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# Higher healthcare cost and utilization before and after diagnosis of AATD in the United States

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## Abstract

**Purpose** Patients with alpha-1 antitrypsin deficiency (AATD) often experience substantial delays from the onset of symptoms to a diagnosis. We explored the impact of delayed diagnosis of AATD on healthcare costs and utilization by assessing costs/utilization before and after diagnosis.

**Methods** Retrospective claims data was used to conduct a longitudinal analysis of a cohort of patients with follow-up over four years in a commercial claims database was conducted. Patients with at least four years of claims experience between the years 2011 – 2017 were included in this study. Outcome measures were calculated for each year (Year 1 pre-index diagnosis, and Years 1, 2, and 3 post-index follow-up). Measures included healthcare costs (pharmacy and medical costs), medical costs, inpatient events, and emergency room visits. Unadjusted measures in the follow-up Year 1, Year 2, and Year 3 were compared to Year 1 pre-index. A separate multivariate analysis adjusting for age, sex, and comorbidities was conducted.

**Results** Among 1258 patients, mean adjusted healthcare costs were significantly higher in Year 1 post-index compared to Year 1 pre-index ($51,785 vs $41,441, $p = < 0.05$). In Year 2 ($36,937 vs $41,441, $p = < 0.05$) and 3 ($28,558 vs $41,441, $p = < 0.05$) post-index, mean adjusted healthcare costs decreased compared to Year 1 pre-index. Adjusted medical costs were similar in Year 1 ($25,034) post-index compared to Year 1 ($22,952) pre-index but were significantly lower in Year 2 ($15,242 vs $25,034, $p = < 0.05$) and Year 3 ($8,779 vs $25,034, $p = < 0.05$) post-index. The frequency of inpatient and emergency room events was significantly lower in all three observation periods following diagnosis in the unadjusted analysis. The adjusted analysis showed similar findings, except for emergency room visits, which were similar across all observation periods.

**Conclusion** Patients with AATD had substantial healthcare costs/utilization in the year before diagnosis. Costs were significantly higher in the first year following diagnosis. However, subsequent years showed cost reductions to levels below pre-diagnosis. These data support the need for strategies to reduce the time from symptom onset to diagnosis.

**Keywords** Alpha-1 antitrypsin deficiency, COPD, PiZZ, Healthcare costs

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## Summary

Alpha-1 antitrypsin deficiency is an inherited disorder that can be associated with lung disease. Early recognition of this condition may provide the opportunity to minimize the progression of lung disease. Unfortunately, patients typically experience symptoms for years before a diagnosis is made. This delay in diagnosis takes a toll on the patient emotionally and physically and is therefore likely to need costly healthcare resources.

To examine the impact of that delay in diagnosis on the use of healthcare resources and cost of care, this study analyzed data from a medical insurance claims database. Medical costs, (defined in this context as all treatment and non-pharmacy costs), and utilization (emergency room visits, and hospitalizations), were examined for 1 year before diagnosis and up to 3 years following diagnosis in 1,258 patients with alpha-1 antitrypsin deficiency. Following diagnosis, patients were less likely to visit the emergency room or be admitted to the hospital. Healthcare costs (the sum of medical and pharmacy costs), were initially higher in the year following diagnosis but declined in subsequent years following diagnosis. This study suggests that strategies to promote diagnosis of alpha-1 antitrypsin deficiency earlier when symptoms are not as severe may reduce emergency room visits and hospitalizations, as well as healthcare costs over time.


## Introduction

Alpha-1 antitrypsin deficiency (AATD) is an inherited autosomal recessive disorder. Mutations in the alpha-1 antitrypsin (AAT) gene may result in reduced levels of AAT, which are associated with an increased risk of emphysema or chronic obstructive pulmonary disease (COPD). There could also be an increased risk for liver disease [1]. Over 100 genetic variants of the AAT gene have been identified [2]. Variants associated with severely reduced levels of AAT, the null-null (no AATD mRNA or protein production), and ZZ (low levels and functionality of AATD) phenotypes, place an individual at a high risk of lung disease compared to the general population. More moderately reduced levels of AAT are seen with the SZ (< 57 mg/dL AATD protein) phenotype, which is associated with a mild increased risk of lung disease [3]. PiZZ is a common single-gene defect found in AATD patients. It is the most common genetic cause of liver disease in children with AATD. A comprehensive review of AATD genotypes and their presentations has recently been published [4].

