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Liver Transplantation for Acute Intermittent Porphyria

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Footnotes

1. **Abbreviations:**

AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, delta-aminolevulinic acid; BMI, body mass index; CKD, chronic kidney disease; CMV, cytomegalovirus; ELITA, European Liver and Intestine Transplant Association; ELTR, European Liver Transplant Registry; GFR, glomerular filtration rate; GnRH, gonadotropin-releasing hormone; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCP, hereditary coproporphyria; HMBS, hydroxymethylbilane synthase; LT, liver transplantation; MELD, model for end stage liver disease; PBG, porphobilinogen; RNA, ribonucleic acid; VP, variegate porphyria.

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3. **Conflicts of interest**

Nothing to declare

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Abstract

Recurrent attacks of acute intermittent porphyria (AIP) result in poor quality of life and significant risks of morbidity and mortality. Liver transplantation (LT) offers cure but published data on outcome after LT are limited. We aimed to assess the pre-transplant characteristics, complications and outcomes for patients transplanted for AIP. Data was collected retrospectively from the European Liver Transplant Registry (ELTR) and from questionnaires sent to identified transplant and porphyria centers.

We studied 38 patients transplanted in 12 countries 2002–2019. Median age at LT was 37 years (range 18-58) and 34 (89%) were female. Two patients were re-transplanted and nine died during follow-up. The 1-year and 5-year overall survival was 92% and 82%, which is comparable to other metabolic diseases transplanted during the same period. Advanced pretransplant neurological impairment was identified as a risk factor for mortality. The 5-year survival was 94% among 19 patients with moderate or no neuropathy at LT, and 83% among 10 patients with severe neuropathy (p=0.04). Pretransplant renal impairment had no significant effect on survival with a 5-year survival of 81% among 18 patients with a pretransplant GFR >60ml/min, and 71% among 14 patients with a pretransplant GFR <60ml/min (p=0.16). While few patients improved their renal function after LT, neurological impairments improved, and no worsening of neurological symptoms was recorded. No patient had AIP attacks after LT, except for a patient who received an auxiliary graft.

Liver transplantation is a curative treatment option for patients with recurrent attacks of AIP. Severe neuropathy and impaired renal function are common and increase the risk for poor outcome. If other treatment options fail, evaluation for liver transplantation should be performed early.

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Introduction

Acute intermittent porphyria (AIP) with recurrent attacks, defined as four or more attacks per year, is a rare condition with severe morbidity and high mortality(1, 2). Liver transplantation offers cure, but few centers are experienced and limited data is available on the outcome of patients and their porphyria related comorbidities.

AIP is a genetic disease caused by deficiency of the third enzyme in the heme biosynthetic pathway (3). Typical symptoms are acute attacks that can include abdominal pain, hypertension, gastrointestinal, neurological and psychiatric symptoms. Most mutation carriers have few attacks or are asymptomatic (3-5). A minority of patients, approximately 5%, (1) who develop recurrent attacks of AIP are frequently hospitalized and have a poor quality of life (2, 6, 7). Therapy includes symptomatic treatment and infusion of exogenous heme during attacks to improve clinical symptoms and reduce mortality (8). Preventive therapy with regular heme infusions is used for AIP with recurrent attacks, despite disadvantages such as iron accumulation and risk of venous thrombophlebitis (9, 10). GnRH-analogues are often tried in women with cyclical attacks (11). Givosiran, an RNA interference therapy, was recently approved for treatment of AIP (12). Givosiran may reduce the frequency of attacks in many patients, but long-term data is still limited. Patients with AIP are at risk for long term complications, such as hypertension, renal impairment (13) neuropathy (14) and primary liver cancer (15, 16). Data on comorbidity and outcomes in patients with recurrent attacks of AIP are scarce. Renal impairment has been reported in up to 64% (2, 9) in patients with recurrent attacks. High rates of depression (9), daily use of opioid pain treatment (17), and increased risk of long-term sick leave and disability pension (18) have also been reported. Liver transplantation is currently the only curative treatment option (19). Earlier published data is limited to a few case studies (19-22) and a case series on liver transplantation (23) and on combined liver-kidney transplantation (24).

