Review Article

Pi*ZZ-related liver disease in children and adults—narrative review of the typical presentation and management of alpha-1 antitrypsin deficiency

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Abstract: Alpha-1 antitrypsin deficiency (AATD) is a genetic disease affecting both children and adults. It is caused by >100 different mutations in *SERPINA1*, the α1-antitrypsin (*AAT*) gene. While the lung is the main afflicted organ in adults, the liver can be affected in both children and adults. The classical form of AATD is the homozygous "Pi*Z" mutation ("Pi*ZZ" genotype) which may result mainly in neonatal hepatitis syndrome and in liver fibrosis in later adulthood. This narrative review focusses on the highly heterogeneous Pi*ZZ-related liver disease (LD) in children and adults and the transition of care. While in a minority of children Pi*ZZ-related LD typically presents as neonatal cholestasis which is largely self-limiting, the majority of Pi*ZZ children do not develop clinically relevant LD. In Pi*ZZ adults, around one third develop signs of significant liver fibrosis. Consequently, Pi*ZZ-related LD is a relatively common cause of liver transplantation which is the only available cure yet. Risk factors for accelerated fibrosis progression in adults are male sex, age ≥50 years, alcohol misuse, obesity, diabetes mellitus, or metabolic syndrome while there are no well-established risk factors in children. The workup of LD is similar in both age groups and includes liver biochemistry, ultrasound, and non-invasive assessment of fibrosis (e.g., elastography). Further workup including liver biopsy might become necessary. While no guidelines exist, in our view, children and adults with signs of Pi*ZZ-related LD should be offered referral to a specialized center in order to counsel the patients and their families regarding their risk of Pi*ZZ-related complications, to define the individual monitoring plan, and to evaluate whether a patient qualifies for a novel treatment modality or liver transplant. Moreover, transition from pediatric to adult hepatologic care should be warranted.

Keywords: Liver fibrosis; neonatal cholestasis; liver stiffness; elastography; *SERPINA1*; genetic liver disease; rare liver disease; transition

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Alpha-1 antitrypsin deficiency (AATD)—general

AATD is an inherited rare disease. It is one of the most common potentially lethal genetic diseases worldwide in both children and adults (1,2). AATD is inherited via an autosomal-codominant route. Most persons carry two normal copies (termed "Pi*M" allele) of *SERPINA1* (*Serpin family A member 1*), the alpha-1 antitrypsin (*AAT*) gene. Accordingly, the wild-type genotype is termed "Pi*MM". Pi*MM individuals have normal serum levels of the AAT protein. While over 100 mutations of *SERPINA1* are known and while up to 10% of Europeans carry a *SERPINA1* mutation (3,4), the manifold mutations have variable effects and not every mutation results in manifest disease or measurable reduction of AAT serum levels. The "Pi*Z" allele is the most relevant mutation and results from a substitution of a single amino acid (lysine instead of glutamine at codon 342, "Glu342Lys"). Homozygosity of the Pi*Z variant is termed as "Pi*ZZ" genotype and represents the classical, severe form of AATD. It occurs in up to 1:2,000 subjects of European descent and can on its own result in manifest disease in both children and adults. Presence of the Pi*Z variant in conjunction with the wild-type allele Pi*M is termed as "Pi*MZ" and occurs in up to 1:25 subjects of European descent (1,3). In contrast to Pi*ZZ, Pi*MZ heterozygosity is thought to be a genetic disease modifier in children and adults (1,5). As Pi*ZZ is the classical, severe form of AATD and by some authors meant as AATD in the narrower sense, this narrative review focusses on the hepatic presentation of Pi*ZZ children and adults.

In terms of pathophysiology, AAT is mainly synthesized in hepatocytes but also, among others, in alveolar cells and neutrophils (1). After synthesis, AAT is translocated to the endoplasmic reticulum (ER), where it becomes folded. Then, AAT passes the intracellular secretory pathway before it is secreted into the circulation. Circulating AAT has various tissue-protective and immunomodulatory functions (1). The name "alpha-1 antitrypsin" arose from its abundance in the alpha-1 fraction of electrophoresis and its inhibitory role against the protease trypsin (6). While AAT can inhibit multiple proteases, its main target is neutrophil elastase which destroys lung tissue. AAT is one of the most highly abundant serum glycoproteins and its concentration can double during the acute phase reaction (1,7).

