

## PERSPECTIVE ARTICLE

# Alpha 1-antitrypsin deficiency and chronic liver disease in adults: Molecular basis and clinical aspects

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## Abstract

Alpha 1-antitrypsin deficiency (A1ATD) is a codominant genetic disorder primarily caused by PiZ mutations in the serpin family A member 1 (*SERPINA1*) gene. A1ATD is typically associated with the early-onset lung emphysema. However, the misfolding and accumulation of alpha 1-antitrypsin (A1AT) in hepatocytes can also lead to chronic liver disease (CLD). This perspective paper discusses the genetic and molecular factors, the epidemiological features, and clinico-pathological spectrum of A1ATD-related CLD in adults. Emphasis is given to steatosis, cirrhosis, and primary liver cancer, the risks of which critically depend on the PiZ genotype. We discuss the diagnostic strategy, including non-invasive assessment of liver fibrosis. While augmentation therapy plays a role in treating the pulmonary manifestations of A1ATD, this approach carries no benefit for the liver, and early detection is critical to slow the progression of CLD. New approaches comprise gene-editing, innovative pharmacological chaperones, and personalized medicine that target the underlying protein misfolding defect. Enhancing early diagnosis and refining precision treatment strategies promise to significantly improve clinical outcomes.

**Keywords:** Cirrhosis; Fibrosis; Gene defect; Genetic disease; Liver; Lung; Steatosis; Primary liver cancer

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## 1. Introduction

Alpha 1-antitrypsin (A1AT) deficiency (A1ATD) is one of the most prevalent hereditary conditions affecting the liver in adults and is frequently underdiagnosed due to its broad spectrum of clinical presentations, variable onset, and impact of environmental factors.<sup>1</sup> A1AT, the primary protease inhibitor of neutrophil elastase, is integral in regulating inflammatory and proteolytic pathways in various tissues, most notably in the lungs and the liver.<sup>2</sup>

A1AT is encoded by the polymorphic serpin family A member 1 (*SERPINA1*) gene, located on human chromosome 14q32.1 and composed of four coding exons and three untranslated exons.<sup>3</sup> In its native state, the A1AT protein has 418 amino acids, including a 24-amino acid signal peptide. The mature form, therefore, contains 394 amino acids, has a mass of approximately 52 kDa, and is typically glycosylated at the Asn46, Asn83,

and Asn247 residues.<sup>3</sup> Structurally, A1AT includes three  $\beta$ -sheets, nine  $\alpha$ -helices, and a reactive central loop, which is critical for its initial interaction with the target protease.<sup>3</sup>

When A1AT levels are deficient or the protein is structurally abnormal, downstream tissue damage and organ dysfunction can occur. In adults, the disease is frequently associated with chronic liver injury, cirrhosis, and primary liver cancer (PLC), namely, hepatocellular carcinoma (HCC) and cholangiocarcinoma.<sup>4</sup>

From an epidemiological standpoint, A1ATD is generally considered as a relatively rare condition, although its true prevalence may be underestimated due to limited systematic screening in the general population. Estimates suggest that the PiZZ genotype, which is the most clinically significant and severe variant of A1ATD, occurs in approximately 1 in 2,000 to 1 in 5,000 individuals of European descent.<sup>5</sup> However, the broader prevalence of A1ATD as determined by various deficiency alleles (including PiZ, PiS, and others) and the occurrence of rare variants can be considerably higher.<sup>6,7</sup> Geographic and ethnic factors strongly influence allele frequency, for example, the PiZ allele is particularly common in Northern and Western Europe but less frequent in Mediterranean, African, and East Asian populations.<sup>5</sup> This distribution can help clinicians anticipate where clusters of A1ATD might emerge, though there is no complete exemption for other regions, given global population movement.

Despite the actual number of cases, many individuals with A1ATD are asymptomatic or exhibit only mild clinical signs, allowing the disease to remain undetected until adulthood and resulting in highly variable quality of life.<sup>8</sup> When overt liver disease exists, early symptoms may present as non-specific fatigue, mild elevations in liver enzymes, or subtle evidence of hepatomegaly. Over time, a subset of patients can progress to more severe manifestations, including cirrhosis, portal hypertension, and ultimately PLC.<sup>4</sup> While children with A1ATD often present with cholestatic features early in life, adults more frequently come to clinical attention when cirrhosis or other advanced liver disease symptoms arise.<sup>4</sup> Accordingly, screening for A1ATD among individuals with unexplained chronic liver disease (CLD) is often recommended, especially in populations known to carry a higher burden of deficiency alleles.

A1ATD is an autosomal codominant hereditary disorder, meaning that an individual inherits one allele from each parent. The A1AT protein is encoded by the *SERPINA1* gene, located on chromosome 14q32.13.<sup>9,10</sup> This gene belongs to the serpin superfamily of protease inhibitors (Figure 1). The naming convention divides alleles into “normal” and “deficiency” variants, designated

by letters. The “M” allele, denoted PiM, is considered the normal wild-type variant. The most common deficiency alleles are PiZ (the most severe deficiency variant) and PiS (generally associated with milder reductions in circulating A1AT levels). An individual's phenotype is described by their combination of inherited *SERPINA1* alleles, for instance, PiMM (often associated with normal levels of A1AT), PiMZ, PiMS, PiSZ, or PiZZ, among others. Homozygosity for the PiZZ allele typically confers a high risk of both lung disease (e.g., emphysema) and significant liver disease. Meanwhile, heterozygous states such as PiMZ or PiMS can lead to intermediate reductions in A1AT levels; these individuals may be at increased risk for certain liver or lung pathologies, but often the manifestations are milder or appear later in life. Importantly, A1AT is produced primarily by hepatocytes, though minor extrahepatic production can occur in other cell types of the lungs, stomach, duodenum, small intestine, gallbladder, pancreas, and kidneys.

The genetic penetrance of A1ATD-related liver disease is highly variable (see below). Not all adults with the PiZZ genotype or other deficiency-genotype combinations progress to cirrhosis or severe hepatic impairment. This incomplete penetrance is likely influenced by additional genetic modifiers in the individual's genome, as well as environmental factors such as exposure to hepatotoxic substances (including alcohol) and the presence of hepatitis viruses or other cofactors.<sup>11-13</sup> However, the impact of these cofactors, such as alcohol, remains under discussion.<sup>14</sup> Studies have also examined how heterozygosity for certain variants and the presence of other comorbid conditions such as hepatitis C infection or non-alcoholic fatty liver disease may increase the risk of liver disease.<sup>12</sup> Understanding the complex interplay between genotype, phenotype, and personal risk factors is crucial for accurate prognostication and long-term management.

