Brief Report

The impact of alpha-1 antitrypsin deficiency alleles on lung cancer survival

José María Hernández-Pérez[1]^, Carolina Ramos-Izquierdo[1], Juan Marco Figueira-Gonçalves[1,2], Francisco Martínez-Bugallo[3], Yolanda Ramallo-Fariña[4,5,6], Lorenzo Pérez-Negrín[1]

[1]Respiratory Medicine, University Hospital "Nuestra Señora de Candelaria", Santa Cruz de Tenerife, Spain; [2]University Institute of Tropical Diseases and Public Health of the Canary Islands, University of La Laguna, Santa Cruz de Tenerife, Spain; [3]Genetics Unit, Clinical Analysis Department, University Hospital "Nuestra Señora de Candelaria", Santa Cruz de Tenerife, Spain; [4]Canary Foundation Health Research Institute of the Canary Islands (FIISC), Santa Cruz de Tenerife, Spain; [5]Health Services Research Network in Chronic Diseases (REDISSEC), Madrid, Spain; [6]Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS), Madrid, Spain

Correspondence to: José María Hernández Pérez, MD, PhD. Respiratory Medicine, University Hospital "Nuestra Señora de Candelaria", Carretera del Rosario 145, 38710 Santa Cruz de Tenerife, Spain. Email: jmherper@hotmail.com.

Abstract: Different studies have shown that carrying an alpha-1 antitrypsin (AAT) deficiency allele is an independent risk factor for developing lung cancer (LC). However, to date, little is known regarding whether carrying a deficiency allele may be a prognostic factor in the evolution of LC. A prospective observational study was carried out which consecutively included patients diagnosed with LC in University Hospital "Nuestra Señora de Candelaria" between December 2017 and August 2020. A blood sample was taken from each of the patients in order to determine both AAT serum concentration and genotype. Based on AAT genotype, patients were divided into the deficiency (*Pi**≠MM*) or non-deficiency (*Pi**=MM*) group. One hundred and sixty-four patients were included. The average length of follow-up was 13±10 months. Patients were classified as stage I (4.2%), stage II (8.3%), stage III (31.2%) and stage IV (56.3%), according to tumour, node and metastasis (TNM) staging. Twenty-eight patients (17%) were carriers of a deficiency allele (6 *Pi**MS*, 1 *Pi**MZ*, 1 $Pi^*MM_{beerlen}$). No significant differences were found with respect to baseline characteristics between *Pi**≠MM* and *Pi**=MM*. Patients in the *Pi**≠MM* group had a higher risk of death in the first 6 months after the LC diagnosis compared to *Pi**=MM* subjects (HR =2.04; 95% CI: 1.04–4.0; P=0.038). The presence of an AAT deficiency genotype could be a potential prognostic marker in LC. However, larger studies that justify these findings are needed.

Keywords: Lung cancer (LC); alpha-1 antitrypsin (AAT); mortality; alpha-1 antitrypsin deficiency (AAT deficiency); neoplasia

Submitted Apr 29, 2023. Accepted for publication Dec 07, 2023. Published online Feb 22, 2024.
doi: 10.21037/tcr-23-743
View this article at: https://dx.doi.org/10.21037/tcr-23-743

Introduction

Lung cancer (LC) is considered to be one of the leading causes of cancer-related mortality in many regions around the world (1). Beyond the tumour, node and metastasis (TNM) staging system (2), few prognostic factors have been identified to allow us to predict patients' future evolution in our routine clinical practice.

Alpha-1 antitrypsin (AAT) is a water-soluble glycoprotein primarily synthesized in the hepatocytes (80%) (3). *Pi*M* (Pi: protease inhibitor) is the most common allele and is present in over 90% of normal subjects, with the most common deficiency alleles being *Pi*S* and *Pi*Z* (4).

^ ORCID: 0000-0002-2920-212X.

Different studies have shown that carrying an AAT deficiency allele is an independent risk factor for developing LC (5-9). However, to date, little is known regarding whether carrying a deficiency allele may be a prognostic factor in the evolution of LC. We present this article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-743/rc).

