Systematic review

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THE NATURAL HISTORY OF ALPHA 1 ANTITRYPSIN DEFICIENCY: A SYSTEMATIC REVIEW

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Tables 6 (3 main text, 3 appendix), Figures 3

Abbreviations: AATD, Alpha-1-antitrypsin deficiency, ALT, alanine aminotransferase, GGT, gamma-glutamyl transferase, BMI, body mass index, LFT, liver function tests, HCC, hepatocellular carcinoma, AST, aspartate aminotransferase, LT, liver transplantation, NAFLD, non-alcoholic fatty liver disease, MRE, magnetic resonance elastography, ELF, enhanced liver fibrosis

Key Points

- This is the first systematic review for liver disease in AATD, and includes outcomes for 1564 children and 626 adults with AATD.
- Non-invasive measurement of liver fibrosis for those with AATD may help to identify those with early liver disease who will benefit from emerging therapies.
- AATD can have an aggressive course in children, with 16% developing liver failure and requiring transplantation. Similarly, 14.7% of adults undergo liver transplantation.
- Although phase II trials are anticipated, liver transplantation remains the only treatment for AATD-related liver disease, and has favorable outcomes compared with other indications.

SUMMARY

Background

Alpha-1 antitrypsin deficiency (AATD) is estimated to affect 3 million people worldwide. It causes liver disease in a proportion of carriers of the PiS and PiZ allele due to the formation and retention of polymers within the endoplasmic reticulum of hepatocytes. The reason for this selective penetrance is not known. Although clinical trials are underway, liver transplantation is the only effective treatment for liver disease due to AATD.

Aims

Through systematic review, we report the prevalence and natural history of liver disease among individuals with AATD, and assess the outcomes of liver transplantation.

Methods

A comprehensive search was conducted across multiple databases. Two independent authors selected the articles and assessed bias using the Newcastle-Ottawa Scale. Data was pooled for analysis where comparable outcomes were reported.

Results

35 studies were identified related to disease progression and 12 for the treatment of AATD. 7% of children were reported to develop liver cirrhosis, with 16.5% of individuals presenting in childhood requiring liver transplantation. Of those surviving to adulthood, 10.5% had liver cirrhosis and 14.7% required transplantation. Liver transplantation was the only effective treatment reported and outcomes compare favourably to other indications, with five-year survival reported as over 90% in children and over 80% in adults.

Discussion

The clinical course of liver disease in individuals with AATD remains poorly understood, but affects about 10% of those with AATD. More research is required to identify those patients at risk of developing liver disease at an early stage, and to provide alternative treatments to liver transplantation.

INTRODUCTION

Alpha-1-antitrypsin deficiency (AATD) is estimated to affect 3 million people worldwide (1), with patients typically developing lower zone emphysema at a relatively young age. Point mutations lead to altered folding during AT biogenesis, and misfolded proteins form polymers that are retained within the endoplasmic reticulum of hepatocytes, rather than being systemically secreted (PMID: 17464974). In the lung, lack of AT permits uninhibited proteolytic damage to the connective tissue matrix, leading to emphysema in approximately 75% of PiZZ patients (5). Liver disease occurs due to aggregation of AT polymers within the endoplasmic reticulum (ER) of liver cells, which form periodic acid-Schiff positive inclusions, a hallmark biopsy feature in AATD-related liver disease (8). Hepatocyte injury is believed to be related to ER stress, mitochondrial dysfunction, and triggering of autophagy, although the true pathophysiology is yet to be fully understood (PMID: 21421920). There is considerable variability of phenotypic expression in both liver and lung disease (3), which is believed to reflect genetic (2) and environmental modifiers (4). Cigarette smoking has been demonstrated to be the greatest predictor of lung function impairment in AATD cohorts (5) and smoking cessation is the most effective treatment strategy (6).

In children AATD-related liver disease may present only transiently, being diagnosed after investigation for prolonged neonatal jaundice, whilst in others disease may persist, progressing to fibrosis and cirrhosis requiring childhood liver transplantation (9). In adults liver disease has been reported in several cohorts or case series, with prevalence varying depending on the modality used to diagnose disease. In one study, clinical signs or symptoms suggestive of liver disease were reported in up to 63% of homozygous patients, (10) whereas other studies describe abnormalities of liver enzymes (e.g. ALT) in less than 10% of adult patients (11, 12). Another paper published in 1986 reported biopsy-defined fibrosis/cirrhosis in 17.5% of patients (7).

Serum tests have also been investigated as possible predictors of significant liver disease with mixed results (11-14). Measurement of GGT may be of benefit (15) but is possibly confounded by its probable relation to oxidative lung injury and airflow obstruction (16). Tests intended to detect liver fibrosis are currently likely to be the most useful, such as the serum enhanced liver fibrosis (ELF) test (17) and/or transient elastography (which has a sensitivity of 71% and specificity of 91% using a cut off of 8KPa to detect advanced fibrosis) (18), but more data in this cohort is needed.

The heterogeneity of liver disease in AATD implies that like lung disease, intrinsic factors such as genetics interact with environmental factors to determine clinical phenotype. Some studies have shown that heterozygosity for the Z allele (e.g. PiMZ) confers an increased risk of fibrosis or cirrhosis compared to the general population (16,17) but it seems likely that co-factors such as alcohol consumption and non-alcoholic steatohepatitis (NASH) play a greater role in heterozygous forms of AATD (19, 20).

In this systematic review the aims were to describe liver disease progression in AATD and assess the clinical effectiveness of liver transplantation.

METHODS

Standard systematic review methodology aimed at minimising bias was employed. The main protocol was registered with PROSPERO (CRD42016040134).

Searches

The search strategy is shared in the supplementary material; it was initially broad and included the terms: alpha 1-antitrypsin deficiency; disease monitoring; disease progression; humans; liver; mortality; incidence. The following sources were searched from inception, with no language restrictions or study design filters: Bibliographic databases (MEDLINE, MEDLINE In Process and EMBASE via Ovid, CINAHL via EBSCO, Cochrane Library (CDSR, DARE, HTA, NHS

EED and CENTRAL databases), Science Citation Index (ISI); current controlled trials metaRegister, ISRCTN database, UKCRN, WHO ICTRP Portal and ClinicalTrials.gov; specialist abstract and conference proceeding resources (British Library's ZETOC and ISI Proceedings). In addition we checked citation lists of included studies and relevant reviews and made contact with study authors and researchers of ongoing trials where appropriate to do so. A combination of text words and index terms relating to AATD, liver fibrosis and liver cirrhosis were used, and results then entered into electronic databases to facilitate record keeping, duplicate removal, study selection and document writing.

Study selection criteria

Studies eligible for inclusion contained children or adults with AATD, as defined by AAT level and genotype (e.g. PiZZ, PiSZ). Some studies included small numbers of individuals with non-polymerogenic forms of AATD, and were retained as outcomes could not be distinguished according to genotype. Systematic reviews and primary study designs that included individuals with liver disease of non-AATD aetiology (e.g. "jaundice in neonates") were eligible if they assessed progression or treatment in ≥10 AATD patients. Studies which consisted solely of patients heterozygous for AATD were excluded.

Interventions eligible for inclusion were any treatment said to be for liver disease, and the comparator was usual care. In the case of searches for manuscripts describing progression of liver disease a comparator was not relevant. Outcomes sought for the treatment review included mortality, graft survival, and quality of life. Where studies reported outcomes in AATD and non-AATD patients we specifically sought comparisons of the treatment effect between the two groups. Outcomes of relevance for the progression review included mortality, liver transplantation, presence of chronic liver disease, and incidence of HCC.

Review methodology, data extraction and assessment of bias

Studies were reviewed independently by two reviewers for relevance. Data from manuscripts included after review of the full manuscript was extracted by one reviewer and checked by

another. Bias was assessed by one reviewer and checked by another using the Newcastle Ottawa scale.

Evidence synthesis

Narrative synthesis of evidence was undertaken for all included studies. We divided the synthesis into sub-groups of childhood and adult disease. Meta-analytic methods could not be employed due to heterogeneity of study design and outcomes.