The classical role of A1AT lies in protecting against proteolytic damage, especially in the lung, where it prevents excessive destruction of alveolar structures by neutrophil elastase. Under normal physiology, A1AT is secreted into the bloodstream after proper folding and glycosylation in the endoplasmic reticulum (ER). In A1ATD, particularly the PiZ variant, the protein is misfolded and prone to polymerization within hepatocyte ER.<sup>15</sup> This abnormal protein folding and inefficient export from the liver cells lead to the intracellular accumulation of A1AT aggregates. The aggregated protein can trigger an endoplasmic overload response, ER stress, protein degradation, unfolded protein response (UPP), autophagy, and cell death pathways, ultimately resulting in hepatocellular injury when these



intracellular aggregates grows over decades. Ultimately, this can set the stage for fibrosis, cirrhosis, and PLC.

Further complicating this molecular pathogenesis is the potential role of autophagy in responding to A1AT aggregates.<sup>25</sup> Autophagy, a process that degrades and recycles cellular components, can be beneficial by mitigating the toxic buildup of misfolded proteins.<sup>24</sup> Experimental research in mice suggests that pharmacological manipulation of autophagy can enhance the clearance of aberrant A1AT aggregates, highlighting a potential therapeutic direction.<sup>26</sup> Nonetheless, if autophagy becomes chronically activated or remains insufficient to clear these aggregates, hepatocytes may succumb to apoptosis or necroinflammation. Thus, the molecular mechanisms linking protein misfolding to adult liver disease in A1ATD hinge on the interplay of ER stress, inflammatory reactions, proteasomal and autophagic pathways, and ongoing hepatocellular damage.

Recent insights from experimental models and clinical observations further underscore how epigenetic factors, modifier genes, and lifestyle choices affect the course of liver disease in A1ATD, potentially altering the 5-methylcytosine genomic landscape.<sup>27,28</sup> Alcohol consumption and other toxins (e.g., smoking) can heighten the stress placed on the protein-folding and detoxification pathways of the liver.<sup>8</sup> In addition, studies have suggested that pharmacological activation of genes associated with the UPR or inflammatory cascades can reduce the accumulation of pathogenic A1AT variants, including PiZ, and modulate susceptibility or resilience to hepatic damage.<sup>29</sup> These complexities highlight that while the PiZ allele represents the principal culprit in severe A1ATD, the ultimate outcome in an individual patient reflects a network of genetic, molecular, and environmental variables.

From a clinical perspective, understanding the epidemiology, genetics, and molecular basis of A1ATD is crucial for anticipating disease progression, guiding diagnostic strategies, and suggesting potential interventions (see below). Screening in at-risk populations, particularly among individuals with unexplained cryptogenic cirrhosis or chronic liver enzyme elevations, often focuses on measuring serum A1AT levels and performing genotype/phenotype assays. Since standard laboratory assays may not adequately detect dysfunctional forms of A1AT, confirmatory genetic testing and Pi-typing are valuable in establishing a definitive diagnosis. Identifying individuals with PiZZ or other high-risk genotypes helps clinicians to implement appropriate follow-up and preventive strategies, which may include lifestyle modifications (e.g., minimizing alcohol use and managing weight to reduce fatty liver burden) and vigilance for early signs of hepatic decompensation.

Ultimately, a nuanced understanding of how mutations in the *SERPINA1* gene disrupt protein folding and lead to liver disease is crucial for developing targeted therapies in A1ATD. Current clinical management involves supportive care, liver transplantation for end-stage disease, and augmentation therapy aimed primarily at protecting the lungs. However, ongoing research aims to address the root cause of protein misfolding. Potential approaches include pharmacological chaperones that stabilize variant A1AT conformations,<sup>30</sup> as well as gene-editing technologies designed to replace or correct the mutant allele.<sup>31</sup> On March 10, 2025, Beam Therapeutics announced successful results from a Phase 1/2 trial of BEAM-302, a liver-targeted lipid nanoparticle formulation containing a guide RNA and an mRNA encoding a base editor specifically designed to correct the disease-causing PiZ mutation.<sup>32</sup> The drug was well tolerated, with only mild-to-moderate adverse effects and no dose-limiting toxicities reported at the data cutoff.<sup>32</sup> These advances offer hope that future generations may be spared the progressive liver damage associated with A1ATD.

## 2. Mechanisms of molecular interaction of A1AT with proteases

A1AT neutralizes proteases by forming a stable complex after cleavage of its reactive center loop (RCL).<sup>33</sup> To achieve this, a “bait-and-switch” strategy is utilized, exposing the RCL as a target for enzymes like neutrophil elastase. When the protease cleaves the RCL, A1AT changes its shape, trapping the protease. This conformational change in A1AT inactivates the “trapped” protease by forming a stable and irreversible covalent complex. A specific methionine in the A1AT structure is essential for its binding to proteases and, therefore, their inactivation. This molecular process requires a dramatic conformational rearrangement for protease inhibition and has therefore been referred to as “molecular gymnastics,” which helps protect tissues from protease damage, especially during inflammation.<sup>33-36</sup>

Factors affecting these molecular interactions include oxidation (e.g., from cigarette smoke) and polymerization (e.g., due to pathogenic mutations causing A1AT self-association into polymeric chains), as oxidized or polymerized A1AT may not effectively inhibit proteases, either by accumulating intracellularly or by deviating from the secretory pathway.<sup>33,37</sup> In addition, alterations within the RCL of A1AT can potentially compromise its interaction with proteases, diminishing inhibitory efficacy or promoting increased protease-mediated cleavage of the A1AT molecule by hindering the formation of stable complexes.<sup>38</sup>

The molecular mechanisms of the interaction of A1AT with proteases have broader implications. In addition to



inhibiting proteases, A1AT also modulates innate immunity and inflammation through various protein, cytokine, and cell surface interactions.<sup>39</sup> Furthermore, A1AT assists in tissue repair and wound healing by protecting fibronectin from protease degradation in chronic wounds.<sup>40</sup> Finally, the ability of A1AT to bind proteases may help regulate serine protease activity in systems such as coagulation and complement pathways.<sup>34</sup>