Based on more extensive experience than previously available, we address in this paper several important issues regarding liver transplantation in AIP. What is the prognosis of AIP-associated

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renal and neurological complications after transplantation? Are there risk factors for poor outcome? What disease specific transplant complications needs to be considered? Is hepatic artery thrombosis (HAT) frequent, as previously reported (23)? Timing of the decision to transplant is challenging. Patients have been reported to improve after years with regular heme infusions as treatment for AIP with recurrent attacks (9, 17), but waiting too long for spontaneous improvement before considering LT increases the risk of complications such as renal impairment, iron accumulation, progressive neurological impairment and worse outcome after transplantation.

With the aim to improve the understanding of these outstanding issues, we performed a retrospective cohort study based on questionnaires and registry data to assess the pre-liver transplant characteristics, complications and outcomes for patients liver transplanted for AIP in Europe.

Patients and Methods

Case identification and study inclusion

Study inclusion criteria were diagnosis[1] of AIP, or the rarer forms of acute hepatic porphyria (AHP); variegate porphyria (VP) or hereditary coproporphyria (HCP), and a liver transplantation done in Europe. Patients were identified by searching the European Liver Transplant Registry (ELTR) database, by personal communications and by literature search. Patients identified in the ELTR by a first or second diagnosis "other porphyria"[2] were excluded unless a definitive AHP diagnosis could be confirmed by the identified transplant or porphyria center. Patients who were identified from literature searches or personal communications were excluded if they could not be confirmed in the ELTR or if no questionnaire was obtained.

Except for a single variegate porphyria patient (21), who was not identified in the ELTR, no patients with the usually more benign forms of acute hepatic porphyria, VP or HCP, were identified. This case was not included, and the study therefore focused only on AIP.

[1] AIP diagnosis was confirmed by each reporting center based on local diagnostic guidelines.
[2] The ELTR list of disease codes include F9: protoporphyria (mainly erythropoietic protoporphyria (EPP)) and F10: other porphyria.

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Questionnaires

A questionnaire (case form) to collect basic information was constructed and sent to identified centers that had managed the patients (Supplementary file 1). Data was collected on baseline demographics, pre-transplant morbidity, peri- and post-operative complications and outcomes, including survival, re-transplantation, neurological impairment and renal impairment. Porphyria-related data was collected regarding pre-transplant disease activity, disease duration, treatment, AIP mutation type and porphyrin precursor excretion pre- and post-transplantation. The questionnaire was designed to be concise and user friendly, mainly checkbox based with predetermined options, in order to enhance the response rate, the reliability of the data and reduce issues of missing data. Some items were open to free text comments, such as for pre-transplant comorbidity (other than renal, neurologic, or hepatocellular carcinoma (HCC)) and for histology of the explanted liver.

Complications, renal and neurological impairment

Peri- and post-transplantation complications were graded using the Clavien-Dindo classification (25). Complications were grouped into minor (grade I-II) and major (grade III-IV).

Renal function was assessed by GFR: the latest recorded before LT, one year after LT and most recently recorded. If results from renal function tests (e.g. iohexol plasma clearance) were not available, GFR was estimated using the Cockcroft-Gault equation. Renal impairment was defined as chronic kidney disease (CKD) stage 3 or higher (GFR< 60ml/min). GFR generally decrease after LT, especially during the first year, mainly related to perioperative acute kidney injury and calcineurin inhibitors (26). We defined stable GFR after LT as < 30% decline from pre-LT GFR.

Neurological impairment was assessed by the reporting centers from medical records at three time points: before, at, and after LT. Three parameters were recorded: 1) Motor function graded as normal function, impaired function or paresis; 2) Mobility graded as normal, walking with aid, wheelchair-dependent or bedridden; 3) Neuropathic pain graded as none, moderate or severe.

Overall survival, defined as the time from LT to death or last recorded observation, was compared to survival data from the ELTR for all patients transplanted for other metabolic diseases[3] as well as all patients transplanted within the ELTR collaboration 2002-2019. (27)

[3] ELTR Metabolic disease includes Wilson disease (17%), Hemochromatosis (8%), Alpha-1 - Antitrypsin deficiency (10%), Glycogen storage disease (2%), Homozygous Hypercholesterolemia (0.5%), Tyrosinemia (2%), Familial

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Statistical analysis

STATA/SE version 15:1 for Windows was used for all statistical analyses (Stata Corp Stata Statistical Software: College Station, TX, USA). Descriptive study results are presented as percentages, medians and ranges. Survival analysis was done by the Kaplan-Meier method and log-rank test for equality of survivor functions. Comparisons of categorical variables were performed using the chi-squared association test. For continuous variables two sample t-test for the means was used. All p-values <0.05 were considered statistically significant.

