Digestive and Liver Disease 53 (2021) 606–611

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Long term results of liver transplantation for alpha-1 antitrypsin deficiency ☆

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ARTICLE INFO

Article history:
Received 21 April 2020
Accepted 13 October 2020
Available online 1 November 2020

Keywords:
Alpha1 antitrypsin
Liver transplantation
Outcome
Survival

ABSTRACT

Introduction: Liver transplantation (LT) is the therapeutic option for end-stage liver disease associated with alpha1 antitrypsin (A1AT) deficiency. The aim of the present retrospective study was to report on long-term outcomes following LT for A1AT deficiency.
Methods: The medical records of 90 pediatric and adult patients transplanted between 1982 and 2017 in France and Geneva (Switzerland) were reviewed.
Results: The study population consisted of 32 adults and 58 children; median age at transplant was 13.0 years (range: 0.2–65.1), and 65 were male (72.2%). Eighty-two patients (94.8% of children and 84.4% of adults) had the PI*ZZ genotype/phenotype and eight patients (8.9%) had the Pi*SZ genotype/phenotype. Eighty-four patients (93.3%) were transplanted for end-stage liver disease and six (all Pi*ZZ adults) for HCC. Median follow-up after LT was 13.6 years (0.1–31.7). The overall cumulative patient survival rates post-transplant were 97.8% at 1 year, and 95.5%, 95.5%, 92.0%, 89.1% at 5, 10, 15, 20 years respectively.

☆ This study did not receive funding.
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https://doi.org/10.1016/j.dld.2020.10.016

The overall cumulative graft survival rates were 92.2% at 1 year, and 89.9%, 89.9%, 84.4%, 81.5% at 5, 10, 15 and 20 years, respectively.
Conclusions: In a representative cohort of patients having presented with end-stage-liver disease or HCC secondary to A1AT, liver transplantation offered very good patient and graft survival rates.

1. Introduction

Alpha1 antitrypsin (A1AT) deficiency is an autosomal recessive disorder with codominant expression, involving lungs and/or liver. Its prevalence in Northern Europe nears 1/2500 and 1/6000 in France and Western Europe [1–4]. A1AT is a protein predominantly synthesized by the liver, and then released into the circulation. Its function is to protect lung tissue by inhibiting neutrophil elastase and several other destructive neutrophil proteinases. The classical form of severe A1AT deficiency is due to a homozygous point mutation (Glu342Lys, Z allele, PI*ZZ genotype) in the SERPINA gene that leads to misfolding of the mutant protein, intracellular polymerization, and consequent accumulation of protein aggregates in the endoplasmic reticulum (ER) of hepatocytes. This toxic gain of function induces chronic ER stress, development of fibrosis, and in some cases progression to cirrhosis and/or hepatocellular carcinoma. On the other hand, decreased secretion leads to a lack of circulating antiprotease activity in the lung, which can in turn cause emphysema [5].

The clinical presentation of PI*ZZ disease is extremely variable [3]. In children with the PI*ZZ genotype/phenotype, transient elevation of aminotransferases has been reported in as many as 73% of infants while it may only affects 15% of patients by 12 years of age [6,7]. Prolonged cholestastic jaundice was reported in 11% of children with the PI*ZZ, while clinical features of chronic liver disease developed in 6%. While clinical symptoms usually resolved by the second year of life, 15% of children with cholestatic jaundice developed cirrhosis, mostly with severe portal hypertension. In adults, akin to what is known in children, the risk of cirrhosis related to PI*ZZ A1AT deficiency has been recognized for many decades [8]. Nevertheless, the natural history is still incompletely understood. The prevalence of advanced liver disease in adults with A1AT deficiency varies widely from 2 to 63% in available reported cohorts and increases with age (age>50), gender (male) and metabolic syndrome [9–14]. A recent cross-sectional biopsy study in an adult PI*ZZ population (not previously known to have cirrhosis) showed a prevalence of clinically significant liver fibrosis (≥F2) in 35% and severe fibrosis (≥F3) in 6% of patients [15]. This variability suggests that other genetic and environmental modifiers influence the development of significant liver disease both in children and adults.