Evidence-based guidance for the management of AATD recommends preventive strategies, such as smoking cessation and minimization of exposure to respiratory irritants, to prevent the development of emphysema [5]. In addition, patients with serum levels of AAT less than 11 μM who have moderate emphysema ($FEV_1$ in the range of 30%—65% predicted) may benefit from a slower decline in lung function with augmentation therapy consisting of purified plasma-derived AAT for intravenous administration. For patients with more severe emphysema, augmentation offers the potential to prolong survival [6, 7].

Early recognition of AATD provides the opportunity to implement these preventive strategies and treatment interventions to potentially minimize the progression of lung disease. AATD testing is recommended for all COPD patients and others with symptomatic fixed airway obstruction and unexplained bronchiectasis or liver disease [6, 7]. Despite these testing guidelines, findings from patient surveys indicate that patients experience extended periods and multiple medical visits before diagnosis. Findings from these surveys report a mean time interval from the onset of symptoms to the diagnosis of AATD ranging from 5.6 to 8.3 years [8–11]. The delay in diagnosis may have an impact beyond the progression of lung damage. Unfavorable effects on work, relationships with family and friends, and health insurance status have been reported. The utilization of healthcare resources is also impacted as patients report healthcare visits to multiple providers in search of a diagnosis [8].

Existing data on healthcare costs and utilization in the management of AATD describe costs in managing the disease following diagnosis. Two early studies explored the cost-effectiveness of augmentation therapy in patients with AATD and COPD based on models assessing efficacy, life expectancy, and cost of therapy. Both studies concluded that the cost-effectiveness of augmentation therapy for individuals with severe AATD and COPD was comparable to other widely accepted medical interventions [12, 13]. A later study, using a statistical model incorporating disease progression, impact of quality of life, and incremental costs of augmentation therapy over a lifetime, found differing results. The authors concluded that augmentation therapy was not cost-effective when compared to other conventional therapies, but recognized that as the only available therapy, AAT therapy should be considered in appropriate patients [14].

Additional studies examining the healthcare cost and utilization for patients with AATD include patient surveys and claims data analyses. Survey responses from patients in the Alpha-1 Registry showed that direct healthcare costs for patients with PiZZ were higher than those with a non-PiZZ phenotype and that augmentation therapy accounted for most of the cost [15, 16]. An analysis of Medicare data suggested that patients with AATD had higher costs, more emergency room visits, and more inpatient events than non-AATD patients with COPD [17]. The most recent study published analyzed

health plan and out-of-pocket costs using a large claims database. This study found that both health plan cost and patient out-of-pocket expenses were significantly higher for patients with AATD who were receiving augmentation therapy compared to those who were not receiving augmentation [18].

The focus of these studies was to describe the direct costs and healthcare utilization associated with the management of AATD once the initial diagnosis is made and to explore the impact of augmentation therapy on healthcare costs and resource utilization. Despite the reports of delays in diagnosis and the impact on physician visits, there are no data describing healthcare costs during the extended period leading up to the diagnosis of AATD.

Early recognition of AATD offers an opportunity to minimize environmental risk factors and potentially reduce lung damage [19, 20]. Shortening the delay in diagnosis may provide clinical benefits for patients with AATD in the management of their lung disease. Little is known about the impact of the delay in diagnosis on healthcare cost and utilization. The objective of this analysis was to explore this impact by assessing healthcare costs and utilization before and after diagnosis of AATD in a cohort of commercially insured patients. This is important because, due to the progressive nature of AATD, the impact of earlier diagnosis and treatment should be assessed over a longer analytic period.