SERPINA1 mutations can lead to misfolding of the resulting AAT protein and thereby to retention of AAT in hepatocytes. Misfolded AAT (i.e., Pi*Z AAT) can aggregate to polymers which build intra-hepatocytic inclusions representing the histologic hallmark of Pi*ZZ-related liver disease (8). Accumulation of misfolded AAT in hepatocytes can lead to chronic inflammation and liver fibrosis ("toxic gain of function"). As accumulated AAT is retained in hepatocytes, a deficiency of intact AAT in the circulation develops resulting in an increased activation of proteases such as the neutrophil elastase. This, in turn results in accelerated destruction of lung parenchyma typically leading to early-onset, often pan-lobular lung emphysema ("loss of function" phenotype). This pulmonary manifestation has the highest clinical relevance in adults and the low AAT serum levels led to the name "AATD" (1,6).

Although AATD was first described in 1963 (9) and although AATD is a relatively common disease, it belongs to the most underdiagnosed diseases (10,11). Some authors estimate that up to 90% of Pi*ZZ subjects remain undiagnosed (12,13). Until recently, the natural history of Pi*ZZ-related liver disease was poorly defined (14). Liver disease typically presents with a biphasic pattern: Early childhood (<4 years) as well as later adulthood (>50 years) (1,15). However, the risks that children with clinically apparent liver disease are facing later on in their adult life still need to be further investigated .

This narrative review is written from both the perspective of pediatric and adult hepatologists to holistically review the current data on Pi*ZZ-related liver disease across the whole lifespan and to encourage transition from pediatric to adult care. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/dmr-21-9). Therefore, we have reviewed the literature available on Medline from the first description of AATD until recently. The selected research is summarized in six paragraphs, critically discussed and areas with need for future research are identified.

Liver disease in Pi*ZZ children—typical presentation

AATD constitutes the most common cause of metabolic liver disease in children and accounts for approximately 3.5% of all liver transplantations in pediatric patients (16). However, presentation, course and progression of disease are highly variable with a large proportion of children staying clinically unimpaired without any obvious signs of disease. These children therefore often remain undiagnosed (17,18). Most of the current literature originates from tertiary care centers, thus reporting mainly of patients with

a certain degree of liver involvement (19,20). In contrast, an epidemiological study in which 200,000 Swedish newborns were screened for AATD, resulted in the detection of 127 Pi*ZZ children, who were then longitudinally observed. This study provides the most unbiased data on liver disease in Pi*ZZ children to date (17,18).

The most frequent age for diagnosis is the neonatal period and the following months. Children typically present with neonatal cholestasis, also known as neonatal hepatitis syndrome, with laboratory abnormalities including elevated bilirubin (including the conjugated form), elevation of aspartate transaminase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) (19,21). As there are many reasons for a newborn and young infant to develop neonatal cholestasis, the prompt diagnosis might be delayed. As AAT belongs to the acute phase proteins and is therefore elevated during inflammation (22), there is a general restraint in measuring its serum concentration. In the authors´ opinion, a Pi*ZZ child will not be able to have AAT serum levels in normal range independent of any acute phase reaction. Hence, the quantitative determination of AAT serum concentration is a fast, widely available and cheap diagnostic tool and should be applied in early differential diagnosis of neonatal cholestasis. In case of pathologically low AAT serum concentration genotyping should be performed for confirmation. It must be mentioned that Pi*SZ children [i.e., compound heterozygosity for Pi*S and Pi*Z—Pi*S is the second most relevant mutation (Glu264Val)] might have AAT serum levels in the normal range during acute phase reaction and could be overlooked. This needs to be kept in mind especially in countries with a higher prevalence of Pi*SZ patients like France or Spain (23). However, the risk of Pi*SZ individuals to develop a clinically relevant liver disease seems to be substantially lower than in Pi*ZZ subjects (17,18).

Beside the most frequent clinical presentation of neonatal cholestasis, several patients are diagnosed later in childhood. Presentation is extremely variable, ranging from asymptomatic patients with elevated liver enzymes or hepatosplenomegaly, noticed in the course of regular check-ups, up to acute liver failure on a basis of an underlying progressive cirrhosis and portal hypertension. The latter is certainly a rare exception, though it is not unusual that older children are diagnosed with AATD and already have a severe liver dysfunction, while seeming perfectly healthy.

The reasons for development of liver disease, its time of onset and especially its severity have been addressed in several studies but remain poorly understood. Only a small proportion of patients will develop severe liver damage, and even fewer will need a liver transplantation. In the epidemiological study of Sveger *et al.* fourteen children showed prolonged obstructive jaundice (12%), of whom nine initially had evidence of severe liver disease (8%). In the long-term, overall risk for death caused by cirrhosis during childhood was reported to be 2–3% (17,18). As must be expected, in hospital-based series, the amount of severe liver disease is reported to be higher. In a French cohort, 25 of 114 Pi*ZZ children (22%) developed a severe liver disease, defined as the presence of portal hypertension, liver failure, liver transplantation or death (19). In a cohort from the United States (US), Teckman *et al.* found that 111 of 246 Pi*ZZ children (45%) showed severe liver affection (24). In addition to the selection bias of tertiary care centers, different genetic and environmental disease modifiers might differ between countries and continents (20).