This study was approved by the institutional review board of the European Liver and Intestine Transplant Association (ELITA).

Results

Patient characteristics and transplant indications

We identified 42 AIP patients in 13 European countries, who received a liver transplant 2002–2019. Sufficient data for study inclusion was available for 38 patients transplanted at 21 centers in 12 countries. Some patients were previously included in publications (Supplementary file 2). ELTR data was available for 20 and questionnaire data for 36. Patient characteristics are presented in Table 1. The median age at liver transplantation was 37 years (18 – 58) and 34 patients (89%) were female. The most common transplant indication was frequent porphyria attacks (89%). Two female patients were transplanted for HCC, both without cirrhosis, aged 48 and 50 years at LT, respectively. None of these had recurrent attacks of AIP in the year prior to LT. There were no reports of HCC-recurrence at latest follow up. One patient had an urgent LT due to acute liver failure induced by an accidental heme overdose (28).

Pretransplant morbidity

The most common comorbidities were neuropathy (68%) and renal impairment (51%) defined as a GFR<60ml/min (CKD stage >2). Some had complications to heme treatment in the form of central venous thrombosis (20%) or secondary hemochromatosis (20%). Arterial hypertension, opioid dependency, recurrent infections, depression and anxiety were other reported comorbid conditions.

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amyloidotic polyneuropathy (17%), Primary hyperoxaluria (4%), Protoporphyria (0.3%), NASH (10%), Crigler-Najjar (4%), Cystic fibrosis (4%), Byler disease (3%) and other metabolic diseases (21%). Percentages from the 2018 Annual Report of the European Liver Transplant Registry (ELTR). (26)

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The AIP disease

The median age at onset of AIP symptoms was 27 (16-44) and the median duration of active disease, defined as the time from first documented AIP attack to LT, was 13 years (3-35). Most patients (87%) had recurrent attacks of AIP, defined as four or more attacks per year, and 74% had >10 attacks annually. Most (94%) were treated with heme and 29% had been treated with GnRH-analogues. Mutation data were available for 17 patients who had 13 different mutations. The two most common hydroxymethylbilane synthase (HMBS) mutations were W198X (593G>A) (17%, all from the Nordic countries[4]) and R173W (517C>T) (17%). Data on pretransplant urinary excretion of porphobilinogen (U-PBG) and delta-aminolevulinic acid (U-ALA) was reported for 18 patients. All had significantly elevated levels. Follow-up analyses one to three days after LT showed normalized urinary excretion in all reported (n=19) cases.

Transplantation

The median waiting list time was 30 weeks (range 1 day to 31 months). The median MELD score was 8 (range 5-32), with most patients having low MELD scores (n=27, median 7, range 5-15. The higher MELD scores (range 19-32) reported in six patients were related to renal impairment (n=4), warfarin treatment (n=1) and acute liver failure (n=1). Seven centers in five countries used different forms of MELD exception systems that were applied for their ten patients. Most (97%) received grafts from deceased donors and one from a live donor. Five patients (13%) received a combined liver-kidney transplantation. One patient had an auxiliary transplant; implantation of a partial donated liver without removing the native liver and suffered continued AIP attacks after transplantation. Exogenous heme was administrated immediately before surgery in 32% of the transplantations.

Patient survival

At the most recent follow-up, 29 patients (76%) were alive and nine (24%) had died. The 1-year and 5-year overall patient survival was 92% and 82%, similar to ELTR-survival data on patients transplanted for other metabolic diseases and all patients transplanted 2002-2019 (Fig 1). Severe neurological impairment was associated with an increased mortality. Patients with any motor paresis, wheelchair dependent, bedridden or suffering severe neuropathic pain at time of LT

[4] W 198 X is also known as the Nordic founder mutation. In this study, patients with this mutation were from Norway and Sweden.

