


Retrospective Database Analysis of Liver-Related Clinical Events in Adult and Pediatric Patients with Alpha-1 Antitrypsin Deficiency in the United States

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Background and Aims: Real-world analyses on burden of illness in patients with alpha-1 antitrypsin deficiency (AATD) are limited. We investigated the real-world burden of liver-related clinical events among adult and pediatric patients with AATD in the USA.

Methods: This was a retrospective, observational analysis of administrative claims data from the IQVIA PharMetrics[®] Plus and Ambulatory Electronic Medical Records databases from 2011 to 2022. Patients had a diagnosis of liver and/or lung disease with ≥ 180 days of continuous enrollment in the IQVIA PharMetrics Plus database before and ≥ 90 days after their first diagnosis. Follow-up time was assigned to the AATD with liver disease health state or AATD with both liver and lung disease health state (for patients aged ≥ 18 years only). Baseline demographic characteristics and liver-related clinical events of interest were reported.

Results: Of 5136 eligible patients, 771 adult and 123 pediatric patients contributed time to the AATD with liver disease health state; 541 adults contributed time to the AATD with both liver and lung disease health state. Among adults, patients with both liver and lung disease had higher rates of liver-related clinical events than patients with liver disease alone. Ascites was the most frequently observed clinical event among adults in both health states, and the median time to the composite of any liver-related clinical event was 26.5 days among all adults combined. Across all pediatric age groups, ascites, gastrointestinal bleed and hepatic encephalopathy were more common than spontaneous bacterial peritonitis and hepatocellular carcinoma, but median time to liver-related clinical event varied by age group at index date and type of event. No liver transplantations occurred in patients aged 6–17 years.

Conclusion: Diagnosed AATD with liver disease carries a substantial burden on adult and pediatric patients; new treatment options are warranted to avoid disease progression to decompensating events.

Keywords: alpha-1 antitrypsin deficiency, genetic disease, liver disease, lung disease, pediatric, adult

Introduction

Alpha-1 antitrypsin deficiency (AATD) is a rare autosomal codominant genetic disease, primarily affecting the lungs and/or liver,¹ occurring in ~1 in 3000–5000 people in the USA.^{1–3} The disorder is characterized by low levels of serum alpha-1 antitrypsin (AAT) leading to lung disease, and accumulation of misfolded AAT in hepatocytes, which can result in liver disease.¹

The most severe AATD phenotypes are associated with the protease inhibitor (Pi)*ZZ genotype, caused by a single homozygous substitution (Glu342Lys) in *SERPINA1* leading to the accumulation of misfolded AAT (a protease inhibitor produced in the liver to maintain the protease-antiprotease balance within the lungs) in hepatocytes and increased risk of developing liver disease.¹ The heterozygous Pi*MZ genotype is generally considered a risk factor for developing advanced liver disease, particularly in the context of obesity and diabetes, while the Pi*Z null genotype results in lung manifestations owing to low levels of serum AAT.^{1,4} The Pi*SZ genotype (caused by a double mutation in *SERPINA1* of the S allele

[Glu264Val] and the Z allele) causes protein misfolding and reduced levels of AAT, leading to liver disease and/or lung disease; however, lung function is less severe in individuals with the Pi*SZ genotype than the Pi*ZZ genotype.¹

Although the Pi*ZZ genotype is defined by a single point mutation, the phenotypic presentation can be variable, making diagnosis challenging.⁵ In pediatric patients, the most common manifestation of AATD with liver disease is neonatal cholestasis; toddlers and older children may present with asymptomatic chronic hepatitis; and in adults, AATD with liver disease is often asymptomatic.^{6,7} As a result, liver disease is frequently undetected until cirrhosis or hepatocellular carcinoma are evident.^{5,7} Although most pediatric patients with a Pi*ZZ phenotype show no pulmonary changes pre-adolescence, the main lung manifestation in patients with AATD is emphysema-predominant chronic obstructive pulmonary disease (COPD).⁸ As a result, treatment for AATD with lung disease typically includes conventional therapies for COPD and specific therapy for AATD (intravenous infusion with plasma-derived AAT).⁹

While treatments are in development for AATD with liver disease,¹⁰ there are currently no licensed pharmacological therapies available. Consequently, liver transplantation is recommended in patients with AATD and advanced liver cirrhosis or liver failure.¹¹ Real-world evidence on the clinical burden of AATD and associated health states (liver and/or lung disease) is limited. Nevertheless, a large prospective study of 200 000 Swedish pediatric patients (consisting of 127, 2 and 54 pediatric patients with AATD and Pi*ZZ, Pi*Z null and Pi*SZ genotypes, respectively) reported that 22 patients (17.3%) aged ≤ 6 months with the Pi*ZZ genotype had clinical signs of liver disease.¹² Additionally, in a study of 350 patients aged 0 to 25 years with a Pi*ZZ or Pi*SZ genotype, 28 developed definite or possible portal hypertension (defined as either ascites or endoscopic evidence of esophageal or gastric varices or other findings consistent with portal hypertension) during follow-up and 32 patients had a liver transplantation or died.¹³ Finally, in a Swedish registry of 1595 adults with the Pi*ZZ genotype followed for a mean of 12 (range 0.3–24) years, 3% of patients manifested liver disease at inclusion, and an additional 7% developed liver disease during the follow-up period;⁵ in support, data from the UK Biobank demonstrated that the risk of developing liver fibrosis or cirrhosis was 20 times higher in patients with AATD and a Pi*ZZ genotype than non-carriers.¹⁴

