

Improving Survival among ZZ patients in the AlphaNet Program

Radmila Choate, MPH¹, David M. Mannino, MD¹, Robert A. Sandhaus, MD, PhD², Daniel Barber, MPH, CPH¹, Kristen E. Holm, PhD, MPH²

¹Department of Preventive Medicine and Environmental Health, University of Kentucky- Lexington, KY/US

²National Jewish Health, Denver, CO/US



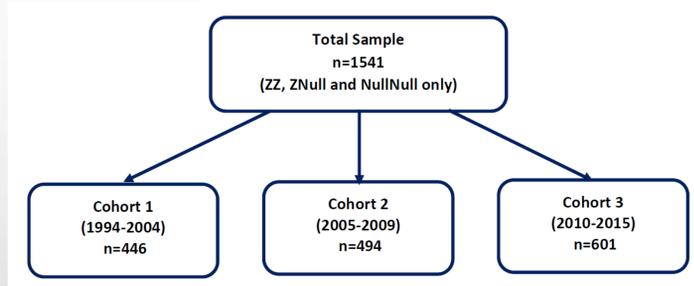
INTRODUCTION

- **AlphaNet** - a non-for-profit organization founded in 1995. It is a health management company that coordinates management and treatment of Alpha-1 antitrypsin deficient patients.
- **Alpa-1 Antitrypsin deficiency (AATD)** - an autosomal co-dominant disorder that results from mutations of the SERPINA1 gene and typically is associated with the increased risk of early onset pulmonary emphysema in adult population, liver disease in children as well as adults and, more rarely, panniculitis- inflammation of the subcutis
- Previous studies of the survival of Alpha-1-antitrypsin (AAT) deficient patients mostly focused on the effects of smoking, gender or overall mortality.
- The aim of the present study is to determine the difference in survival between three cohorts of AAT deficient patients defined by the time of entry into the study in five year intervals- 1) 1999-2004; 2) 2005-2009; 3) 2010-2015.



METHODS

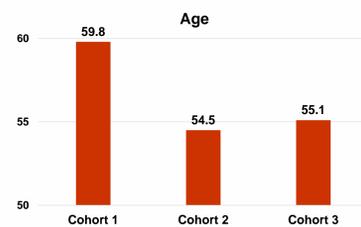
- We analyzed data collected from a sample of 1541 patients with AATD (all members of AlphaNet) including 1517 patients with phenotype “ZZ”, 18 – “ZNull” and 6 “NullNull” variants,
- Our study intended to evaluate survival in a homogenous group of patients who carry a PiZ allele, therefore observations with all other phenotypes were excluded from the analysis. All subjects enrolled in AlphaNet were receiving augmentation therapy (some stop their therapy because of choice, financial issues, or lung transplantation)
- Out of the total sample, 482 died and 1059 were censored.



Flow chart of study participants

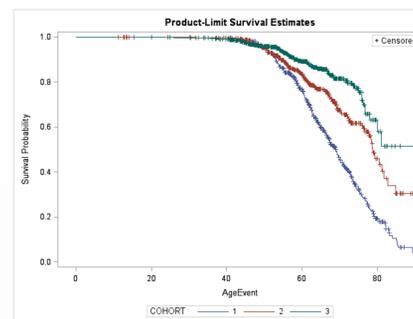
- Survival analysis was performed using Kaplan-Meier method with log-rank test to measure the differences in survival curves between the three cohorts. Cox proportional hazard models were also developed. Hazard rates were compared between the three cohorts.
- The results for categorical variables were reported by frequencies and proportions, and for continuous variables as mean + SD (min, max). Values between the groups were compared using t-test and ANOVA, and Chi-squared test respectively.
- SAS software (SAS 9.4 for Windows) was used for the statistical analysis. The significance level was set at 0.05.