### 3. Disease spectrum

The most important disease-causing genotypes among the multiple A1ATD alleles are PiZZ and PiSZ.<sup>41</sup> In its heterozygous form, A1ATD may predispose adults to CLD, namely, fibrosis, cirrhosis, and HCC and, and less frequently to antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, intestinal Wegener's granulomatosis, neutrophilic subcutaneous nodular panniculitis, chronic kidney disease, gallstones, diabetes, and hypolipidemia.<sup>42,43</sup> Symptomatic ZZ infants and children are diagnosed efficiently and quickly because their symptoms related to growth, nutrition, and development are unique, and pediatricians are generally more familiar with rare diseases than other healthcare providers. A1ATD is the most frequent genetic cause of pediatric liver disease and liver transplantation.<sup>44,45</sup>

Early onset (e.g., in the fourth and fifth decade) of panacinar, predominantly basal, and emphysema with pronounced tissue destruction was recognized as the first clinical manifestation of A1ATD in 1964.<sup>46</sup> In 1969, liver cirrhosis was also reported to be associated with A1ATD.<sup>47</sup> However, the spectrum of non-cirrhotic manifestations of A1ATD also comprises hepatic steatosis and liver fibrosis (Table 1).<sup>16,48,49</sup>

The accumulation of misfolded, insoluble globular proteins in the ER may trigger not only the development of liver fibrosis but also PLC.<sup>45</sup>

The globules represent polymerized, misfolded Z protein retained, and accumulated within hepatocytes, serving as the hallmark feature of A1ATD on a liver biopsy.<sup>50,51</sup> Although not essential for diagnosing A1ATD-related liver disease, liver biopsy can help determine the severity of liver injury in specific cases.<sup>51</sup>

An analysis of over 1,500 adult patients with the PiZZ phenotype reported that 2% developed HCC over an average follow-up period of 12 years.<sup>13</sup> PLC in these individuals remains an incompletely characterized disease entity, although A1ATD is associated with a 20- to 50-fold increased risk of PLC.<sup>4</sup> Risk factors for PLC among carriers of A1ATD include male sex, diabetes, advanced age, and fibrosis or cirrhosis.<sup>4</sup> Importantly, PLC

may occur in non-cirrhotic PiZZ subjects with healthy livers, indicating that the neoplastic risk is a downstream pathogenic consequence of intrahepatocyte storage of Z-alpha antitrypsin *per se*, rather than a result of malignant transformation of cirrhosis.<sup>4</sup> However, it is well documented that A1AT globules are notably absent in HCC cells, and additional histological studies are necessary to determine whether PLC arises exclusively in globule-free areas and how this should be interpreted mechanistically.<sup>4</sup>

The notion that A1ATD is associated with hypolipidemia resulting from the impaired ability of hepatocytes to excrete fatty substrates implies that this genetic condition, while predisposing to steato-fibrosing CLD, might protect from coronary artery disease. In this regard, A1ATD closely resembles the disease model of other gene variants, such as patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), familial heterozygous hypobetalipoproteinemia, transmembrane 6 superfamily member 2 (*TM6SF2*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*),<sup>52-55</sup> and dissociates steatotic liver disease from the risk of cardiovascular disease, as typically seen in metabolic dysfunction-associated steatotic liver disease.<sup>56</sup> Finally, it is important to note that the risk of the most severe forms of CLD, namely, fibrosis, cirrhosis, or PLC, is strictly associated with the Pi genotype (Table 2).<sup>57</sup>

### 4. Diagnosis of A1ATD-related liver disease

Attributing otherwise "cryptogenic" CLD to A1ATD is a two-step procedure: (a) diagnosing A1ATD genetic status and (b) staging the severity of liver damage.

#### 4.1. Diagnosing A1ATD

A strategy for assessing A1AT circulating serum concentrations must include genetic testing (Figure 2). An initial screening blood test is typically used to determine the serum level of A1AT protein, with low concentrations possibly suggesting A1AT deficiency and leading to additional tests.<sup>58</sup> Screening programs in newborns, blood donors, or random population samples may help determine the prevalence of deficiency genes within the general population.<sup>59</sup> Alternatively, another feasible approach is targeted detection in potential patients, achieved by focusing on cohorts of symptomatic individuals with a higher risk for gene mutations.<sup>59</sup> Quantitative measurement of A1AT serum levels with radial immunodiffusion, nephelometry, and latex-enhanced immunoturbidimetry is typically the first screening test.<sup>59</sup> Whether targeted PCR for PiS and PiZ is used initially or reserved for low-level samples depends on available funding and the algorithm's main objective.<sup>59</sup> Using nephelometry or immunoturbidimetry, serum A1AT levels are considered normal at 90–200 mg/dL, with a protective threshold for lung emphysema risk set at 50 mg/dL.<sup>59</sup> When

Table 1. Overview of studies on the prevalence of steatotic and fibrotic liver disease in A1ATD

Author, year <sup>Ref</sup>	Study design	Findings	Conclusion
Clark <i>et al.</i> <sup>16</sup>	94 adults with PiZZ A1ATD	More than one-third of individuals with A1ATD who were asymptomatic or had lung issues also had asymptomatic liver fibrosis at stage F2 or higher. This liver damage was linked to higher levels of liver enzymes, the MetS, and histological features such as abnormal alpha-1 storage within hepatocytes, portal inflammation, and hepatocellular degeneration. The prevalence of HS, which may be interpreted in different ways, was over greater than 40%.	HS may be due to concurrent MASLD or result from A1ATD.
Mandorfer <i>et al.</i> <sup>48</sup>	315 individuals with CSPH	Carriage of the Z allele was associated with a higher risk of CSPH (OR: 2.47; 95% CI, 1.03–5.9; $P=0.042$ ). Non-invasive identification of HS was found in 65% of PiZZ and 52% of PiSZ individuals.	Heterozygosity for the Z allele is a risk factor for the development of CSPH. HS may contribute to the progression of liver fibrosis.
Hamesch <i>et al.</i> <sup>49</sup>	554 PiZZ adults with A1ATD homozygous for the PiZ mutation, and 234 adult controls without the PiZ mutation, all without pre-existing liver disease. Histological assessment of livers from transgenic mice overexpressing the A1ATD-associated PiZ variant	Signs of significant fibrosis without invasive procedures were present in 20–36% of PiZZ carriers, while indications of advanced fibrosis were 9- to 20-fold more common in PiZZ carriers compared to non-carriers. Factors such as male sex, age over 50 years, elevated ALT, AST, or GGT levels, and decreased platelet count were linked to a higher burden of liver fibrosis. CAP greater than or equal to 280 dB/m, indicating severe HS, was observed in 39% of PiZZ carriers versus 31% of controls. PiZZ carriers had lower levels of serum TG, LDL, and VLDL compared to controls, suggesting impaired liver lipid secretion. Livers from mice overexpressing PiZ showed signs of HS and downregulation of genes involved in lipid secretion.	Lung function was not associated with liver fibrosis. Hypolipidemia, resulting from impaired lipid secretion by hepatocytes, is characteristic of individuals carrying the PiZZ allele.

