

Mortality in Individuals With Severe Deficiency of α_1 -Antitrypsin*

Findings From the National Heart, Lung, and Blood Institute Registry

James K. Stoller, MD, MS, FCCP; Joseph Tomashefski, Jr., MD; Ronald G. Crystal, MD, FCCP(Hon); Alejandro Arroliga, MD, FCCP; Charlie Strange, MD, FCCP; Dermot N. Killian, MD, FCCP; Mark D. Schluchter, PhD; and Herbert P. Wiedemann, MD, FCCP; for the α_1 -Antitrypsin Deficiency Registry Study Group†

Study objective: To clarify the mortality rate and causes of death of individuals with α_1 -antitrypsin (AAT) deficiency, the Death Review Committee (DRC) of the National Heart, Lung, and Blood Institute Registry of Individuals with Severe AAT Deficiency reviewed all available medical records regarding the deaths of study subjects during Registry follow-up (up to 7.2 years).

Methods: Individual determinations by each member of the three-person DRC led to consensus judgments regarding the underlying cause and the immediate and contributing causes of death.

Results: Of the 1,129 Registry subjects, 204 died (18.1%) [approximately 3%/yr]. Record availability permitted detailed review in 120 decedents, and death certificates were available in 56 of the remaining 84 subjects (67%). Emphysema and cirrhosis were the most common underlying causes of death (72% and 10%, respectively), with malignancy and diverticulitis accounting for 3% of deaths each. To assess attributable mortality, standardized mortality ratio analysis was performed and indicated that excess mortality was ascribable entirely to lung and liver disease.

Conclusions: We conclude that severe AAT deficiency poses a significant threat to health, that severe airflow obstruction is a major determinant of mortality, and that liver and lung disease account for the excess mortality in affected individuals. These findings support current efforts to enhance diagnostic recognition and treatment of AAT-deficient individuals.

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Key words: α_1 -antitrypsin deficiency; cause of death; mortality; registry; standardized mortality ratio

Abbreviations: AAT = α_1 -antitrypsin; CI = confidence interval; DRC = Death Review Committee; NHLBI = National Heart, Lung, and Blood Institute; SMR = standardized mortality ratio

Severe deficiency of α_1 -antitrypsin (AAT) confers risk of early onset emphysema and, in the case of AAT-deficient variants with the Z or several other alleles, the risk of liver disease.^{1,2} To address gaps in

existing knowledge about the natural history of AAT deficiency, the National Heart, Lung, and Blood Institute (NHLBI) Registry of Individuals with Severe Deficiency of AAT was launched in 1989 and conducted a long-term follow-up of the largest available cohort of severely AAT-deficient individuals

*From the Section of Respiratory Therapy (Dr. Stoller), Department of Pulmonary, Allergy, and Critical Care Medicine, Cleveland Clinic Foundation, Cleveland, OH; Department of Pathology (Dr. Tomashefski), MetroHealth Medical Center, Cleveland, OH; Department of Genetic Medicine (Dr. Crystal), Division of Pulmonary and Critical Care Medicine, Weill Medical College, Cornell University, New York, NY; Section of Critical Care Medicine (Dr. Arroliga), Department of Pulmonary, Allergy, and Critical Care Medicine, Cleveland Clinic Foundation, Cleveland, OH; Division of Pulmonary and Critical Care Medicine (Dr. Strange), Medical University of South Carolina, Charleston, SC; Department of Pulmonary Medicine (Dr. Killian), Mercy Hospital, Portland ME; Department of Pediatrics and Biostatistics and Epidemiology (Dr. Schluchter), Case Western Reserve University, Cleveland, OH; and Department of Pulmonary, Allergy, and Critical Care Medicine (Dr. Wiedemann), Cleveland Clinic Foundation, Cleveland, OH.

†A list of Alpha 1-Antitrypsin Deficiency Registry Study Group members is given in the Appendix.

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Correspondence to: James K. Stoller, MD, MS, FCCP, Department of Pulmonary, Allergy, and Critical Care Medicine, The Cleveland Clinic Foundation, 9500 Euclid Ave, A90, Cleveland, OH 44195; e-mail: stollej@ccf.org

(n = 1,129) at 37 participating clinical centers throughout North America.^{3,4} To date, the Registry has provided insights into the clinical features of affected individuals, the rate of progression of obstructive lung disease, the efficacy of IV augmentation therapy, and adverse experiences and patterns of prescribing augmentation therapy.³⁻⁶

As part of the activities of the Data Coordinating Center in the Registry, a Death Review Committee (DRC) reviewed all available records on individuals who died over the course of Registry follow-up in order to determine the specific causes of death. The current report extends available findings from the Registry by presenting the results of the DRC analysis regarding the mortality rate and the specific causes of death for these decedents.