RESULTS

The PRISMA flow diagram in Figure 1 demonstrates the inclusion of papers related to prognosis and treatment of AATD. Participant characteristics and outcomes are summarized in tables 1 and 2 respectively, with a more detailed description of relevant studies shown in tables 3 and 4.

Of 1191 identified records related to prognosis in AATD, 48 full articles were retrieved and 35 met the inclusion criteria. Twenty-eight papers reported the outcomes for individuals with AATD presenting in children under the age of 16, and seven reported the outcomes of those presenting in adulthood.

7298 records were identified for the treatment of AATD, thirteen articles were retrieved and twelve met inclusion criteria. Some studies included participants with the heterogeneous phenotypes PiMZ and PiMS; these studies were only included where the majority (>90%) of participants had polmerogenic AATD phenotypes (i.e. PiZZ, PiSZ).

Risk of bias

There was a high risk of bias for the majority of the studies (figures 2, 3 and table 6 of the appendix). Nearly all were conducted retrospectively, and participants were often selected following clinical presentation with manifestations of AATD. The quality of reporting and

conduct of the included studies was often low, especially among smaller, older studies. Participant characteristics were often poorly described, with baseline characteristics such as age, sex and ethnicity incompletely defined. Few studies included an appropriate control and for those that did, the composition of the control group varied widely. Follow-up was often incomplete and/or relatively short-term outcomes were reported, so that important outcomes such as mortality were not always included.

Prognosis and outcomes in AATD related liver disease

Children

Twenty-eight papers reporting the prognosis and outcomes of children diagnosed with AATD under the age of 16 were reviewed (Table 3). A series of six papers reported the outcomes of 127 Swedish children identified at birth through screening and are recorded only once using data from the follow-up study at 16 years (21-26).

Participant characteristics:

There were a total of 1536 participants; characteristics were extracted from papers where they were adequately defined, and are summarised in table 1. Follow up ranged from 3 months to 27 years.

Disease prevalence and progression

Only studies using definitive clinical end-points or requirement for liver transplantation were included, and the results are summarised in table 2. There were no reports of Hepatocellular carcinoma (HCC). Mortality was reported in 17 studies but overall mortality could not be

reported due to data heterogeneity; mortality ranged from 0% in 10 children with PiZZ who presented with neonatal cholestasis followed up until 20 years of age (27), to 25.5% in a cohort of 98 participants with PiZZ/PiSZ referred to a tertiary centre with liver disease (28). Outcomes following liver transplantation are discussed in the treatment results section.

Adults

Seven papers primarily reported the outcomes of adult populations (14, 15, 38-42) (Table 3). All studies reported outcomes in adulthood, but in three data was collected from presentation at birth until adulthood, whereas in the remaining papers follow-up was from adulthood until a maximum age of 68.

Participant characteristics:

In total there were 626 participants, characteristics are summarized in table 1. Different reporting styles precluded reporting of age for adults.

Disease prevalence and progression:

Chronic liver disease in adults was adequately defined in five studies (14, 15, 38, 39, 41), and 4 reported liver transplantation as an outcome; the results are shown in table 2. Mortality was reported in four of the seven adult studies. As with the paediatric studies, there was significant heterogeneity between studies for age, phenotype and length of follow up, so overall mortality could not be accurately determined. One paper reported a liver-related mortality of 2.3% in 44 PiZZ children and adults presenting with abnormal LFTs after a minimum follow up of 4 years(14); another study of 160 adults with mixed AATD phenotypes referred to a tertiary gastroenterology centre with abnormal LFTs reported a non-liver related mortality of 8% in

106 patients with AATD but no clinical signs of liver disease. Of the remaining 54 patients that had signs of liver disease, mortality was 22% over 14 years follow-up, 85% of which was liver-related (41). However, 38% of these patients were found to be hepatitis C (HCV) carriers, and a further 40% have evidence of either current or previous Hepatitis B infection, and unsurprisingly viral infection was a risk factor for chronic liver disease in this study (41).

Participant Characteristics	**Number (%)**
Paediatric studies	
Sex	Male: 223 (36.9%)
Age	0-18 yrs
Phenotype	
PiZZ	1154 (75.1%)
PiSZ	69 (4.5%)
PiMZ	28 (1.8%)
PiSS/PiMS/PiFS	12 (0.7%)
Rare variants	12 (0.7%)
Unknown	261 (17.0%)
Ethnicity	
Caucasian	97.2%
Adult studies	
Sex	Male: 270 (53.6%)
Age	16-75 yrs
Phenotype	
PiZZ	345 (55.1%)
PiMZ	171 (27.3)
PiSZ	87 (13.9%)
PiSS/PiMS/PiFS	7 (1.1%)
Unknown	16 (2.6%)
Ethnicity (from transplant data)	
Caucasian	93.1%

Table 1. Basic participant characteristics, paediatric and adult studies.

Outcomes	**Number of participants**
Paediatric studies	
Liver transplantation	95 (16.5%)
Cirrhosis	36 (7.5%)
Portal hypertension	33 (6.9%)
Jaundice	9 (1.9%)

Abnormal LFT/prolonged PT	43 (9.0%)
HCC	0 (0.0%)
Adult studies	
Liver transplantation	46 of 312 (14.7%)
Cirrhosis	49 (10.5%)
Portal hypertension	16 (3.4%)
Jaundice	Not reported
Abnormal LFTs	12 (3.6%)
HCC	

Table 2. Outcomes for children and adults with AATD

Factors associated with development of liver disease

Although a meta-analysis could not be performed, twelve paediatric and four adult studies investigated possible risk factors for the development of liver disease in subjects with AATD.

Children

In paediatric studies, neonatal hepatitis was believed to be a possible factor for the development of subsequent chronic liver disease in the study by Ghishan *et al* (9), whilst Camarena *et al* reported that 44.6% of those who had neonatal cholestasis died or underwent transplant, compared with no requirement for transplant for those that presented later in life (34). In contrast, neonatal cholestasis was not found to be a risk factor for progression of liver disease in the studies by Nemeth *et al* (27, 43).

There are similarly conflicting results for serum markers. Francavilla *et al* found that in children requiring transplantation compared with those that did not, aspartate aminotransferase (AST) was significantly higher at presentation ($p<0.0001$), and when combined with gamma-glutamyl transferase (GGT) also higher at 6 months ($p<0.001$), one year ($p<0.0003$) and five years ($p<0.01$)(30). Pferdmenges also found that GGT at presentation was predictive of death or liver

transplantation in infants (12). However, serum AST at presentation was not noted to be a factor in the study by Filipponi et al, although this was an uncontrolled study of 16 children who all underwent liver transplantation (11).

Clinical jaundice and synthetic function have also been investigated as potential prognostic factors. Three studies found that raised bilirubin levels, in the "early stages" of the disease (34), or at presentation (12, 35) were a risk factor for future progression ($p<0.001$ in the study by Pferdmenges et al)(12), while another study reported that prolonged jaundice (>6 months) in those presenting with neonatal hepatitis was more common in those who went on to require liver transplantation (30). A retrospective study of 16 children referred for liver transplantation (11) suggested that recurrence of jaundice in children who present with neonatal cholestasis should be regarded as an alarm feature, although it is likely that this signifies a deterioration in synthetic function. Of note, the study by Moroz et al found no correlation between jaundice and clinical outcomes, and although it included fewer patients than the other studies that followed up patients from presentation, no other reason for this difference could be identified (44).

Prolonged international normalized ratio (INR), a marker of synthetic function, was found to be a risk factor for poorer outcomes in the study by Pferdmenges ($p<0.001$) when measured in "early disease," or at diagnosis in the study by Pfister ($p<0.001$), with a similar, non-significant trend being seen in the study by Volpert (12-14). The same study by Volpert *et al* saw a trend for lower serum albumin at diagnosis in those that later developed cirrhosis, but the findings were not significant, (14) and not replicated in other studies, though for the majority of studies serum albumin was used as a marker of severity rather than investigated for prognostic purposes.