Abbreviations: A1ATD: Alpha 1-antitrypsin deficiency; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CAP: Controlled attenuation parameter; CI: Confidence interval; CSPH: Clinically significant portal hypertension; GGT: Gamma-glutamyl transferase; HS: Hepatic steatosis; LDL: Low-density lipoprotein; MASLD: Metabolic dysfunction-associated steatotic liver disease; MetS: Metabolic syndrome; OR: Odds ratio; TG: Triglyceride; VLDL: Very low-density lipoprotein.

Table 2. Risk of CLD in relation to the A1ATD genotype<sup>57</sup>

Pi genotype	aOR of fibrosis/cirrhosis (CI)	aOR of PLC (CI)	Others
ZZ	21.7 (8.8–53.7)	44.5 (10.8–183.6)	----
MZ	1.7 (1.2–2.2)	----	Cholelithiasis aOR (CI) = 1.3 (1.2–1.4)
SS	----	----	No hepatobiliary abnormalities were, except for slightly elevated ALT levels.
SZ	3.1 (1.1–8.2)	6.6 (1.6–26.9)	-----

Abbreviations: ALT: Alanine transaminase; aOR: Adjusted odds ratio; CI: Confidence interval; CLD: Chronic liver disease; PLC: Primary liver cancer.

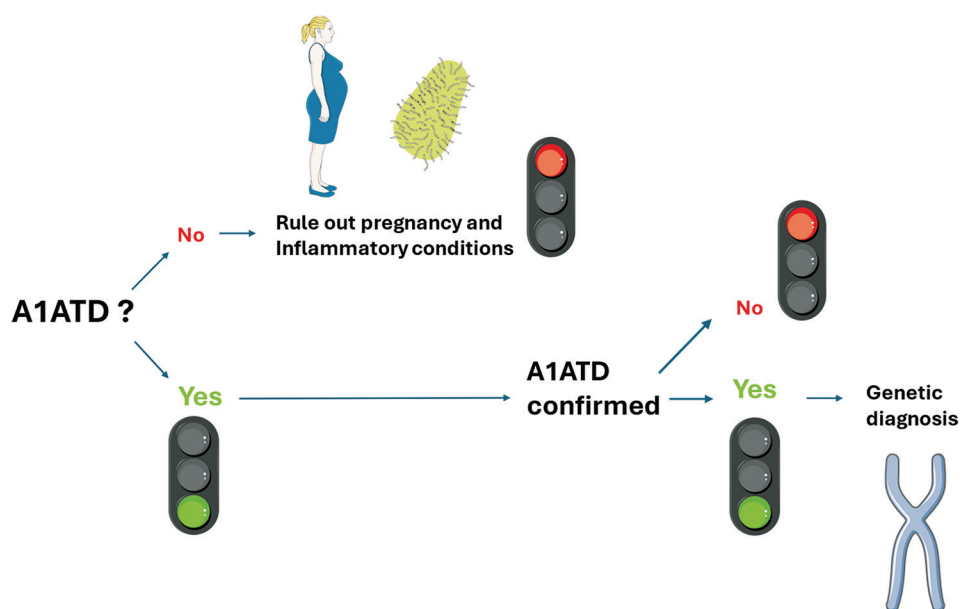
A1AT serum levels and PCR results conflict, or when protein confirmation is needed, isoelectric focusing (IEF) is preferred, as it separates proteins by isoelectric points and identifies A1AT isoforms. IEF is cost-effective but requires expertise and has long been the diagnostic standard, though many labs now favor combined determinations of serum measurement with PCR. SERPINA1 gene sequencing is used if low serum levels remain unexplained after PCR or IEF.<sup>59,60</sup>

Rather than being a genuinely rare condition, A1ATD is underdiagnosed, with fewer than 10% of the affected population being diagnosed with A1ATD and an average

diagnostic delay of 6 years.<sup>41</sup> Therefore, PiZZ carriers should be monitored at a center specializing in A1AT deficiency.<sup>61</sup>

#### 4.2. Staging the severity of A1ATD-related liver disease

Staging A1ATD-related liver disease involves evaluating fibrosis and cirrhosis, monitoring complications, and considering the impact of the A1ATD genotype, particularly PiZZ, on progression. Monitoring the enzymatic profile is a simple, non-invasive, and universally available laboratory technique that can be repeated over time to determine the trend of liver disease. However,



**Figure 2.** A1ATD can be diagnosed by analyzing serum protein electrophoresis or by directly measuring A1AT levels. Inflammatory conditions and pregnancy can lead to falsely normal A1AT levels, so these should be ruled out. Phenotyping through IEF is considered the gold standard for diagnosing A1ATD. Once confirmed, A1ATD should be further characterized with appropriate genetic analysis.

Abbreviations: A1AT: Alpha 1-antitrypsin; A1ATD: Alpha 1-antitrypsin deficiency; IEF: Isoelectric focusing.

these changes are non-specific and must be alongside other non-invasive biomarkers.

