# Progression of liver disease in newly diagnosed patients with alpha-1 antitrypsin deficiency and PiZZ genotype

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## Introduction

- Alpha-1 antitrypsin deficiency (AATD) is a rare and underdiagnosed genetic disorder associated with lung and/or liver disease (LD) in children and adults.[1]
- AATD is caused by mutations in *SERPINA1*, which encodes alpha-1 antitrypsin (AAT); the protease inhibitor (Pi) Z genotype (Glu342Lys) is the most common disease-causing variant.[2]
  - In PiZZ homozygous individuals, AAT misfolds in hepatocytes, leading to accumulation of AAT aggregates in the liver and liver damage.[2]
  - Reduced levels of secreted AAT lead to lung damage, due to tissue attack by neutrophil elastase, which is normally inhibited by AAT.[2]
- Patients with AATD-associated LD and with PiZZ genotype (AATD-LD-PiZZ) experience variable disease progression and may remain asymptomatic despite advanced liver fibrosis.
  - Factors contributing to the progression of AATD-LD-PiZZ are poorly understood.[3]

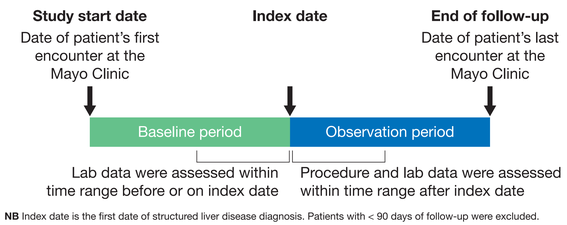
## Objectives

- To define and characterize patients with AATD-LD-PiZZ in a large tertiary referral center.
- To examine the relationship between LD progression and LD-related clinical events (LD events) in patients with AATD-LD-PiZZ.

## Methods

- A retrospective longitudinal study in patients with AATD-LD-PiZZ was conducted in the Mayo Clinic Healthcare System.
- Data were extracted from the Mayo Clinic Healthcare System nference electronic medical record database for the period January 2004 to September 2021.
- Eligible patients had > 3 clinical encounters > 3 months apart over a period of > 1 year.
  - The baseline and observation periods were defined as occurring before and after the date of LD diagnosis (index date) (**Figure 1**).
- Patients with AATD were defined by structured diagnosis codes for AATD or serum AAT level < 100 mg/dL.
  - PiZZ genotype was defined by genotyping results or unstructured data through Bidirectional Encoder Representations from Transformers natural language processing (NLP) models.
  - LD was defined based on structured diagnosis codes and biochemical, radiological and histopathological findings where available.

**Figure 1. Study design**




**NB** Index date is the first date of structured liver disease diagnosis. Patients with < 90 days of follow-up were excluded.

- Fibrosis stage (F1–F4) was assessed at baseline (± 90 days from index date) and during follow-up using a hierarchical approach: liver biopsy (METAVIR staging), magnetic resonance elastography (MRE), vibration-controlled transient elastography (VCTE; Fibroscan), aspartate aminotransferase to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) score.
  - **F4 decompensated cirrhosis (dc):** Model for End-stage Liver Disease score increased by ≥ 15 from baseline value < 12, or Child–Turcotte–Pugh score increased > 2 from baseline
  - **F4 compensated cirrhosis (cc):** MRE > 5.0 kPa, APRI > 1.5 or FIB-4 > 3.25
  - **F3:** 5.0 ≥ MRE > 4.0 kPa, VCTE > 12.5 kPa, APRI > 0.63 or FIB-4 > 1.90
  - **F2:** 4.0 ≥ MRE > 3.5 kPa, VCTE > 8.45 kPa, APRI > 0.43 or FIB-4 > 1.43
  - **F1:** 3.5 ≥ MRE ≥ 3.0 kPa
- LD events were defined as development of ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, and listing for or undergoing liver transplantation.
  - LD events were identified using structured diagnosis codes and NLP of unstructured data.