Additionally, it needs to be stressed out that most of the patients who present with neonatal cholestasis also experience improvement, with disappearance of jaundice for several months or years. This honeymoon phase should not lead to a false sense of security, as a significant portion of patients show a second deterioration of liver function, often necessitating a liver transplantation before five years of age (17,25). On the other hand, the absence of neonatal cholestasis does not rule out a progressive disease throughout childhood (25). If liver transplantation gets necessary, it is most commonly before school age, although some patients with severe liver dysfunctions remain stable for longer periods of time (26). Thus, transplantation occasionally takes place in school-aged children and adolescents (27,28).

Regarding the natural history of liver disease in children with AATD, it is also important to keep in mind that the majority of patients have a favorable prognosis (18). There is a large share of children that show abnormal liver values in the first years of life, which later disappear without developing clinically significant liver disease (18). In their systematic review, Townsend *et al.* suggested that patients with severe liver dysfunction, who do not need liver transplantation, might recover completely in the long term (29).

One, yet unanswered, key question for every pediatrician is whether there are predictors for poor outcome. The likeliest prognostic factor is a history of neonatal cholestasis, which was shown to be associated with a worse outcome by several studies, as reviewed by Townsend (29). Contrarily, findings have been reported

lately by Teckman *et al.*, showing that neonatal cholestasis cannot be confirmed as a strong risk factor in their large study population (20). Although male sex is an unmodifiable risk factor in adults, there is no clear evidence for this assumption in children (28). Hinds *et al.* were able to show that siblings of Pi*ZZ children more often develop a liver disease, in case the older sibling did so. However, the concordance for its severity was reported to be only 29% (30). The follow-up examinations from the only longitudinal population-based cohort from Sweden indicate that children with pediatric liver disease who survive until adulthood are not likely to develop an advanced liver disease until the age of 40 (31). However, only a limited number of children with pediatric liver disease were included in these studies. Moreover, adult liver disease often becomes apparent at a later age (i.e., after 50 years of age) that is not covered by the existing studies. Hence, we recommend to continue hepatologic monitoring of Pi*ZZ adults who survived Pi*ZZ-related liver disease in their childhood.

Liver disease in Pi*ZZ children—management

Although diagnosing homozygous Pi*ZZ children is quite simple by quantifying serum alpha-1 antitrypsin levels (most commonly below 0.3 mg/dL), it is still difficult to predict which of them may develop severe liver disease, as well as when this may develop. Therefore, standardized regular monitoring is essential (*Figure 1*). The control interval is mainly dependent on the severity of liver dysfunction and needs to be individually adjusted. The majority of patients may present asymptomatically, with only slightly elevated liver enzyme values (17,18). In the author´s opinion, a yearly follow-up for these patients should be sufficient. Additionally, the families of these patients should be informed that the progression of liver dysfunction can appear at any time and that several years free of symptoms should not indicate an end of yearly follow-ups.

As well as the regularly performed diagnostic screening—including physical examination, liver function tests, and sonography to assess the liver, spleen, and portal vasculature—liver elastography (non-invasive measurement of liver stiffness) should be implemented, if possible, in order to increase experience with this promising and non-invasive diagnostic tool (32). Moreover, medical care should be carried out by a pediatric hepatologist or gastroenterologist, due to the complexity of clinical development, particularly in Pi*ZZ children. In cases where health care structure, geographical remoteness, family compliance or other similar reasons prevent access to a specialized center, it is imperative that sufficient education is given to the attending pediatrician. Not only the awareness of less common symptoms, such as failure to thrive, but also a profound knowledge of the pathogenesis is needed in order to make an adequate family counselling possible (33). Potential disease modifiers, such as obesity, should be avoided. Preventive measures such as vaccination against hepatitis A and B should be encouraged. There is some evidence suggesting a negative effect of non-steroidal anti-inflammatory drugs on AATD-related liver disease, thus we recommend our patients to prefer acetaminophen if needed, for instance due to fever (34,35). However, as acetaminophen is known to be hepatotoxic when overdosed, parents´ knowledge of correct dosage is essential (maximum 10–15 mg/kg bodyweight every 6 hours). Families need to be informed about the pulmonary course of AATD and the importance of abstinence from smoking (including inhalation of second-hand smoke), as well as the avoidance of environmental pollutants. Fortunately, the usefulness of medical information has been verified by prospective studies with a low share of AATD patients who smoke (36).