Adults

In adults, a possible increased risk of chronic liver disease in men was observed in a retrospective review of 19 individuals with AATD and liver disease (40), and male gender was a risk factor (p=0.006) for end-stage liver disease requiring liver transplantation in a retrospective follow up of 139 individuals from a US AATD registry with self-reported liver disease (42). In the same study, BMI was also a risk factor (p=0.01) for end-stage liver disease requiring liver transplantation (42). Concurrent viral infection (41, 42) and increased alcohol intake (39, 42) have not consistently been shown to be risk factors or cofactors for development of liver disease in AATD.

Liver biopsy

12 paediatric and 1 adult study included biopsy findings; and seven studies attempted to correlate clinical outcomes with histological features. A summary of biopsy findings is in table 5. One retrospective review of 97 children referred to a liver transplant centre found that those who developed end-stage liver disease requiring transplantation were more likely to have bile duct proliferation ($p<0.01$), severe fibrosis with bridging septa ($p<0.02$), and established cirrhosis ($p<0.04$) in biopsies taken at presentation, compared with those who had no requirement for transplantation (30). Hadchouel *et al* also found that infants with AATD who presented with neonatal cholestasis who had bile duct proliferation and portal fibrosis at biopsy aged 1-6 months, showed a tendency to develop early cirrhosis and portal hypertension compared with those with predominant features of cholestasis, hepatocellular damage, or ductular hypoplasia (45). Portal fibrosis was also a risk factor for cirrhosis in children with AATD who presented with neonatal cholestasis at <6 months (84.6% vs 26.3%, $p<0.01$) in the study by Nebbia et al (46).

Paucity of bile ducts has also been suggested as a factor for poor prognosis (11, 44). In the study by Nebbia *et al*, a higher proportion of children who later developed cirrhosis had this feature at biopsy before 6 months of age (31.6% vs 15.8% p=n.s)(11, 46), however, the difference between the groups was not significant, and other studies have not replicated these findings (46-48). Rujner *et al* performed a case-control study to investigate whether serum procollagen III levels were associated with histological severity of fibrosis in individuals with AATD, but found no correlation (49).

Liver Transplantation for AATD-related liver disease

Although the initial search was designed to encompass all treatments for AATD, the only reported therapy in humans was liver transplantation. Twelve retrospective studies discussed liver transplantation as a treatment for AATD (see table 4), six studies reported paediatric populations (11, 30, 31, 37, 50, 51), and six included both paediatric and adult patients (42, 52-56).

Children

The studies included 425 children who underwent liver transplantation for AATD. Phenotypes were reported in 297 children; 95.6% were PiZZ, with the remaining children having PiSZ, PiMZ, or unknown phenotypes. 60.5% were male, and median ages ranged from 1.9 and 6 years, with a full range of 1-17 years. Ethnicity was reported in two studies and 254 (97.2%) were described as Caucasian.

Only one study reported the indications for transplantation, with five studies reporting clinical features at the time of transplantation. In 198 participants, ascites was reported in 89 (44.9%), jaundice in 48 (24.2%), varices or gastrointestinal bleeding in 78 (39.4%) and encephalopathy

Comment [ST1]: I could summarise this into a table but this may be repetitive?

in 12 (6.1%). Outcomes following liver transplantation were reported in eight studies and are shown in table 4. Five year survival ranged from 74% from transplant data in the 1980s (51) to 92% in two studies published since 2000 (30, 52). Most studies report an excellent quality of life in survivors, with no recurrence of AATD in the liver, no pulmonary complications, and favourable outcomes compared with other indications for liver transplantation.

Adults

The studies included up to 656 adults who underwent liver transplantation for AATD. Phenotypes were reported in 130 participants, and were PiZZ in 96 (73.8%), and PiSZ in 24 (18.5%). 74.0% participants were male, and median ages ranged from 34 to 54 years. 93.1% of individuals were described as Caucasian. The indications for transplantation were not reported in sufficient numbers to draw conclusions.

Outcomes following liver transplantation are shown in table 4, and were included in four studies. Five year survival was 80% in the most recent study published in 2013 (53). Survivors report an excellent quality of life, and had no recurrence of liver or lung disease. Only one study showed decline in lung function, as measured by FEV_1/FVC, in 11 of 17 adults who had pre and post-transplant lung function measured; the remaining 6 showed improvement. A search for data on the outcomes of combined liver and lung transplantation for AATD yielded single case-reports only, although the study by Kemmer et al reported a 100% 8 year survival rate for three patients that received separate liver and lung transplantation for AATD-related disease (54).

DISCUSSION

This is the largest study and only systematic review of AATD-related liver disease, and includes over 1000 child and adult participants, drawing data from 47 studies. Despite being a recognised cause of liver disease, only 10% of those with polymerogenic AATD phenotypes

develop cirrhosis/chronic liver in either childhood or adulthood. In children, possible predictive factors for the development of significant liver disease could be elevated serum AST, GGT and prolonged or recurrent jaundice, but it adults it seems likely that additional liver injury such as NASH, alcohol or viral infection play a role.

It is still unknown why some individuals develop AATD related liver disease while others do not. The bimodal distribution of clinical presentation in children and adults is a unique characteristic of the disease adding another dimension of complexity. In children, serum bilirubin level at presentation or the pattern of clinical jaundice may help predict progression of liver disease, but no clear pattern or algorithm has been established. Portal fibrosis, and possibly bile duct proliferation, observed on liver biopsy at presentation or within the first six months of life, also seemed to distinguish those children likely to develop cirrhosis and potentially require liver transplantation. Serological and histological factors such as these should be further examined in a prospective, case-control study.

In adults, male sex and increasing BMI were the only potential risk factors identified for the development of end-stage liver disease requiring transplantation. However, non-alcoholic steatohepatitis (NASH) is increasingly recognized as a cause of cirrhosis in individuals with the metabolic syndrome, and may be responsible for liver disease in those with AATD and raised BMI. Although it seems feasible that cofactors such as alcohol intake or concurrent viral infection contribute to the development of liver disease in adults, this was not validated in any of the studies. However, given that such a small proportion of those with AATD develop cirrhosis, alternative aetiologies should always be excluded, particularly in individuals with non-polymerogenic forms of AATD.

Only 10% of individuals with AATD develop cirrhosis, and 16.5% of children and 14.7% of adults who presented with AATD-related liver disease required transplantation. However, in children it was observed that studies with longer follow up appeared to have better long-term outcomes, suggesting that even those presenting with significant liver disease at a young age

can fully recover if transplantation is not required. It is likely that this, in addition to ascertainment bias (most study data was reported from transplant centres), accounts for the discrepancy between the proportion of those with cirrhosis and those requiring transplantation.

HCC was not reported in children suggesting it is extremely rare. In adults, the overall incidence of 1.3% was similar to published data for aetiologies such as alcohol-related liver cirrhosis and primary biliary cholangitis (57). A slightly higher incidence was recorded in one paper investigating patients with AATD, but this study included heterozygotes with concurrent hepatitis B and C, and the majority of HCC cases involved subjects with cirrhosis and viral liver disease (58). Histological studies have associated cholangiocarcinomas and combined hepatocholangiocarcinomas with the PiZZ phenotype, but these were not reported in our follow up studies (59, 60).

Mortality due to AATD related liver disease in both children and adults has significantly declined since the late 1980s when liver transplantation became standard practice for end-stage liver disease secondary to AATD. Outcomes following liver transplantation for both paediatric and adult studies were excellent and comparable with other common indications for transplantation (61).

Limitations of the study.

Unfortunately heterogeneity of data and risk of bias was such that we were unable to perform a meta-analysis. The majority of studies were retrospective and there was significant selection bias; basic demographic data such as age and sex of participants was missing in several studies and long-term follow up was often incomplete. In addition, many of the studies included heterozygous and/or non-polymerogenic phenotypes and liver related outcomes for these individuals were usually inseparable from those with PiZZ phenotype. In addition, a number of

studies were written by a small number of authors, contributing to the detection, selection and attrition bias already discussed and outlined in figures 2 and 3.