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(n=10) had a 5-year survival of 83%, compared to 94% in patients (n=19) with moderate or no neuropathy (p=0.04) (Fig 2a). Pre transplant renal impairment tended to increase mortality after LT. Patients with a GFR <60 ml at pre LT assessment (n=14) who did not receive a combined liver kidney transplant had a 5-year survival of 71% compared to 81% for patients (n=18) with GFR >60 ml/min (p=0.16) (Fig 2b). All five patients who received combined liver kidney transplants were alive at last follow-up. Two patients were re-transplanted. The causes of death for the nine deceased patients are described in Table 2.

Transplant-related complications

The rate of complications in the perioperative phase was low (9%). No complications were reported in 39% of the transplanted patients. Minor complications (Clavien-Dindo grade I-II), such as acute rejection, cytomegalovirus (CMV) viremia, other infections, cholangitis and deep venous thrombosis were recorded in 26%. Major complications (Clavien-Dindo grade III-IV), such as bile duct leakage or obstruction, wound tissue rupture, human herpes virus-6 (HHV-6) infection with multi organ failure and late bleeding requiring surgical intervention were recorded in 35%. Hepatic artery thrombosis (HAT) occurred in 4 patients (11%), all females. One patient had early HAT within one month after LT, was re-transplanted and recovered. One patient (exact time for HAT missing) was re-transplanted after 4.5 months but died 18 months later from cerebral hemorrhage. A third patient developed HAT after about one month, was listed for re-LT but deteriorated and died. A fourth patient developed HAT after three years and recovered without re-transplantation.

Neurological impairment

Almost all patients (93%) had paresis, impaired motor function, impaired mobility or neuropathic pain before LT. Most improved after LT and no patient experienced worsening of symptoms after LT. One third (33%) of the patients with moderate or severe neuropathic pain had no motor or mobility impairment before LT. The frequencies of neurological impairment symptoms were lower in all three categories at follow up after LT compared to the pre-LT assessments (Fig 3 a-c). Severe mobility impairment and paresis at LT and lower age at onset of symptomatic porphyria were associated with residual neuropathy after LT (Table 3).

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Renal impairment

At pretransplant assessment, 4 patients (11%) had GFR >90ml/min, 14 (38%) had a GFR 60-90ml/min, 12 (32%) had a GFR 30-60ml/min and 7 (19%) had a GFR <30ml/min. Four of the patients with GFR <30 ml were on hemodialysis or peritoneal dialysis and received combined liver kidney transplantations. All patients had calcineurin inhibitor based initial immune suppression, tacrolimus (n=36, 97%) and ciclosporin (n=1, 3%). The median GFR before LT in patients who did not receive a combined liver kidney transplant was 62 ml/min, decreased to 52 ml/min at the one-year follow up and was 46 ml/min at the most recent follow up.
Post-LT GFR varied in patients with a pre-LT GFR <60ml/min, who received only LT and had complete GFR information (n=12). While seven had stable GFR (defined as less than 30% decline from pre-LT GFR) or improved GFR, five had more than a 30% decline in GFR after LT (Fig 4). All three patients with CKD stage 4 (GFR <30 ml/min) at LT had a further worsening in renal function after LT with more than 30 % decline in GFR at latest follow-up. The five patients who received combined liver-kidney were all alive with a median GFR of 63 ml/min (range 36-73) at latest follow-up.

Explanted livers

Data was collected on 25 explanted livers (Table 4). The most common finding was increased iron deposits (67%), presumably from pre-LT heme therapy. Fibrosis stage 2 was found in 20%, only one (4%) had stage 3 fibrosis and no liver was cirrhotic (stage 4). The explanted livers from the two patients transplanted for HCC showed no advanced fibrosis or cirrhosis. HCC was not found in any other explanted livers.

Discussion

In this, the largest case series to date, we report on the characteristics and outcomes of 38 liver transplantations done for AIP in 12 European countries 2002-2019. We confirm that LT is a curative option for patients with severe AIP with recurrent attacks. Survival rates are comparable to similar transplant indications. Neurological impairment improves after transplantation while

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renal impairment in most patients does not. At least three of the women in this study gave birth to healthy children after LT.