MATERIALS AND METHODS

As described previously,³⁻⁵ eligibility criteria for Registry enrollment included the following: age ≥ 18 years; severe AAT deficiency, defined as a serum level $< 11 \mu\text{mol/L}$ (as confirmed by the Central Phenotype Laboratory of the Registry); and written informed consent. Altogether, 1,129 eligible participants enrolled between March 1989 and October 31, 1992. Registry participants were followed up for a mean of 4.4 years (range, 0 [for subjects who died before the first follow-up visit at 6 to 12 months] to 7.2 years).

Participant deaths were ascertained in reports from the 37 clinical centers (where follow-up visits were conducted every 6 to 12 months throughout the Registry) or by inquiries to death review services, the National Death Index (National Center for Health Statistics, Hyattsville, MD) and Equifax (McLean, VA). For each death, medical records were sought that would best describe the events surrounding the death; these records included medical charts from the terminal hospitalization, final outpatient visits (especially if the subject died at home), and the death certificate. Importantly, determinations of the cause of death reported in this series were based on independent review of records and not causes stated on the death certificate.

Using these available records, the cause of each subject's death was determined by a DRC comprised by three of the study investigators (H.P.W. [Chair], J.K.S., and J.T.). Definitions of causes of death were decided *a priori*, were distributed to each DRC member, and were based on coding definitions for death certificate completion. Specifically, for each evaluable decedent, the DRC was asked to determine the following: (1) a single underlying cause of death (defined as "the single disease or injury that influenced the events resulting in death"); (2) a single immediate cause of death (defined as the "single final disease, injury, or complication directly causing the death"); (3) other causes deemed contributing to death; (4) all conditions being present but not contributing to death; and (5) whether or not the death was deemed attributable to a complication of augmentation therapy.

To assign the cause of death, each DRC member independently reviewed all available records and assigned the aforementioned death-related categories. Consensus ratings by the three DRC members were achieved in a series of face-to-face meetings, and consensus ratings were used for all analyses in this study.

Reports of postmortem examinations were available for 58 decedents. In another 126 decedents, postmortem examinations

were known not to have been performed, and postmortem examination status was uncertain in 20 decedents. Pathology findings in these postmortem examinations are the subject of a separate report.⁷

Statistical Analysis

Univariate comparisons of two groups were made using the two-sample *t* test for continuous outcomes and the χ^2 test for categorical outcomes. Cumulative mortality curves since enrollment in the Registry were estimated using the Kaplan-Meier method using data from all 1,129 subjects in the Registry in which surviving patients were censored at the time of last Registry contact. Survival curves were compared using the log-rank test. The Cox proportional hazards model was used to examine the independent effects of baseline and time-varying predictors on survival. In this model, baseline factors examined included gender, education, age, and level of postbronchodilator FEV₁ percentage of predicted at enrollment. Lung transplant status and whether the subject was currently receiving IV augmentation therapy were treated as binary, time-varying covariates. Following our previously reported approach,⁵ when fitting the Cox regression models, we used a landmark analysis approach in which only patients who had been contacted ≥ 6 since enrollment (1,048 subjects, 147 deaths) were included. This approach reduced the possibly biasing effects of those patients who were very ill when enrolled and who died before they could begin augmentation therapy or return for an additional follow-up visit. Because we previously reported on the relationship of augmentation therapy to survival using a more detailed analysis and model,⁵ we do report risk ratios for augmentation therapy in this article. To compare death rates in the Registry to the general population, standardized mortality ratios (SMRs) were computed as the ratio of observed to expected deaths, in which expected numbers of deaths were obtained using age/gender-specific death rates published in the 1992 Statistical Abstract of the United States,⁸ which was concurrent with the Registry. Confidence intervals for SMRs were computed from the exact Poisson distribution.⁹

RESULTS

Of the 1,129 Registry enrollees, 204 subjects (18.1%) died over the course of follow-up, at a relatively linear rate of approximately 3%/yr (Fig 1). Univariate comparison of baseline features of 204 decedents with those of the 925 survivors (Table 1) showed that subjects who died over the course of Registry follow-up were older (51 ± 11 years vs 45 ± 10 years, $p < 0.0001$) [mean \pm SD], had a slightly higher serum AAT level ($6.2 \pm 1.3 \mu\text{mol/L}$ vs $5.7 \pm 1.4 \mu\text{mol/L}$, $p < 0.0001$), had a lower post-bronchodilator FEV₁ percentage of predicted ($29.4 \pm 18.8\%$ vs $50.5 \pm 30.4\%$, $p < 0.0001$), were more frequently ex-smokers or current smokers ($p = 0.02$), and had a lower educational level ($p < 0.0001$). Also, receipt of any kind of a transplant or of a lung transplant was more common among decedents than survivors ($p < 0.0001$ for both comparisons).