The clinical course of liver disease in individuals with AATD remains poorly understood, but approximately 10% of those with deficient phenotypes are likely to experience significant morbidity secondary to liver disease at some point during their lifetime. Further prospective studies are required to better understand which individuals are prone to develop liver disease and the mechanism behind liver injury in these individuals. Detecting early fibrosis in individuals with AATD is currently the best method of identifying those at risk of significant liver disease, and non-invasive methods as an alternative to liver biopsy may soon be validated in this population. It is hoped that drugs currently in phase 2 trials will become available in the future and can be used to target those with fibrosis, providing a long-awaited treatment alternative to liver transplantation.

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Sarah Townsend and Ross Edgar performed the research, Sarah Townsend and Paul Ellis collected and analysed the data, Sarah Townsend designed the research study and wrote the paper, and Philip Newsome and Alice Turner contributed to the design of the study and provided critical appraisal of the manuscript.

All authors approved the final version of the manuscript.

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Conflict of Interest: None to declare

Table 3. A summary of all included studies for AATD related liver disease in children and adults.

AATD, alpha-1-antitrypsin deficiency; BA, biliary atresia; CLD, chronic liver disease; HCC, hepatocellular carcinoma; HTN, hypertension; LFTs, liver function disease; LT, liver transplantation; M, male; mth, month; pt, patient; wk, week; yr, year

Author and year	Study design	Description	Sample Size	Phenotype (%)	Sex (% male)	Mean age (range)	Control/Comparator	Primary outcomes	Follow up
PAEDIATRIC STUDIES									
Rujner et al, 1991 (49)	Case control study	Case control, comparing fibrosis with levels of procollagen III	31	PiZZ – 23 (74.2%) PiMZ – 6 (19.4%) PiSS – 1 (3.2%) PiFZ – 1 (3.2%)	24 (77.4%)	NR	Cholestasis vs no cholestasis Degrees of fibrosis compared	No association between collagen III and degree of hepatic fibrosis found	2.5 mths - 14 yrs
Moroz et al, 1976 (44)	Prospective study	Prospective review of AATD cases identified by screening those with liver disease between 1969 and 1979, plus 7 healthy PiZZ siblings	25	All PiZZ	NR	NR	No control	Death – 4 (16%) Severe Liver disease – 3 (12.0%) Asymptomatic – 11 (44.0%)	10 yrs
Hadchouel et al, 1976 (45)	Prospective study	Prospective follow up of 15 children with neonatal cholestasis diagnosed with AATD	15	All PiZZ	NR	16 mths – 19 yrs	No control	Jaundiced – 4 (26.7%) Not Jaundiced –10 (73.3%) Portal HTN – 5 (35.7%) Splenomegaly – 3 (21.4%)	NR
Sveger et al, 1976 (21)	Prospective study	Prospective follow up of 183 individuals with AATD (any genotype) identified by screening 200000 children between 1972 and 1974. 6 month follow up	176	PiZZ – 125 (71.0%) PiSZ – 48 (27.2%) PiMS – 1 (0.6%) PiMZ – 2 (1.2%)	NR	NR	No control	Severe obstructive jaundice – 12 (7.0%) Subclinical jaundice – 5 (3.0%)	2 yrs
Sveger et al, 1978 (22)	Prospective study	Prospective follow up of 176 individuals with AATD (any genotype) identified by screening 200000 children between 1972 and 1974. 2 year follow up	176	PiZZ – 125 (71.0%) PiSZ – 48 (27.3%) PiMS – 1 (0.6%) PiMZ – 2 (1.1%)	NR	NR	PiMZ, PiSZ and PiMS pts	Cirrhosis – 3 (1.7%) all PiZZ Hyperbilirubinamia – 19 (11.0%), all PiZZ Liver Disease –10 (6.0%), all PiZZ No Liver Disease –146 (83.0%)	2 yrs
Odievre et al, 1981 (48)	Prospective study	Follow up of patients with prolonged cholestasis before age of 3 months	103	PiZZ – 17 (100%)	Not reported for AATD	NR	No control	Liver disease – 5 (29.4%)	NR
Sveger et al, 1981 (23)	Prospective study	Prospective follow up of 172 individuals with AATD (any genotype) identified by screening 200000 children between 1972 and 1974. Follow up age 4	183	PiZZ – 126 (68.9%) PiSZ – 53 (29.0%) PiZ- – 2 (1.1%) PiS- – 1 (0.5%) PiFZ – 1 (0.5%)	NR	AATD 4.3 yrs (3.9 - 5) Control 4.2 yrs (4.0 - 4.6)	80 random controls (not screened)	Death – 1 (0.5%), PiZZ aged 3.7 yrs, aplastic anaemia, cirrhosis at post mortem Cirrhosis – 2 (1.1%), both PiZZ Neonatal Jaundice – 14 (7.7%), all PiZZ Hepatomegaly/deranged LFTs – 1 (0.5%), PiZZ	4 yrs
Nemeth et al, 1982 (43)	Prospective study	Thirteen children aged 4-6 with PiSZ or PiZZ with no history of neonatal cholestasis, identified through screening, prospectively followed up	13	PiZZ – 8 (61.5%) PiSZ – 5 (38.5%)	PiZZ – 7 (87.5%) PiSZ – 4 (80.0%)	NR	No control	Death – 1 (7.7%), GI bleed Asymptomatic 12 (92.3%) Biospy (N = 7) • Cirrhosis – 1 (7.7%), PiZZ phenotype • Fibrosis – 4 (30.0%), 1 PiSZ	NR

Nemeth et al, 1982 (27)	Prospective study	Ten children with PIZZ and neonatal cholestasis followed up to ages 4-20 years	10	All PiZZ	NR	NR	No control	Cirrhosis– 3 (30%) Portal Hypertension –2 (20%) Prolonged Jaundice 2 (20%)	NR
Nebbia et al, 1983 (46)	Prospective study	Prospective follow up of 45 children with AATD who had been referred with neonatal cholestasis; 25 who developed cirrhosis before the age of 8 compared with those who did not	45	PiZZ – 44 (97.8%) PiMZ – 1 (2.20%)	25 (56.8%)	NR	No control	Death – 6 (13.3%) Cirrhosis – 25 (55.0%) Jaundice • Resolved by 6 mths – 19 (42.2%) • Resolved by 88 mths – 2 (4.4%) • Progressive liver disease – 6 (13.3% - all died) • Portal HTN – 12 (26.6%)	NR
Sveger et al, 1984(24)	Prospective study	Prospective follow up of 176 individuals with AATD (any genotype) identified by screening 200000 children between 1972 and 1974. 8 year follow up	176	PiZZ – 125 (71.0%) PiSZ – 48 (27.2%) PiMS – 1 (0.6%) PiMZ – 2 (1.2%)	NR	NR	No control	Death – 9 (5.1%) Asymptomatic –146 (83.0%)	8 yrs
Mellado et al, 1986 (47)	Prospective study	Review of 14 children with AATD, divided into 2 groups according to age at diagnosis	14	PiZZ – 12 (85.7%) PiMZ – 2 (14.3%)	NR	NR	No control	No significant difference between biopsies in the 2 groups	23 days – 6 yrs
Sveger et al, 1988 (25)	Prospective study	Prospective follow up of 176 individuals with AATD (any genotype) identified by screening 200000 children between 1972 and 1974. 12 year follow up	185	PiZZ– 127 (68.6%) PiSZ – 54 (29.2%) PiZ- – 2 (1.1%) PiS- – 1 (0.5%) PiFZ – 1 (0.5%)	NR	NR	PiMZ and PiMS pts	Deaths: 5 (3.2%), all PiZZ, 3 liver cirrhosis, 1 accidental, 1 anaphylaxis 1 PiSZ, sudden infant death syndrome	12 yrs
Pittschieler et al, 1992 (29)	Prospective study	14 PiSZ children detected by screening of all children at one centre between 1985-1989	14	All PiZZ	7 (50.0%)	NR	No control	No negative outcomes	NR
Sveger et al, 1995 (26)	Prospective study	Prospective follow up of 176 individuals with AATD (any genotype) identified by screening 200000 children between 1972 and 1974. 18 year follow up	185	PiZZ – 127 (68.6%) PiSZ – 54 (29.2%) PiZ – 2 (1.1%) PiS – 1 (0.5%) PiFZ – 1 (0.5%)	NR	NR	No control	Death – 6 (3.2%), 5 PiZZ and 1 PiSZ Raised LFTs – 2 (1.1%)	16 - 18 yrs
Ghishan et al, 1988 (9)	Retrospective study	Retrospective follow up of 18 patients with PIZZ AATD	18	All PiZZ	15 (83.3%)	2 mths	No control	Death – 2 (11.1%), variceal bleed and histoplasmosis Cirrhosis – 3 (16.7%) Elevated AST – 18 (100%)	3.7 yrs +/-2.4 yrs
Ibarguan et al, 1990 (28)	Retrospective study	Retrospective observational study of 98 children with AATD referred to paediatric department between 1967 and 1988	98	PiZZ – 95 (96.9%) PiSZ – 3 (3.1%)	54 (55.1%)	NR	No control	Death, N = 25 (25.5%), 9 male (44%), 14 female (56.0%), mean age 5 yrs (range 6 wks - 19 yrs) Transplanted, N = 26, 16 male , 10 female (38.5%), mean age at transplant, female 8.4 yrs (range 7 mths - 19 yrs), male 7.8 yrs (range 1-18yrs) • Alive – 18 (69.2%) • Death – 8 (30.8%), 5 female, 3 male	Mean 5.3 yrs (1 mth - 27 yrs)
Filipponi et al, 1994 (11)	Retrospective study	Retrospective review of children referred for transplant with AATD	16	All PiZZ	9 (56.3%)	NR	No control	Transplant (N = 16) • Hepatosplenomegaly – 16 (100%) • Varices – 16 (100%) • Jaundice – 9 (56.3%) • Ascites – 9 (56.3%) • Histological cirrhosis – 16 (100%) Neonatal jaundice – 7 (43.8%)	22 mths
Francavilla et al, 2000 (30)	Retrospective study	Retrospective observational study of 97 children with	97	All PiZZ	58 (60.0%)	1.9 mths (1 wk to 11.5 yrs)	No control	Jaundice – 82 (84.5%) Transplant – 24 (24.7%)	Median follow up