The S allele, another allele associated with A1AT deficiency, forms polymers of AAT at a much slower rate than the Z allele, and leads to higher circulating levels of A1AT. However, PI*SZ compound heterozygote patients have been reported to present with less severe liver disease both in childhood [16,17] and adulthood [18]. Case reports and family studies have also described an association between liver disease and rarer A1AT variants also causing protein misfolding such as S_{Iiyama}, M_{malton}, M_{Duarte}.

Like for other forms of end-stage-liver disease, LT is the ultimate treatment of severe liver complications of A1AT deficiency, both in children and adults. Based on the UNOS (United Network for Organ Sharing, US) database, it has been reported that this rare indication could represent 1% of all indications [19]. Nevertheless, there is little data on outcomes. Therefore, the aim of the present study was to evaluate the long-term outcome after LT for A1AT deficiency, in a large multicenter adult and pediatric cohort.

2. Patients and methods

2.1. Study design

Pediatric and adult patients having undergone LT for A1AT deficiency in France (all centers) and in Geneva (Switzerland) were identified from medical records spanning October 1982 and December 2017. Data collection was performed by comprehensive medical chart review. All PI*ZZ, PI*SZ patients were included. Dual-organ (lung-liver) transplant recipients were includedA1AT serum levels and phenotyping and/or genotyping data were collected. Other comorbid causes of liver disease such as alcohol-related liver disease, non-alcoholic fatty liver disease, autoimmune liver disease, chronic viral hepatitis, and other conditions (iron overload, Wilson disease) were recorded. According to French law (Loi Jardé), anonymous retrospective studies do not require Institutional Review Board (IRB) approval. In Switzerland, the study was approved by the local IRB (CER 11–010R).

2.2. Liver transplantation

All patients received grafts from cadaveric or living donors. Initial immunosuppressive regimen was based on a calcineurin-inhibitor: cyclosporine or tacrolimus. Some patients could also receive 500 mg IV methylprednisolone after reperfusion and/or basiliximab. As from 1985, patients initially received cyclosporine (Sandimmun® or Neoral®, Novartis Pharma). Since 1996, patients may also have received tacrolimus (Prograf®, Astellas). Starting on postoperative day 1, methylprednisolone was tapered to reach a maintenance dose of 0 to 5 mg/day at 6 months post-transplantation. Azathioprin,mycophenolate mofetil (MMF) (since 1996) or sirolimus/everolimus (since 2002) was either administered as part of an initial triple immunosuppressive regimen, or introduced during follow-up as a maintenance immunosuppressive agent. Outpatient follow-up visits were tailored to individual patient needs, usually monthly during the first year, and every 3 to 12 months thereafter, regardless of the time elapsed since transplantation. Extensive laboratory investigations were carried out at each visit: hematology, liver parameters, coagulation, electrolytes, total protein, renal parameters, fast blood glucose, lipid profile and blood CNI trough levels.

2.3. Statistics

Statistical analysis was performed with SPSS 23.0 (IBM, Armonk, NY, US). Survival rates were evaluated using the Kaplan-Meier method starting from the date of LT to that of death, the last clinical visit or the data cut-off point (May 1st, 2018). Graft survival was calculated from the date of LT to that of retransplantation, death, last visit or data cut-off point if no retransplantation. Survival curves were constructed with the Kaplan–Meier method and compared with the log-rank test. The Cox proportional hazards regression model was used in univariate analysis for continuous variables. Values in this paper are shown as median with ranges and mean. Continuous variables were compared using Mann-Whitney's test. P values lower than or equal to 0.05 were considered to be statistically significant.