As an example of the longitudinal effect of base-

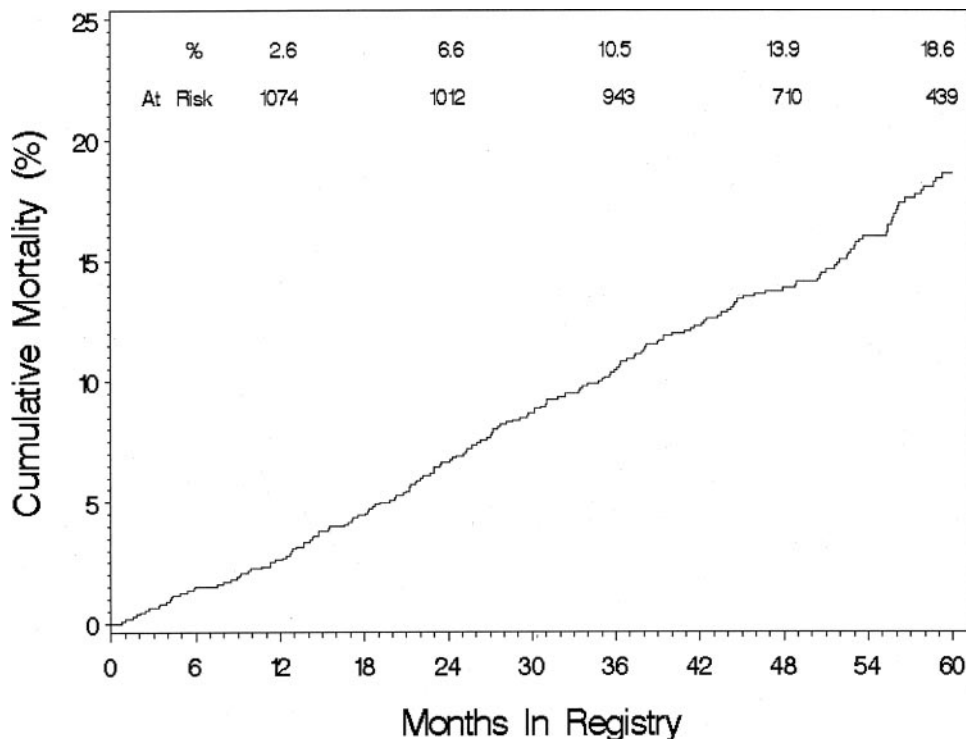


FIGURE 1. Kaplan-Meier estimate of the overall cumulative mortality rate in the Registry.

line categories on the crude mortality rate over Registry follow-up, Figure 2 presents cumulative mortality rates in subgroups of Registry subjects categorized according to initial postbronchodilator FEV₁ percentage of predicted. Participants whose initial FEV₁ was < 15% predicted had a significantly higher mortality rate (eg, 36.2% at 36 months) than subjects with FEV₁ percentage of predicted > 50%

(2.6%, $p < 0.0001$). As shown in Table 2, multivariate Cox proportional hazards analysis of features associated with mortality (in which gender, age [in five categories], initial postbronchodilator FEV₁ percentage of predicted [in five categories as in Fig 2] and education [in four categories] were included [and in which transplant and augmentation therapy status were included as time-varying covariates])

Table 1—Univariate Analysis of Features of Decedents vs Survivors in the Registry*

Variables	Decedents (n = 204)	Survivors (n = 925)	p Value
Male gender	59.8	54.6	NS
Age at death, yr	54 ± 11		
Age at enrollment, yr	51 ± 11	45 ± 10	< 0.001
Serum AAT level, μmol/L	6.2 ± 1.3 (n = 183)	5.7 ± 1.4 (n = 843)	< 0.001
Baseline postbronchodilator FEV ₁ % predicted	29.4 ± 18.8 (n = 201)	50.5 ± 30.4 (n = 922)	< 0.001
Smoking status			
Never smoked	13.7	21.5	0.02
Ex-smoker	79.4	69.8	NS
Current smoker	6.9	8.7	NS
Education			
< High school	19.3	7.4	< 0.001
High school	37.6	34.1	NS
1–4 yr college	30.2	43.3	NS
> 4 yr college	12.9	15.3	NS
Any kind of transplant	21.1	8.2	< 0.001
Lung transplant	20.1	7.7	< 0.001

*Data are presented as % or mean ± SD. NS = not significant.

