


Liver Transplantation for Acute Intermittent Porphyrria

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Recurrent attacks of acute intermittent porphyria (AIP) result in poor quality of life and significant risks of morbidity and mortality. Liver transplantation (LT) offers a cure, but published data on outcomes after LT are limited. We assessed the pretransplant characteristics, complications, and outcomes for patients with AIP who received a transplant. Data were collected retrospectively from the European Liver Transplant Registry and from questionnaires sent to identified transplant and porphyria centers. We studied 38 patients who received transplants in 12 countries from 2002 to 2019. Median age at LT was 37 years (range, 18–58), and 34 (89%) of the patients were women. A total of 9 patients died during follow-up, and 2 patients were retransplanted. The 1-year and 5-year overall survival rates were 92% and 82%, which are comparable with other metabolic diseases transplanted during the same period. Advanced pretransplant neurological impairment was associated with increased mortality. The 5-year survival rate 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 was common. A total of 19 (51%) patients had a GFR < 60 mL/minute. Although 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. LT 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 outcomes. If other treatment options fail, an evaluation for LT should be performed early.

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Acute intermittent porphyria (AIP) with recurrent attacks, defined as 4 or more attacks per year, is a rare condition with severe morbidity and high mortality.^(1,2) Liver transplantation (LT) offers a cure, but few centers are experienced, and limited data are available on the outcomes 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, and 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 the infusion of exogenous heme during attacks to improve clinical symptoms and reduce mortality.⁽⁸⁾ Preventive therapy with regular heme infusions is used to treat AIP with recurrent attacks despite disadvantages such as iron accumulation and the risk of venous

thrombophlebitis.^(9,10) Gonadotropin-releasing hormone (GnRH) analogs are often tried in women with cyclical attacks.⁽¹¹⁾ Givosiran, a ribonucleic acid (RNA) interference therapy, was recently approved for the treatment of AIP.⁽¹²⁾ Givosiran may reduce the frequency of attacks in many patients, but long-term data are 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) of patients with recurrent attacks. High rates of depression,⁽⁹⁾ daily use of opioid pain treatment,⁽¹⁷⁾ an increased risk of long-term sick leave, and the use of disability pensions⁽¹⁸⁾ have also been reported. LT is currently the only curative treatment option.⁽¹⁹⁾ Earlier published data are limited to a few case studies⁽¹⁹⁻²²⁾ and a case series on LT⁽²³⁾ and on combined liver-kidney transplantation.⁽²⁴⁾

Based on more extensive experience than previously available, in this article we address several important issues regarding LT in AIP. What is the prognosis of AIP-associated renal and neurological complications after LT? Are there risk factors for poor outcomes? What disease-specific transplant complications need 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 a 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 outcomes after LT.

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-LT characteristics, complications, and outcomes for patients in Europe who received an LT for AIP.

Patients and Methods

CASE IDENTIFICATION AND STUDY INCLUSION

Study inclusion criteria were diagnosis of AIP (an AIP diagnosis was confirmed by each reporting center based on local diagnostic guidelines) or the rarer forms of acute hepatic porphyria (AHP), variegate porphyria (VP), or hereditary coproporphyrinuria (HCP) and a LT

Abbreviations: AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; CKD, chronic kidney disease; ELTR, European Liver Transplant Registry; GFR, glomerular filtration rate; GnRH, gonadotropin-releasing hormone; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCP, hereditary coproporphyrinuria; HMBS, hydroxymethylbilane synthase; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RNA, ribonucleic acid; VP, variegate porphyria.

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done in Europe. Patients were identified by searching the European Liver Transplant Registry (ELTR) database, personal communications, and literature. Patients identified in the ELTR by a first or second diagnosis of “other porphyria” were excluded unless a definitive AHP diagnosis could be confirmed by the identified transplant or porphyria center. (The ELTR list of disease codes include F9, protoporphyria [mainly erythropoietic protoporphyria], and F10, other porphyria.) Patients who were identified from the 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 patient with VP⁽²¹⁾ who was not identified in the ELTR, no patients with the usually more benign forms of AHP, VP, or HCP were identified. This case was not included, and the study therefore focused only on AIP.