Methods

A prospective observational study was carried out which consecutively included patients diagnosed with LC in University Hospital "Nuestra Señora de Candelaria" between December 2017 and August 2020.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the University Hospital "Nuestra Señora de Candelaria" (Code PI 75-17), and informed consent was taken from all the patients. The inclusion criteria were: >18 years old with an LC diagnosis confirmed with histological study. The existence of a concomitant infection at the time of diagnosis, starting active oncological treatment before the blood extraction (determining AAT protein serum levels/AAT genotype) and/or the patient declining to participate in the study were reasons for exclusion. Patients' age, tobacco history, body mass index, AAT serum levels at the time of diagnosis, AAT genotype, histological LC type and comorbidities (arterial hypertension, dyslipidemia, diabetes mellitus, heart failure, atrial fibrillation, ischemic heart disease, stroke and chronic kidney disease) were recorded. LC extension was determined using the 8th edition TNM staging system (2), and the age adjusted Charlson comorbidity index (CCI) was calculated.

A blood sample was taken from each of the patients in order to determine both AAT serum concentration and genotype. AAT serum values were determined using nephelometry (BN ProSpec System, Siemens, Berlin, Germany). Genomic DNA was purified from EDTA whole blood (MagCore® Genomic DNA Whole Blood Kit, RBC Bioscience, Buenos Aires, Argentina). The two most common deficiency alleles (*PI*S* and *PI*Z*) were genotyped using real-time polymerase chain reaction (PCR) with TaqMan probes (Applied Biosystems 7500, Thermo Fisher Scientific, Waltham, USA). The genotypes obtained were correlated with the reference AAT plasma values at University Hospital "Nuestra Señora de Candelaria". Patients with AAT serum levels that did not match those expected for the S/Z genotypes obtained underwent complete sequencing of the coding exons and flanking intronic regions of the SERPINA1 gene using an AB3500 capillary sequencing instrument (Applied Biosystems), comparing the results obtained with the reference sequence NM_001127701.1 (SeqScape 3.0, Thermo Fisher Scientific). Based on AAT genotype, patients were divided into the deficiency (*Pi*≠MM*) or non-deficiency (*Pi*=MM*) group.

Student's *t*-test was used for continuous variables and the Chi-square test and Fisher's exact test were used for categorical variables. The survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate survival analyses were carried out using the Cox proportional hazards regression model and confidence intervals of 95% were estimated for the hazard ratio (HR). The assumed constant HR was verified (χ^2=0.43; P=0.511). This statistical analysis used IBM SPSS (Statistical Package for the Social Sciences) version 22.0 (IBM Corp., Armonk, NY, USA). P values ≤0.05 (bilateral) were considered significant.

Results

Of the 167 patients initially included, the analysis was carried out in 164 (3 patients were lost to follow-up). They were primarily male (63.4%), with an average age of 64.5±9.1 years and 52.4% were current smokers; the average CCI score was 8±2. The average length of follow-up was 13±10 months. Ninety-two patients (56.1%) passed away, with an average follow-up of 9±7 months. The most frequent histological type of LC was adenocarcinoma (40.9%). Patients were classified as stage I (4.2%), stage II (8.3%), stage III (31.2%) and stage IV (56.3%), according to TNM staging.

Twenty-eight patients (17%) were carriers of a deficiency allele (26 *Pi*MS*, 1 *Pi*MZ*, 1 $Pi^*MM_{heerlen}$). No significant differences were found with respect to baseline characteristics between *Pi*≠MM* and *Pi*=MM*, including AAT serum levels (*Tables 1*,*2*). Patients in the *Pi*≠MM* group had a higher risk of death in the first 6 months after the LC diagnosis compared to *Pi*=MM* subjects (HR =2.04; 95% CI: 1.04–4.0; P=0.038) (*Figure 1A*). A second analysis was performed excluding small cell LC, maintaining an increase in mortality in the first 6 months in those subjects carrying deficient alleles (HR =2.24; 95% CI: 1.11–4.55; P=0.025) (*Figure 1B*). This difference is diluted if we

Table 1 Baseline characteristics of patients with lung cancer according to the existence of AAT deficiency