		AATD referred to a paediatric transplant unit between 1989 and 1998							(transplanted) 3.9 yrs (1-9)
Prachalias et al, 2000 (31)	Retrospective study	A study of 21 patients all receiving liver transplant due to AATD	21	All PiZZ	NR	NR	No control	Transplanted – 21 (100%) Clinical features at transplant: Portal HTN – 18 (85.7%) Jaundice – 16 (76.0%) Hepatosplenomegaly – 15 (71.0%) Ascites – 14 (67.0%) Oesophageal Varices – 9 (42.8%) Gastrointestinal bleed – 6 (28.5%) Encephalopathy – 1 (9.5%)	8 yrs
Hinds et al, 2006 (33)	Retrospective study	Retrospective review of patients and their siblings with PiZZ AATD presenting between 1978 and 2002	235 Liver involvement 74	PIZZ – 58 (24.7%)	32 (55.2%)	NR	No control	Transplant – 7 (12.1%) Liver Disease – 21 (72.0%) No Liver disease – 8 (29.0%) No concordance in liver disease severity between siblings with PiZZ	80 mths (30 - 240)
Bakula et al, 2007 (37)	Retrospective study	Fifty nine children admitted for cholestasis/hepatitis, homozygous for AATD	59	All PiZZ	NR	NR	No control	Death 3 (5.1%) Varices • 5 yrs –2 (3.4%) • 8-11 yrs – 9 (15.3%)	From diagnosis to LT 4-17 yrs No LT 7-14 yrs
Camarena et al, 2010 (34)	Retrospective study	Retrospective review of patients presenting in infancy or later with liver disease and found to have AATD	79	PiZZ – 73 (92.4%) PiSZ – 6 (7.6%)	NR	NR	No control	Death or Transplant – 35 (44.6%), all had presented with neonatal cholestasis, 34 PiZZ, 1 PiSZ	10 – 16 yrs
Pfister et al, 2011 (13)	Retrospective study	Retrospective follow up of all PIZZ carriers presenting to unit	53	All PiZZ	NR	NR	No control	Death – 8 (15.1%) Transplant – 17 (32.1%)	1.5 – 2 yrs (transplant only)
Kekez et al, 2015 (35)	Retrospective study	Retrospective analysis of database of PIZZ children diagnosed between 1979 and 2012	292	All PiZZ	113 (38.7%)	NR	No control	Death – 3 (3.5%), all pre transplant era Severe disease – 21 (21.9%) Moderate Disease – 4 (4.2%) Mild Disease – 23 (23.9%) Asymptomatic – 6 (6.3%) Normal – 42 (43.7%)	15 yrs
Lang et al, 2005 (36)	Retrospective study	Retrospective analysis of 48 patients with AATD, prevalence of liver disease at time of diagnosis	48	PiZZ – 12 (25.0%) PiMZ – 17 (35.4%) PiMS – 7 (14.5%) PiSZ – 2 (4.2%) PiVZ – 2 (2.1%) PiMP – 2 (2.1%) Rare Variants – 8 (16.7%)	21 (43.7%)	NR	No control	Death – 2 (4.20%) Transplanted – 1 (2.1%) , later died of fungal disease Liver disease – 3 (6.3%)	NR
Pferdmenges et al, 2013 (12)	Retrospective study	Retrospective review of patient's files with AATD with telephone follow up, those with good and poor outcomes and compared	53	All PiZZ	Group 1 (poor outcome) 9 (37.5%)	0 - 18 yrs	Those with good and poor outcomes compared	Asymptomatic – 29 (4.7%) Liver disease – 24 (45.3%) Transplant – 22 (41.0%) Death – 9 (17%), 8 transplanted, 1 died on waiting list	NR
Karitzky et al, 1978 (62)	Retrospective study	Review of 12 patients with PiZZ, five of whom had liver disease	12	All PiZZ	NR	NR	No control	Death – 1 (0.8%)	NR
<u>ADULT STUDIES</u>									
Bernspang et al 2009 (38)	Prospective study	Follow up of a cohort of patients with AATD at 30 years	129	PiZZ – 89 (69.0%) PiSZ – 40 (31.0%)	PiZZ – 37 (41.5%) PiSZ – 20 (50.0%) Control – 37	31 yrs	No control	All well Abnormal LFTs – 6 (5.0%)	Aged 30 yrs