In case of progressive and life-threatening liver disease, early listing for liver transplantation is needed as it is the only curative approach. Median age for liver transplantation is approximately 4–5 years and it is associated with an excellent outcome (27,28). In many centers, ursodeoxycholic acid (UDCA) is administered when signs of liver involvement appear (19). This seems plausible because of its protective role in many other cholestatic diseases. However, there is only one retrospective study about its use in children with AATD that reports a beneficial effect on the clinical and biochemical status (37,38). Due to lack of alternatives and the fact that UDCA is safe and well tolerated, its use as a supportive treatment may be considered acceptable.

Transition from pediatric to adult care of Pi*ZZ subjects

When a patient enters adulthood, the transfer of all patient information is of vital importance during the transition from the pediatrician to a physician that will overtake the patient's care for the remainder of her/his life. This need is obvious in patients with severe liver disease, but the main share of patients will have no or very little affection of the liver at the age of transition. At the same time, the responsibility for clinical check-ups on a regular basis shifts

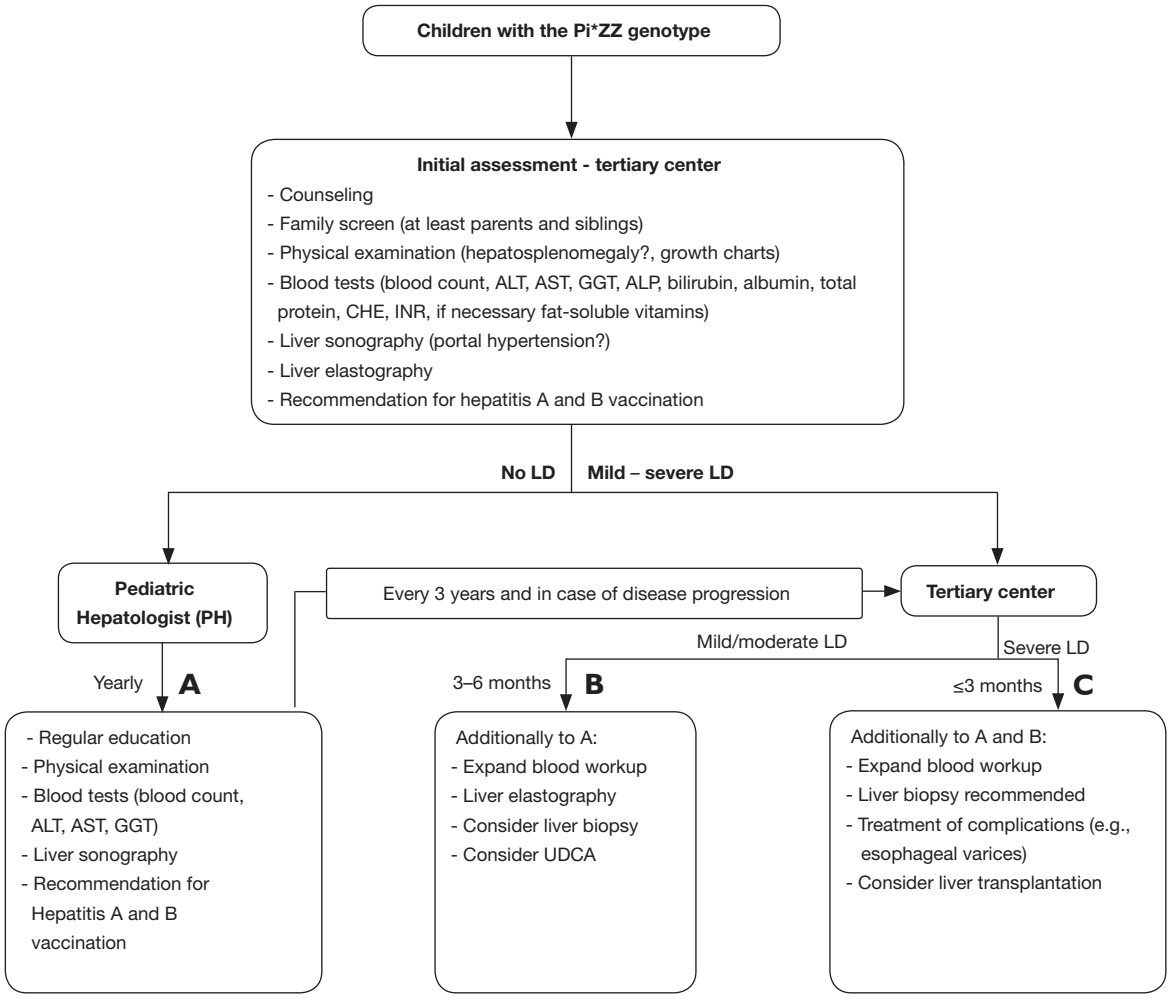

Figure 1 Suggestion of surveillance for children with the classical Pi*ZZ genotype of AATD. Given the highly variable course of disease in children, the actual medical care needs to be adjusted individually. Severe LD: portal hypertension, liver failure. Moderate liver disease: ALT and/or GGT >2× upper limit of normal (ULN) without criteria of severe liver disease. Mild liver disease: ALT and/or GGT <2× ULN without criteria of severe liver disease. LD, liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; CHE, cholinesterase; UDCA, ursodeoxycholic acid.