Baseline characteristics	Overall population	According to the existence of AAT deficiency alleles		P
		Pi=MM*, n=136 (82.9%)	*Pi*≠MM*, n=28 (17.1%)	
Male	104 (63.4)	88 (64.7)	16 (57.1)	0.449
Age (years)	64.5±9.1	64.8 (63.3–66.4)	63.4 (60.3–66.5)	0.433
Smoking status				0.387
Former smoker	63 (38.4)	49 (36.0)	14 (50.0)	
Current smoker	86 (52.4)	74 (54.4)	12 (42.9)	
Arterial hypertension	70 (42.7)	59 (43.4)	11 (39.3)	0.690
Dyslipidemia	54 (32.9)	45 (33.1)	9 (32.1)	0.923
Diabetes mellitus	30 (18.3)	23 (16.9)	7 (25.0)	0.313
Heart failure	3 (1.8)	1 (0.7)	2 (7.1)	0.076
Arrhythmia	7 (4.3)	6 (4.4)	1 (3.6)	0.999
Ischemic heart disease	16 (9.8)	12 (8.8)	4 (14.3)	0.481
Stroke	6 (3.7)	3 (2.2)	3 (10.7)	0.063
Chronic kidney disease	7 (4.3)	6 (4.4)	1 (3.6)	0.999
BMI (kg/m^2)	25.9 (24.7–27.2)	25.9 (24.5–27.3)	26.2 (23.8–28.6)	0.854
AAT serum levels (mg/dL)	194.9 (186.3–203.5)	195.9 (186.4–205.4)	185.1 (162.6–207.6)	0.357
Lung cancer histology				0.909
Adenocarcinoma	67 (40.9)	53 (39.0)	14 (50.0)	
Squamous	42 (25.6)	35 (25.7)	7 (25.0)	
Small-cell	20 (12.2)	17 (12.5)	3 (10.7)	
Other	35 (21.3)	31 (22.8)	4 (14.3)	

Data are expressed as n (%), mean (95% CI), or mean ± standard deviation. AAT, alpha-1 antitrypsin; CI, confidence interval; BMI, body mass index; *Pi*=MM*, AAT non-deficiency genotype; *Pi*≠MM*, AAT deficiency genotype.

consider the entire follow-up of the patients (HR =1.44; 95% CI 0.87–2.40; P=0.156 and HR =1.48; 95% CI: 0.88–2.51; P=0.142, respectively), this may be motivated because the group of patients with a genotype from 6 months of follow-up is small in size sample (*Figure 1*). The treatments (surgical or pharmacological) used in both groups according to staging were evaluated, however, no differences were observed in terms of treatment.

Discussion

Different studies have shown that those subjects who are carriers of deficiency alleles, regardless of their degree of tobacco consumption, have a greater risk of developing LC (9,10). With a described prevalence of around 13% (8,9), these figures are slightly lower than those detected in our study, which could be justified by the high prevalence of deficiency alleles in our setting (11). In light of these findings, some authors postulate the theory that in subjects with deficiency alleles, there is a clear protease-antiprotease imbalance originating from low AAT concentrations in the blood and tissues, which would predispose them to a tissue environment that favors carcinogenic action and consequently the development of LC. Other hypotheses postulate that the presence of low AAT levels can promote neoplasm progression by inhibiting the apoptotic capacity of tumor cells that, along with neutrophil elastase, can activate matrix metalloproteinases, a group of enzymes that play a fundamental role in tumor invasion and the origin of metastases (12,13).

Table 2 Baseline characteristics of patients with lung cancer according to the existence of AAT deficiency excluding patients with small cell lung tumor

Baseline characteristics	Population excluding small cell lung tumor	According to the existence of AAT deficiency alleles		P
		Pi=MM*, n=119 (82.6%)	*Pi*≠MM*, n=25 (17.4%)	
Male	91 (63.2)	76 (63.9)	15 (60.0)	0.716
Age (years)	64.6 (63.1–66.1)	64.9 (63.2–66.5)	63.8 (60.6–67)	0.594
Smoking status				0.204
Former smoker	58 (40.3)	44 (37.0)	14 (56.0)	
Current smoker	73 (50.7)	64 (53.8)	9 (36.0)	
Non-smoking	13 (9.0)	11 (9.2)	2 (8.0)	
Arterial hypertension	60 (41.7)	50 (42.0)	10 (40.0)	0.852
Dyslipidemia	50 (34.7)	42 (35.3)	8 (32.0)	0.753
Diabetes mellitus	24 (16.7)	18 (15.1)	6 (24.0)	0.279
Heart failure	3 (2.1)	1 (0.8)	2 (8.0)	0.078
Arrhythmia	7 (4.9)	6 (5.0)	1 (4.0)	0.826
Ischemic heart disease	15 (10.4)	11 (9.2)	4 (16.0)	0.315
Stroke	6 (4.2)	3 (2.5)	3 (12.0)	0.065
Chronic kidney disease	7 (4.9)	6 (5.0)	1 (4.0)	0.999
BMI (kg/m^2)	25.7 (24.4–26.9)	25.6 (24.1–27)	26.2 (23.8–28.6)	0.697
AAT serum levels (mg/dL)	194.6 (185.5–203.7)	195.4 (185.4–205.4)	185.3 (160.7–210)	0.412
Lung cancer histology				0.483
Adenocarcinoma	67 (46.5)	53 (44.5)	14 (56.0)	
Squamous	42 (29.2)	35 (29.4)	7 (28.0)	
Other	35 (24.3)	31 (26.1)	4 (16.0)	
TNM stage				0.302
I	6 (4.2)	4 (3.4)	2 (8.0)	
II	12 (8.3)	10 (8.4)	2 (8.0)	
III	45 (31.2)	40 (33.6)	5 (20.0)	
IV	81 (56.3)	65 (54.6)	16 (64.0)	

