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Systematic review: the natural history of alpha-1 antitrypsin deficiency, and associated liver disease

S. A. Townsend[1,2,3] | R. G. Edgar[2,4] | P. R. Ellis[5] | D. Kantas[2] | P. N. Newsome[1,2,3] | A. M. Turner[4,5]

[1]National Institute for Health Research Liver Biomedical Research Unit, University Hospitals Birmingham, NHS Foundation Trust, University of Birmingham, Birmingham, UK

[2]Centre for Liver Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

[3]Liver Unit, BirminghamInstitute of Inflammation and Ageing, University Hospitals Birmingham NHS Foundation Trust, University of Birmingham, Birmingham, UK

[4]Institute of Applied Health Research, University of Birmingham, Birmingham, UK

[5]Heart of England NHS Foundation Trust, Birmingham, UK

Correspondence
Dr. A M Turner, Institute of Applied Health Research, University of Birmingham, Birmingham, UK.
Email: a.m.turner@bham.ac.uk

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Summary

Background: Alpha-1 antitrypsin deficiency (AATD) is estimated to affect three 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: To report the prevalence and natural history of liver disease among individuals with AATD, and assess the outcomes of liver transplantation through systematic review.

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

Results: Thirty-five studies were identified related to disease progression and 12 for the treatment of AATD. Seven per cent 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 5-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.

The Handling Editor for this article was Professor Peter Hayes, and this uncommissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Alpha-1-antitrypsin deficiency (AATD) is estimated to affect three million people worldwide,[1] with patients typically developing lower zone emphysema at a relatively young age. Point mutations lead to altered folding during alpha-1 antitrypsin biogenesis, and misfolded proteins form polymers that are retained within the endoplasmic reticulum of hepatocytes, rather than being systemically secreted.[2] In the lung, lack of alpha-1 antitrypsin permits uninhibited proteolytic damage to the connective tissue matrix, leading to emphysema in approximately 75% of PiZZ patients.[3] Liver disease occurs due to aggregation of alpha-1 antitrypsin 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.[4] 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.[5] There is considerable variability in phenotypic expression in both liver and lung disease,[6] which is believed to reflect genetic[3] and environmental modifiers.[7] Cigarette smoking has been demonstrated to be the greatest predictor of lung function impairment in AATD cohorts[8] and smoking cessation is the most effective treatment strategy.[4]

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 (eg alanine aminotransferase, 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.[11]

Serum tests have also been investigated as possible predictors of significant liver disease with mixed results.[12-15] Measurement of gamma-glutamyl transferase (GGT) may be of benefit,[16] but is possibly confounded by its probable relation to oxidative lung injury and airflow obstruction.[17] Tests intended to detect liver fibrosis are currently likely to be the most useful, such as the serum enhanced liver fibrosis (ELF) test [18] and/or transient elastography (which has a sensitivity of 71% and specificity of 91% using a cut off of 8 KPa to detect advanced fibrosis),[19] but more data in this cohort are 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 (eg PiMZ) confers an increased risk of fibrosis or cirrhosis compared to the general population[16,17] but it seems likely that cofactors such as alcohol consumption and non-alcoholic steatohepatitis (NASH) play a greater role in heterozygous forms of AATD.[20,21]

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

2 | METHODS

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

2.1 | Searches

The search strategy is shared in the Data S1; it was initially broad and included the terms: alpha 1-antitrypsin deficiency, disease monitoring, disease progression, humans, liver, mortality and 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.

2.2 | Study selection criteria

Studies eligible for inclusion contained children or adults with AATD, as defined by alpha-1 antitrypsin level and genotype (eg PiZZ, PiSZ). Some studies included small numbers of individuals with nonpolymerogenic 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 (eg "jaundice in neonates") were eligible if they assessed progression or treatment in $\geq$ 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 hepatocellular carcinoma (HCC).

2.3 | 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.

2.4 | 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.