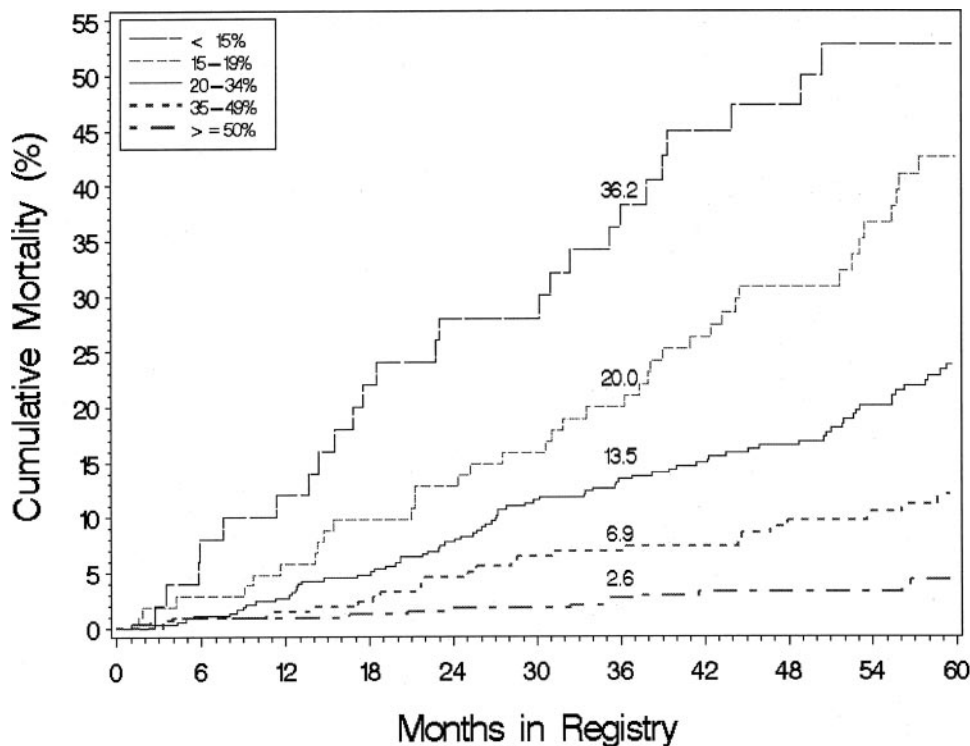


FIGURE 2. Kaplan-Meier analysis of mortality, stratified by baseline value of FEV₁ percentage of predicted.

showed that increased age, lower initial postbronchodilator FEV₁ percentage of predicted, receipt of a lung transplant, and lower education level were significantly associated with mortality (all $p \leq 0.001$).

Regarding specific causes of death, records were available for DRC review in 120 of the 204 subjects who died (60%) over the course of Registry follow-up. For the remaining 84 decedents lacking records, death certificates were available in 56 cases (67%). Comparison of the gender, smoking status, and ascertainment method (*ie*, how the subject came to be considered for recruitment to the Registry) of the 120 decedents for whom records were available for DRC review with the 84 others showed no differences (Table 3), suggesting that the 120 decedents reviewed in detail by the DRC were representative of the entire group of 204.

Underlying causes of death were ascertained in 118 of the 120 decedents (98%) for whom records were available. In two instances, the DRC could not ascertain the specific underlying cause despite the availability of records. The most common underlying causes of death (Table 4) were emphysema (72%) and cirrhosis (10%), with malignancy and diverticulitis accounting for 3% of deaths each. Sepsis/infection, trauma, and other causes accounted for the remainder. Notably, hepatocellular carcinoma was not found to be the underlying malignant cause of

death in any of these instances. Rather, the underlying cancers were malignant glioma, leiomyosarcoma of the duodenum, and renal cell carcinoma in one subject each.

To assess the potential impact of bias by smoking status, underlying causes of death were evaluated in the subset of never-smokers. Of the 204 decedents, 7.8% ($n = 16$) were never-smokers, in whom emphysema was still deemed the underlying cause of death in the majority (56%, $n = 9$). Cirrhosis accounted for 25% ($n = 4$) of the deaths among never-smokers, and portal fibrosis, trauma, and renal cell carcinoma in one instance each.