No previous study has used the same methodology to analyze liver-related clinical events in both adult and pediatric patients, thus permitting a direct comparison of age-related differences. In addition, no previous study has compared liver-related clinical events between adults with AATD with liver disease and adults with AATD with both liver and lung disease. Therefore, the aim of this study was to investigate the burden of liver-related clinical events among a cohort of adult and pediatric patients with AATD. To enable the inclusion of a sufficient number of patients with AATD from across the USA, this study leveraged data from a national administrative claims database in the USA.

Materials and Methods

Study Design

This was a non-interventional, retrospective, observational analysis of administrative claims data from the IQVIA PharMetrics® Plus database. As genotype data and laboratory results are not available in claims databases, linkage to the IQVIA Ambulatory Electronic Medical Records (AEMR) database was utilized, if available. The IQVIA PharMetrics Plus database comprises fully adjudicated medical and pharmaceutical claims for more than 190 million unique and commercially insured patients across the USA. The data are longitudinal, with approximately 20 million patients with both medical and pharmacy coverage and at least 3 years of continuous enrollment. The IQVIA AEMR database comprises approximately 75 million patient records collected from more than 40 000 physicians and sourced from an “opt-in” provider research network.

Study Population

Patient data were identified from each database separately, and then combined, before stratification by patient age (pediatric: <1 years, 1–5 years, 6–17 years; adult: ≥ 18 years). Patients from the IQVIA PharMetrics Plus database were included if they had records for one or more inpatient medical claim based on the International Classification of Diseases,

Ninth Revision, Clinical Modification (ICD-9-CM) code 273.4 or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code E88.01, or two or more outpatient medical claims for AATD at least 90 days apart in the IQVIA PharMetrics Plus database during the selection period (January 1, 2012–October 31, 2021). Patients from the IQVIA AEMR database were included if they had at least one diagnosis of AATD based on a Systematized Nomenclature of Medicine (SNOMED; January 1, 2006–June 30, 2022) code, with at least one problem name (eg a disease or symptom) or laboratory test result that indicated a Pi*ZZ or Pi*MZ genotype, and were required to have linkage to the IQVIA PharMetrics Plus database during the study period (July 1, 2011–January 31, 2022). Patients with AATD and liver disease or AATD with liver and lung disease were required to have at least 180 days of continuous enrollment prior to the date of first liver or lung disease diagnosis (unless they were aged <1 year on that date) and at least 90 days of continuous enrollment after the date of first liver or lung disease diagnosis.

A person–time approach was taken to maximize the use of data. At the patient level, for a patient's identified continuous enrollment period in the IQVIA PharMetrics Plus database, patient time was assigned to different health states based on the presence of a liver and/or lung disease diagnosis code. Follow-up time was assigned to the AATD with liver disease health state (for time with liver disease only) or the AATD with both liver and lung disease health state (for time with both liver and lung disease); most pediatric patients (<18 years of age) do not manifest lung disease and were therefore assigned to the AATD with liver disease health state only.⁸ The date of the first identified medical claim with a liver disease diagnosis code was termed the index date for time in the AATD with liver disease health state ([Supplementary Table 1](#)). For the AATD with both liver and lung disease health state, the date of the first identified medical claim with a lung disease diagnosis code (after a liver disease diagnosis) or date of first medical claim with a liver disease diagnosis code (after lung disease diagnosis) was termed the index date ([Supplementary Figure 1](#) and [Supplementary Table 2](#)). If a patient had a first liver disease diagnosis and first lung disease diagnosis code within 90 days of each other, the index date was the date of the first occurring liver or lung disease diagnosis. The presence of asthma alone was not sufficient to assign follow-up time to the AATD with both liver and lung disease health state. Patients had a variable follow-up period (≥ 3 months) through to the end of their available continuous enrollment.