## Methods

### Data source and description

The source of data for this analysis was the PharMetrics™ Plus Commercial Database, a proprietary database licensed for use from IQVIA, for the years 2011 through 2017. The PharMetrics database comprises fully adjudicated medical and pharmaceutical claims for approximately 70 million unique patients from over 70 health plans across the United States. Records in the PharMetrics database are representative of the U.S. commercially insured population on demographic measures including age and sex. The data are longitudinal, with an average member enrollment time of over two years. The database includes inpatient and outpatient diagnoses as identified in the International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM formats, respectively); procedures identified in the Current Procedural Terminology and Healthcare Common Procedure Coding System (CPT-4 and HCPCS formats, respectively); and both retail and mail-order prescription records.

The PharMetrics Plus Commercial Database utilizes de-identified, HIPAA-compliant data. The use of de-identified, publicly available data does not constitute human subjects research as defined at 45 CFR 46.102. Therefore, this study was exempt from review by an institutional review board/ethics committee. Also, all data reported are in the aggregate and impossible to link to individual participants, so individual informed consent was not required.

Claims data is generated whenever healthcare providers submit requests for payment for services rendered. The components of claims data—service dates tracking the delivery of patient care; standardized diagnosis codes describing patient conditions; and uniform procedure codes identifying medical services – are combined to create a valuable source of healthcare utilization information. Large databases can be particularly useful for studying uncommon conditions such as AATD. However, there are widely acknowledged limitations associated with claims data. Among these, concerning AAT patients, is the inability to recognize important clinical information indicative of disease severity.

### Study population / study design

A cohort of patients was constructed by identifying patients at index (first) diagnosis on a claim for AATD. Patients were required to:

- Have at least one index claim (alpha-1 antitrypsin deficiency ICD-9-CM code 273.4 or ICD-10-CM code E88.01)
- Have at least one additional confirmatory claim (ICD-9-CM code 273.4 or ICD-10-CM code E88.01) at least 90 days before or after the first index claim
- Be enrolled in a health plan with medical and pharmacy benefits that contributes to PharMetrics Plus Data for at least 12 months before index diagnosis and at least 12 months post index diagnosis

In this longitudinal study, data were analyzed, and outcome measures were calculated for the cohort over four observational periods (baseline, 12 months post-index, 24 months post, and 36 months post-index) associated with the diagnosis of AATD. Outcome measures were calculated for each of the four observation periods (0–12 months pre-index diagnosis of AATD, and 0–12 months, 13–24 months, and 25–36 months post-index diagnosis of AATD).

### Measures

Patient demographic characteristics including age and sex were summarized. The Elixhauser Comorbidity Index was used to provide baseline clinical characteristics (Appendix A) [21].

Study outcomes included:

- All-cause healthcare costs (defined as the summation of pharmacy and medical costs)
- All-cause medical costs (defined as all non-pharmacy/treatment costs)
- All-cause inpatient events
- All-cause emergency room events

### Statistical analysis

Demographic and medical characteristics for the cohort were described using counts and percentages for categorical variables and measures of central tendency (mean/median/standard deviation) for continuous variables. Characteristics were presented by total sample and for each subset with 24 months and 36 months follow-up. Outcomes including healthcare costs and utilization events were assessed within the follow-up periods and compared to the pre-index period (mean/median/standard deviation). All statistical analyses were conducted using SAS version 9.4. Comparisons were made for outcomes within the cohort/sub-groups.

### Bivariate analysis

Healthcare costs, medical costs, and utilization were calculated and described with means, medians, and standard deviations for each observation period for the patients who contributed data for that period. Alpha was set at 0.05. For continuous variables, statistical comparisons to Year 1 pre-index diagnosis were conducted with paired t-tests for Year 1 post-index and independent t-tests for Year 2 and Year 3 post-index for those subgroups with corresponding follow-up times. For percentages, statistical comparisons to Year 1 pre-index diagnosis were conducted with Chi-square tests.