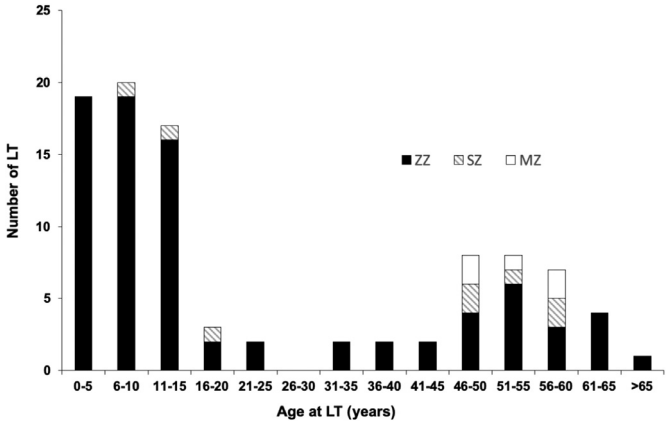

Fig. 1. Number of LT according to the age bracket and the genotype/phenotype.

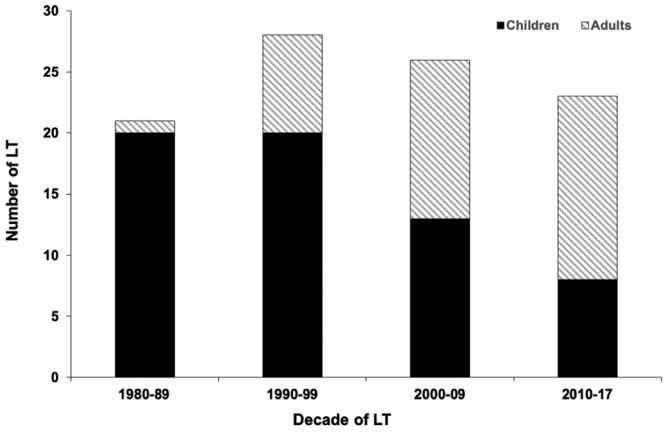

Fig. 2. Number of LT according to the period in children and adults.

3. Results

3.1. Study population

This report included 32 adults (age >18 years) and 58 children having undergone LT for A1AT deficiency between October 1982 and December 2017 in 18 different transplant centers throughout France and Geneva (Switzerland). Fig. 1 displays the number of LT according to age bracket and genotype/phenotype. In this study, we observed a main peak of LT during childhood and a second peak in adulthood after 45 years of age. Fig. 2 shows the number of LT according to era in children and adults. The overall number of LT for A1AT deficiency remained stable over decades. However, the distribution between pediatric and adults recipients has varied somewhat. During the eighties and nineties there were more children than adults who underwent LT, but this proportion reversed since 2000. Patient characteristics are summarized in Table 1. The median age of all patients was 13.0 years (range: 0.2–65.1), and 65/90 were male (72.2%). The vast majority of patients (91.1%) had the PI*ZZ genotype/phenotype. When considering only children, 55/58 (94.8%) had the PI*ZZ genotype/phenotype and three children were PI*SZ. In adults, 26/32 (81.2%) were PI*ZZ, 6/32 (18.8%) were PI*SZ. Before transplantation, the median serum A1AT level was lower for the PI*ZZ patients (0.31 g/L, range: 0.13–0.52), compared to the PI*SZ patients (0.56 g/L, range: 0.23–0.70) ($p<0.05$). One child had a coexisting liver disease (biliary atresia). In adults, coexisting liver disease was identified in 10/26 (38.5%) PI*ZZ patients: alcohol-related ($n=6$), non-alcoholic fatty liver disease (NAFLD) ($n=3$), HCV ($n=1$). Likewise, 4/6 (66.7%) PI*SZ patients also had evidence of a comorbid condition affecting the liver: alcohol-related ($n=3$), NAFLD ($n=1$). All patients ($n=6$) presenting with an HCC were adults (median age 51.8, range 37.0–61.9); HCC was diagnosed before LT in all cases. Eight patients, all adults with PI*ZZ genotype/phenotype, had emphysema at the time of LT, and three of them underwent a combined lung-liver transplantation.

3.2. Complications after liver transplantation

Surgical complications included hepatic artery stenosis ($n=5$, 5.6%), hepatic artery thrombosis ($n=2$, 2.2%) and biliary stenosis ($n=20$, 22.2%).

Thirty-two (32/90) patients (35.6%) experienced at least one episode of biopsy-proven acute rejection, 11 of whom developed histological features of chronic rejection. Sixty seven (67/90) (74%) patients had normal liver function tests at their last follow-up visit.