Outcomes

Analyses were descriptive with no formal statistical comparisons performed. Baseline demographics were collected at the index date and clinical characteristics were collected during the 6 months before the index date (baseline period). Liver-related clinical events of interest (identified by ICD-9/-10-CM or procedure codes as applicable) included ascites, gastrointestinal bleed, hepatic encephalopathy, hepatocellular carcinoma, liver transplantation and spontaneous bacterial peritonitis. Event rates per person-year (PPY) for liver-related clinical events were calculated as unique patients with the event in the numerator and the denominator was censored patient time contributed to each health state (up until the first event if one occurred). Events were evaluated separately and as a composite (defined as the first occurrence of any liver-related clinical event). Time to event was reported at the patient level for liver-related clinical events of interest, starting from the first occurring liver disease diagnosis for patients in the AATD with liver disease health state, or first liver or lung disease diagnosis for patients in the AATD with both liver and lung disease health state ([Supplementary Figure 1](#)). For the combined analysis of the AATD with liver disease and AATD with both liver and lung disease health states, follow-up time from each group was merged.

Results

Patient Demographics and Baseline Characteristics

Of 5136 patients, 771 and 541 adults contributed time to the AATD with liver disease and AATD with both liver and lung disease health states, respectively (combined, 1147 patients [164 patients contributed time to both health states]). In addition, 123 pediatric patients (aged <1 [n=41], 1–5 [n=24] and 6–17 [n=58] years) contributed time to the AATD with liver disease health state ([Figure 1](#)). Of the remaining patients, 1804 (adults and pediatric) were excluded from further analysis owing to the absence of a liver and/or lung disease diagnosis, and 2218 adults contributed time to the AATD with lung disease health state only.

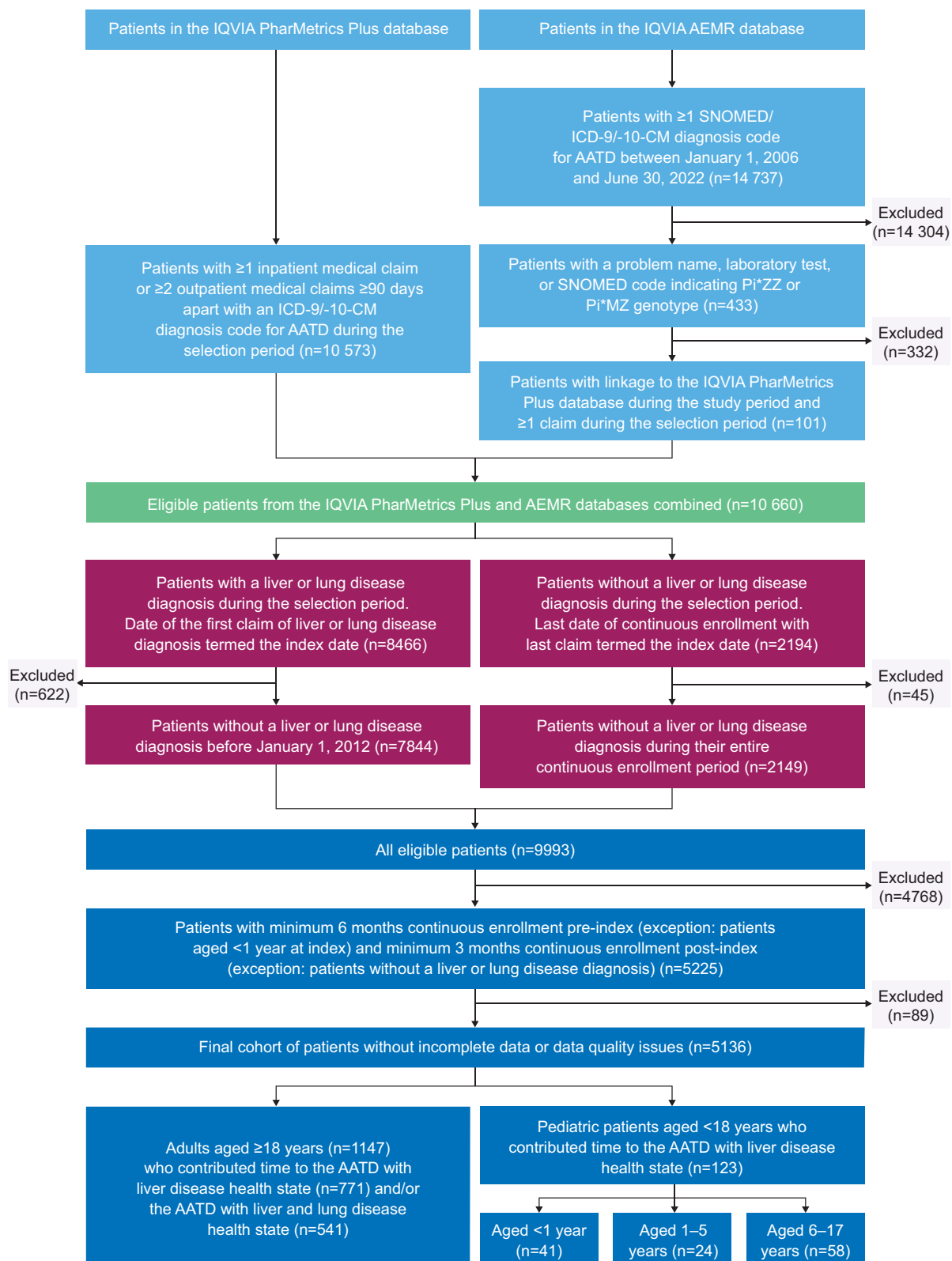


Figure 1 Patient Disposition.