## Results

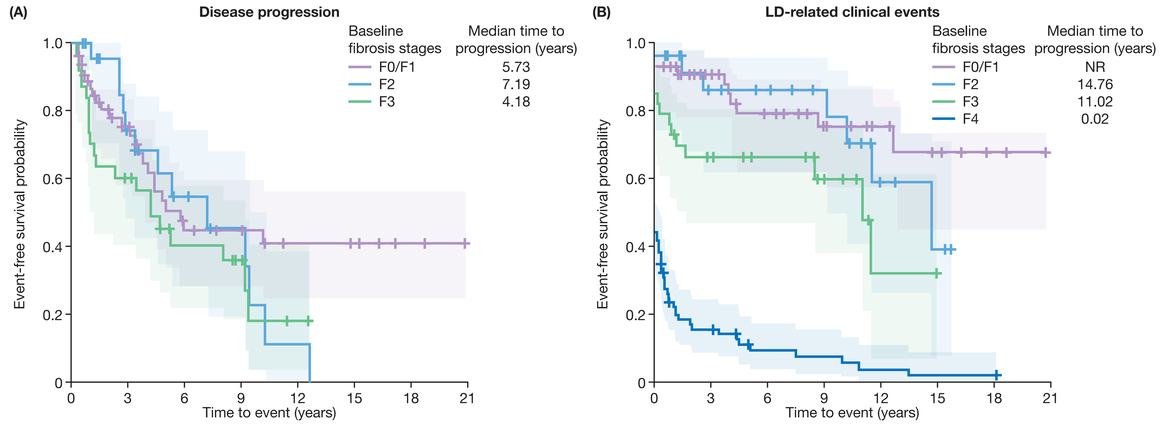
- Of the approximately 685 000 patients in the nference database (January 2004 to September 2021), 6315 had AATD, of whom 501 had the PiZZ genotype and 316 had AATD-LD-PiZZ and qualified for the study.
- In patients with AATD-LD-PiZZ (N = 316), the mean age at baseline was 50.5 years; 58.5% were male and 96.8% were White (**Table 1**).
  - Baseline fibrosis stage was evaluable in 197/316 patients (**Table 1**).
  - Very few patients had baseline liver biopsy (< 2%) or MRE (0%).
- Among 316 patients, the median time from LD diagnosis date (or index date) to last encounter was 2717 days, or approximately 7.4 years.
  - Disease progression (≥ 1 fibrosis stage from baseline) occurred in 31/197 patients (15.7%) within 2 years of LD diagnosis (F0/F1, 22.2%; F2, 4.8%; F3, 36.5%) and in 53/197 (26.9%) within 5 years (F0/F1, 49.5%; F2, 38.5%; F3, 54.8%) (**Figure 2A**).
  - LD events (any event of interest) occurred in 160/316 patients (50.6%) at any time during follow-up (median 7.4 years), with a higher frequency in patients with baseline fibrosis stage F4cc (98.2%) than in those with F3 (68.3%) or F2 (61.0%) (**Figure 2B**).
  - In total, 14.3% of patients with F2 at baseline had an LD event within 3 years (**Figure 2B**).
  - Of 316 patients, 55 (17.4%) underwent liver transplantation (F0/F1, 1.9%; F2, 4.2%; F3, 12.1%; F4cc, 43.7%).

**Table 1. Demographics and baseline characteristics**

| | Patients with AATD-LD-PiZZ (N = 316) |
|---|---|
| Age, mean (SD)* | 50.5 (16.4) |
| Male, n (%) | 185 (58.5) |
| BMI, mean (SD)† | 28.5 (6.3) |
| Weight, mean (SD) | 84.4 (21.4) |
| White, n (%) | 306 (96.8) |
| Fibrosis stage, n (%) | |
| F0/F1 | 53 (26.9) |
| F2 | 24 (12.2) |
| F3 | 33 (16.8) |
| F4cc | 87 (44.2) |
| Not evaluable‡ | 119 |

*At liver disease diagnosis date. †Closest to liver disease diagnosis date. ‡Variables for calculating the fibrosis staging were not available.
AATD-LD-PiZZ, alpha-1 antitrypsin deficiency-associated liver disease protease inhibitor ZZ; BMI, body mass index; SD, standard deviation.

**Figure 2. Kaplan–Meier analysis of time to (A) disease progression and (B) LD events by baseline fibrosis stage**




| | Baseline F0/F1 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| At risk | 53 | 30 | 15 | 13 | 9 | 8 | 2 | 0 |
| Censored | 0 | 11 | 15 | 17 | 20 | 21 | 27 | 29 |
| Events | 0 | 12 | 23 | 23 | 24 | 24 | 24 | 24 |
| **Baseline F2** | | | | | | | | |
| At risk | 24 | 13 | 7 | 4 | 1 | 0 | 0 | 0 |
| Censored | 0 | 6 | 9 | 11 | 11 | 11 | 11 | 11 |
| Events | 0 | 5 | 8 | 9 | 12 | 13 | 13 | 13 |
| **Baseline F3** | | | | | | | | |
| At risk | 33 | 17 | 9 | 5 | 1 | 0 | 0 | 0 |
| Censored | 0 | 4 | 7 | 10 | 12 | 13 | 13 | 13 |
| Events | 0 | 12 | 17 | 18 | 20 | 20 | 20 | 20 |