3 | 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 summarised in Tables 1 and 2 respectively, with a more detailed description of relevant studies shown in Tables S5 and S6.

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.

TABLE 1 Basic participant characteristics, paediatric and adult studies

Participant characteristics	Number (%)
Paediatric studies	
Sex	Male: 223 (36.9%)
Age	0-18 y
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 y
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%

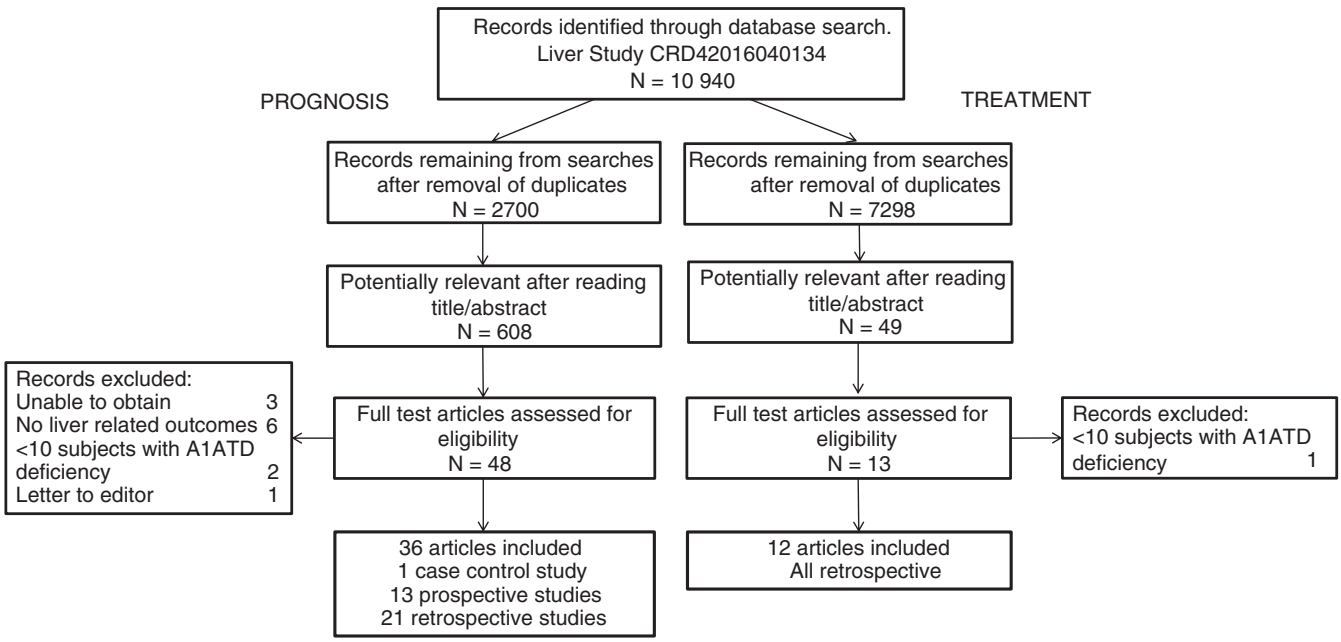

FIGURE 1 PRISMA flow diagram for all included studies, which were divided into those related to prognosis, and those related to treatment of AATD

TABLE 2 Outcomes for children and adults with AATD

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 LFTs/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	6 (1.3%)

LFT, liver function test; PT, prothrombin time; HCC, hepatocellular carcinoma.

Seven thousand two hundred and ninety-eight records were identified for the treatment of AATD, thirteen articles were retrieved and 12 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 (ie PiZZ, PiSZ).

3.1 | Risk of bias

There was a high risk of bias for the majority of the studies (Figures 2, 3 and Table S6 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.