RESULTS



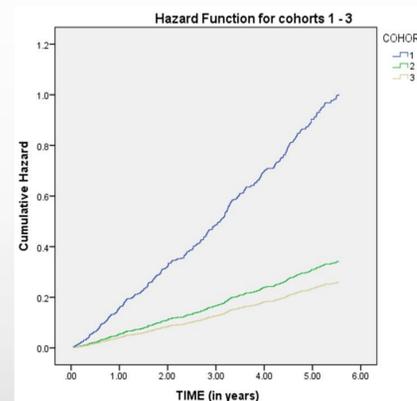
Results of survival analysis:

- The average age of the total cohort was 56.3+11.3 years. Respondents in the first cohort were older compared to the second and third cohort ($p=0.001$)
- A little over half of the respondents (51.1%) were males, predominantly Caucasian (98.8 %)
- The overall median survival age was 75.65 years (95% CI 73.85 - 76.79).
- Significant cohort effect was found in survival among AAT deficient patients when stratified by cohort of entry into the study.
- **Median survival age:**
 - cohort 1 - 68.9 years (95% CI: 66.9 - 70.2)
 - cohort 2 - 78.8 years (95% CI: 76.7 – 81.8);
 - cohort 3 - 80.4 years (95% CI: 78.1 – 82.7)



COHORT 1- 1999-2004; COHORT 2- 2005-2009; COHORT 3- 2010-2015;

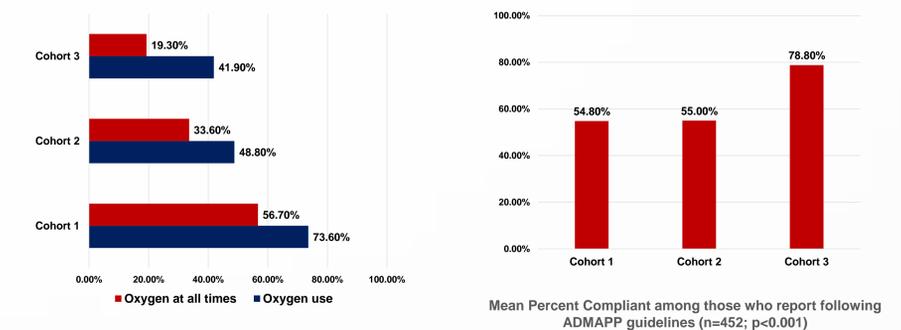
Results of the Cox proportional hazard models:



COHORT 1- 1999-2004; COHORT 2- 2005-2009; COHORT 3- 2010-2015;

- When stratified by cohort of entry into the study:
 - patients in cohort 1 were found to have a hazard ratio of 3.5 (HR=3.47; 95% CI 2.61-4.60) compared to respondents in cohort 3 (controlling for age, gender, income, smoking status and exacerbation frequency)
 - There was no statistically significant difference in hazard rates between cohorts 2 and 3, with hazard ratio of 1.1 (HR=1.12; 95% CI 0.83- 1.52)
- Follow up period was calculated from the date the patient answered the baseline survey questions (the earliest answer date was May 2008) to the date of death, discharge from the study or March 31, 2015.

Variable	Cohort 1 (N=446) (%)	Cohort 2 (N=494) (%)	Cohort 3 (N=601) (%)	p
High Blood Pressure	167 (47.3)	182 (47.2)	194 (36.5)	<0.001*
Diabetes	44 (12.5)	34 (8.8)	32 (6.0)	0.004*
Emphysema/ Chronic Bronchitis/ COPD	411 (94.3)	406 (90.0)	440 (84.5)	<0.001*
Perception of Weight- Overweight	168 (38.3)	218 (46.9)	249 (49.1)	<0.001*
Perception of Health- Poor	101 (23.1)	78 (16.9)	94 (18.4)	0.15
Ever Smoked - Yes	344 (78.0)	329 (70.9)	349 (68.2)	0.003*



STRENGTHS AND LIMITATIONS

Strengths:

- Large sample of patients with AATD available for analysis, extensive demographic and other baseline data.
- The findings are generalizable due to wide geographic distribution of the patients within the US

Limitations:

- Unavailability of complete death data prior to 2008; no information on cause of death
- Data were not available on lung function measurements (FEV1, FEV1/FVC (%)) as well as clinical findings including CT. Responses on augmentation dose and frequency are not complete

CONCLUSION

- In the most recent cohorts of patients (2010-2015 and 2005-2009), we observe improved survival relative to the earlier cohort (1999-2004). The reasons for this are not clear, but may be related to the affect of comorbidities, improved disease management, or other factors.
- Further research will continue to explore the specifics and etiology of the improved survival

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