### Multivariable analysis

Multivariable models were developed to predict estimates for each period for the patients who contributed data for that period. Healthcare costs and medical costs in each of these periods were estimated using a generalized linear model with a gamma family distribution and a log link while adjusting for age, sex, and the 31 Elixhauser comorbidities for those patients who contributed data to that observation period.

Healthcare utilization (inpatient and emergency room events) in each of the periods was estimated using a negative binomial model while adjusting for age, sex, and the 31 Elixhauser comorbidities for those patients who contributed data to that observation period.

Alpha was set at 0.05. All adjusted statistical comparisons to year 1 pre-index diagnosis of AATD were conducted with paired t-tests for Year 1 post-index and independent t-tests for Year 2 and Year 3 post-index.

## Results

A total of 1,258 patients who met the study criteria were identified within the database. Data were available for 602 of those patients at 24 months post-index diagnosis and for 167 patients at 36 months post-index diagnosis. The mean age and percentage of female patients remained stable across the Year 1, Year 2, and Year 3 post-index date follow-up periods (Appendix B). There was a trend for a lower frequency of comorbidities in the Year 3 post-index period compared with the Year 1 post-index period, specifically for cardiac arrhythmias, COPD, diabetes (complicated), alcohol abuse, and depression. There was a higher frequency of lymphoma in the year 3 period compared to the Year 1 period. The frequency of other comorbidities remained similar over time.

### Unadjusted healthcare costs and utilization

Unadjusted healthcare costs were significantly higher in Year 1 post-index compared to Year 1 pre-index (mean costs \$42,116 vs \$33,695, $p < 0.05$). However, the healthcare costs decreased in Year 2 and Year 3 post-index to similar or slightly lower levels compared to Year 1 pre-index (Table 1; Fig. 1).

Although medical costs (excluding pharmacy costs) were similar in Year 1 post-index compared to Year 1 pre-index, medical costs were significantly lower in Year 2 and Year 3 post-index. Additionally, the frequency of inpatient events and emergency room visits was significantly lower in all three observation periods following the diagnosis of AATD compared to the year before diagnosis (Table 1).

### Adjusted healthcare costs and utilization

Further analyses adjusting for age, sex, and Elixhauser comorbidities also demonstrated a significant increase in healthcare costs Year 1 post-index compared to Year 1 pre-index (mean \$51,785 vs \$41,441, $p = < 0.05$). In Year 2 and Year 3, costs were reduced to below Year 1 pre-index levels. (Table 2; Fig. 2).

Adjusted medical costs were similar in Year 1 post-index compared to Year 1 pre-index but were significantly lower in Year 2 and Year 3 post-index. As observed in the unadjusted analysis, there were significantly fewer inpatient events during Year 1, Year 2, and Year 3 compared to Year 1 pre-index. However, emergency room visits were similar across all four observation periods in the adjusted analysis (Table 2).

### Sub-group analysis

A sub-group analysis of the patient population included in this study was conducted. Liver disease, a condition that poses an increased risk for many AATD patients, is a defined Elixhauser comorbidity.

**Table 1** Unadjusted Healthcare Costs and Utilization

| | Year 1 pre-index | Year 1 post-index | Year 2 post-index | Year 3 post-index |
|---|---|---|---|---|
| Total (*n*) | 1258 | 1258 | 602 | 167 |
| Healthcare cost<br>Mean ± SD<br>Median | $33,695 ± 67,308<br>$7,773 | $42,166 ± 120,306[a]<br>$7,303 | $31,333 ± 57,029<br>$6,773 | $25,933 ± 50,035<br>$5,327 |
| Medical cost<br>Mean ± SD<br>Median | $19,303 ± 50,460<br>$4,520 | $21,153 ± 107,546<br>$4,213 | $12,930 ± 29,374[a]<br>$3,662 | $8,067 ± 11,982[a]<br>$3,133 |
| Inpatient events<br>*n* (%)<br>Mean ± SD<br>Median | 455 (36.17)<br>0.53 ± 1.00<br>0.00 | 277 (22.02)[b]<br>0.37 ± 0.97[a]<br>0.00 | 69 (11.46)[b]<br>0.20 ± 0.85[a]<br>0.00 | 12 (7.19)[b]<br>0.13 ± 0.58[a]<br>0.00 |
| Emergency room events n<br>(%)<br>Mean ± SD<br>Median | 348 (27.66)<br>1.14 ± 3.39<br>0.00 | 213 (18.36)[b]<br>0.87 ± 3.92<br>0.00 | 110 (18.27)[b]<br>0.96 ± 4.96<br>0.00 | 31 (18.56)[b]<br>0.83 ± 2.68<br>0.00 |