from the parents to the patients themselves as they grow up. Therefore, a comprehensive information of the adolescent is essential in order to make an optimal transition possible. The time before transition, in which the adolescent gains more personal responsibility and self-determination, is very well-suited to repeat and expand several recommendations that might have been discussed mainly with the parents during childhood. To avoid environmental pollutants, the choice of suitable profession should be discussed. Beside the abstinence from smoking and hepatotoxic drugs, the importance of cautious alcohol consumption is advisable. The adolescents need to be informed about the necessity of regular hepatologic and pulmonary monitoring throughout the rest of their life even in case of full health at the time of transition. Contact info of experienced centers and specialists has to be handed over and at least one visit for initial assessment should be recommended. A continuation of regular check-ups in the young adulthood is also important in order to foster healthy life-style and to provide clear prognostic information. In our own experience, young adults with AATD often either under- or overestimate the severity of their condition which is not surprising given the limited evidence and a low awareness even among hepatologists. Consulting the whole family, i.e., the parents

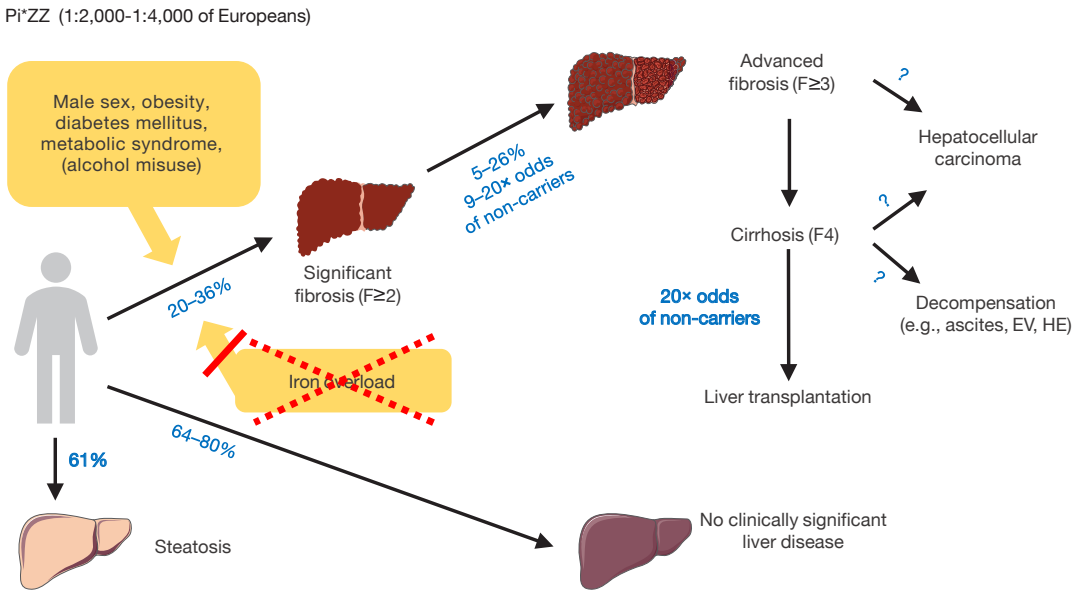

Figure 2 Liver phenotype and disease course in adults with the classical Pi*ZZ genotype of alpha-1 antitrypsin deficiency. Male sex, obesity, diabetes mellitus and metabolic syndrome are established risk factors of Pi*ZZ-related liver disease, while age ≥50 years is, if at all, a rather weak risk factor and alcohol misuse a highly likely, yet not firmly established, risk factor. In contrast, iron overload does not appear to be a pro-fibrogenic factor in Pi*ZZ-related liver disease. "?" indicates that the rate of developing the described disease course is not exactly known. EV, esophageal varices; F, fibrosis stage; HE, hepatic encephalopathy.