					(44.0%)				
Tanash et al, 2015 (15)	Prospective study	Prospective follow up of 176 individuals with AATD (any genotype) identified by screening 200000 children between 1972 and 1974. 18 year follow up	122	PiZZ – 88 (72.1%) PiSZ – 34 (27.9%)	NR	NR	No control	Deranged LFTs – 7 (5.7%) one had Hepatitis C All well	34 yrs
Triger et al, 1976 (39)	Retrospective study and case series	Retrospective analysis of 13 pts aged 16-73 with AATD	13	PiZZ – 9 (69.2%) PiMZ – 2 (15.4%) Unknown – 2 (15.4%)	7 (53.8%)	Presentation 48.2 yrs (4 mths - 73 yrs) Follow up/death 52.8 yrs (16 - 74)	No control	Death – 7 (53.8%), 1 respiratory failure, 3 hepatic coma (two with alcohol excess), 2 varices, 1 hepatic rupture) Alive – 6 (46.2%)	1 mth - 26 yrs
Rakela et al, 1987 (40)	Retrospective study	Review of electronic records of 19 adult patients with AATD and liver disease	19	PiMZ – 8 (42.1%) PiZZ – 9 (42.1%) PiSZ – 3 (15.8%)	Total 13 (68.4%) PiZZ – 7 (87.5%) PiSZ – 1 (33.3%) PiMZ – 5 (62.5%)	NR	No control	Death – 8 (42.1%)	NR
Propst et al, 1995 (41)	Retrospective study	Review of 6890 patients referred to gastroenterology tertiary centre between 1978 and 1993. Those with CLD compared with those that did not develop CLD	160 Grp 1: 54 Grp 2: 106	Grp 1 (CLD) PiZZ – 3 (6%) PiMZ – 42 (78%) PiFZ – 5 (9%) PiSZ – 4 (7%) Grp 2 (No CLD) PiMZ – 94 (88%) PiFZ – 2 (2%) PiZZ – 4 (4%) PiSZ – 6 (6%)	Grp 1 – 34 (63.0%) Grp 2 – 64 (59.3%)	CLD 55.7 yrs No CLD 50.4 yrs	Those with signs of CLD compared with those without	Group 1 outcome only (CLD): Death – 4 (8.0%) Cirrhosis – 32 (59.2% - Child Pugh A 34%, B 39%, C 27%) HCC – 6 (11.1%) Chronic hepatitis –22 (40.7%)	NR
Volpert et al, 2000 (14)	Retrospective study	All patients known to have AATD taken from a database of patients with abnormal liver biochemistry results	44	All PIZZ	25 (56.8%)	16-73 yrs	No control	Death – 1 (2.3%) Cirrhosis or Portal HTN – 17 (38.6%) Liver Transplant – 5 (11.4%) Lost to follow up – 2 (4.5%)	1 mth – 26 yrs
Bowlus et al, 2005 (42)	Retrospective study	Retrospective study of patients who self-reported having AATD	139	PiZZ – 99 (71.3%) PiMZ – 25 (18.0%) Unknown 14 (10.70%) (Self-reported)	NR	43.5 yrs (1-75 yrs)	No control	Liver transplant – 41 (29.5%)	NR

Table 4. All included studies for transplant in AATD in children and adults

Author and year	Study design	Description	Characteristics of treated group	Treatment	Control/Comparator	Indications for transplant/clinical features at transplantation	Survival – patient/graft	Duration of follow up
Filipponi et al, 1994 (11)	Retrospective review	Retrospective review of children with AATD referred for liver transplantation	N = 16 Phenotype: PiZZ – 16 Gender: M – 9 (56.3%)	LT	No control	Varices – 16 (100%), Ascites – 9 (56.3%), Encephalopathy – 0 (0%).	15 patients (94%) were alive after a median follow-up of 22 mths. 2 required regraft	22 mths
Francavilla et al, 2000 (30)	Retrospective observational	Retrospective observational study of 97 children with AATD referred to a paediatric transplant unit between 1989 and 1998	N = 26 Phenotype: PiZZ – 26 Gender: not reported for treated group Median age at referral: NH group 1.9 mths (range 1 wk to 11.5 yrs), Chronic liver disease group 11.3 mths, range (4.8 to 11.5 yrs) Ethnicity: Caucasian N = 26	LT	Divided into neonatal hepatitis (NH) transplanted and (LT) non-transplanted, and chronic liver disease (CLD) transplant and non-transplant	Recurrent ascites – 19 (79%), Coagulopathy – 15 (61%), Recurrent jaundice – 12 (50%).	Pt survival, 1 year: 96%, 5 yr 92%, Graft survival at 1 and 5 yrs 79% 2 deaths. One at 3 mths (intracranial haemorrhage), one at 3 yrs (sepsis) Survival data unavailable for control group. One patient received 2 grafts and 1 received 3 grafts.	Median follow up (transplanted) 3.9 yrs (1-9 yrs)
Hughes et al, 2011 (50)	Retrospective observational	Retrospective review of LT in recipients with AATD compared with those with biliary atresia (BA)	N = 35 Phenotype: PiZZ – 34, PiSZ – 1 Median age at transplantation: 6 yrs (1-10) Gender: M –20 (57.1%)	LT	Patients with BA	Ascites – 24 (69.0%), Bacterial peritonitis – 7 (20.7%), GI bleeding – 13 (37.5%), Encephalopathy – 8 (24.1%).	Pt survival AATD: 1 yr 82.7%, 5 yr 76.5%, 10 yr 76.5% Graft survival 1 yr 68.4%, 5 yr 68.4%, 10 yr 68.4% Pt survival BA: 1 yr 70.0%, 5 yr 60.3%, 10 yr 55.9% Graft survival BA: 1 yr 66.2%, 5 yr 55.8%, 10 yr 52.5%	>10 yrs in 50%
Prachalias et al, 2000 (31)	Retrospective observational	A study of 21 patients all receiving liver transplant due to AATD	N = 21 Phenotype: PiZZ – 21 Gender: not reported Age at diagnosis: <6 mths in 1, >5 yrs in 2 children.	LT	No control	Jaundice (BR > 20 ymol/l) – 16 (76.1%) Ascites – 14 (66.6%) Oesophageal varices – 9 (42.8%), Encephalopathy – 1 (9.5%).	21 children are alive at a median follow-up of 40 mths (range 3-97 mths). 4 pts underwent a re-transplant.. The indication for re-transplantation was hepatic artery thrombosis N = 3, chronic rejection N = 1 (well 8 yrs post-transplant).	Median 40 mths
Migliazza et al, 2000 (51)	Retrospective	Review of 198 children undergoing LT at a single centre	Sixteen patients with AATD No other demographics reported	LT	No control	Not reported	Outcomes for pts with AATD not defined. All Pt survival: 1 yr 80%, 3 yrs 76%, 5 yrs 74%, 10 yrs 74%. Graft survival at 1 yr 63%, 3 yrs 60%, 5 yrs 58%, 10 yrs 58%.	Median 41 mths (0 to 154 mths)
Bakula et al, 2007 (37)	Retrospective	Fifty nine children admitted for cholestasis/hepatitis, homozygous for AATD	N = 59 Treated N = 11 (LT) Phenotype: PiZZ – 59 Gender: not reported Age: range 10.3-17.1 yrs	LT	No control	Not reported	Transplant outcomes not reported.	From diagnosis to LT 4-17 yrs No LT 7-14 yrs
Carey et al, 2013 (52)	Retrospective	Review of pts undergoing LT for AATD across three transplant centres	N = 123 Phenotype: PiZZ – 50, PiSZ – 23 Control PiMZ – 50 Gender: M PiSZ – 18 (78.3%), PiZZ – 38 (76.0%), PiMZ – 37 (74.0%). Age at LT: PiSZ – 53.0 yrs (28-69), PiZZ –47.8 (1-69), PiMZ – 57.7 (30-70) Ethnicity: not reported *includes paediatric pts	LT	PiMZ – 50 Transplanted for other indications	Not reported	PiZZ group: 1yr 94%, 3 yrs 92%, 5 yrs 92%, 10 yrs 86%. PiSZ group: 1 yr 86%, 3 yrs 83%, 5 yrs 80%, 10 yrs 72% MZ control group: 1 yr 91%, 3 yrs 86%, 5 yrs 79%, and 10 yrs 79%. 23 pts died during the follow-up period. 1 pt in the ZZ and SZ grps died of pulmonary complications. No pts required regraft	Up to 25 yrs
Esquivel et al, 1987 (53)	Retrospective	Single centre experience of all patients transplanted for AATD between 1980 and 1986	N = 39 **Paediatric N = 29** Mean age at LT: 5 yrs (0.66-13) Phenotype: PiZZ – 22 (76.0%), PiSZ – 2 (7.0%), PiMZ – 3 (7.0%), unknown – 3 (10.0%)	LT	No control	Paediatrics: Ascites 23 (79.0%), GI bleeding 17 (59.0%), Jaundice 11 (38.0%), Encephalopathy 3 (10.0%). Adults: Ascites – 8 (80.0%)	Paediatrics 5 yr survival: 83% 3 patients required regraft All survivors are attending school	Paediatric: mean 26 mths (8 to 60)