Immediate causes of death (Table 5) were most commonly infectious, including pulmonary bacterial infection (14%), sepsis of nonpulmonary cause (13%), and pulmonary fungal infection (5%). Respiratory failure accounted for 33% of the immediate causes of death, liver failure for 4%, and other causes for four or fewer deaths each. Notably, in no instance was receipt of augmentation therapy deemed to be an underlying, immediate, or contributing cause of death.

To further evaluate causes of death in the context of an illness predisposing to end-stage lung and/or liver disease, a specific analysis was undertaken of causes of death in the lung and liver transplant recipients who died. Overall, of the 1,129 Registry

Table 2—Multivariate Cox Proportional Hazards Analysis of Features Associated With Death Among Registry Subjects*

Variables	Risk Ratio	95% CI	p Value
Gender			0.78
Male	0.95	0.7, 1.3	0.78
Female	1.0		
Age, yr			< 0.001
≤ 30	1.0		
30–44	2.4	0.3, 17.7	
45–54	3.4	0.5, 24.8	
55–64	8.3	1.1, 61.2	
≥ 65	19.3	2.5, 147.2	
Initial postbronchodilator FEV ₁ % of predicted			< 0.001
< 15	15.2	6.5, 35.3	
15–19	11.8	5.7, 24.5	
20–34	5.7	2.9, 11.0	
35–49	3.0	1.4, 6.4	
≥ 50	1.0		
Lung transplant			0.001
No	1.0		
Yes	2.5	1.5, 4.2	
Education			< 0.001
< High school	3.5	1.8, 6.5	
High school	1.6	0.9, 2.8	
1–4 college	1.2	0.7, 2.1	
> 4 college	1.0		

*Lung transplant (yes/no) is a time-varying covariate. The model also adjusts for augmentation therapy (on vs. not on) as a time-varying covariate.

enrollees, 112 underwent lung transplantation (10%), 6 of whom underwent transplantation before Registry enrollment. Seven subjects underwent liver transplantation. Of the 106 recipients of a lung transplant during Registry follow-up, 38 patients died (36%). Records were available for DRC review in 25 of these decedents. Two of the seven liver transplant recipients died (28.5%), and records were available for both. Of the 25 lung transplant decedents reviewed by the DRC, emphysema was deemed the underlying cause of death in 24 patients (96%) and hepatitis in 1 patient (4%). For the two liver transplant recipients who died, cirrhosis was deemed the underlying cause in one patient and portal fibrosis in the other.

Immediate causes of death in lung and liver transplant recipients included nonpulmonary sepsis in both liver transplant recipients and in 24% of lung transplant recipients. Pulmonary infection was deemed the immediate cause of death in 32% of lung transplant recipients, most commonly due to bacterial (16%) and fungal (12%) infection. Taken together, transplant recipients for whom infection was deemed the immediate cause of death accounted for 21.1% of all such deaths.

Finally, to assess attributable mortality in Registry

Table 3—Comparison of Features of Decedents in Whom Records Were Available for Review by the DRC vs. Those for Whom Records Were Unavailable*

Variables	Had DRC Review (n = 120)	Not Reviewed by DRC (n = 84)
Male gender	62.5	56.0
Smoking		
Never smoked	13.3	14.3
Ex-smoker	81.7	76.2
Current smoker	5.0	9.5
Ascertainment		
Pulmonary symptoms	80.8	90.5
Family screening	11.7	6.0
Other	7.5	3.6
FEV ₁ % predicted (postbronchodilator)		
< 35%	77.5	79.0
35–49%	13.2	13.6
50–79%	4.2	3.7
≥ 80%	5.0	3.7
Age at enrollment, yr	51 ± 10	51 ± 12
FEV ₁ % predicted	29.8 ± 19.8	28.8 ± 17.3
FEV ₁ , mL	1,060 ± 827	994 ± 748
Serum AAT, μmol/L (No.)	6.2 ± 1.4 (106)	6.1 ± 1.2 (77)
Self-reported liver disease	20.0	13.1
Self-reported lung disease	95.0	97.6

*Data are presented as % or mean ± SD. None of the comparisons between groups achieved statistical significance.

subjects who died, SMRs were calculated. For the Registry cohort overall, the SMR was 6.3 (95% confidence interval [CI], 5.5 to 7.3). Gender-specific SMRs were, respectively, 5.8 for male subjects (95% CI, 4.8 to 6.9) and 7.4 for female subjects (95% CI, 5.9 to 9.2). Stratifying SMR by quintiles of initial postbronchodilator FEV₁ percentage of predicted showed that the SMR was > 1 for subgroups with

Table 4—Underlying Causes of Death Among the 118 Evaluable Decedents*

Variables	No. (%)†
Emphysema	85 (72)
Cirrhosis	12 (10)
Malignancy	3 (3)
Diverticulitis	3 (3)
Sepsis/infection	2 (2)
Trauma/accident	2 (2)
Other‡	12 (10)
Total	118 (100)

*Medical records were available for review in 120 subjects; underlying cause of death could not be determined for two cases reviewed.