Data are expressed as n (%) or mean (95% CI). AAT, alpha-1 antitrypsin; *Pi**=MM, alpha-1 antitrypsin non-deficiency genotype; *Pi*≠MM*, alpha-1 antitrypsin deficiency genotype; BMI, body mass index; TNM, tumour, node and metastasis; CI, confidence interval.

Studies analyzing whether the presence of a deficiency genotype can have any sort of impact on LC prognosis are scarce. Li *et al.* (14) did not find any difference in survival according to carrier status in patients diagnosed with non-small cell LC. However, in our study, those patients with LC (small cell and non-small cell LC) who carried a deficiency allele did show worse survival at 6 months after diagnosis, results that is maintained even after excluding those patients with small cell LC. Compared to the patients included in the study by Li *et al.*, the majority of the subjects in our sample are in advanced stages of the disease and are not suitable for curative surgery, which will influence their prognosis. Given the fact that our sample primarily focuses on stages III and IV, our results provide clinical value in these patients for whom there is not a curative option.

It is important to note that in our sample, there were no

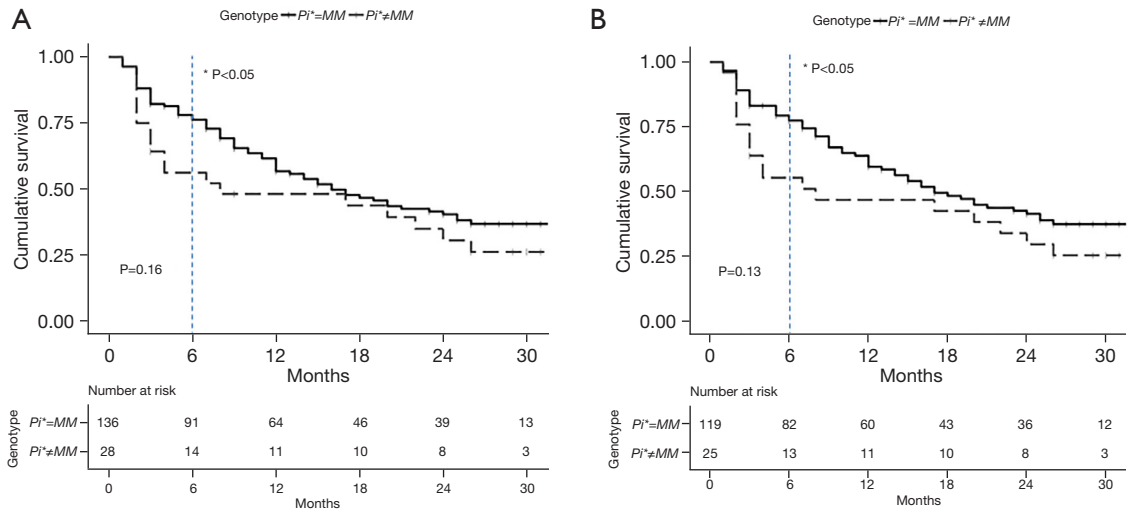

Figure 1 Survival of patients with lung cancer based on the presence of an alpha-1 antitrypsin deficient allele. (A) Kaplan-Mayer curve of cumulative survival between patients with lung cancer with and without altered genotype throughout the follow-up. (B) Kaplan-Mayer curve of cumulative survival between patients with lung cancer with and without altered genotype throughout the follow-up excluding patients with small cell lung tumor. *, P<0.05. *Pi*=MM*, alpha-1 antitrypsin non-deficiency genotype; *Pi*≠MM*, alpha-1 antitrypsin deficiency genotype.

significant differences between AAT serum levels in patients carrying a deficiency allele compared to non-deficiency patients. This leads us to believe that the problem may stem from AAT activity. Its dysfunction would cause an imbalance between protease-antiprotease, not in quantity but rather functionality, where despite normal or even elevated AAT levels, said protein has little or no anti-elastase activity (4,15,16).