*SD* Standard deviation

[a] $p < 0.05$, statistical comparison to year 1 pre-index with paired t-test for year 1 post-index and independent t-tests for year 2 and 3 post-index

[b] $p < 0.05$, statistical comparison to year 1 pre-index with Chi-square test

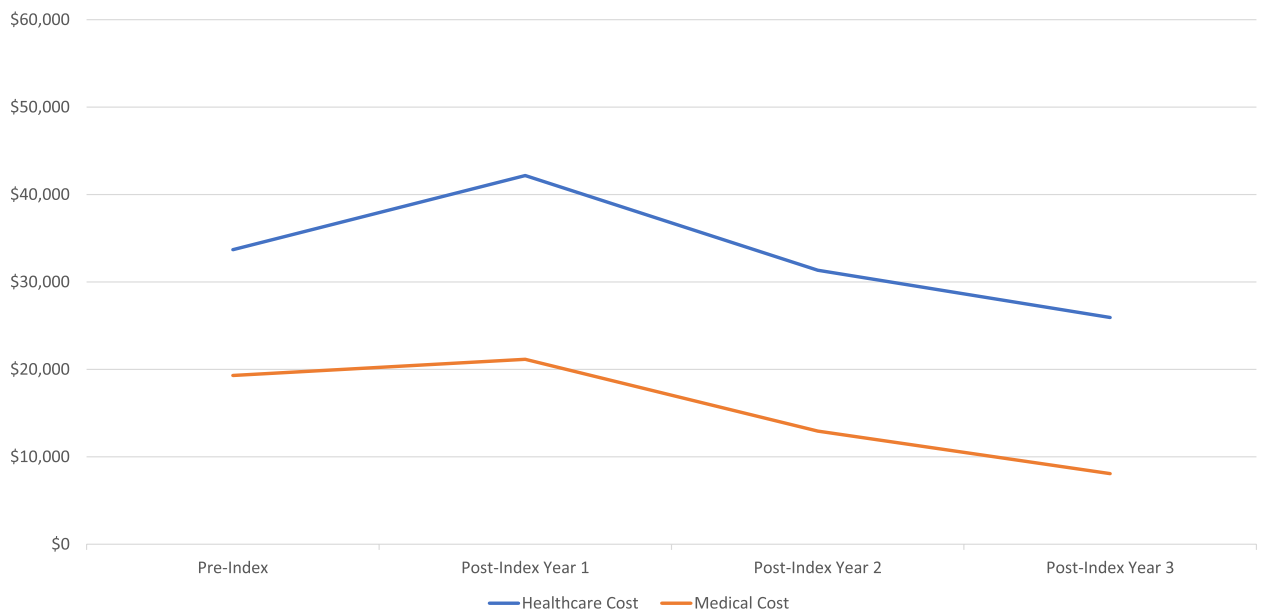


**Fig. 1** Mean unadjusted healthcare cost among patients with alpha-1 antitrypsin deficiency

The sub-group consisted of all study patients with any ICD-9 and/ or ICD-10 codes for liver disease in their claims history during the study period (Appendix A). These codes, however, are not indicative of disease severity. Due to the low patient counts, a negative binomial model was employed to predict outcomes.