| | Baseline F0/F1 | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| At risk | 50 | 35 | 25 | 18 | 11 | 8 | 2 | 0 |
| Censored | 0 | 13 | 19 | 25 | 32 | 34 | 40 | 42 |
| Events | 3 | 5 | 9 | 10 | 10 | 11 | 11 | 11 |
| **Baseline F2** | | | | | | | | |
| At risk | 23 | 16 | 14 | 11 | 4 | 2 | 0 | 0 |
| Censored | 0 | 5 | 7 | 10 | 14 | 15 | 17 | 17 |
| Events | 1 | 3 | 3 | 3 | 6 | 7 | 7 | 7 |
| **Baseline F3** | | | | | | | | |
| At risk | 29 | 19 | 14 | 8 | 2 | 0 | 0 | 0 |
| Censored | 0 | 3 | 8 | 13 | 17 | 19 | 19 | 19 |
| Events | 4 | 11 | 11 | 12 | 14 | 14 | 14 | 14 |
| **Baseline F4** | | | | | | | | |
| At risk | 56 | 12 | 5 | 4 | 2 | 1 | 1 | 0 |
| Censored | 0 | 3 | 6 | 6 | 6 | 6 | 6 | 7 |
| Events | 31 | 72 | 76 | 77 | 79 | 80 | 80 | 80 |

| Baseline stage | Proportion of patients with progression from baseline at n years, % | | | | | |
|---|---|---|---|---|---|---|
| | ≤ 1 y | ≤ 2 y | ≤ 3 y | ≤ 4 y | ≤ 5 y | ≤ 20 y |
| F0/F1 (n = 53) | 11.5 | 22.2 | 24.5 | 35.4 | 49.5 | 59.0 |
| F2 (n = 24) | 0.0 | 4.8 | 25.9 | 31.6 | 38.5 | 100.0 |
| F3 (n = 33) | 29.8 | 36.5 | 39.8 | 43.6 | 54.8 | 81.9 |

| Baseline stage | Proportion of patients with clinical event from baseline at n years, % | | | | | |
|---|---|---|---|---|---|---|
| | ≤ 1 y | ≤ 2 y | ≤ 3 y | ≤ 4 y | ≤ 5 y | ≤ 20 y |
| F0/F1 (n = 53) | 7.5 | 9.6 | 9.6 | 15.3 | 21.0 | 32.5 |
| F2 (n = 24) | 4.2 | 9.2 | 14.3 | 14.3 | 14.3 | 61.0 |
| F3 (n = 33) | 27.3 | 33.9 | 33.9 | 33.9 | 33.9 | 68.3 |
| F4 (n = 87) | 76.5 | 84.4 | 84.4 | 85.8 | 88.9 | 98.2 |

In panel B, reported fibrosis stages were baseline stages.
LD, liver disease; NR, not reachable; y, years.

## Limitations

- The use of non-invasive surrogate markers helped to define fibrosis staging but created the potential for misclassification of fibrosis staging owing to a lack of validation in the AATD cohort. Yet the high percentage of patients developing a clinical endpoint typical of decompensated LD corroborated the late diagnosis of the disease.
- Further validation of these non-invasive markers and thresholds in this cohort is warranted to support the clinical management of AATD-LD.
- These study findings might not be representative of the broader population with AATD-LD.

## Conclusions

- Disease progression was characterized and examined in 316 patients with AATD-PiZZ-LD, one of the largest AATD-LD cohorts defined in a real-world setting.
- In patients with an LD diagnosis before AATD, the average time to receive an AATD diagnosis was 4.7 years, demonstrating the widespread delayed diagnosis of AATD.
- Approximately one-third of patients with AATD-LD-PiZZ and fibrosis stage F3 at baseline progressed to F4 or had LD events within 2 years. More than 75% of patients with fibrosis stage F4cc at baseline had LD events within 1 year.
- This study shows that a considerable percentage of patients with fibrosis stage F3 progress to F4cc/F4dc within 2 years, highlighting the need for early diagnosis.

### References

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