Liver biopsy, which is not required for the diagnosis of A1ATD and is reserved for selected, complicated cases, typically shows diastase-resistant bright pink globules with PAS reagent.<sup>45</sup> Electron microscopy can identify multiple globular inclusions within dilated, congested rough ER cisterns adjacent to secondary lysosomes; mitochondrial damage develops as the globules accumulate.<sup>45</sup> Since abnormal A1AT accumulates in the ER, the definition of A1ATD as an “ER storage disease” has been proposed, in contrast to the better-known concept of “lysosomal storage diseases”.<sup>45</sup>

Staging of liver fibrosis, the primary determinant of CLD progression, should ideally be conducted using non-invasive techniques that can be repeated over time. These techniques include transient elastography, the fibrosis-4 (FIB-4) index, and the aspartate transaminase (AST) to platelet ratio (APRI) index.<sup>61,62</sup> Among liver enzymes, gamma-glutamyl transferase (GGT), which serves as both a liver test and a marker of cardiovascular risk, outperforms APRI, FIB-4, and transaminase measurements.<sup>61,63</sup> Liver stiffness measurement, which correlates with fibrosis, is a first-line approach to non-invasively assessing fibrosis. This can be done using techniques such as FibroScan (transient elastography).<sup>64</sup> While a specific cut-off for liver stiffness measurement (LSM) in A1ATD is still debated, a value

of  $\geq 7.1$  kPa may be useful in identifying liver disease.<sup>65</sup> Individuals with cirrhosis and/or portal hypertension should undergo biannual liver ultrasound scanning to facilitate early detection of HCC.<sup>61,66</sup>

## 5. Management of A1ATD-related liver disease

At present, liver transplantation is the only definitive treatment for advanced A1ATD-related liver disease. However, emerging therapies, including gene therapy, small molecules, and enhanced autophagy, are being studied to target protein misfolding, reduce liver damage, and prevent or reverse liver fibrosis.<sup>58</sup>

In a pioneering small proof-of-concept study,<sup>67</sup> fazirsiran, an investigational RNA interference therapeutic that degrades Z-A1AT messenger RNA, thereby decreasing synthesis of the deleterious protein, was associated with a strong reduction in serum and hepatic in Z-A1AT concentrations, leading to an improvement in liver enzyme profiles. More recently, Clark *et al.*<sup>68</sup> assessed the safety and efficacy of fazirsiran in an ongoing Phase 2 study involving 40 patients randomized to receive either placebo subcutaneously or fazirsiran at doses of 25, 100, or 200 mg. The data showed a significant, dose-dependent decrease in serum Z-A1AT concentration compared to placebo. Similarly, post-dose liver biopsy showed that fazirsiran treatment significantly reduced liver Z-A1AT

concentration, resulting in a reduction of hepatic globule burden in subjects with portal inflammation and liver fibrosis, all without adverse events leading to drug discontinuation and with stable lung functional tests.<sup>68</sup>

Intravenous “augmentation therapy” with pooled human A1AT protein, which is used in adults with lung disease, is not considered appropriate for CLD due to A1ATD.<sup>45</sup> In individuals with end-stage CLD, liver transplantation restores normal levels of A1AT since the transplanted liver expresses the donor’s A1AT phenotype.<sup>45</sup> The survival rate of children and adults with A1ATD who undergo liver transplantation is excellent.<sup>69</sup> Standard supportive care for cirrhosis and the prevention and management of cirrhosis complications should be administered similarly to all other types of cirrhosis, regardless of the etiology.<sup>70</sup> Potential innovative approaches to A1ATD-related liver disease include neutrophil elastase inhibitors, gene-directed therapy, gene silencing, small molecules, and cell-based therapies.<sup>44</sup>

On March 10, 2025, the manufacturer announced initial safety and efficacy data from its Phase 1/2 trial of BEAM-302. This dosing study showed that BEAM-302 was well tolerated and led to long-lasting correction of the pathogenic mutation, providing proof-of-concept evidence that *in vivo* base editing may represent a potential treatment for A1ATD.<sup>32</sup> However, more robust evidence of safety and efficacy in humans is awaited before this promising approach can enter the clinical arena.

A1ATD provides a disease model for studying protein linkages, the propagation of polymeric structures, and therapeutic strategies for other conformational diseases.<sup>61</sup> Moving forward, it will be important to increase the detection rate of A1ATD to expand the pool of patients eligible for therapeutic trials and to improve hepatic outcomes by reducing diagnostic delays through early detection.<sup>44</sup>

## 6. Conclusion

A1ATD is a codominant genetic disorder caused by pathogenic variants of the *SERPINA1* gene, most notably the PiZ allele. While intravenous augmentation therapy has significantly improved the management of A1ATD-associated lung disease, it does not benefit liver disease, which can lead to cirrhosis and PLC. Emerging approaches, including novel augmentation therapies, gene-editing approaches, innovative pharmacological chaperones, and personalized medicine strategies, hold promise for more effective treatment. Ongoing research focusing on improved screening, early diagnosis, novel gene-editing strategies, and interventions targeting disease pathophysiology will be crucial in preventing disease

progression and reducing the burden of A1ATD-related liver complications.

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The authors declare that they have no competing interests.

## Author contributions

*Conceptualization:* All authors

*Visualization:* All authors

*Writing—original draft:* All authors

*Writing—review & editing:* All authors

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Not applicable.

## Consent for publication

Not applicable.

## Availability of data

Not applicable.

## Further disclosure

The author, Amedeo Lonardo retired from Department of Internal Medicine, Azienda Ospedaliero-Universitaria of Modena, Modena, Italy in 2023.

## References

1. Rangaraju M, Turner AM. Why is disease penetration so variable in Alpha-1 Antitrypsin Deficiency? The contribution of environmental factors. *Chronic Obstr Pulm Dis.* 2020;7(3):280-289.  
doi: 10.15326/jcopdf.7.3.2019.0177
2. Janciauskiene S, Wrenger S, Immenschuh S, *et al.* The multifaceted effects of alpha1-antitrypsin on neutrophil functions. *Front Pharmacol.* 2018;9:341.  
doi: 10.3389/fphar.2018.00341
3. Gonzalez A, Belmonte I, Nuñez A, *et al.* New variants of alpha-1-antitrypsin: Structural simulations and clinical expression. *Respir Res.* 2022;23(1):339.  
doi: 10.1186/s12931-022-02271-8
4. Schneider CV, Decraecker M, Beaufrère A, *et al.* Alpha-1 antitrypsin deficiency and primary liver cancers. *Biochim Biophys Acta Rev Cancer.* 2025;1880(2):189290.



