non-carriers | Reference | |
| Carriers | 0.93 (0.77, 1.12) | 0.43 |
| **Serum level of $\alpha_1$AT** (50 unit increase) | | |
| In all patients[†] | 1.13 (1.09, 1.18) | <.0001 |
| In patients whose blood were drawn before initial treatment[‡] | 1.39 (1.19, 1.63) | <.0001 |

Abbreviations: $\alpha_1$ATD, alpha 1-antitrypsin deficiency; $\alpha_1$AT, alpha 1-antitrypsin; HR, hazard ratio; CI: confidence interval.

Other cell type includes large cell, not specified non-small-cell lung cancer, adenosquamous carcinoma, sarcomatoid, and other mixed cell types.

[¶]N=1321, number of events= 995.

[†]Cox Proportional Hazard model with Landmark Approach. Survival time was calculated from the date of the blood draw to death. N= 1303, number of events= 982.

[‡]N= 128, number of events= 110.

## Table 3

### Multivariate analysis

| | Adjusted HR (95% CI) | *P* value |
|---|---|---|
| **$\alpha_1$ATD carrier status**[¶] | | |
| Non-Carriers | Reference | |
| Carriers | 0.98 (0.82, 1.18) | 0.83 |
| **Serum level of $\alpha_1$AT (50 mg/dL increase)** | | |
| In all patients[‡†] | 1.15 (1.11, 1.21) | <0.0001 |
| In patients whose blood were drawn before initial treatment[‡] | 1.43 (1.21, 1.70) | <0.0001 |

Abbreviations: $\alpha_1$AT, alpha1-antitrypsin; $\alpha_1$ATD, alpha 1-antitrypsin deficiency; HR, hazard ratio; CI: confidence interval.

[¶]Adjusted for gender, cell type, and stage.

[†]Cox Proportional Hazard model with Landmark Approach. Survival time was calculated from the date of the blood draw to death. Adjusted for gender, stage, cell type, and carrier status. N= 1303, number of events=982.

[‡]Adjusted for gender, stage, cell type, and carrier status. N= 128, number of events=110.