Approximately 20% of the overall study patient population in each year, were found to have at least one of the liver disease ICD codes in their medical record. It was noted that the patients in the liver disease subgroup population followed a pattern similar to that of the overall study patient population of higher healthcare and medical costs in the Year 1 Pre-index and Year 1 Post-index years. Similarly, Year 2 Post-index and Year 3 Post-index healthcare and medical costs decreased among both groups (Appendix C).

**Table 2** Adjusted Healthcare Costs and Utilization[a]

| | Year 1 pre-index | Year 1 post-index | Year 2 post-index | Year 3 post-index |
|---|---|---|---|---|
| Total (*n*) | 1258 | 1258 | 602 | 167 |
| Healthcare cost<br>Mean ± SD<br>Median | $41,441 ± 161,896<br>$24,782 | $51,785 ± 80,792[a]<br>$34,744 | $36,937 ± 51,186<br>$21,079 | $28,558 ± 46,594<br>$12,215 |
| Medical cost<br>Mean ± SD<br>Median | $22,952 ± 89,936<br>$10,825 | $25,034 ± 52,953<br>$13,129 | $15,242 ± 26,600[b]<br>$10,034 | $8,779 ± 9,838[b]<br>$5,639 |
| Inpatient events<br>Mean ± SD<br>Median | 0.53 ± 0.75<br>0.34 | 0.38 ± 0.58[b]<br>0.27 | 0.21 ± 0.42[b]<br>0.10 | 0.13 ± 0.35[b]<br>0.00 |
| Emergency room events<br>Mean ± SD<br>Median | 1.21 ± 1.95<br>0.75 | 1.03 ± 3.41<br>0.50 | 1.45 ± 9.25<br>0.47 | 0.92 ± 1.83<br>0.23 |

*SD* standard deviation

[a] Cost estimates predicted using generalized linear models with gamma family distribution and a log link while adjusting for age, sex, and Elixhauser comorbidities; Utilization estimates predicted using negative binomial models while adjusting for age, sex and Elixhauser comorbidities

[b] $p < 0.05$, statistical comparison to year 1 pre-index with paired t-test for year 1 post-index and independent t-tests for year 2 and 3 post-index