†Data are rounded to the nearest percentage.

‡Other cases include coronary artery disease, myocardial infarction, drug reaction/toxicity (unrelated to augmentation therapy), venous stasis, hepatitis, septal fibrosis of liver, perforated abdominal viscus, biliary tract obstruction, bronchiectasis, idiopathic thrombocytopenic purpura, monoclonal gammopathy, depression.

Table 5—Immediate Causes Of Death Among 120 Evaluable Decedents*

Variables	No. (%)
Respiratory failure	39 (33)
Pulmonary bacterial infection	17 (14)
Sepsis/infection of nonrespiratory cause	15 (13)
Pulmonary fungal infection	6 (5)
Liver failure	5 (4)
Other ($\leq n = 4$ deaths/cause)	38 (31)
Total	120 (100)

*Medical records were available for review in 120 subjects.

FEV₁ values < 20% predicted (SMR, 21.8; 95% CI, 17.1 to 27.5), FEV₁ 20 to 34% predicted (SMR, 7.6; 95% CI, 6.1 to 9.4), and FEV₁ 35 to 49% predicted (SMR, 3.3; 95% CI, 2.1 to 4.7), with decreasing SMR values for lesser degrees of airflow obstruction. Notably, the SMR for subjects with FEV₁ \geq 80% predicted also was significantly > 1, with nine deaths observed vs 3.2 deaths expected (SMR, 2.8; 95% CI, 1.3 to 5.3). However, when the SMR for subjects with FEV₁ \geq 80% predicted was recalculated after removing five of the nine decedents deemed to have died from liver-related causes, the residual SMR for subjects with FEV₁ \geq 80% predicted did not differ significantly from unity (SMR, 1.3). This observation suggests that excess mortality in Registry subjects was ascribable entirely to lung and liver disease.

DISCUSSION

In this analysis of the rates and causes of death among decedents in the NHLBI Registry of Individuals with Severe Deficiency of Alpha 1-antitrypsin,³⁻⁵ the main findings are as follows: (1) The overall mortality rate over approximately 5 years of follow-up was approximately 3%/yr. (2) Features that were significantly associated with a higher mortality rate included increased age, lower initial postbronchodilator FEV₁ percentage of predicted, receipt of a lung transplant, and lower education level. In particular, the 3-year mortality rate among individuals with baseline FEV₁ < 15% predicted was 36%. Notably, an earlier report⁵ from the NHLBI Registry showed that receipt of augmentation therapy was associated with enhanced survival among Registry participants. Specifically, the odds ratio for death among augmentation therapy recipients was 0.79 compared with nonrecipients ($p = 0.02$). (3) In this detailed analysis of the immediate and underlying causes of death in evaluable patients, the most common underlying causes of death were emphysema (72%) and cirrhosis (10%), and the most common underlying causes were infection (32%),

respiratory failure (33%), and liver failure (4%). (4) SMR analysis to assess whether observed deaths exceeded expected rates for an age- and gender-matched population suggests that the excess mortality in patients with severe AAT deficiency is entirely attributable to lung and liver disease.

The current report extends available experience regarding mortality in AAT by providing detailed analyses by a review committee of immediate and underlying causes of death in a large group of severely AAT-deficient decedents. Indeed, as reflected by the sparse number of series describing long-term survival and/or cause-specific mortality in individuals with severe AAT deficiency,¹⁰⁻¹² these issues have received relatively little attention, likely due to the difficulty of assembling a large cohort of individuals with this underrecognized condition.^{13,14} Importantly, because Registry eligibility required severe deficiency of AAT (*ie*, measured serum levels < 11 μ mol/L), our results apply only to severely deficient individuals and not to PI*MZ heterozygotes.

In the earliest available analysis of long-term survival, Larsson¹⁰ described the long-term outcomes in a cohort of 246 PI*Z individuals followed up for up to 14 years (from 1963 to 1977). The crude mortality rate in this series was 37% (91 of 246 patients), with causes of death ascertained on the basis of review of hospital records, postmortem examination results, or death certificates. Respiratory failure from COPD accounted for 59% of the deaths (54 of 91 deaths), with complications of liver disease deemed responsible for 13% (12 of 91 deaths). Miscellaneous causes of death included pulmonary embolism ($n = 4$), pneumonia ($n = 3$), and pneumothorax, congestive heart failure, subarachnoid hemorrhage, intracerebral bleeding, subdural hematoma, and peritonitis in two patients each.