Table 1
Characteristics of the study population ($n=90$).

Characteristic	
Age at LT (years, median and range, *mean*)	13.0 (0.2–65.1), *22.3*
Male/female [n (%)]	65/25 (72.2%/27.8%)
Children/adult [n (%)]	58/32 (64.4%/35.6%)
A1AT serum level before LT (g/L, median and range, *mean*)	0.38 (0.13–0.70), *0.43*
A1AT phenotype: ZZ/SZ [n (%)]	82/8 (91.1%/8.9%)
Child-Pugh class at listing for LT: A/B/C [n (%)]	22/43/25 (24.4%/47.8%/27.8%)
Coexisting liver disease [n (%)]	15 (16.7%)
HCC (from explanted liver) [n (%)]	6 (6.7%)
Combined lung transplantation [n (%)]	3 (3.3%)
Liver graft [n (%)]	
-whole liver	61 (67.8%)
-partial liver (split, reduced or living donor)	29 [4,7,18] (32.2%)
Donor age (years, median and range, *mean*)	24.0 (0.7–86.0), *30.9*
Initial immunosuppressive regimen [n (%)]	
-cyclosporine/tacrolimus	41/49 (45.6%/54.4%)
-azathioprine/mycophenolate mofetil/none	40/26/24 (44.4%/28.9%/26.7%)
-steroids	90 (100.0%)
Maintenance immunosuppressive regimen (last follow-up) [n (%)]	
-cyclosporine/tacrolimus/none	18/69/3 (20.0%/76.7%/3.3%)
-azathioprine/mycophenolate mofetil/none	5/29/56 (5.6%/32.2%/62.2%)
-steroids	10 (11.1%)
-mTOR inhibitor	4 (4.4%)
-monotherapy/ double therapy/triple therapy	49/35/6 (54.4%/38.9%/6.7%)

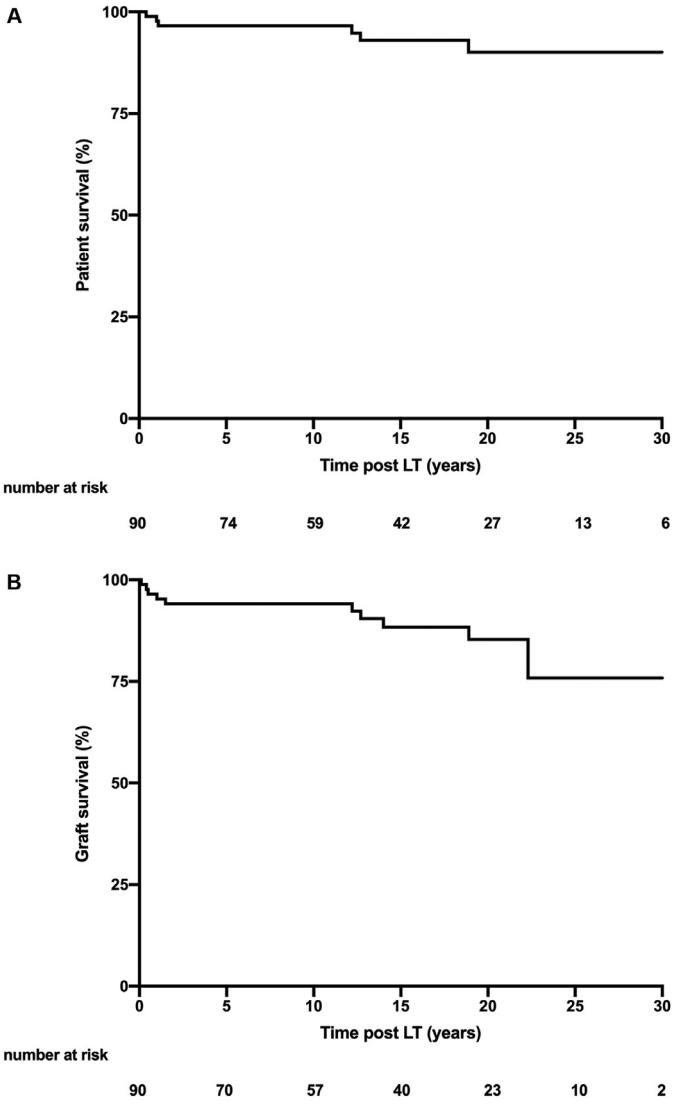

Fig. 3. Graft and patient actuarial survival according to Kaplan-Meier estimates. (A) Overall patient survival. (B) Overall graft survival.