(who typically both have the Pi*MZ genotype) and siblings (who might also have the Pi*ZZ genotype or carry the Pi*MZ genotype), is of high value and helps to improve the consciousness about this genetic condition. For all family members, whether Pi*Z homo- or heterozygous, information on the risk of liver fibrosis in case of metabolic dysfunction (e.g., obesity or diabetes mellitus) and risky alcohol consumption is important. At the same time, these individuals should be consulted regarding the risk of lung emphysema in case of smoking.

Liver disease in Pi*ZZ adults—typical presentation

In adults, liver disease is the second most common organ manifestation after lung disease in terms of morbidity and mortality. As expected, the relative proportion of AATD-related liver disease is higher in never-smokers compared to smokers (39,40). The prevalence of AATD-related liver disease is expected to increase due to (I) the decreasing proportion of smokers in the European population; (II) the increasing proportion of obesity and metabolic syndrome that constitute important co-factors in liver disease development (41,42); (III) the expanding awareness of AATD-related liver disease among both patients and physicians especially as there are therapeutic options on the horizon (1,43).

Pi*ZZ-related liver disease in adults was, until recently, poorly understood. The current textbook knowledge on Pi*ZZ-related liver disease relies on a few studies with smaller, less representative cohorts (17,29,31,44,45). Another challenge is, that liver disease, regardless of the underlying etiology, usually does not present with specific symptoms until late stage of disease (5,46). Another challenge specific to AATD is that serum liver enzymes are often within normal limits, even in patients with histologically proven liver fibrosis (14,47,48). Hence, routine measurement of liver enzymes appears not sufficient and (serial) liver biopsies in all Pi*ZZ adults are not justified due to their invasive character. This emphasizes the need for a reliable and non-invasive assessment of liver disease in these patients (*Figure 2*). As it is not known whether a relationship between Pi*ZZ-related liver disease during childhood and during adulthood exists, questioning patients about associated symptoms (e.g., prolonged newborn icterus) is of uncertain diagnostic yield.

A recent European registry study non-invasively assessing 554 Pi*ZZ adults and an US study invasively assessing 94 Pi*ZZ adults were able to provide robust data regarding the presentation of liver disease (14,48). Depending on the used test, 20–36% of Pi*ZZ adults had signs of significant liver fibrosis [fibrosis (F) stage 2 on a 0–4 scale] while 5–26% had signs of advanced liver fibrosis (F ≥3) using either blood-based tests, liver elastography (non-invasive measurement of liver stiffness), or liver biopsy. Several studies assessing Pi*ZZ adults with an elastography method were published in recent years. The data for transient elastography (TE, also known as FibroScan®) are the only stiffness measurements that were cross-validated with liver biopsy, the current yet suboptimal gold standard (48), and assessed in a large multicentric cohort (14). Apart from TE, other elastography modalities were assessed in smaller, less representative cohorts limiting their usefulness (29,31,44,49-52). While elastography is helpful to rule-in advanced liver fibrosis (i.e., F ≥3) it is less well suited to rule-out mild or significant liver fibrosis (i.e., F ≤2). This is in line with the situation in other chronic liver diseases (53).

Despite recent data (14,48,54,55), the heterogeneous presentation of liver disease in Pi*ZZ individuals, ranging from no liver disease until old age to decompensated cirrhosis necessitating liver transplantation in early adulthood, is not well understood. At the same time, the risk of a Pi*ZZ adult needing liver transplant is 20× higher than for non-carriers of an AAT mutation (56,57). These observations suggest that a "second hit", is needed to develop a clinically significant liver disease. Hence, it is crucial to keep the potential co-factors in mind.

Liver disease in adults, if at all, usually presents in later life (>50 years) if no other hepatic comorbidities exist that may accelerate disease progression. However, there is no clear association between age and presence of significant liver fibrosis (14). Another unmodifiable risk factor is male sex (14,45,58). Among potentially modifiable risk factors, obesity, diabetes mellitus, and metabolic syndrome seem to be particularly relevant and point to the metabolic footprint of Pi*ZZ-related liver disease (14,48). Typical hepatotoxic toxins such as chronic alcohol misuse are also relevant disease modifiers of Pi*ZZ-related liver fibrogenesis (14,59). Unlike other chronic liver diseases, iron overload does not appear to play a major role in Pi*ZZ-related liver fibrogenesis or might be important only in a small subset of patients (60).