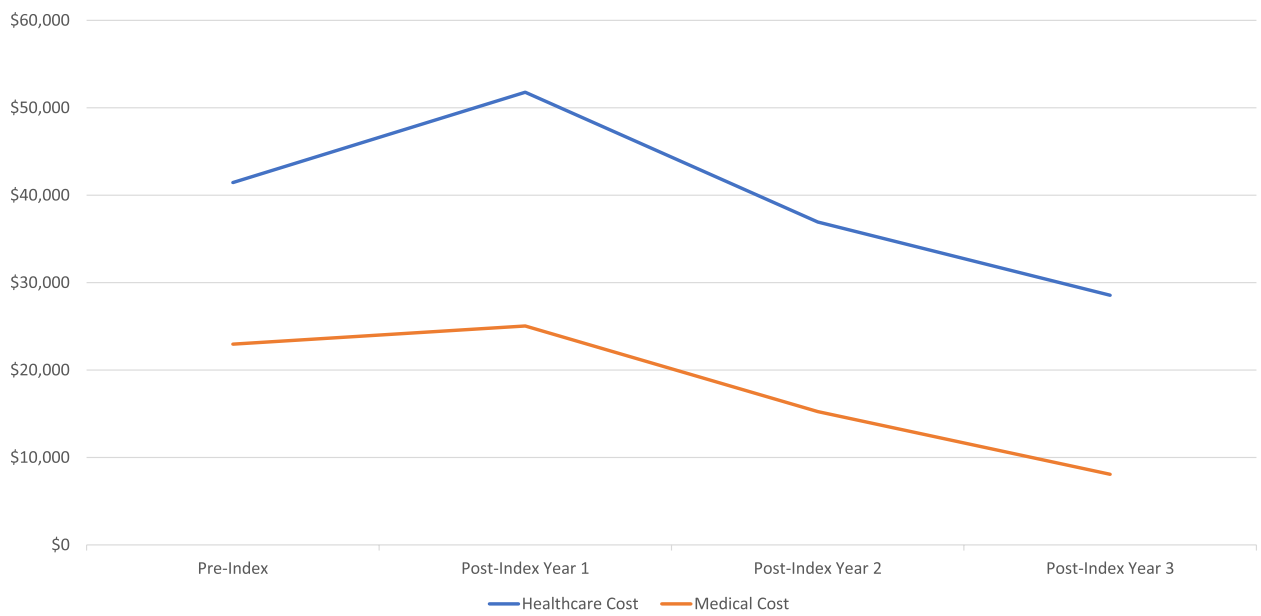


**Fig. 2** Mean adjusted healthcare cost among patients with alpha-1 antitrypsin deficiency

## Discussion

This is the first longitudinal data analysis describing healthcare cost and utilization before diagnosis of AATD. Using a claims database, this study examined trends in healthcare costs and utilization for 1 year before the diagnosis (first claim) of AATD through 3 years post-diagnosis. The findings suggest that the year leading up to the diagnosis of AATD is associated with substantial healthcare costs and utilization of inpatient services and emergency room visits. While the first year following diagnosis was associated with significantly higher healthcare costs, which include pharmacy costs, compared to the year before diagnosis, the costs were reduced below pre-diagnosis costs in the subsequent years. The reductions in healthcare costs in Year 2 and Year 3 did not reach statistical significance, however, medical costs, inpatient hospitalizations, and unadjusted emergency room visits were all significantly lower than the year before diagnosis.

In this study, based on claims data for the years 2011 through 2017, the mean adjusted healthcare costs for patients in the year before diagnosis was $41,441. In the first year following diagnosis, the mean adjusted

healthcare costs significantly increased to $51,785 ($p < 0.05$) and then dropped below the pre-diagnosis level in Year 2 and Year 3 following diagnosis ($36,937 and $28,558, respectively) (Table 2).

The first report of annual healthcare costs for patients with AATD in the United States was an analysis of data from a survey of patients from the Alpha-1 Foundation Registry from 1997 through 1999 [14]. Survey responses showed an annual healthcare cost of $30,948 for patients with PiZZ phenotype and $20,673 for patients with non-PiZZ phenotypes. Healthcare costs included estimates of cost for medical visits, medications, and all other expenditures for healthcare services, including out-of-pocket expenses [14]. A follow-up survey was conducted with this same cohort of patients to gain a clearer breakdown of healthcare costs, including health insurance premiums, prescription drugs, physician visits, emergency room visits, hospitalizations, and long-term care [16]. In the follow-up report, the mean annual healthcare cost for all AATD patients ranged from $36,471 to $46,114. Costs for patients with PiZZ were higher than costs for patients with non-PiZZ phenotypes [16].

In a more recent study evaluating the healthcare costs among patients with AATD in the United States, investigators conducted a retrospective analysis using a claims database (OptumLabs™ Data Warehouse 1993 through 2015). Mean healthcare costs in this cohort of 9,117 patients was $22,975 [18].

While direct comparisons between the current findings and previous studies cannot be made due to differences in methodology and timeframes for data collection, the studies consistently show that healthcare costs and resource utilization for patients with AATD are substantial. Recognizing the high cost and utilization of resources for the management of AATD, the aim of this study was to explore trends in costs incurred before diagnosis of AATD and in the years after the diagnosis.