Abbreviations: AATD, alpha-1 antitrypsin deficiency; AEMR, Ambulatory Electronic Medical Records; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; Pi, protease inhibitor; SNOMED, Systematized Nomenclature of Medicine.

Among adults, baseline characteristics were broadly similar across the two health states (Table 1). Patients in the AATD with both liver and lung disease health state were slightly older (median [interquartile range (IQR)] 55 [46–61] vs 49 [38–57] years) than patients in the AATD with liver disease health state, while patients in the AATD with liver disease health state had a higher proportion of males (58.5% vs 50.8%) than patients in the AATD with both liver and lung disease health state. The most common comorbidities in both health states were hypertension and hyperlipidemia. The

Table 1 Patient Demographics and Characteristics

	AATD with Liver Disease				AATD with Both Liver and Lung Disease
	Patients Aged <1 Year (n=41)	Patients Aged 1–5 Years (n=24)	Patients Aged 6–17 Years (n=58)	Patients Aged ≥18 Years (n=771)	Patients Aged ≥18 Years (n=541)
Age, years, median (IQR)	0 (0–0)	3 (2–5)	14 (10–16)	49 (38–57)	55 (46–61)
Sex, male, n (%)	25 (61)	13 (54)	36 (62)	451 (58)	275 (51)
Time in health state, months, median (IQR) ^a	37 (22.6–55)	22 (9.0–36)	36 (15.0–60)	22 (10–40)	21 (10–38)
Most common comorbidities, n (%) ^b	N/A ^c				
Asthma		2 (8)	8 (14)	62 (8)	90 (17)
Diabetes mellitus		0	2 (3)	107 (14)	107 (20)
Hyperlipidemia		0	3 (5)	208 (27)	166 (31)
Hypertension		2 (8)	2 (3)	221 (29)	217 (40)
Liver cirrhosis		0	0	15 (2)	60 (11)
Liver/gall bladder/pancreatic disease		1 (4)	0	80 (10)	132 (24)
Obesity		1 (4)	8 (14)	124 (16)	129 (24)
Sleep disorders		0	2 (3)	97 (13)	100 (18)
Study liver disease definition ^d		0	0	0	93 (17)
Study lung disease definition ^d		1 (4)	4 (7)	0	127 (23)
Charlson Comorbidity Index, n (%)	N/A ^c				
0		21 (88)	48 (83)	515 (67)	191 (35)
1		2 (8)	8 (14)	138 (18)	162 (30)
2		0	1 (2)	73 (10)	74 (14)
3		0	0	30 (4)	52 (10)
≥4		1 (4)	1 (2)	15 (2)	62 (11)
Payer type, n (%)					
Commercial	25 (61)	12 (50)	42 (72)	511 (66)	353 (65)
Self-insured	12 (29)	9 (38)	13 (22)	224 (29)	151 (28)
Medicare risk	0	0	0	21 (3)	25 (5)
Medicaid	4 (10)	3 (13)	3 (5)	12 (2)	8 (1)
Other/unknown	0	0	0	3 (<1)	4 (<1)
Geographic region of the USA, n (%)					
South	13 (32)	10 (42)	22 (38)	341 (44)	272 (50)
Midwest	13 (32)	10 (42)	16 (28)	187 (24)	129 (24)
Northeast	8 (20)	2 (8)	12 (21)	147 (19)	76 (14)
West	7 (17)	2 (8)	7 (12)	86 (11)	57 (11)
Unknown/missing	0	0	1 (2)	10 (1)	7 (1)

Notes: ^aDifference in time from first lung disease diagnosis (after liver disease diagnosis), or first liver disease diagnosis (after lung disease diagnosis), or first liver or first lung disease diagnosis (if within 90 days of each other) to last day of continuous enrollment period. ^bPresent in ≥10% of patients in at least one of the subgroups. ^cPatients <1 year were indexed at age 0 years and therefore did not have a 6-month baseline period for the collection of clinical characteristics. ^dClinician determined specific liver/lung disease diagnosis codes as AATD-specific; separately reported comorbidities may include broader definitions (eg alcoholic liver cirrhosis).

Abbreviations: AATD, alpha-1 antitrypsin deficiency; IQR, interquartile range; N/A, not available.

median (IQR) duration of observation was 22.2 (10.3–39.7) months in the AATD with liver disease health state and 20.8 months (9.9–38.4) in the AATD with both liver and lung disease health state.