Few other series^{11,12} have addressed long-term survival and cause-specific mortality in individuals with severe AAT deficiency. For example, in the Danish registry of AAT-deficient individuals, Seersholm et al¹¹ reported a 2-year crude mortality rate of 34% among 282 PI*ZZ individuals. Cause-specific mortality was not reported and, as in the current series, decreased FEV₁ correlated significantly with the mortality rate. Specifically, the rate of survival was high in individuals whose FEV₁ was > 35% predicted but then fell exponentially as FEV₁ declined to < 35% predicted. In follow-up of a larger subset of Danish registry participants ($n = 397$), Seersholm et al¹² reported that 112 patients with severe AAT deficiency died over the follow-up interval (for up to 14 years). As in the earlier 2-year analysis from the smaller cohort, specific causes of death were not reported and smoking correlated

importantly with mortality; the median survival age of smokers was 51.8 years, vs 66.8 years for never-smokers ($p < 0.05$).

The finding that excess mortality in AAT deficiency is completely attributable to lung and liver disease accords with the observation that emphysema and chronic liver disease are the main clinical manifestations of PI*Z AAT deficiency,^{1,2} that PI*ZZ AAT-deficient individuals comprised 97% of Registry participants,⁴ and that deficiency associated with the Z allele likely accounts for most clinically significant disease. Indeed, while other illnesses have been clearly associated with AAT deficiency, including classic-pattern antineutrophil cytoplasmic antibody-positive vasculitis^{15,16} and panniculitis,^{17,18} these are very uncommon, even in the context of a relatively uncommon entity like AAT deficiency.

Our finding that cirrhosis was deemed the cause of death in 10% of the analyzed decedents invites comparison with other studies in which the frequency of cirrhosis among PI*ZZ individuals has been evaluated.^{10,19} Our findings agree closely with those of Larsson,¹⁰ who described cirrhosis in 11.8% of 246 PI*Z individuals and who reported that cirrhosis was the cause of death among 13.1% of the 91 individuals who died over the 14 years of follow-up. More recent insights suggest that the frequency of cirrhosis among PI*ZZ individuals may be underestimated during life and that, among nonsmokers with longer survival, cirrhosis may occur more commonly. Specifically, Eriksson¹⁹ reported that cirrhosis occurred in 34% ($n = 14$) of 41 PI*ZZ decedents in Malmo, Sweden (of the 58 expected PI*ZZ individuals in that city), and that cirrhosis was suspected in life in 9 of the 14 individuals (64%). Notably, cirrhosis was significantly more common at postmortem examination among nonsmokers (71%) than among smokers (9%, $p < 0.001$). In the context that the nonsmokers lived longer (mean age at death, 73 years vs. 56 years [smokers], $p < 0.01$), the results suggest that cirrhosis will ultimately affect a large proportion of older PI*ZZ individuals. Our finding that cirrhosis was more frequent as the underlying cause of death among never-smokers (25%) is consistent with this idea. To the extent that 91% of the 204 decedents in this Registry series had severe emphysema (*ie*, FEV₁ < 50% predicted) and the mean age of death was 54 ± 11 years, it is conceivable that the frequency of cirrhosis is lower than would have been observed in a series of never-smokers.

Overall, this report of long-term follow-up from the NHLBI Registry with detailed review of cause-specific mortality confirms that severe deficiency of AAT poses a significant threat to health, that severe airflow obstruction is a major determinant of mor-

tality, and that emphysema and cirrhosis account for the excess mortality rate in affected individuals. In the context of recommended current interventions for AAT-deficient individuals (including smoking cessation, avoidance of dusty occupational settings^{20,21} and, for individuals with established emphysema, augmentation therapy with pooled human plasma antiprotease^{1,5,22-25} and promising new treatments), these observations provide further support for enhanced diagnostic recognition and optimal management of affected individuals.

APPENDIX 1: ALPHA 1-ANTITRYPSIN DEFICIENCY REGISTRY PARTICIPANTS

The following institutions and individuals were participants in the Registry of Patients with Severe Deficiency of Alpha 1-Antitrypsin for a period of ≥ 6 months.

NHLBI

Carol E. Vreim, PhD (Program Director), and Margaret Wu, PhD.