3.2 | Prognosis and outcomes in AATD-related liver disease

3.2.1 | Children

Twenty-eight papers reporting the prognosis and outcomes of children diagnosed with AATD under the age of 16 were reviewed (Table S5). 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.[22–27]

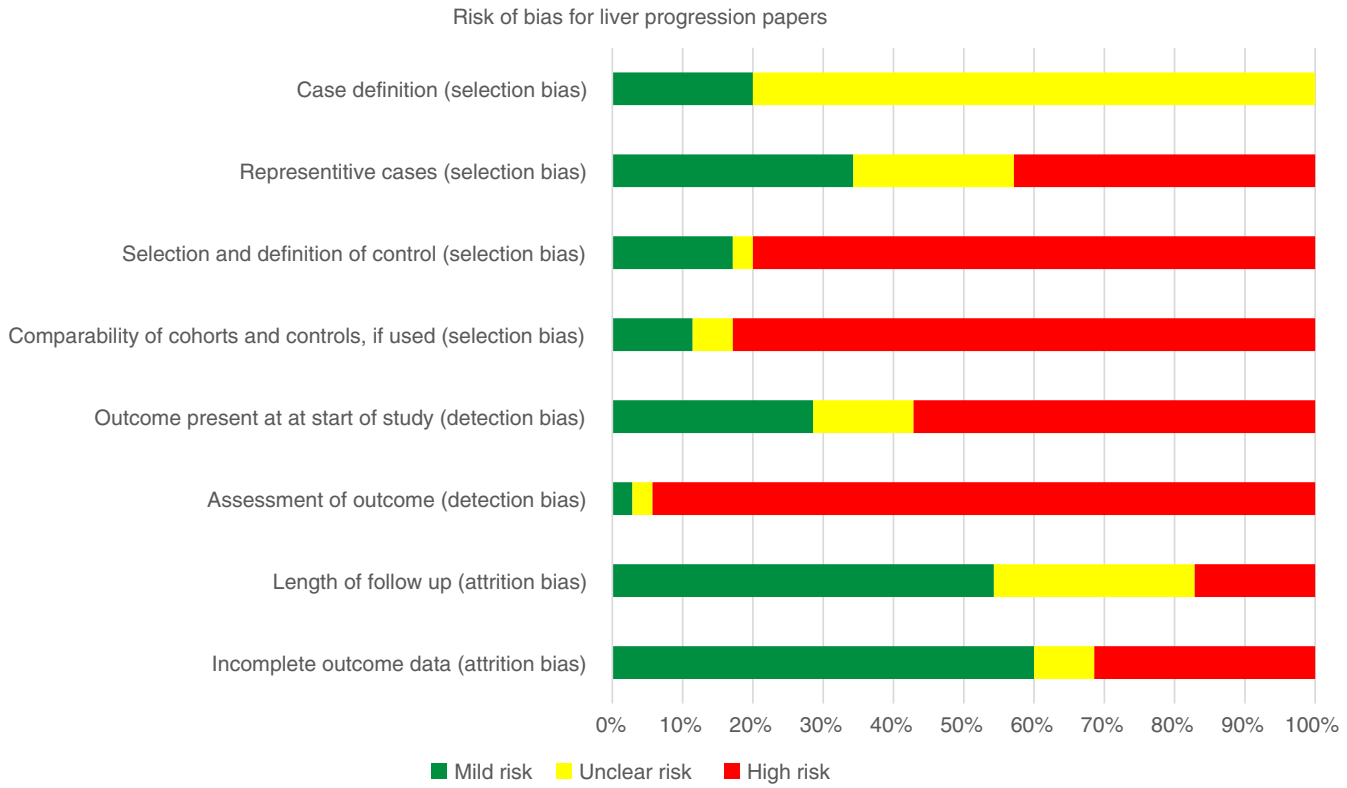

FIGURE 2 Risk of bias for studies reporting the progression of AATD using the Newscastle-Ottawa Scale. A summary of the relative risk of bias for each study is shown. This represents two authors' judgements regarding risk of bias for each item presented as the mean percentage across all studies. Individual bias assessments are available in the supplement