- doi: 10.1016/j.bbcan.2025.189290
5. Blanco I, Bueno P, Diego I, *et al.* Alpha-1 antitrypsin Pi\*Z gene frequency and Pi\*ZZ genotype numbers worldwide: An update. *Int J Chron Obstruct Pulmon Dis.* 2017;12:561-569.  
doi: 10.2147/COPD.S125389
  6. Matamala N, Gomez-Mariano G, Perez JA, *et al.* New cis-acting variants in PI\*S background produce null phenotypes causing alpha-1 antitrypsin deficiency. *Am J Respir Cell Mol Biol.* 2020;63(4):444-451.  
doi: 10.1165/rcmb.2020-0021OC
  7. Ferrarotti I, Wencker M, Chorostowska-Wynimko J. Rare variants in alpha 1 antitrypsin deficiency: A systematic literature review. *Orphanet J Rare Dis.* 2024;19(1):82.  
doi: 10.1186/s13023-024-03069-1
  8. Miravittles M, Herepath M, Priyendu A, *et al.* Disease burden associated with alpha-1 antitrypsin deficiency: Systematic and structured literature reviews. *Eur Respir Rev.* 2022;31(163):210262.  
doi: 10.1183/16000617.0262-2021
  9. Schroeder WT, Miller MF, Woo SL, Saunders GF. Chromosomal localization of the human alpha 1-antitrypsin gene (PI) to 14q31-32. *Am J Hum Genet.* 1985;37(5):868-872.
  10. Yamamoto Y, Sawa R, Okamoto N, Matsui A, Yanagisawa M, Ikemoto S. Deletion 14q(q24.3 to q32.1) syndrome: Significance of peculiar facial appearance in its diagnosis, and deletion mapping of Pi(alpha 1-antitrypsin). *Hum Genet.* 1986;74(2):190-192.  
doi: 10.1007/BF00282092
  11. Propst T, Propst A, Dietze O, Judmaier G, Braunsteiner H, Vogel W. High prevalence of viral infection in adults with homozygous and heterozygous alpha 1-antitrypsin deficiency and chronic liver disease. *Ann Intern Med.* 1992;117(8):641-645.  
doi: 10.7326/0003-4819-117-8-641
  12. Regev A, Guaqueta C, Molina EG, *et al.* Does the heterozygous state of alpha-1 antitrypsin deficiency have a role in chronic liver diseases? Interim results of a large case-control study. *J Pediatr Gastroenterol Nutr.* 2006;43 Suppl 1:S30-S35.  
doi: 10.1097/01.mpg.0000226387.56612.1e
  13. Tanash HA, Piitulainen E. Liver disease in adults with severe alpha-1-antitrypsin deficiency. *J Gastroenterol.* 2019;54(6):541-548.  
doi: 10.1007/s00535-019-01548-y
  14. Fromme M, Schneider CV, Guldiken N, *et al.* Alcohol consumption and liver phenotype of individuals with alpha-1 antitrypsin deficiency. *Liver Int.* 2024;44(10):2660-2671.  
doi: 10.1111/liv.16044
  15. Lawless MW, Mankan AK, Gray SG, Norris S. Endoplasmic reticulum stress--a double edged sword for Z alpha-1 antitrypsin deficiency hepatotoxicity. *Int J Biochem Cell Biol.* 2008;40(8):1403-1414.  
doi: 10.1016/j.biocel.2008.02.008
  16. Clark VC, Marek G, Liu C, *et al.* Clinical and histologic features of adults with alpha-1 antitrypsin deficiency in a non-cirrhotic cohort. *J Hepatol.* 2018;69(6):1357-1364.  
doi: 10.1016/j.jhep.2018.08.005
  17. Schneider CV, Hamesch K, Gross A, *et al.* Liver phenotypes of European adults heterozygous or homozygous for Pi\*Z variant of AAT (Pi\*MZ vs Pi\*ZZ genotype) and noncarriers. *Gastroenterology.* 2020;159(2):534-548.e11.  
doi: 10.1053/j.gastro.2020.04.058
  18. Borel F, Tang Q, Gernoux G, *et al.* Survival advantage of both human hepatocyte xenografts and genome-edited hepatocytes for treatment of  $\alpha$ -1 antitrypsin deficiency. *Mol Ther.* 2017;25(11):2477-2489.  
doi: 10.1016/j.ymthe.2017.09.020
  19. de Seynes C, Ged C, de Verneuil H, Chollet N, Balduyck M, Raherison C. Identification of a novel alpha1-antitrypsin variant. *Respir Med Case Rep.* 2016;20:64-67.  
doi: 10.1016/j.rmcr.2016.11.008
  20. Huang X, Zheng Y, Zhang F, *et al.* Molecular mechanism of Z  $\alpha$ 1-antitrypsin deficiency. *J Biol Chem.* 2016;291(30):15674-15686.  
doi: 10.1074/jbc.M116.727826
  21. Faull SV, Elliston ELK, Gooptu B, *et al.* The structural basis for Z  $\alpha$ 1-antitrypsin polymerization in the liver. *Sci Adv.* 2020;6(43):eabc1370.  
doi: 10.1126/sciadv.abc1370
  22. Belorgey D, Häggglöf P, Karlsson-Li S, Lomas DA. Protein misfolding and the serpinopathies. *Prion.* 2007;1(1):15-20.  
doi: 10.4161/pri.1.1.3974
  23. Fischer HP, Ortiz-Pallardó ME, Ko Y, Esch C, Zhou H. Chronic liver disease in heterozygous alpha1-antitrypsin deficiency PiZ. *J Hepatol.* 2000;33(6):883-892.  
doi: 10.1016/s0168-8278(00)80119-1
  24. Wu SA, Li ZJ, Qi L. Endoplasmic reticulum (ER) protein degradation by ER-associated degradation and ER-phagy. *Trends Cell Biol.* 2025;35:576-591.  
doi: 10.1016/j.tcb.2025.01.002
  25. Leon C, Bouchecareilh M. The autophagy pathway: A critical route in the disposal of alpha 1-antitrypsin aggregates that holds many mysteries. *Int J Mol Sci.* 2021;22(4):1875.  
doi: 10.3390/ijms22041875
  26. Hidvegi T, Ewing M, Hale P, *et al.* An autophagy-enhancing drug promotes degradation of mutant alpha1-antitrypsin Z