The pediatric patients were mostly male (60.2%), from the south of the USA (36.6%), had commercial health insurance (64.2%) and had a Charlson Comorbidity Index of 0 (89.4%). The most common comorbidities were asthma (8.1%) and obesity (7.3%), and the median (range) duration of time contributed in the AATD with liver disease health state was 31.5 (3.1–115.5) months.

Liver-Related Clinical Events

For adult patients, there was a trend towards more frequent liver-related clinical events in the AATD with liver and lung disease health state than the AATD with liver disease health state alone; the event rate PPY for composite events was 0.20 in the AATD with liver and lung disease health state and 0.13 in the AATD with liver disease health state only. For liver-related clinical events PPY in the AATD with liver disease health state and the AATD with both liver and lung disease health state, the most common were ascites (0.09 and 0.12, respectively), hepatic encephalopathy (0.07 and 0.10, respectively) and gastrointestinal bleed (0.05 and 0.08, respectively; Figure 2A). The event rate PPY for liver transplantation in adult patients was 0.01 and 0.03, respectively.

For the <1 year, 1–5 years and 6–17 years groups in the AATD with liver disease health state, ascites (0.07, 0.08, 0.01 events PPY), gastrointestinal bleed (0.04, 0.08, 0.02 events PPY) and hepatic encephalopathy (0.03, 0.10, 0.04 events