AIP is a rare disease and only a small fraction of symptomatic patients develop recurrent attacks (four or more attacks per year). These patients, mostly women in their 20s and 30s, suffer repeated painful attacks, poor quality of life, frequent hospitalizations, temporary or progressive neurological impairment, vascular, renal and psychiatric comorbidity and a high mortality risk. The economic burden on the healthcare systems is substantial (2). Medical treatment options have been limited. Since the first report on LT for AIP in 2004 (19), this option has become an established rescue therapy even if published data have been limited. The aim of this study was to assemble and offer comprehensive data to aid clinicians when liver transplantation is considered for severe AIP with recurrent attacks.

One- and five-year survival of 92% and 82% are comparable to patients transplanted for other metabolic diseases and to all patients transplanted during the same time period (Fig 1). Compared to other liver transplant indications, the median age of 37 in this cohort is however low and higher survival rates would be desirable. Identification of risk factors for worse outcome after LT is of value to support optimal selection and timing. We found that most patients had a long duration of AIP before LT was done, 13 years in average, and that the majority had developed AIP-related comorbidities. This suggests that LT generally is considered late in the disease course and highlights the importance of assessment for LT before comorbid conditions become too advanced. Severe neuropathy at LT, was associated with an increased risk of mortality.

Among the patients who died, we identified three factors that deserve attention:

1) At least two patients were in poor clinical condition at the time of transplantation and one patient was ventilator dependent due to AIP neuropathy. Generally, LT should, when possible, be considered earlier in the disease course.

2) An earlier case series (23) reported HAT in 40 % of AIP LT recipients. We identified four patients (11%) with HAT in this study, which led to re-transplantation in two and death in one. The HAT rate of 11% is low compared to the previously reported 40 %, but higher than an expected rate of 3-9% in general LT (29). Two of the previously reported cases of HAT (23) are however not included in this study due to non-response from the transplant center, suggesting a real HAT rate of more than 11%. The occurrence of both early and very late HAT suggests that

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the cause or causes may not be AIP-related. Some of the previously described risk factors for early HAT are low recipient age, low recipient weight, metabolic disease and female gender (30, 31). These factors apply to the patients in this AIP cohort. Based on the limited data presented here and previously, an individual assessment of thromboembolic risk and close monitoring after LT is recommended for AIP patients who are transplanted. Anticoagulant prophylaxis should be considered based on individual risk factors.

3) Renal dysfunction was linked to several deaths, both early and late after LT. Data on the outcome of renal impairment after LT for AIP has been scarce. Half the patients in this cohort (51%) had CKD stage 3 or worse at LT. The trends in GFR after LT varied considerably between patients. The median GFR was 62ml/min at pre-LT assessment, 52 ml/min one-year post-LT and 46 ml/min at last follow-up. A progressive decline in GFR, particularly in the first year after LT, is not uncommon and post LT renal impairment is an independent risk factor for morbidity and mortality (26, 32). Almost half of the patients with a pre-LT GFR < 60ml/min but no patients with GFR<30 ml/min who received only LT had stable or improved GFR after transplantation. A minority of patients with impaired renal function at LT improved their GFR after LT. AIP-related renal impairment appears to have multifactorial causes (33, 34) and may in some be reversible with LT (Fig 4). All five patients who received a combined liver-kidney transplant in this study were alive with preserved renal function. Hence, progressive renal impairment in a patient with severe AIP with recurrent attacks is a finding that should hasten decisions on evaluation for LT. In patients approaching severely impaired renal function (GFR <30 ml/min) a combined liver-kidney transplantation should be thoroughly considered since expected further decline in renal function following LT imposes a significant risk of the patient deteriorating to end stage renal disease.

Neurological impairment is frequent in AIP with recurrent attacks (14) and was a common contributing factor for transplant referral. Most patients improved and no patients progressed in neurological impairment after LT. The rates of patients with paresis or impaired motor function, impaired mobility or neuropathic pain was lower after transplantation (Fig 3a-3c). Severe motor neuropathy at LT, often in combination with lower age at onset of symptomatic AIP, was associated with an increased risk of residual neuropathy after LT

AIP patients have an increased risk of developing primary liver cancer, most commonly hepatocellular carcinoma (HCC) but also, less frequently, cholangiocarcinoma or mixed forms (15, 16). Most non-AIP HCC occur in male patients with cirrhotic liver disease. In contrast, most

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AIP-related primary liver cancers are diagnosed in females without significant fibrosis (35). In the two female patients with HCC in this study, aged 48 and 50 at LT, liver histology showed no advanced fibrosis or cirrhosis. Histology reports on explanted livers were available from in total 25 patients in this study. In line with a previous observations (22), few significant histopathological findings were reported except for mild to moderate fibrosis, and iron accumulation that was presumably caused by pre-LT heme treatment.