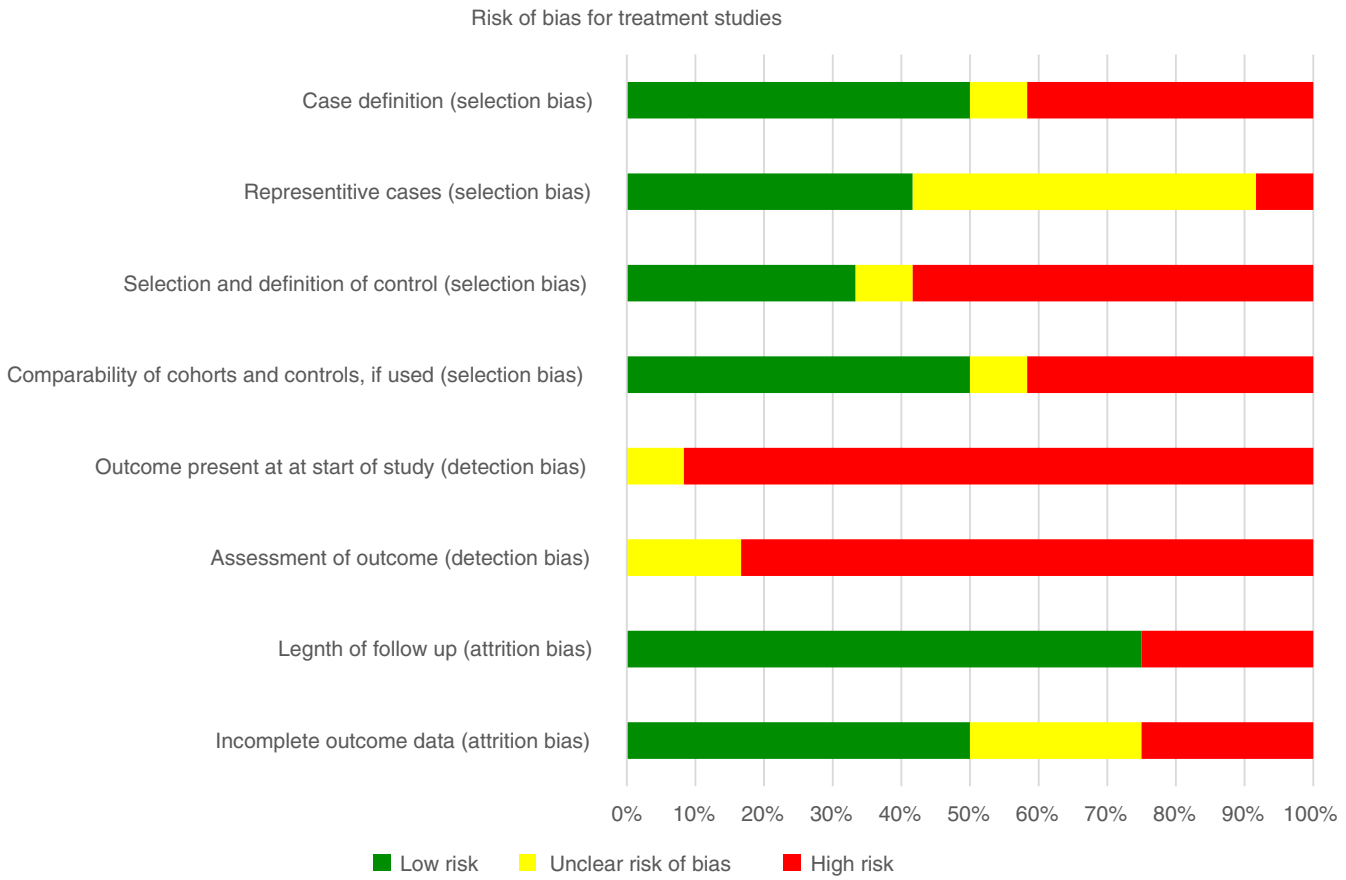

FIGURE 3 Risk of bias for treatment studies using the Newcastle-Ottawa Scale. A summary of the relative risk of bias for each study is shown. This represents two authors' judgements regarding risk of bias for each item presented as the mean percentage across all studies. Individual bias assessments are available in the supplement

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,[28] to 25.5% in a cohort of 98 participants with PiZZ/PiSZ referred to a tertiary centre with liver disease.[29] Outcomes following liver transplantation are discussed in the treatment results section.