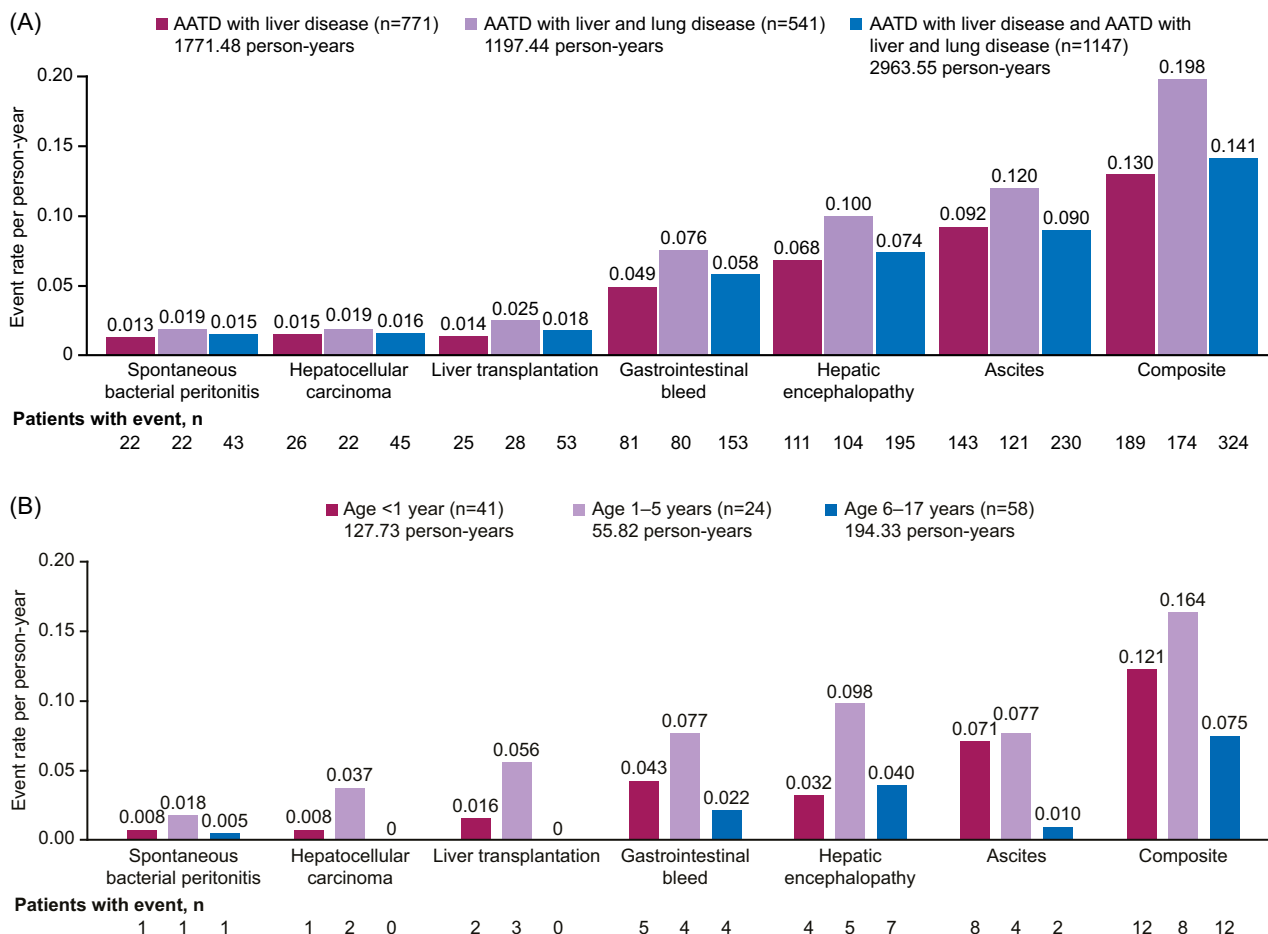


Figure 2 Liver-Related Clinical Event Rates per Person-Year in (A) Adult Patients (Aged ≥18 Years)^a and (B) Pediatric Patients^{b,c}. ^aThe sum of patients in each health state is higher than the number of patients included in the study owing to patients contributing time in more than one health state during the study, according to their disease status. ^bData are reported for pediatric patients (stratified by age group [<1 year, 1–5 years and 6–17 years]) with AATD with liver disease. Number of events were calculated per person-year (365.25 days); composite data (≥1 liver-related clinical event) are shown for any patient with >1 clinical event. **Abbreviation:** AATD, alpha-1 antitrypsin deficiency.

PPY) were more common than spontaneous bacterial peritonitis (0.01, 0.02, 0.01 events PPY) and hepatocellular carcinoma (0.01, 0.04, 0.00 events PPY; Figure 2B). For all liver-related clinical events in pediatric patients (Figure 2B), event rates PPY were highest in the 1–5 years group and lowest in the 6–17 years group (except for hepatic encephalopathy). No liver transplantations occurred in patients aged 6–17 years, whereas the event rates PPY were 0.02 and 0.06 in the <1 year and 1–5 years groups, respectively.

Time to Liver-Related Clinical Event

In a combined analysis of adults in the AATD with liver disease and AATD with both liver and lung disease health states, the median time to the composite of any liver-related clinical event (among patients with an event) was 26.5 days (Figure 3A). Ascites had the shortest median time to event of 20.5 days while liver transplantation had the longest median time to event of 410.0 days. Further, 10/53 patients (18.9%) had a recorded event of hepatocellular carcinoma prior to their first event of liver transplantation.

Median time to first liver-related clinical event was generally longer in pediatric patients in the AATD with liver disease health state than in adults. Although time to event varied by age group at diagnosis and type of event (Figure 3B), the median time to the composite of any liver-related clinical event increased with age: 85.5, 95.0 and 184.5 days, for the <1 year, 1–5 years and 6–17 years groups, respectively. The shortest and longest reported time to first liver-related clinical event were in the <1 year age group: 3.5 days for hepatic encephalopathy and 846.0 days for spontaneous bacterial peritonitis.