The under-recognition and delay in diagnosis of AATD are well-documented. Patients report seeking care from multiple healthcare providers in the 5.6 to 8.3 years from the onset of first symptoms to the diagnosis of AATD [7–11]. The findings from the current study reflect high healthcare costs and resource utilization in the years leading up to the diagnosis of AATD. While costs are significantly higher in the first year after the diagnosis of AATD compared to pre-diagnosis, those costs are reduced below pre-diagnosis levels in Year 2 and Year 3. Hospitalizations and unadjusted emergency room visits were significantly lower following diagnosis, which may account for the reduction in healthcare costs. In addition, the reduction in healthcare costs is consistent with studies suggesting that comprehensive healthcare management programs can reduce resource utilization through reductions in the rate of severe exacerbations of COPD and hospitalizations [22, 23]. One could also speculate that decreases in some comorbidities, including cardiac arrhythmias, COPD, diabetes (complicated), alcohol abuse, and depression, could be related to life style changes and more patient education associated with the delivery of augmentation therapy. However, further studies would be needed to confirm such an association. These data suggest that an earlier diagnosis, which could result in the patient being treated with appropriate therapy for AATD and participation in a comprehensive disease management program, may lead to a reduction in healthcare costs and utilization.

### Strengths and limitations

Interpretation of this study should be considered within the context of several limitations. Claims data have the potential for errors or miscoding, which could potentially introduce misclassification bias into the study by incorrectly identifying patients diagnosed with AATD. All treatment use is inferred from the claims. Claims data cannot identify important clinical information, such as severity of disease or genotype/phenotype, which may influence healthcare resource utilization. Finally, the sample sizes are relatively small and may result in high variance on point estimates and affect statistical significance on comparisons between groups, especially with patients who had 3 years of post-index follow-up. The reasons for the loss of patients to follow-up in Year 2 and Year 3 post-index are unknown. Potential reasons include a change in health insurance programs, migration to Medicare or Medicaid, or death.

## Conclusion

In summary, this analysis found that patients with AATD had an adjusted mean healthcare cost of $41,441 in the year before the diagnosis of AATD. Healthcare costs were significantly higher in the first year following diagnosis; however, in subsequent years following diagnosis healthcare costs and resource utilization were reduced to levels below pre-diagnosis. These data support the need for increased awareness of symptoms and risk for AATD and enhanced strategies to drive a reduction in the time from symptom onset to diagnosis. Reducing the delay in diagnosis offers the opportunity for earlier intervention with lifestyle modifications and treatment, which may provide clinical benefits as well as reduce healthcare costs and utilization. Therefore, this study may benefit a broad range of actors in the healthcare system, including but not limited to, healthcare providers and payers, both nationally and internationally.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03396-w.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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**Clinical trial number**
Not applicable.

**Authors' contributions**
Christopher M Blanchette — Conceptualization and Project administration Sarah Whitmire —Writing (original draft and editing) Joshua Oh —Data curation and Formal analysis Joshua Noone— Data curation and Methodology Reuben Howden— Investigation and Writing-review & editing Thomas Ardiles—Investigation review and editing Glenda Stone—Investigation and writing—review and editing.

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**Data availability**
Data is from a proprietary data source that licenses the data and access to the data files would not be allowed under the data use agreement, however, we can supply data in aggregate at the request of the editors.

## Declarations

**Ethics approval and consent to participate**
*Higher healthcare cost and utilization before and after diagnosis of AATD in the United States*, is a retrospective claims analysis. A Clinical Trial Number is therefore not applicable in this case. The source data for this analysis was the PharMetrics™ Plus Commercial Database. This database utilizes de-identified, HIPAA compliant data. The use of de-identified, publicly available data does not constitute human subjects research as defined at 45 CFR 46.102. Therefore, this study was exempt from review by an institutional review board/ethics committee.

**Consent for publications**
All data reported are in the aggregate and impossible to link to individual participants, so individual informed consent was not required.

**Competing interests**
Drs. Blanchette, Howden, Oh, Noone, and Ms. Whitmire have each received consultation fees from Grifols, Inc. in the past. Dr. Ardiles is an employee of Grifols Shared Services of North America, a subsidiary of Grifols, Inc. Dr. Stone was an employee of Grifols Inc., at the time the research was conducted. Grifols, Inc. a manufacturer of a marketed therapy for the treatment of AATD, funded this study and preparation of this manuscript.

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