			Adults N = 10 Median age: 34 yrs (18-48) Phenotype: PiZZ – 8 (80.0%), PiMZ – 2(20.0%)			Jaundice – 2 (20.0%) Encephalopathy – 4 (40.0%)	Adults 5 yr survival 60% 2 adults required regraft	
Kemmer et al, 2008 (54)	Retrospective	Review of LT for AATD from the UNOS database	567 LT recipients for AATD **Children N = 161** Gender: M – 98 (60.9%) Median age: 3 yrs (0.5-17) Ethnicity: White – 144 (89.4%), Hispanic – 10 (6.2%), other – 7 (4.4%) **Adults N = 406** Gender: M – 294 (72.4%) Median age: 52 yrs (18-70) Ethnicity: White – 396 (97.5%), Hispanic – 6 (1.5%), other – 4 (1%) Phenotypes: not reported	LT	No control	Not reported	Pt survival paediatrics: 1 yr 84%, 3 yrs 81%, 5 yrs 78%. Pt survival adults: 1 yr 83%, 3 yrs 79%, 5 yrs 77%.	Up to 9 yrs
Kilpe et al, 2003 (55)	Retrospective	Review of LT data from 37 centres	5180 cases reviewed N = 116 with AATD Age 0-14 N =12 Age ≥14 yrs, n=104	LT	Compared with other indications for transplantation	Not reported	Outcomes for AATD not given separately	Up to 9 yrs
Vennarecci et al, 1996 (56)	Retrospective	All pts referred for LT for AATD, single centre	N = 81 total Transplanted grp **Children N = 13** Gender: M – 11 (84.6%) Median age: 4.6 yrs (0.4-11.9 yrs) All PiZZ All British born, ethnicity not specified **Adults N = 22** Gender: M – 19 (86.4%) Median age: 44 yrs (16-68.8 yrs) Phenotypes: PiZZ – 3 (13.6%), PiSZ – 1 (4.5%), PiMZ – 9 (40.9%), PiMM – 3 (13.6), PiMS – 2 (9.1%), not recorded 4 (18.2%)	LT	Those referred and not transplanted	Not reported	Paediatric Survival (overall): 1yr 69%, transplanted after 1990 87.5% 2 pts re-transplanted because of chronic rejection. Five children died of the following: cardiac arrest of uncertain cause, fulminant rejection in an ABO-incompatible donor LT, chronic rejection (2), and left ventricular failure secondary to myocarditis. Adults Survival (overall 60%, transplanted after 1990, 73%. Two patients were re-transplanted for hepatic artery thrombosis and ischemic graft failure. Seven patients died of the following: cardiac arrest, pneumonia (3), haemorrhage from hepatic artery anastomosis dehiscence, primary non-function, and myocardial infarct.	Median 48 mths (8 -114 mths)
Bowlus et al 2005 (42)	Retrospective	Retrospective review of self-reported outcomes in a cohort of patients with AATD	**Children N = 15** Gender: M – 8 (53.3%) Mean age at transplantation (diagnosed in childhood): 16.9 ± 21.7 yrs Phenotype: PiZZ – 13 (86.7%), other 2 (13.3%) Ethnicity: White – 13 (86.7%), non-white – 2 (13.3%) **Adults N = 25** Gender: M - 20 (80%) Mean age at transplantation: 51.6 ± 8.3 yrs Phenotype: PiZZ – 16 (64.0%), other 9 (36.0%) Ethnicity: white – 23 (92.0%), non-white – 2 (8.0%)	LT	No control	Indication not reported	Transplant - 41 (29.5%) were transplant recipients or on waiting list – outcomes not reported	Not reported

Table 5. A summary of biopsy findings from included studies.

Author and year	Study design	Description	Sample Size	Phenotype (%)	Biopsy Findings
Children					
Hadchouel et al, 1976 (45)	Prospective study	Prospective follow up of 15 children with neonatal cholestasis diagnosed with AATD	15	All PiZZ	Performed at 1 - 6 mths PAS +ve globules present in all pts Pts were divided into 3 groups: G1, n=6, cholestasis, hepatocellular damage, mild portal fibrosis; improvement in liver injury seen G2, n=5, significant portal fibrosis and bile duct proliferation; all developed cirrhosis, G3, n=4, ductular hypoplasia; suffered prolonged cholestasis
Odieve et al, 1976 (48)	Retrospective study	Retrospective analysis of 424 children screened for AATD over 3.5 years	36	PiZZ – 19 (52.8%) PiMS – 7 (19.4%) PiMZ – 6 (16.7%) PiSZ – 4 (11.4%)	4 biopsies performed in PiZZ pts aged between 2 mths and 6.5 yrs Features: PAS +ve granules, absent intrahepatic bile ducts in all Mixed genotype - no intracellular PAS positive deposits (+ve in all PiZZ)
Nemeth et al, 1982 (43)	Prospective study	Thirteen children aged 4-6 with PiSZ or PiZZ with no history of neonatal cholestasis, identified through screening, prospectively followed up	13	PiZZ – 8 (61.5%) PiSZ – 5 (38.5%)	Features at diagnosis Cirrhosis – 1 Fibrosis – 5 Steatosis – 5 Nuclear vacuolisation – 2 Normal – 1
Nemeth, 1982 (27)	Prospective study	Ten children with PIZZ and neonatal cholestasis followed up to ages 4-20 years	10	All PiZZ	Performed ages 4-20 Cirrhosis – 3 Fibrosis – 1 Normal – 2 poor biopsy – 1 not done – 1
Nebbia et al, 1983 (46)	Prospective study	Prospective follow up of 45 children with AATD who had been referred with neonatal cholestasis; 25 who developed cirrhosis before the age of 8 compared with those who did not	45	PiZZ – 44 (97.8%) PiMZ – 1 (2.20%)	Grp 1, cirrhosis, n=25 infancy Grp 2, no cirrhosis, n=20
Ghishan et al, 1988 (9)	Retrospective study	Retrospective follow up of 18 pts with PIZZ AATD	18	All PiZZ	Performed at presentation in 14 Cirrhosis – 3 Portal fibrosis – 1 Bridging fibrosis – 3 Mild fibrosis – 1 Cholestasis – 13 Neonatal hepatitis – 7 Decreased bile ducts – 1
Rujner et al, 1991(49)	Case control study	Case control, comparing fibrosis with levels of procollagen III	31	PiZZ – 23 (74.2%) PiMZ -6 (19.4%) PiSS – 1 (3.2%) PiFZ – 1 (3.2%)	No correlation was found between the degree liver fibrosis determined by histological examination and the serum concentration of procollagen type III peptide
Pittschieler et al, 1992 (29)	Prospective study	14 children with PiSZ detected by screening of all children at one centre between 1985 and 1989, prospectively followed up	14	All PiZZ	Performed in 1 pt - normal
Filipponi et al, 1994 (11)	Retrospective study	Retrospective review of children referred for transplant with AATD	16	All PiZZ	Performed at diagnosis PAS positive diastase-resistant cellular inclusions – 11 Cirrhosis – 6 Extensive portal fibrosis with ductular proliferation – 5 Mild portal fibrosis – 3 Paucity of IL bile ducts – 2
Francavilla et al, 2000 (30)	Retrospective study	Retrospective observational study of 97 children with AATD referred to a paediatric transplant unit between 1989 and 1998	97	All PiZZ	Median age at biopsy 1.8 mths (range 2 wks-16 mths) Group with neonatal hepatitis requiring transplantation (NH,LT): cirrhosis 4, bridging septa 6, cholestasis 11, bile duct reduplification 9, PAS granules 3, bile duct hypoplasia 2, portal inflammation 2 Neonatal hepatitis, no liver transplant (NH,no LT): cirrhosis – 2, bridging septa – 5, cholestasis – 32, bile duct reduplification – 8,