3.2.2 | Adults

Seven papers primarily reported the outcomes of adult populations [15,16,30-34] (Table S5). 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 summarised 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,[15,16,30,31,33] 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 liver function tests (LFTs) after a minimum follow-up of 4 years[15]; another study of 160 adults with mixed AATD phenotypes referred to a tertiary gastroenterology centre with abnormal LFTs reported a nonliver-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.[33] 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.[33]

3.2.3 | Factors associated with development of liver disease

Although a meta-analysis could not be performed, 12 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.[35] In contrast, neonatal cholestasis was not found to be a risk factor for progression of liver disease in the studies by Nemeth et al.[28,36]

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 ($P < 0.001$), 1 year ($P < 0.0003$) and 5 years ($P < 0.01$).[37] Pferdmenges also found that GGT at presentation was predictive of death or liver transplantation in infants.[13] 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.[12]

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,[35] or at presentation[13,38] were a risk factor for future progression ($P < 0.001$ in the study by Pferdmenges et al),[13] 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.[37] A retrospective study of 16 children referred for liver transplantation[12] 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 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.[39]

Prolonged international normalised 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, nonsignificant trend being seen in the study by Volpert.[13-15] 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,[15] 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,[32] 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.[34] In the same study, body mass index (BMI) was also a risk factor ($P = 0.01$) for end-stage liver disease requiring liver transplantation.[34] Concurrent viral infection[33,34] and increased alcohol intake[31,34] have not consistently been shown to be risk factors or cofactors for development of liver disease in AATD.

Liver biopsy

Twelve 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 S5. 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.[37] 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.[40] 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.[41]

Paucity of bile ducts has also been suggested as a factor for poor prognosis.[12,39] 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),[12,41] however, the difference between the groups was not significant, and other studies have not replicated these findings.[41-43] 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.[44]

3.3 | 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 (Table S6), six studies reported paediatric populations[12,37,45-48] and six included both paediatric and adult patients.[34, 49–53]

3.3.1 | 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 to 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 in 12 (6.1%). Outcomes following liver transplantation were reported in eight studies and are shown in Table S6. Five-year survival ranged from 74% from transplant data in the 1980s[48] to 92% in two studies published since 2000.[37,49] 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.

3.3.2 | 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%). A total of 74.0% participants were male, and median ages ranged from 34 to 54 years. A total of 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 S6, 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 ratio, 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.[51]

4 | 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 non-alcoholic steatohepatitis (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 6 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, NASH is increasingly recognised 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 nonpolymerogenic 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 were reported from transplant centres), accounts for the discrepancy between the proportion of those with cirrhosis and those requiring transplantation.

Hepatocellular carcimona 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.[54] 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.[55] Histological studies have associated cholangiocarcinomas and combined hepatocholangiocarcinomas with the PiZZ phenotype, but these were not reported in our follow-up studies.[56,57]

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.[58]

4.1 | 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 nonpolymerogenic 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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AUTHORSHIP

Guarantor of the article: Sarah Townsend.

Author contributions: Sarah Townsend, Alice Turner and Ross Edgar performed the research, Sarah Townsend and Paul Ellis collected and analysed the data, Sarah Townsend and Alice Turner designed the research study and wrote the paper, and Philip Newsome and Alice Turner provided critical appraisal of the manuscript. All authors approved the final version of the manuscript.

ORCID

S. A. Townsend http://orcid.org/0000-0002-6811-3939
P. R. Ellis http://orcid.org/0000-0003-3817-3882
P. N. Newsome http://orcid.org/0000-0001-6085-3652

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SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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