A novel RNA interference therapy, givosiran, was recently approved by the EMA and FDA for treatment of AIP (12). Givosiran may reduce the frequency of attacks in many patients, but liver transplantation will remain an option when this and other treatment options are ineffective.

Based on these and previous results we recommend that evaluation for liver transplantation should be considered at an early stage in all AIP patients suffering from recurrent attacks with insufficient response to available therapies. Evaluation should include careful assessment of several interacting factors such as frequency and severity of attacks; response, tolerance and adherence to treatments; severity and disease course of comorbidities, particularly renal and neurological; age and, not least, the patient's quality of life. A liver transplant unit, preferably with experience in AIP, should be involved in the evaluation. Combined liver-kidney transplant should be considered if renal impairment is severe (CKD stage > 3) or progressive.

The strengths of this study include the large number of cases (in an AIP context), up to 16 years of clinical follow-up and registry data that may provide support in the often difficult decision about if and when to consider liver transplantation in AIP. This study has several limitations. Retrospective registry and questionnaire data based on medical records should be interpreted with caution considering the risk of information bias. The questionnaires that were send to the identified transplant and porphyria centers were intentionally designed to encourage compliance and response rate and reduce issues of missing data. Accordingly, the amount and level of detail in the collected data was less than what would be desirable. Data was not available for four (10%) transplanted patients. Two of these had HAT, as commented above, and data from these might have added valuable information on this rare complication. Information about neurological impairment was collected from patients' medical records. The simple scales for grading impairment offer little information about time-lag between LT and improvement or about symptom details.

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In conclusion, this study confirms that liver transplantation offers cure from AIP symptoms with good survival rates. Porphyria-related neuropathy improves but severe neuropathy and advanced pretransplant renal impairment increase the risk of poor outcome. AIP patients with recurrent attacks, signs of renal impairment and/or severe neuropathy, who do not respond to other therapeutic options, should therefore be considered for LT and a transplant center should be involved in the discussion at an early stage, before AIP-related comorbidity is complex or severe.

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Table 1. Liver transplantation for AIP 2002-2019, patient characteristics.

Female/male: n/n (%/%)	34/4 (89/11)
Age at LT (median), years (range)	37 (18 – 58)
Stated main indications for LT: n (%)	
Frequent AIP attacks	33(89)
Frequent AIP attacks and renal impairment and/or neuropathy	13 (35)
HCC	2 (5)
Acute liver failure (accidental heme overdose)	1 (3)
Porphyria characteristics:	
Median age at onset of symptoms, years (range)	27 (16-44)
Median time from first porphyria symptom to LT, years (range)	13 (3 - 35)
Previous treatment: n (%)	
Exogenous heme	32 (94)
GnRH-analogue	10 (29)
Annual number of AIP attacks during two pre-LT years: n (%)	
>3 (AIP with recurrent attacks)	27 (87)
- >10	23 (74)
- Comorbidities at time of LT: n (%)	
Renal impairment, CKD stage > 2 (GFR<60ml/min)	19 (51)
Any neuropathy*	23 (68)
Central vein thrombosis	7 (20)
Type of transplantation: n (%)	
Deceased donor	36 (97)
Living donor	1 (3)
Combined Liver-Kidney transplant	5 (14)
Auxiliary transplant	1 (3)
Time (weeks) on waiting list: median (range)	30 (0-135)

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LT, liver transplantation; BMI, body mass index; AIP, acute intermittent porphyria; HCC, hepatocellular carcinoma; GnRH, gonadotropin-releasing hormone; CKD, chronic kidney disease; GFR, glomerular filtration rate. *Includes any paresis, impaired motor function, impaired mobility or neuropathic pain at time of liver transplantation.

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Table 2. Causes of death.