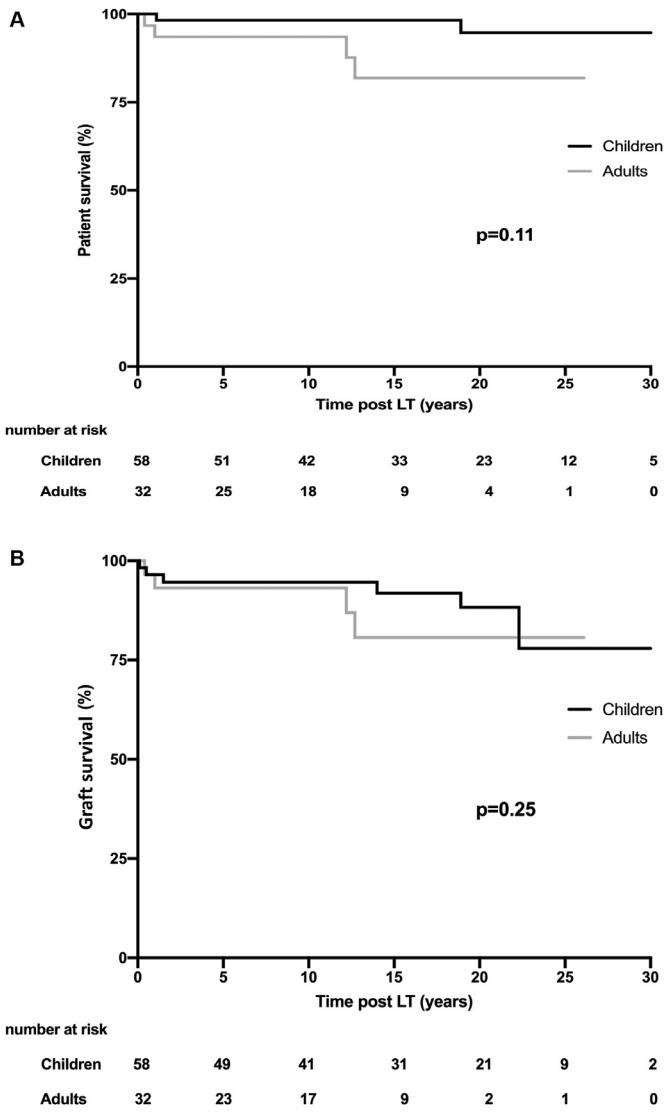

Fig. 4. Graft and patient actuarial survival according to Kaplan-Meier estimates. (A) Overall patient survival (adults *vs.* children). (B) Overall graft survival (adults *vs.* children).

Medical complications included arterial hypertension ($n=20$, 22.2%), hyperlipidemia ($n=8$, 8.9%) and diabetes ($n=7$, 7.8%). At the time of the last visit, median glomerular filtration rate (estimated using the Cockroft formula) was 90 µmol/L (10->120); 13 patients (10 adults) (14.4%) suffered from stage II renal insufficiency (*i.e.* 30 mL/min <clearance <60 mL/min), and 3 (1 adult) (3.3%) had ≥ stage III renal insufficiency (*i.e.* clearance <30 mL/min). One patient developed respiratory failure due to emphysema. One adult patient developed a solid organ (non-skin) *de novo* malignancy (head and neck carcinoma).