- and reduces hepatic fibrosis. *Science*. 2010;329(5988):229-232.  
doi: 10.1126/science.1190354
27. Rondanelli M, Gasparri C, Razza C, *et al.* Practical dietary advices for subjects with alpha-1 antitrypsin deficiency. *Biomed Pharmacother*. 2023;163:114753.  
doi: 10.1016/j.biopha.2023.114753
  28. Wang L, Marek GW 3<sup>rd</sup>, Hlady RA, *et al.* Alpha-1 antitrypsin deficiency liver disease, mutational homogeneity modulated by epigenetic heterogeneity with links to obesity. *Hepatology*. 2019;70(1):51-66.  
doi: 10.1002/hep.30526
  29. Sun S, Wang C, Zhao P, *et al.* Capturing the conversion of the pathogenic alpha-1-antitrypsin fold by ATF6 enhanced proteostasis. *Cell Chem Biol*. 2023;30(1):22-42.e5.  
doi: 10.1016/j.chembiol.2022.12.004
  30. Burrows JA, Willis LK, Perlmuter DH. Chemical chaperones mediate increased secretion of mutant alpha 1-antitrypsin (alpha 1-AT) Z: A potential pharmacological strategy for prevention of liver injury and emphysema in alpha 1-AT deficiency. *Proc Natl Acad Sci U S A*. 2000;97(4):1796-1801.  
doi: 10.1073/pnas.97.4.1796
  31. Pires Ferreira D, Gruntman AM, Flotte TR. Gene therapy for alpha-1 antitrypsin deficiency: An update. *Expert Opin Biol Ther*. 2023;23(3):283-291.  
doi: 10.1080/14712598.2023.2183771
  32. Beam Therapeutics. Press Release. *Beam Therapeutics Announces Positive Initial Data for BEAM-302 in the Phase 1/2 Trial in Alpha-1 Antitrypsin Deficiency (AATD), Demonstrating First Ever Clinical Genetic Correction of a Disease-causing Mutation*. Available from: <https://investors.beamtx.com/news-releases/news-release-details/beam-therapeutics-announces-positive-initial-data-beam-302-phase> [Last accessed on 2025 Jul 27].
  33. Gooptu B, Ekeowa UI, Lomas DA. Mechanisms of emphysema in alpha1-antitrypsin deficiency: Molecular and cellular insights. *Eur Respir J*. 2009;34(2):475-488.  
doi: 10.1183/09031936.00096508
  34. O'Brien ME, Murray G, Gogoi D, *et al.* A review of alpha-1 antitrypsin binding partners for immune regulation and potential therapeutic application. *Int J Mol Sci*. 2022;23(5):2441.  
doi: 10.3390/ijms23052441
  35. Scherr F, Darisipudi MN, Börner FR, *et al.* Alpha-1-antitrypsin as novel substrate for *S. aureus* Spt proteases - implications for virulence. *Front Immunol*. 2024;15:1481181.  
doi: 10.3389/fimmu.2024.1481181
  36. Whisstock JC, Bottomley SP. Molecular gymnastics: Serpin structure, folding and misfolding. *Curr Opin Struct Biol*. 2006;16(6):761-768.  
doi: 10.1016/j.sbi.2006.10.005
  37. Fazleen A, Wilkinson T. The emerging role of proteases in  $\alpha_1$ -antitrypsin deficiency and beyond. *ERJ Open Res*. 2021;7(4):00494-2021.  
doi: 10.1183/23120541.00494-2021
  38. Denardo A, Ben Khelifa E, Bignotti M, *et al.* Probing of the reactive center loop region of alpha-1-antitrypsin by mutagenesis predicts new type-2 dysfunctional variants. *Cell Mol Life Sci*. 2023;81(1):6.  
doi: 10.1007/s00018-023-05059-1
  39. Han L, Wu X, Wang O, *et al.* Mesenchymal stromal cells and alpha-1 antitrypsin have a strong synergy in modulating inflammation and its resolution. *Theranostics*. 2023;13(9):2843-2862.  
doi: 10.7150/thno.83942
  40. Rao CN, Ladin DA, Liu YY, Chilukuri K, Hou ZZ, Woodley DT. Alpha 1-antitrypsin is degraded and non-functional in chronic wounds but intact and functional in acute wounds: The inhibitor protects fibronectin from degradation by chronic wound fluid enzymes. *J Invest Dermatol*. 1995;105(4):572-578.  
doi: 10.1111/1523-1747.ep12323503
  41. Manne V, Kowdley KV. Alpha1-antitrypsin deficiency: A cause of chronic liver disease. *Clin Liver Dis*. 2020;24(3):483-492.  
doi: 10.1016/j.cld.2020.04.010
  42. Balbi B, Benini F, Corda L, *et al.* An Italian expert consensus on the management of alpha1-antitrypsin deficiency: A comprehensive set of algorithms. *Panminerva Med*. 2022;64(2):215-227.  
doi: 10.23736/S0031-0808.22.04592-X
  43. Lonardo A, Medicina D, Leonelli M, Bagni A, Callea F. Intestinal Wegener's granulomatosis in a patient with severe alpha-1-antitrypsin deficiency resulting from a unique combination of two deficiency alleles (PiZ and PiMProcida). *Eur J Gastroenterol Hepatol*. 2002;14(12):1389-1392.  
doi: 10.1097/00042737-200212000-00017
  44. Brantly M, Campos M, Davis AM, *et al.* Detection of alpha-1 antitrypsin deficiency: The past, present and future. *Orphanet J Rare Dis*. 2020;15:96.  
doi: 10.1186/s13023-020-01352-5
  45. Mitchell EL, Khan Z. Liver disease in alpha-1 antitrypsin deficiency: Current approaches and future directions. *Curr Pathobiol Rep*. 2017;5(3):243-252.  
doi: 10.1007/s40139-017-0147-5. Erratum in: *Curr Pathobiol Rep*. 2018;6(1):97.  
doi: 10.1007/s40139-018-0164-z