					PAS granules – 10, bile duct hypoplasia– 6, portal inflammation – 5. (Significantly more cirrhosis, bridging septa, severe fibrosis, bile duct reduplification compared to those without TP). Group with chronic liver disease (CLD, LT) requiring transplantation: cirrhosis – 3, bridging septa – 2, PAS granules– 5, portal inflammation – 2, CLD and no liver transplant (CLD, no LT): cirrhosis – 1, bridging septa – 2, PAS granules – 4, portal inflammation – 1. Follow up biopsy after a median 6.3 mths in TP group (n=18) and 26 mths non-TP group (n=38). NH,LT: cirrhosis – 11, bridging septa – 15, cholestasis – 6, bile duct reduplification – 10, PAS granules – 9, portal inflammation – 9, NH,no LT: cirrhosis – 3, bridging septa – 11, cholestasis – 2, bile duct reduplification – 4, PAS granules – 21, portal inflammation – 3. (Significantly more cirrhosis, bridging septa, severe fibrosis, bile duct reduplification compared to those without TP). CLD, LT: cirrhosis – 3, PAS granules – 3, portal inflammation – 2, CLD CLD, no LT=cirrhosis – 1, PAS granules – 2, portal inflammation– 0
Camarena et al, 2010 (34)	Retrospective study	Retrospective review of patients presenting in infancy or later with liver disease and found to have AATD	79	PiZZ – 73 (92.4%) PiSZ – 6 (7.60%)	N=30, all of whom had neonatal cholestasis: ductopenia – 8, ductal proliferation – 6, giant cells – 6, nonspecific cholestasis/fibrosis – 13.
Mellado et al, 1986 (47)	Prospective study	Review of 14 children with AATD, divided into 2 groups according to age at diagnosis	14	PiZZ – 12 (85.7%) PiMZ – 2 (14.3%)	Considerable histological variation between pts, no consistent pattern seen.
Adult					
Triger et al, 1976 (39)	Retrospective study and case series	Retrospective analysis of 13 patients aged 16-73 with AATD	13	PiZZ – 9 (69.2%) PiMZ – 2 (15.4%) Unknown – 2 (15.4%)	Cirrhosis – 8 (macronodular – 7, micronodular – 1), bile duct proliferation present in cirrhotics. Fibrosis with enlarging portal tracts – 5 Piecemeal necrosis – 5 Hepatoma – 1 All PiZZ: PAS positive globules and diastase resistant globules.

Appendix. Table 6. Bias assessment for all included studies for disease progression in AATD

Author and year	Study design	Description	Sample Size	Control/Comparator	Bias
Rujner et al, 1991 (49)	Case control study	Case control, comparing degrees of fibrosis with levels of procollagen III	31	No control	High
Moroz et al, 1976 (44)	Prospective study	Prospective review of cases diagnosed with AATD from screening of those with liver disease between 1969 and 1979, plus 7 healthy siblings that were tested	25	No control	High
Hadchouel et al, 1976 (45)	Prospective study	Follow up of 15 children diagnosed with neonatal cholestasis and AATD	15	No control	High
Sveger et al, 1976 (21)	Prospective study	Results of 200000 children screened for AATD between 1972 and 1974. 183 found to have AATD	176	No control	Moderate
Sveger et al, 1978 (22)	Prospective study	176 children with AATD (any genotype) identified from screening 200000 infants between 1972 and 1974 and prospectively followed up	176	PiMZ, PiSZ and PiMS pts	Moderate
Odievre et al, 1981 (48)	Prospective study	Follow up of patients with prolonged cholestasis before age of 3 months	102	No control	High
Sveger et al, 1981 (23)	Prospective study	Results of 200000 children screened for AATD between 1972 and 1974. 183 were found to have AATD at examination aged 4 years	183	80 random controls (not screened)	Moderate
Nemeth et al, 1982 (43)	Prospective study	Thirteen children aged 4-6 examined either with PiSZ or PiZZ who had not had neonatal cholestasis, 10 through screening, one presented later. These 10 children were checked regularly from birth	13	No control	High
Nemeth 1982 (27)	Prospective study	Ten children with PIZZ and neonatal cholestasis were followed up to ages 4-20 years	10	No control	High
Nebbia et al, 1983 (46)	Prospective study	Prospective follow up of 45 children found to have AATD, who had been referred with neonatal cholestasis – 12/25 in first week of life and before 8th week of life in the other participants	45	No control	High
Sveger et al, 1984 (24)	Prospective study	Results of 200000 children screened for AATD between 1972 and 1974. 183 found to have AATD at 8 year follow up	176	No control	Moderate
Mellado et al, 1986 (47)	Prospective study	Review of 14 children with AATD and their biopsies, divided into 2 groups according to when they were diagnosed	14	No control	High
Sveger et al, 1988 (25)	Prospective study	Results of 200000 children screened for AATD between 1972 and 1974 – follow up aged 12	185	PiMZ and PiMS pts	Moderate
Pittschieler et al, 1992 (29)	Prospective study	Fourteen PiSZ children detected by screening of all children at one centre between 1985-1989 with follow up	14	No control	High
Sveger et al 1995 (26)	Prospective study	Results of 200000 children screened for AATD between 1972 and 1974. There were 183 patients found to have AATD with 16 and 18 year follow up	185	No control	Moderate
Ghishan et al, 1988 (9)	Retrospective study	Retrospective follow up of 18 pts with PIZZ AATD	18	No control	High
Ibarguan et al, 1990 (28)	Retrospective study	Retrospective observational study of 98 children with AATD referred to paediatric department between 1967 and 1988	98	No control	High
Filipponi et al, 1994 (11)	Retrospective study	Retrospective review of children referred for transplant with AATD	16	No control	High
Francavilla et al, 2000 (30)	Retrospective study	Retrospective observational study of 97 children with AATD referred to paediatric transplant unit between 1989 and 1998	97	No control	High
Prachalias et al, 2000 (31)	Retrospective study	A study of 21 patients all receiving liver transplant due to AATD	21	No control	High
Hadzic et al, 2005 (32)	Retrospective study	Retrospective review of children with PiSZ and PiSS AATD referred to a tertiary service between 1988 and 2002	17	No control	High
Hinds et al, 2006 (33)	Retrospective study	Retrospective review of patients and their siblings with PiZZ AATD presenting between 1978 and 2002	235 Liver involvement 74,PiZZ 58	No control	High
Bakula et al, 2007 (37)	Retrospective study	Fifty nine children admitted for cholestasis/hepatitis homozygous for AATD	59	No control	High
Camarena et al, 2010 (34)	Retrospective study	Retrospective review of patients presenting in infancy or later with liver disease found to have AATD	79	No control	High
Pfister et al, 2011 (13)	Retrospective study	Retrospective follow up of all PIZZ carriers presenting to unit	53	No control	High
Kekez et al, 2015 (35)	Retrospective study	Retrospective analysis of database of PIZZ children diagnosed between 1979 and 2012	292	No control	High
Lang et al, 2005 (36)	Retrospective study	Retrospective analysis of 48 patients with AATD, prevalence of liver disease at time of diagnosis	48	No control	High
Pferdmenges et al, 2013 (12)	Retrospective study	Retrospective review of patient's files with AATD and telephone follow up, divided into good and poor outcomes and compared	53	No control	High
Karitzky et al, 1978 (62)	Retrospective study	Review of 12 patients with PiZZ, five of whom had liver disease	12	No control	High
Bernspang et al, 2009 (38)	Prospective study	Follow up of cohort of patients with AATD at 30 years, with blood tests	129	No control	Moderate
Tanash et al, 2015 (15)	Prospective study	Results of 200000 children screened for AATD between 1972 and 1974, looking at quality of life, smoking habit and lung and liver function of patients at 34 years old	122	No control	Moderate
ADULT Triger et al, 1976 (39)	Retrospective study and case series	Retrospective analysis of 13 patients aged 16-73 from 12 families with AATD. Follow up time between 1 month and 26 years	13	No control	High
Rakela et al, 1987 (40)	Retrospective study	Review of electronic records of 19 adult patients with AATD and liver disease	19	No control	High
Propstj et al, 1995 (41)	Retrospective study	Review of 6890 patients referred to gastroenterology tertiary centre between 1978 and 1993	160 Group 1 – 54 Group 2 - 106	AATD but no CLD	High
Volpert et al, 2000 (14)	Retrospective study	All patients known to have AATD taken from a database of patients with abnormal liver biochemistry results	44	No control	High
Bowlus et al, 2005 (42)	Retrospective study	Retrospective study of patients who self-reported having AATD	139	No control	High

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