Steering Committee

Members: Ronald G. Crystal, MD FCCP(Hon) [Chairman], The New York Hospital/Cornell University, New York, NY; A. Sonia Buist, MD, Oregon Health Sciences University, Portland OR; Benjamin Burrows, MD, University of Arizona, Tucson, AZ (through December 1995); Allen B. Cohen, MD (deceased), University of Texas Health Center, Tyler, TX; Robert J. Fallat, MD, California Pacific Medical Center, San Francisco, CA; James E. Gadek, MD, Ohio State University, Columbus, OH; Ralph H. Rousell, MD, Bayer Corporation, Berkeley, CA; Mark D. Schluchter, PhD, The Cleveland Clinic Foundation, Cleveland OH; Richard S. Schwartz, MD, Cutter Biological/Miles, Inc, Berkeley, CA (through September 1992), Gerard M. Turino, MD, St. Luke's/Roosevelt Hospital, New York, NY; and Carol E. Vreim, PhD, National Heart, Lung, and Blood Institute, Bethesda, MD.

Nonvoting Members: Mark L. Brantly, MD, National Institutes of Child Health and Human Development, Human Genetics Branch, Bethesda, MD; James K. Stoller, MD, FCCP, The Cleveland Clinic Foundation, Cleveland, OH; and Margaret Wu, PhD, National Heart, Lung, and Blood Institute, Bethesda, MD.

Clinical Coordinating Center

The Cleveland Clinic Foundation, Cleveland, OH.

Biostatistics Section: Mark D. Schluchter, PhD (through April 1998, Co-director); Ralph O'Brien, PhD (after January 1999, Co-director); George W. Williams, PhD (through June 1991, Co-director); Raghid Ajamoghli, BS; DeAnn M. Barrett; Gerald J. Beck, PhD; Richard Connelly, MS; Janet Doak; Beth Dobish; Lucy Giaimo; Marlene Goormastic, MPH; William Grasser, BS; Jeffrey Hammel, MS; Judith Leatherman, BS; June McMahan; Edward Mascha, MS; Venita Midcalf, MBA; Betty Moore; Paul Sartori, AD; Susan Sherer, BS; Michael J. Tuason, BS; Rebecca Zhang, MS; Sharayu Shanbhag, BSc; and Ronald Stewart, MS.

Pulmonary Section: James K. Stoller, MD, FCCP (Co-director); Herbert P. Wiedemann, MD, FCCP; and Kevin McCarthy, RCPT.

Consultants: Thomas L. Petty, MD, University of Colorado, Denver, CO; Joseph F. Tomashefski, Jr., MD, MetroHealth Medical Center, Cleveland, OH.

Database Preparation: E. Shannon Neeley, Ben Neibaur, Jana Shepherd, Alvin Van Orden, and Aimee Wahle.

Central Phenotyping Laboratory

National Institutes of Health, National Institute of Child Health and Human Development, Bethesda, MD: Mark L. Brantly, MD; Jeffrey Hildesheim, BA; and Barbara Rundquist, BS.

Clinical Centers

Arapahoe Pulmonary Consultants, Denver, CO: Robert A. Sandhaus, MD, PhD; C. William Bell, PhD; Janis Berend, MSN, CNP; C. Allen Burry, CRTT; Kathleen Irvine, BS; Dixie Krantz, RRT, CPFT; and Susan Lewis.

William Beaumont Hospital, Royal Oak, MI: K. P. Ravikrishnan, MD; Robert Begle, MD; David Erb, MD; Karen Burgess, MA; Barbara Cameron, RN; Shirley Cotton, CPFT; David Erb, MD; Chet Jaworsky, RRT, CPFT; Joel Seidman, MD; Stanley Sherman, MD; and Mercedes True, BS, RPFT.

Beth Israel Hospital, Boston, MA: Steven Weinberger, MD; Kristen Armstrong, BA; Richard Johnston, CPFT; Mitchell Rosenberg, MD; Jeanne B. La Rock, BS; and Alison Vargas.

California Pacific Medical Center, San Francisco, CA: Robert J. Fallat, MD; Leonard Moriyama, RRT, RCPT; Michael Snow, RCPT, RPFT; and Keith Willard, RCPT.

The Cleveland Clinic Foundation, Cleveland, OH: Alejandro C. Arroliga, MD, FCCP; David P. Meeker, MD (through June 1994); Eugene Cassidy, CPFT; Joseph A. Golish, MD; Linda Hutchins, MS, CNP; Daniel Laskowski, PPFT; Atul Mehta, MD; Lynn Pagliaccio, PA-C; Richard Pillar, RCPT; Gloria Rhodes, RCPT; Jenera Scott, RCPT; and Linda Soentjen, RPFT, RRT.

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