The main limitations of this study are its small sample size, the limited number of patients in early stages of the disease and the absence of subjects with the severe deficiency genotype, but the results provide a starting point for future lines of research.

Conclusions

Based on all of this, the presence of an AAT deficiency genotype could be a potential prognostic marker in advanced LC. However, larger studies that justify these findings are needed.

Acknowledgments

Funding: This study was supported by a grant from the Asociación Canaria de Neumología y Cirugía Torácica (NEUMOCAN).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-743/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-743/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-743/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the University Hospital Nuestra Señora de Candelaria (Code PI 75-17), and informed consent was taken from all the patients.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
3. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med 2003;168:818-900.
4. Blanco I, Lara B. Déficit de alfa-1 antitripsina: fisiopatología, enfermedades relacionadas y tratamiento. Respira-Fundación Española del Pulmón-SEPAR. Barcelona; 2016.
5. Tubío-Pérez RA, Torres-Durán M, Fernández-Villar A, et al. Alpha-1 antitrypsin deficiency and risk of lung cancer: A systematic review. Transl Oncol 2021;14:100914.
6. Torres-Durán M, Ruano-Ravina A, Parente-Lamelas I, et al. Alpha-1 Antitrypsin Deficiency and Lung Cancer Risk: A Case-Control Study in Never-Smokers. J Thorac Oncol 2015;10:1279-84.
7. Yang P, Wentzlaff KA, Katzmann JA, et al. Alpha1-antitrypsin deficiency allele carriers among lung cancer patients. Cancer Epidemiol Biomarkers Prev 1999;8:461-5.
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;168:1097-103.
9. Topic AS, Jelic-Ivanovic ZD, Spasojevic-Kalimanovska VV, et al. Association of moderate alpha-1 antitrypsin deficiency with lung cancer in the Serbian population. Arch Med Res 2006;37:866-70.
10. Onur ST, Boyracı N, Akyıl FT, et al. Developing lung cancer in COPD: Possible role of carrying Alpha-1 antitrypsin deficiency variants. Respir Med Case Rep 2022;38:101667.
11. Blanco I, Bueno P, Diego I, et al. Alpha-1 antitrypsin Pi*Z gene frequency and Pi*ZZ genotype numbers worldwide: an update. Int J Chron Obstruct Pulmon Dis 2017;12:561-9.
12. Shamamian P, Schwartz JD, Pocock BJ, et al. Activation of progelatinase A (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: a role for inflammatory cells in tumor invasion and angiogenesis. J Cell Physiol 2001;189:197-206.
13. Yamashita J, Ogawa M, Abe M, et al. Tumor neutrophil elastase is closely associated with the direct extension of non-small cell lung cancer into the aorta. Chest 1997;111:885-90.
14. Li Y, Krowka MJ, Qi Y, et al. Alpha1-antitrypsin deficiency carriers, serum alpha 1-antitrypsin concentration, and non-small cell lung cancer survival. J Thorac Oncol 2011;6:291-5.
15. Owen MC, Brennan SO, Lewis JH, et al. Mutation of antitrypsin to antithrombin. alpha 1-antitrypsin Pittsburgh (358 Met leads to Arg), a fatal bleeding disorder. N Engl J Med 1983;309:694-8.
16. Hiller AM, Ekström M, Piitulainen E, et al. Cancer risk in severe alpha-1-antitrypsin deficiency. Eur Respir J 2022;60:2103200.

Cite this article as: Hernández-Pérez JM, Ramos-Izquierdo C, Figueira-Gonçalves JM, Martínez-Bugallo F, Ramallo-Fariña Y, Pérez-Negrín L. The impact of alpha-1 antitrypsin deficiency alleles on lung cancer survival. Transl Cancer Res 2024;13(2):1125-1130. doi: 10.21037/tcr-23-743