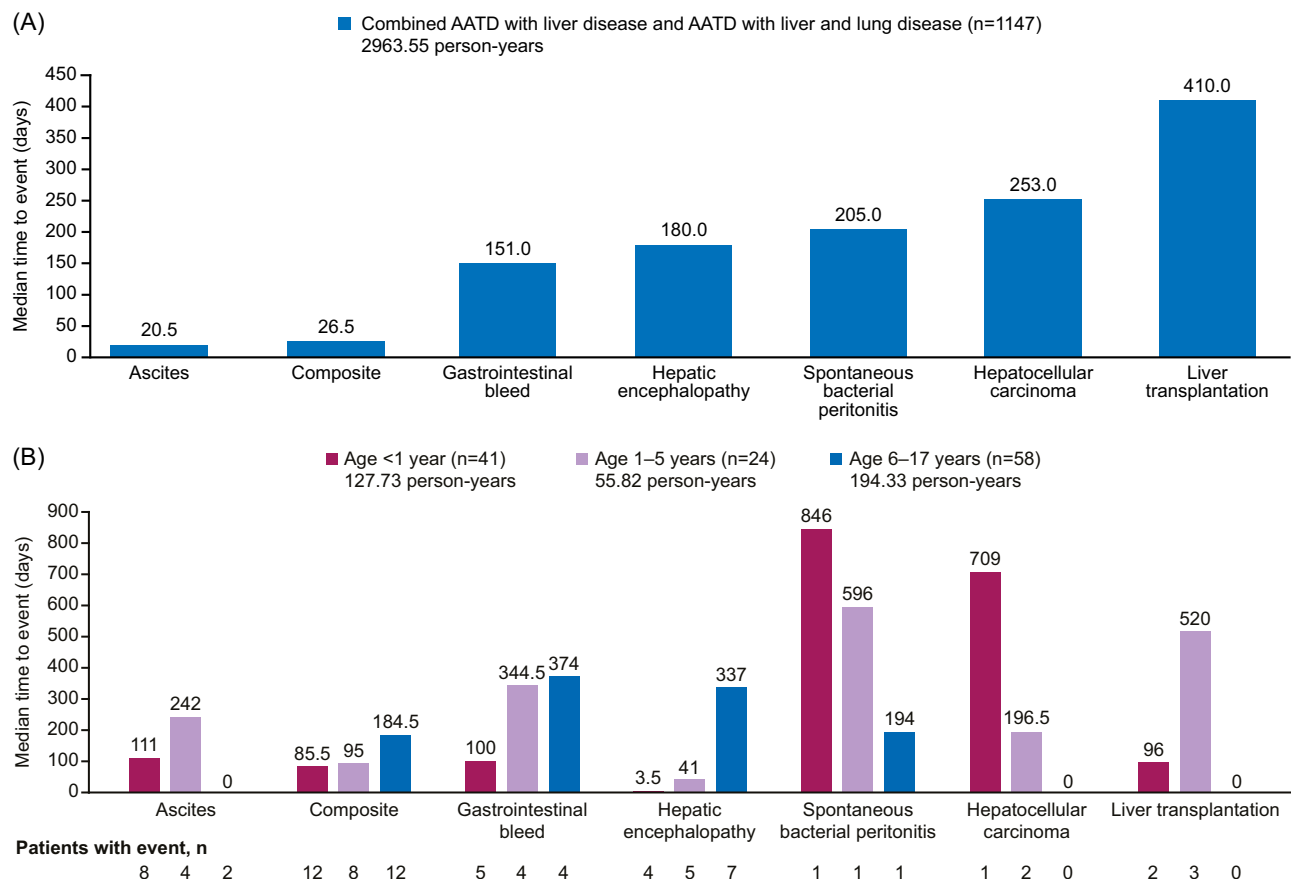


Figure 3 Median Time to First Liver-Related Clinical Event in (A) Adult Patients (Aged ≥18 Years) and (B) Pediatric Patients^a. ^aData are reported for pediatric patients (stratified by age group [<1 year, 1–5 years and 6–17 years]) with AATD with liver disease. Time to first liver-related clinical event was reported from the index date. Patients with ≥1 clinical event are presented in the composite data.

Abbreviation: AATD, alpha-1 antitrypsin deficiency.

Discussion

This real-world study adds to the limited literature on the clinical course of AATD with liver disease alone, AATD with both liver and lung disease in adult patients and AATD with liver disease in pediatric patients, by providing an understanding of the burden of liver-related clinical events. In addition, to the best of our knowledge, this is the first study to measure liver-related clinical events in both adult and pediatric patients using the same methodology.

In adults, the rates of liver-related clinical events were higher when patients had both liver and lung disease than liver disease only. This could be attributed to a higher number of events or shorter time at risk in the AATD with both liver and lung disease health state; however, the difference in average time at risk in person-years between the groups was minimal (2.30 years in the AATD with liver disease health state and 2.21 years in the AATD with both liver and lung disease health state). This may also be related to the higher median age of adult patients with AATD and both liver and lung disease.

For both adult and pediatric patients, ascites, hepatic encephalopathy and gastrointestinal bleed were more frequently observed than spontaneous bacterial peritonitis and hepatocellular carcinoma (Figure 2A and B), although the event rate PPY for ascites was notably lower in the pediatric 6–17 years age group (Figure 2B). Interestingly, for patients aged <1 and 1–5 years, our study reported more cases of hepatocellular carcinoma than prior studies.¹⁵ While hepatocellular carcinoma is seen in pediatric patients with AATD,^{6,16} it is an extraordinarily rare finding, and therefore previously published shorter case series may not have been best suited to identifying patients with hepatocellular carcinoma.¹⁵ As such, more cases of hepatocellular carcinoma may exist than are currently reported in prior studies.

While liver transplantation events were reported in pediatric patients aged <6 years, there were no reported liver transplantation or hepatocellular carcinoma events in patients aged 6–17 years, indicating greater disease burden in younger versus older pediatric patients. Consistent with this, a prior Swedish birth cohort of 127 pediatric patients with Pi*ZZ genotypes identified by isoelectric focusing reported two liver disease-related deaths within the first year of life, and an additional three deaths in patients aged 1–8 years, while fewer liver-related clinical events were identified throughout adolescence.¹² In addition, in a US registry study among 350 patients with AATD and either a Pi*ZZ or Pi*SZ genotype, a median age of 4.2 years at registry enrollment and a median follow-up time of 2.5 years, the rate of development of portal hypertension was 0.02 PPY and the rate of liver transplantation or death was 0.03 PPY.¹³ Collectively, these findings suggest the need for early monitoring of pediatric patients for the development of ascites and progression to severe liver disease.

For adult and pediatric patients, the earliest encountered liver-related clinical events were ascites, gastrointestinal bleed and hepatic encephalopathy (Figure 3A and B). Within the pediatric population, the median time to liver-related clinical events varied by age group; for example, time to gastrointestinal bleed and hepatic encephalopathy increased with age while spontaneous bacterial peritonitis and hepatocellular carcinoma decreased in the older pediatric age groups. The median time to composite event was lower for adults (26.5 days) than pediatric patients (85.5, 95.0 and 184.5 days for the <1 year, 1–5 years and 6–17 years groups, respectively). The short median time to event in adults suggests that the diagnosis is often established at the time of a clinical event at more advanced stages of liver disease, not when prospective follow-up of patients with AATD is ongoing. Therefore, the late diagnosis of AATD with liver disease is a barrier to efficiently enrolling patients in interventional studies at a time prior to the development of cirrhosis and delays the timely intervention of lifestyle modifications and potential treatments.