3.3. Survival

Median follow-up after LT was 13.6 years (0.1–31.7). Seven patients died after LT and eight were re-transplanted. The overall cumulative patient survival rates post-transplant were 97.8% at 1 year, and 95.5%, 95.5%, 92.0%, 89.1% at 5, 10, 15, 20 years post-transplant respectively (Fig. 3A). The cause of death was sepsis ($n=2$), cardiovascular disease ($n=1$), respiratory failure ($n=1$), *de novo* malignancy ($n=1$) or unknown ($n=2$). All 3 patients who received combined lung/liver transplantation survived. The overall cumulative liver graft survival rates post-transplant were 92.2% at 1 year, and 89.9%, 89.9%, 84.4%, 81.5% at 5, 10, 15 and 20 years, respectively (Fig. 3B). The indications for re-transplantation included primary non-function ($n=3$), chronic rejection ($n=4$) and hepatic artery thrombosis ($n=1$).

Gender, recipient age (as a continuous variable or considering adult *vs.* pediatric), genotype/phenotype (Pi*ZZ *vs* Pi*SZ), emphysema, HCC, type of graft (whole *vs* partial), type of donor (living *vs.* cadaveric) were not associated with patient and graft survival in the univariate analysis. Patient (but not graft) survival was slightly higher for pediatric LT recipients, but the difference did not reach statistical significance (Fig. 4).

4. Discussion

Using a large, multi-center cohort comprising 90 pediatric and adult patients, we report that long-term outcomes after LT or combined lung-liver transplantation for A1AT deficiency are favorable and similar to those for other indications

The burden of liver disease associated with A1AT deficiency has been evaluated from registry studies. A large survey focusing on clinical characteristics included 1953 questionnaires returned

in North America (1810 with severe A1AT deficiency) [20]. Lung or liver transplantation was reported by 9% of all respondents ($n = 175$), including 66 single lung transplants, 68 double lung transplants, and 47 LT; additional 6.6% ($n = 128$) reported that they were currently on a transplant list. In the National Heart, Lung, and Blood Institute registry, cirrhosis accounted for 10% of deaths and has been reported as the primary cause of death in 28% of PI*ZZ nonsmoker individuals [21,22]. It can therefore be summarized that A1AT deficiency is a severe illness for many of those affected as reflected in a high incidence of transplantation for liver and/or lung disease.

In A1AT deficiency, LT is able to cure both the liver disease and the underlying metabolic defect. This has been demonstrated from early experience in children, in whom normal levels of A1AT and phenotype change were detected soon after transplant [23]. The first large case series of LT for A1AT deficiency came from Pittsburgh, reporting 39 patients (29 children and 10 adults), transplanted between 1980 and 1986 [24]. Interestingly, 30 of 36 patients with available data (83%) were homozygous PI*ZZ, but 6 were heterozygotes, either PI*MZ or PI*SZ, and 5-year actuarial survival was 83% and 60% in pediatric and adult recipients respectively, suggesting that LT in this indication could be associated with a particularly favorable outcome.

The largest published cohort available was built using the UNOS database, including 567 children and adults, who underwent LT from 1995 to 2004 [19]. A1AT deficiency accounted for 1.06% of all adult LT and 3.51% for pediatric LT during that time interval. The 1-, 3-, and 5-year patient survival was better for pediatric patients compared to adults: 92%, 90%, and 90% respectively, *vs.* 89%, 85%, and 83%, even if graft survival was similar: 84%, 81%, and 78% for pediatric patients *vs.* 83%, 79%, and 77% for adults. Age was the only predictor of patient survival.

Regarding the indication for LT in this specific liver disease, the vast majority of patients, including in the present study, were transplanted for end-stage liver disease or severe portal hypertension rather than hepatocellular carcinoma (HCC). The reported risk and prevalence of HCC in A1AT deficiency are highly variable and dependent on the population studied. In the case-control autopsy study from Sweden, the reported prevalence of HCC was 28% [12], while no cases of HCC were reported in the large UNOS study [19]. It can be surmised that this information was lacking in the UNOS database (or not collected), since subsequent analyses of other LT cohorts reported HCC prevalence from 10.2% to 17.9% [18,25], and 6.3% in our cohort.