Interestingly, a majority of Pi*ZZ adults had signs of liver steatosis either by TE-based controlled attenuation parameter (CAP) or by liver biopsy (14,48,52). While the accuracy of CAP for predicting histological steatosis has not been histologically validated in Pi*ZZ patients yet, CAP is an established surrogate of steatosis in other entities of liver disease (61). The reduced serum levels of triglycerides, low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) cholesterol point to the potential underlying metabolic alterations (14).

Although the liver enzymes ALT, AST, GGT, and alkaline phosphatase (AP) are usually within normal limits, an increase of these liver enzymes might indicate underlying liver disease (14). Among blood-based parameters, GGT was most strongly correlated with the presence of significant liver fibrosis (14,48). The blood-based liver fibrosis test AST-to-Platelet Ratio Index (APRI) is easy to determine and can be used as a first screening test (5,14).

Pi*ZZ-related liver cirrhosis is associated with the typical complications known for other entities of chronic liver disease, i.e., ascites and esophageal varices (EV) (due to portal hypertension), hepatic encephalopathy (among others, due to accumulation of ammonium), or kidney injury (multifactorial nature) (62). Notably, experimental evidence suggests that Pi*ZZ individuals may have an impaired ability to detoxify ammonia, however, the clinical consequences of this observation remain to be determined (1). Moreover, Pi*ZZ cirrhotics may decompensate faster than individuals with other disease etiologies (63).

Several studies point to the fact that Pi*ZZ adults have a higher risk of hepatocellular carcinoma (HCC) (64). However, it appears that this HCC risk is mainly linked to the higher occurrence of cirrhosis. Actually, the data whether HCC can occur in Pi*ZZ adults without concomitant cirrhosis are conflicting. While older studies showed an association (46), recent studies suggest that the Pi*Z variant does not play a major role in carcinogenesis (i.e., a role beyond its impact on liver fibrosis) as several genome-wide association studies showed clear associations for other genetic risk variants but not for *SERPINA1* (65-67). Interestingly, several mechanistic studies suggest a pro-carcinogenic effect of Pi*Z [e.g. by downregulation of hepatocyte nuclear factor 4α (68-70), by genomic hypomethylation (71) or by up-regulation of proteins associated with predisposition to malignancy (72)]. More prospective studies with longitudinal follow-up are needed to clarify the carcinogenic risk of Pi*Z apart from its pro-fibrogenic risk.

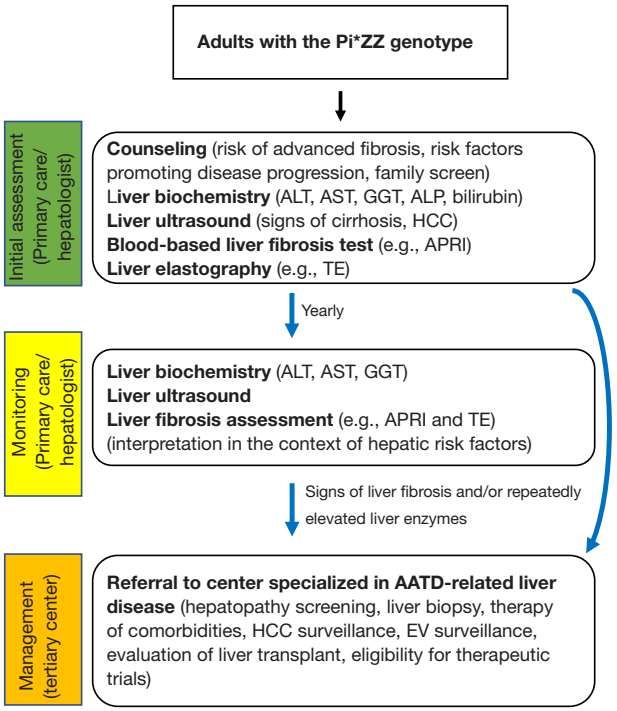

Figure 3 Suggestion of liver surveillance for adults with the classical Pi*ZZ genotype of AATD. All adults with the Pi*ZZ genotype should receive regular hepatologic care until further evidence suggests otherwise. As there are no liver-centered guidelines yet, the authors suggest to offer Pi*ZZ patients with signs of clinically relevant liver disease (i.e., signs of liver fibrosis and/or repeatedly elevated liver enzymes) a referral to a specialized center. ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; EV, esophageal varices; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; TE, transient elastography (FibroScan).

Liver disease in Pi*ZZ adults—management

Liver disease should, in our eyes, be monitored regularly in Pi*ZZ adults as they have 9–20× the odds of developing advanced liver fibrosis (14). The goal should be to detect those patients who need regular hepatologic surveillance (*Figure 3*). As the natural history of Pi*ZZ-related liver disease is still not adequately known and as there is no evidence-based monitoring plan yet, there are no guidelines advising which examinations are helpful in the early stage of liver disease. However, it is likely beneficial for liver-related outcomes to identify patients at risk early in the disease course in order to potentially halt disease progression.