Case nr	Time from LT	Background	Cause of death
1	3 months	Ventilator dependent for months pre-LT. GFR 34ml/min.	Sepsis and multi organ failure.
2	4 months	No data.	No data.
3	7 months	"Very poor vascular condition" pre-LT. GFR 45 ml/min pre-LT.	Pulmonary infection.
4	2 years		Hepatic artery thrombosis, Re-transplantation, died from cerebral hemorrhage
5	3 years		Hepatic artery thrombosis
6	3 years	Auxiliary LT.	Recurrent AIP attacks, cardiac and renal impairment post LT.
7	5 years		Patient ended immunosuppression therapy
8	8 years	GFR 54 ml/min pre-LT	Sepsis, renal failure.
9	8 years	GFR 28ml/min pre LT	Complications from chronic renal failure

LT, liver transplantation; AIP, acute intermittent porphyria; GFR, glomerular filtration rate.

Table 3. Pre-transplantation clinical features associated with persistent neuropathy after LT

Variable	n	Persistent neuropathy	Neuropathy absent	Difference	Chi^2	p
Age at onset of AIP (n), mean years	21	(7) 23	(14) 33	9.4	-	0.01
Time from onset of AIP to LT (n), mean years	23	(7) 16	(15) 10	5.5	-	0.10
Severe paresis at LT, n (%)	5	4 (80)	1 (20)	-	5.5	0.02

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Moderate/no paresis at LT, n (%)	24	6 (25)	18 (75)			
Severe mobility impairment at LT, n (%)	4	3 (75)	1 (25)	-	3.9	0.05
Moderate or no mobility impairment at LT, n (%)	24	6 (25)	18 (75)			

NOTE: Persistent neuropathy includes any residual motor neuropathy, mobility impairment or neuropathic pain at last assessment after LT. Age at LT and time from onset of AIP to LT was compared by the two-sample t-test for the means. Grade of paresis and mobility impairment at LT was compared by chi-squared association test.

AIP, acute intermittent porphyria; LT, liver transplantation.

Table 4. Liver histology, explanted livers (n=25).

Increased iron deposits	n=18	72%
Fibrosis stage* 0-1	n=17	67%
Fibrosis stage 2	n=5	20%
Fibrosis stage 3	n=1	4%
Cirrhosis (stage 4)	n=0	0%
HCC (no cirrhosis)	n=2	8%

*Fibrosis stages according to the Metavir staging system

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Figure legends

Figure 1

Kaplan-Meyer plot of overall patient survival for the AIP patients (n=38), patients transplanted for other metabolic diseases (n=2941) and all patients transplanted within the ELTR collaboration (n=98376) 2002-2019.

Figure 2a

Kaplan-Meyer plots of overall survival for patients with severe neuropathy (any motor paresis, wheelchair dependent, bedridden or severe neuropathic pain) (n=10) and moderate or no neuropathy at LT (n=19), p=0.04

Figure 2b

Kaplan-Meyer plots of overall survival for patients receiving only LT with GFR >60 ml/min (n=18) and GFR<60ml/min (n=14) pre-LT, p=0.16

Figure 3

Rates (%) of three categories of neuropathic symptoms before liver transplantation, at the time of transplantation and at latest recorded follow-up. Numbers (n) are patients with sufficient data to be included in the analysis. a) Motor neuropathy (n=29), b) Impaired mobility (n=28), c) Neuropathic pain (n=24)

Figure 4

Percent change in GFR from before to most recent value after liver transplantation for 12 patients with pre-transplant GFR 30-60 mL/min (black bars, n=9) or <30ml/min (grey bars, n=3).

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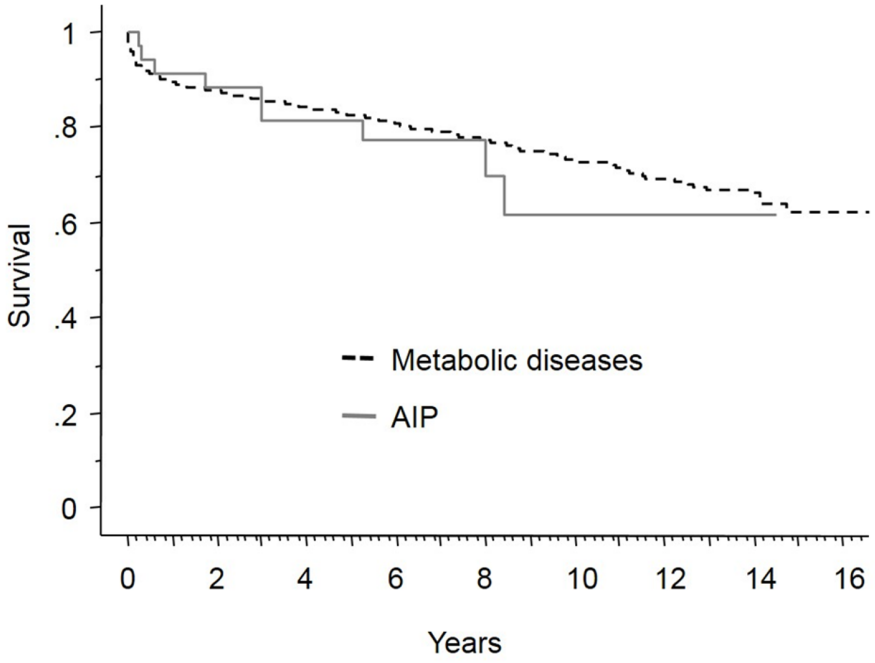