The present report confirms that the clinical spectrum of A1AT patients undergoing LT is wide, spanning young children to adults in their fifties. In summary, among pediatric LT recipients, most were PI*ZZ patients without other cause of liver disease, whereas, adult LT recipients (and probably more and more as their age increases) presented more often with heterozygous phenotypes and frequent liver co-morbidities. Our pediatric study population strongly resembles that of the UNOS study with a median age at LT of 3 years (range 0.5–17), and a male predominance 60.9% [19]. Similarly, 72% of adults were men, and the median age at transplant was 52 years (range 18–70). Nevertheless, limitations of the UNOS study must be pointed out: no A1AT phenotype was available, so the adult population may have included both homozygous and heterozygous individuals and no information on contributing factors such as hepatitis C virus infection, obesity and metabolic syndrome, or alcohol, was available. Before the present report, the best characterized adult A1AT LT population included 50 PI*ZZ patients and 23 PI*SZ patients, a group of 50 PI*MZ patients used for comparison, transplanted from 1987 to 2012 [18]. More than 40% of the PI*SZ patients had an additional cause for liver disease, 8% in the PI*ZZ group, and 90% of the PI*MZ group. This strongly supports the theory that heterozygosity usually requires an additional injury to cause liver cirrhosis and highlights the importance of testing individuals with liver disease for A1AT deficiency.

Given that A1AT deficiency is associated with both liver disease and chronic obstructive pulmonary disease, this warrants special discussion. First, lung disease rarely occurs before the age of 30 [26], therefore only affecting the evaluation of adult patients. Pulmonary function can range from normal to severe airway obstruction. Therefore, LT candidates must undergo an exhaustive pulmonary evaluation including a full set of pulmonary function tests as part of the pre-LT evaluation, taking into account that concurrent ascites, hepatic hydrothorax, and/or malnutrition can interfere with both the patient's ability to perform the test and test results.

In case of combined lung and liver compromise, combined lung/liver transplantation should be discussed. This is a rare occurrence, as illustrated in the present cohort (3/95, 3.2%). Only three other cases have been reported so far [27,28]. Similarly to our 3 patients, outcomes were satisfactory with all patients alive at 4, 7, and 13 years of follow-up. Not only have combined liver-lung transplantations been reported, but sequential transplantations have also been performed: in the large UNOS study, there were 3 liver-after-lung transplants (out of 567 patients, *i.e.* 0.5%) [19].

Another concern is the evolution of the chronic obstructive pulmonary disease after LT, because lung and liver diseases do progress independently [29]. This has not been extensively studied. The largest and most comprehensive series reported paired pre-LT and post-LT pulmonary function tests of 17 patients, all with PI*ZZ phenotype [18]. Despite the normalization of A1AT levels after LT, the forced expiratory volume in 1 second (FEV1) continued to decline for the majority of patients (PI*ZZ or PI*SZ) patients; individual data suggest a continued decline in 65% with an improvement in 35% with wide variations. More importantly, 53% of the PI*ZZ patients had an annual reduction in FEV1 greater than the expected 30 mL/y from aging. In addition, Jain and coll. reported data of 7 adult patients who had pulmonary function tests available before and after LT [30]. The FEV1 was nearly unchanged after LT (mean total interval of nearly 3 years), suggesting, for the authors, that LT could have prevented the progression of pulmonary disease. Further studies on pulmonary function after LT are needed, including children, because long-term pulmonary outcomes after pediatric LT are unknown. However, we do recommend these recipients not to smoke.

Finally, while augmentation therapy can address the loss of A1AT in the lung, no treatment exists for the associated liver disease other than LT for patients with advanced liver disease. Several strategies are currently under evaluation in early-phase clinical trials to address this lack of available treatment: reduction of the production of the mutant protein by gene silencing (siRNA), blockage of intracellular polymerization (small molecules or antibodies), clearance of intracellular polymers by enhancing autophagy (carbamazepine, sirolimus), increasing of secretion of less polymerogenic variants [5,31]. In the future, the need for LT could decrease if efficacy of these treatments is confirmed.

In conclusion, A1AT deficiency is a rare indication for LT but enables a very good long-term outcome for both children and adults. Pulmonary outcomes need further analysis.

Conflict of Interest

The authors have no conflict of interest to declare.

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