Serum liver enzymes should, despite their described limited diagnostic yield, be assessed regularly as they can be measured easily and at low cost. Additionally, we suggest, similar to other causes of chronic liver disease (73), the use of a blood-based liver fibrosis test combined with liver elastography at least once (*Figure 3*). Regarding blood-based tests, the best evidence exists for APRI (14) which is easy to use. Liver elastography is an elegant way to assess the development of liver fibrosis in the long term (53,55). As TE is the best validated method for most entities (and also for Pi*ZZ-related liver disease) and as it is the most broadly available method (53,55), we prefer TE over other methods. Magnetic resonance elastography has the advantage over TE that a whole liver is examined, but remains to be further validated. In addition, MRE is not broadly available, is poorly standardized among the centers and is comparably expensive (5,46). For Pi*ZZ adults with signs of significant liver fibrosis (F≥2) and/or repeatedly elevated serum liver enzymes, and/or patients with inconclusive results (i.e., different results in a blood-based fibrosis test and elastography), we recommend referral to a hepatologist, ideally one with experience in AATD. The hepatologist should evaluate the need to screen for presence of hepatic co-morbidities and the need for liver biopsy. These measures help to clarify whether liver disease is caused by Pi*ZZ alone or whether a, potentially treatable, comorbidity exists. It should also be evaluated whether these patients qualify for a therapeutic trial, and because of that, a referral to or at least a contact with an AATD reference center is recommended (*Figure 3*).

Apart from non-invasive liver fibrosis assessment, we recommend repeated liver ultrasounds. As the risk of HCC without concomitant cirrhosis is not known, we opt for yearly exams. In patients with advanced liver fibrosis (F ≥3), ultrasound should be performed every 6 months by an experienced physician to screen for HCC. Pi*ZZ subjects with signs of advanced fibrosis should also be regularly screened for the potential presence of EV. Individuals with advanced liver disease should be regularly seen by a hepatologist to evaluate further preventive measures (e.g., vaccinations such as against hepatitis A and B) as well as the need for liver transplantation in case of hepatic decompensation. Ideally, these patients should be offered referral to a center specialized in AATD.

Regardless of their test results, Pi*ZZ patients should be counseled to inform their family about testing (i.e., AAT serum level and, if indicated, genetic testing) and to be under a regular pulmonologist surveillance. Furthermore,

every Pi*ZZ adult should be consulted regarding the established risk factors of liver disease progression and counseled how to face them (i.e., weight control, strict diabetes therapy, exercise, alcohol misuse, etc.).

Taken together, Pi*ZZ individuals with a fibrosis stage of ≥3 should receive the same hepatologic care and surveillance as patients with advanced liver fibrosis due to other entities. Pi*ZZ subjects with a fibrosis stage of ≤2 likely require less stringent monitoring. The exact surveillance plan should be based on the availability of diagnostic tests, availability of specialized hepatologists, patient preference, the expected amount of fibrosis, and the presumed disease activity. Moreover, the clinical context including age, sex, presence of risk factors (e.g., obesity, diabetes, metabolic syndrome, or alcohol misuse) should also be taken into consideration.

Therapeutic outlook

The described knowledge gap is not only the reason why no evidence-based management recommendations exist but also why no specific therapy is available. However, almost 60 years after its first description (9), there are several promising therapeutic trials targeting the disease at its origin, i.e., in the liver (1). While an approach increasing Pi*Z degradation via autophagy enhancement is supported primarily by experimental data (e.g., carbamazepine) (74), following three therapeutic concepts are studied in current/recent clinical trials: (I) Blockage of hepatic AAT production by silencing RNA (siRNA) that decreases the hepatic AAT load. As a potential drawback, the lung AAT levels and antiprotease protection decreases and these patients may therefore need a simultaneous intravenous AAT augmentation therapy. First proof-of concept data support the efficacy of this treatment (43). (II) Chaperone-based therapies might change the conformational folding of AAT thereby leading to an enhanced excretion of AAT from the liver into the circulation. While this approach would potentially target both the liver and the lung disease, no proof of concept in humans exists yet. However, this approach was successful in other diseases such as cystic fibrosis (75). (III) Genome editing approaches might correct the disease-causing mutation *in vivo*. While a proof of concept in mice was partially successful (76), its usefulness in humans needs to be further tested (77-79). It is likely that in a few years results from phase 3 trials become available and will hopefully result in one or more therapeutic options for this underserved population.

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Footnote

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