The strengths of this study include the size of the patient population, with 5136 patients characterized, which represents a large sample of patients with AATD. A person–time approach was undertaken to maximize the use of patient data and to standardize reporting of outcomes for each health state given the variable time in each health state. The limitations of this study include that these findings are from commercially insured patients and may not be generalizable to the wider US population. Additionally, ascertainment bias is common in this type of study, which may explain the higher hepatocellular carcinoma event rate in pediatric patients in this study compared with those occurring in the entire population of pediatric patients with AATD with liver disease. Furthermore, the number of pediatric patients in the sample was low, particularly in the 1–5 years group, which warrants additional studies to confirm these findings. The overall burden may also be underestimated owing to an underrepresentation of older patients (≥ 65 years of age) in the databases used, who are more likely to have AATD with liver disease or AATD with both liver and lung disease. In addition, when using administrative claims databases, a diagnosis for AATD is dependent on ICD-9-CM and ICD-10-CM diagnosis codes which do not specify genotype. As such, this results in a lack of genotype data in administrative claims databases. Indeed, no patients were identified with a confirmed Pi*ZZ genotype and only 13 patients were identified with a confirmed Pi*MZ genotype, and therefore stratification of patient data by genotype was not

feasible. Although ICD-9-CM and ICD-10-CM diagnosis codes for AATD exist, it can be challenging to confirm an AATD with liver disease or AATD with lung disease diagnosis as there are no specific diagnosis codes for AATD combined with the manifestations, which may have led to the exclusion of some patients who would have otherwise been eligible. Furthermore, AATD diagnosis codes are required when requesting AATD-related laboratory tests prior to a confirmed AATD diagnosis, which may lead to the inclusion of patients without AATD but with AATD medical records for screening; this limitation was minimized in this study by requiring two diagnosis codes for AATD at outpatient visits at least 90 days apart. Finally, it was not possible to identify the fibrosis stage in patients with liver disease using ICD-9-CM or ICD-10-CM diagnosis codes.

Conclusion

To the best of our knowledge, this is the first study of liver-related clinical events and time to event in a large sample of adult and pediatric patients with AATD (not specifically among patients with a Pi*ZZ genotype). This study adds to the limited literature by providing a real-world understanding of the clinical burden of AATD with liver disease. The high rate of liver-related clinical events reported in our study demonstrates that AATD with liver disease has a substantial burden on adult and pediatric patients. Most notably, younger pediatric patients (aged <6 years) should be monitored for occurrence of liver-related clinical events to avoid decompensating events. The short median time to liver-related clinical events in adults suggests that patients often have advanced liver disease at the initial diagnosis date and are being diagnosed late in their disease journey. New treatment options are warranted to avoid disease progression, which can lead to liver transplantation. Further research should examine the rate of liver-related clinical events by genotype in adult and pediatric patients with AATD with liver disease to understand how genotype may impact disease severity.

Abbreviations

AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin; AEMR, Ambulatory Electronic Medical Records; COPD, chronic obstructive pulmonary disease; EMR, electronic medical records; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; Pi, protease inhibitor; SNOMED, Systematized Nomenclature of Medicine.

Data Sharing Statement

The original de-identified data used in this analysis were obtained from and are the property of IQVIA. IQVIA has restrictions prohibiting the authors from making the data set publicly available. Interested researchers may contact IQVIA to apply to gain access to the study's data in the same way the authors obtained the data (see <https://www.iqvia.com/contact/sf>).

Ethics Statement

Institutional review board approval to conduct this study was not necessary because only de-identified data were used, and the study did not involve the collection, use or transmittal of individually identifiable data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

MH, SP, EGM and KR are employees and stockholders of Takeda Development Center Americas, Inc. VD, SM and MD are employees of IQVIA, which received funding for this study from Takeda Development Center Americas, Inc. CS is an employee of AlphaNet; has grants paid to the Medical University of South Carolina from Adverum Biotechnologies, Arrowhead Pharmaceuticals, AstraZeneca, CSA Medical, Grifols, Krystal, Mereo BioPharma, National Institutes of Health, Novo Nordisk, Nuvaira, Takeda and Vertex Pharmaceuticals; and has consulted for Bronchus, CSL Behring, Dicerna Pharmaceuticals, GlaxoSmithKline, PulManage and Vertex Pharmaceuticals for alpha-1 and/or chronic obstructive pulmonary disease. The authors report no other conflicts of interest in this work.

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