46. Eriksson S. Alpha 1-antitrypsin deficiency: Lessons learned from the bedside to the gene and back again. Historic perspectives. *Chest*. 1989;95(1):181-189.  
doi: 10.1378/chest.95.1.181
47. Sharp HL, Bridges RA, Krivit W, Freier EF. Cirrhosis associated with alpha-1-antitrypsin deficiency: A previously unrecognized inherited disorder. *J Lab Clin Med*. 1969;73(6):934-939.
48. Mandorfer M, Bucsecs T, Hutya V, *et al*. Liver disease in adults with  $\alpha$ 1-antitrypsin deficiency. *United European Gastroenterol J*. 2018;6(5):710-718.  
doi: 10.1177/2050640618764057.
49. Hamesch K, Mandorfer M, Pereira VM, *et al*. Liver fibrosis and metabolic alterations in adults with alpha-1-antitrypsin deficiency caused by the Pi\*ZZ mutation. *Gastroenterology*. 2019;157(3):705-719.e18.  
doi: 10.1053/j.gastro.2019.05.013
50. Norton B, Denson J, Briggs C, Bowles M, Stell D, Aroori S. Delayed diagnosis of alpha-1-antitrypsin deficiency following post-hepatectomy liver failure: A case report. *World J Gastroenterol*. 2016;22(11):3289-3295.  
doi: 10.3748/wjg.v22.i11.3289
51. AASLD Family of Websites. *Liver Fellow Network. Why does Alpha-1 Antitrypsin Deficiency Cause Liver Disease?* Available from: <https://www.aasld.org/liver-fellow-network/core-series/why-series/why-does-alpha-1-antitrypsin-deficiency-cause-liver#:~:text=The%20gold%20standard%20for%20the,protein%20retained%20within%20the%20hepatocyte> [Last accessed on 2025 Jul 25].
52. Weiskirchen R, Lonardo A. PNPLA3 as a driver of steatotic liver disease: Navigating from pathobiology to the clinics via epidemiology. *J Transl Genet Genom*. 2024;8:355-377.  
doi: 10.20517/jtgg.2024.70
53. Tarugi P, Lonardo A, Ballarini G, *et al*. Fatty liver in heterozygous hypobetalipoproteinemia caused by a novel truncated form of apolipoprotein B. *Gastroenterology*. 1996;111(4):1125-1133.  
doi: 10.1016/s0016-5085(96)70082-3
54. Dongiovanni P, Paolini E, Corsini A, Sirtori CR, Ruscica M. Nonalcoholic fatty liver disease or metabolic dysfunction-associated fatty liver disease diagnoses and cardiovascular diseases: From epidemiology to drug approaches. *Eur J Clin Invest*. 2021;51(7):e13519.  
doi: 10.1111/eci.13519
55. Gagnon E, Gill D, Bourgault J, *et al*. RNA interference versus antibody-based PCSK9 inhibition for the prevention of cardiovascular disease: A drug-target Mendelian randomization study. *Cardiovasc Res*. 2025;121:1066-1075.  
doi: 10.1093/cvr/cvaf078
56. Stefan N, Lonardo A, Targher G. Role of steatotic liver disease in prediction and prevention of cardiometabolic diseases. *Nat Rev Gastroenterol Hepatol*. 2024;21(3):136-137.  
doi: 10.1038/s41575-023-00880-2
57. Fromme M, Schneider CV, Pereira V, *et al*. Hepatobiliary phenotypes of adults with alpha-1 antitrypsin deficiency. *Gut*. 2022;71(2):415-423.  
doi: 10.1136/gutjnl-2020-323729
58. Meseeha M, Sankari A, Attia M. Alpha-1 Antitrypsin Deficiency. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK442030> [Last accessed on 2025 Jul 26].
59. Greulich T, Vogelmeier CF. Alpha-1-antitrypsin deficiency: Increasing awareness and improving diagnosis. *Ther Adv Respir Dis*. 2016;10(1):72-84.  
doi: 10.1177/1753465815602162
60. Greene DN, Elliott-Jelf MC, Grenache DG. AAT phenotype identification by isoelectric focusing. *Methods Mol Biol*. 2017;1639:33-44.  
doi: 10.1007/978-1-4939-7163-3\_4
61. Strnad P, McElvaney NG, Lomas DA. Alpha1-antitrypsin deficiency. *N Engl J Med*. 2020;382(15):1443-1455.  
doi: 10.1056/NEJMra1910234
62. Jamalnia M, Lonardo A, Weiskirchen R. Sex and gender differences in liver fibrosis: Pathomechanisms and clinical outcomes. *Fibrosis*. 2024;2:10006.  
doi: 10.70322/fibrosis.2024.10006
63. Lonardo A, Ndrepepa G. Concise review: Gamma-glutamyl transferase - evolution from an indiscriminate liver test to a biomarker of cardiometabolic risk. *Metab Target Organ Damage*. 2022;2:17.  
doi: 10.20517/mtod.2022.20
64. Boeckmans J, Schattenberg JM, Fromme M, Strnad P, Hagström H. Clinical utility of non-invasive tests for liver fibrosis in people living with alpha-1 antitrypsin deficiency. *Liver Int*. 2025;45(7):e70165.  
doi: 10.1111/liv.70165
65. Pons M, Núñez A, Esquinas C, *et al*. Utility of transient elastography for the screening of liver disease in patients with alpha1-antitrypsin deficiency. *J Clin Med*. 2021;10(8):1724.  
doi: 10.3390/jcm10081724
66. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. *J Hepatol*. 2025;82(2):315-374.  
doi: 10.1016/j.jhep.2024.08.028
67. Strnad P, Mandorfer M, Choudhury G, *et al*. Fazirsiran for liver disease associated with alpha<sub>1</sub>-antitrypsin deficiency. *N Engl J Med*. 2022;387(6):514-524.

- doi: 10.1056/NEJMoa2205416
68. Clark VC, Strange C, Strnad P, *et al.* Fazirsiran for adults with alpha-1 antitrypsin deficiency liver disease: A phase 2 placebo controlled trial (SEQUOIA). *Gastroenterology*. 2024;167(5):1008-1018.e5.  
doi: 10.1053/j.gastro.2024.06.028
69. Guillaud O, Jacquemin E, Couchonnal E, *et al.* Long term results of liver transplantation for alpha-1 antitrypsin deficiency. *Dig Liver Dis*. 2021;53(5):606-611.  
doi: 10.1016/j.dld.2020.10.016
70. Zaccherini G, Tufoni M, Bernardi M, Caraceni P. Prevention of cirrhosis complications: Looking for potential disease modifying agents. *J Clin Med*. 2021;10(19):4590.  
doi: 10.3390/jcm10194590