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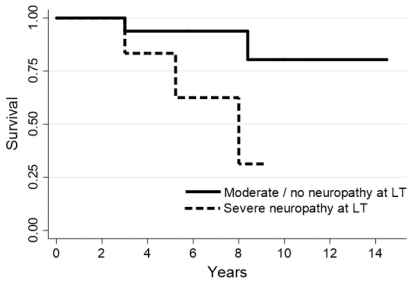

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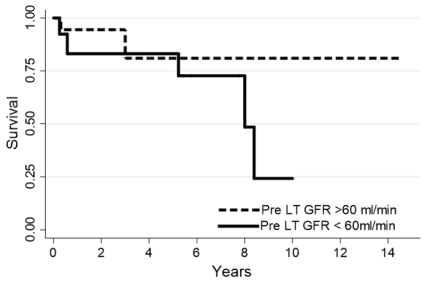

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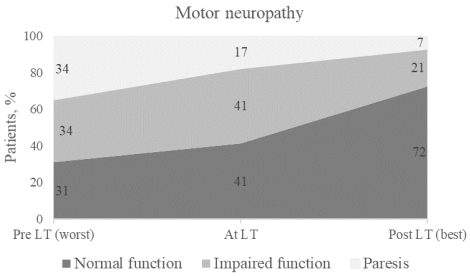

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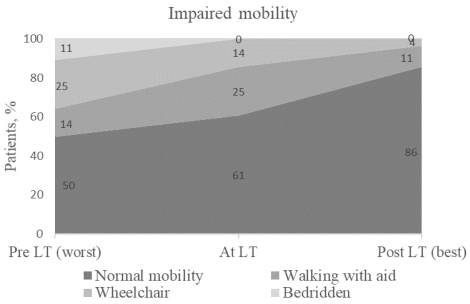

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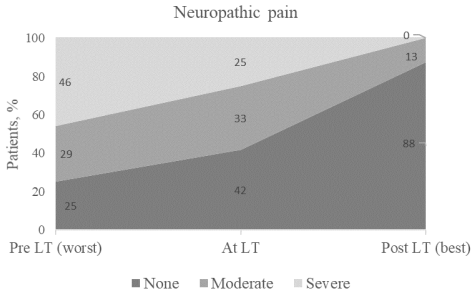

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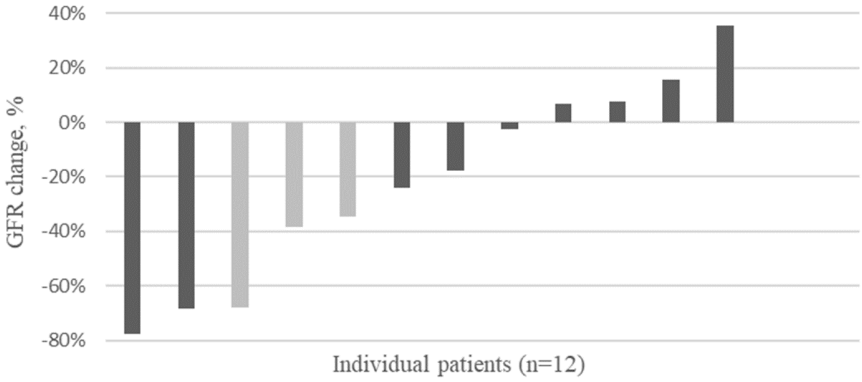

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