QUESTIONNAIRE

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

COMPLICATIONS, RENAL AND NEUROLOGICAL IMPAIRMENT

Peritransplantation and posttransplantation 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 glomerular filtration rate (GFR): the latest recorded before LT, 1 year after LT, and most recently recorded. If results from renal function tests (eg, 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 < 60 mL/minute). GFRs generally decrease after LT, especially during the first year, mainly a result of 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 the 3 time points: before, at, and after LT. The following 3 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; and (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 with survival data from the ELTR for all patients who received transplants for other metabolic diseases as well as for all patients who received transplants during the ELTR collaboration from 2002 to 2019.⁽²⁷⁾ (The ELTR metabolic diseases include Wilson’s disease [17%], hemochromatosis [8%], alpha-1-antitrypsin deficiency [10%], glycogen storage disease [2%], homozygous hypercholesterolemia [<1%], tyrosinemia [2%], familial amyloidotic polyneuropathy [17%], primary hyperoxaluria [4%], protoporphyria [<1%], nonalcoholic steatohepatitis [10%], Crigler-Najjar syndrome [4%], cystic fibrosis [4%], Byler disease [3%], and other metabolic diseases [21%]. Percentages are from the 2018 annual report of the ELTR.⁽²⁶⁾)

STATISTICAL ANALYSIS

Stata special edition version 15:1 for Windows was used for all statistical analyses (StataCorp, College Station, TX). Descriptive study results are presented as percentages and medians and ranges. Survival analysis was done by the Kaplan-Meier curve method and log-rank test for equality of survivor functions. Comparisons of categorical variables were performed using the chi-square association test. For continuous variables, 2-sample *t*-tests 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.

Results

PATIENT CHARACTERISTICS AND TRANSPLANT INDICATIONS

We identified 42 patients with AIP in 13 European countries who received LTs from 2002 to 2019. Sufficient data for study inclusion were available for 38 patients who received transplants at 21 centers in 12 countries. Some patients were previously included in publications (Supporting File 2). ELTR data were available for 20 patients, and questionnaire data were available for 36 patients. Patient characteristics are presented in Table 1. The median age at LT was 37 years (range, 18-58), and 34 patients (89%) were women. The most common transplant indication was frequent porphyria attacks (89%). A total of 2 female patients aged 48 and 50 years at LT received transplants for HCC, both without cirrhosis. None of these patients had recurrent attacks of AIP in the year prior to LT. There were no reports of HCC recurrence at the latest follow-up. One patient had an urgent LT as a result of 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 < 60 mL/minute (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 the other reported comorbid conditions.

AIP DISEASE

The median age at onset of AIP symptoms was 27 (range, 16-44), and the median duration of active disease, defined as the time from first documented AIP attack to LT, was 13 years (range, 3-35). Most patients (87%) had recurrent attacks of AIP, defined as 4 or more attacks per year, and 74% had >10 attacks annually. Most of the patients (94%) were treated with heme, and 29% had been treated with GnRH analogs. Mutation data were available for 17 patients who had 13 different mutations. The 2 most common hydroxymethylbilane synthase (*HMB*S) mutations were W198X (593G > A; 17%, all from the Nordic countries) and R173W (517C > T; 17%).

TABLE 1. LT for AIP from 2002 to 2019: Patient Characteristics (n = 38)

Female/male, n/n (%/%)	34/4 (89/11)
Age at LT, years, median (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 analog	10 (29)
Annual number of AIP attacks during 2 pre-LT years, n (%)	
>3	27 (87)
>10	23 (74)
Comorbidities at time of LT, n (%)	
Renal impairment, CKD stage > 2 (GFR < 60 mL/minute)	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	5 (14)
Auxiliary	1 (3)
Time (weeks) on waiting list, median (range)	30 (0-135)

*Includes any paresis, impaired motor function, impaired mobility, or neuropathic pain at time of LT.

(W198X is also known as the Nordic founder mutation; in this study, patients with this mutation were from Norway and Sweden.) Data on pretransplant urinary excretion of porphobilinogen and delta-aminolevulinic acid were reported for 18 patients. All of the patients had significantly elevated levels. Follow-up analyses 1 to 3 days after LT showed normalized urinary excretion in all reported (n = 19) cases.

TRANSPLANTATION

The median waitlist time was 30 weeks (range, 1 day to 31 months). The median Model for End-Stage Liver Disease (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) was reported in 6 patients were related to renal impairment ($n = 4$), warfarin treatment ($n = 1$), and acute liver failure ($n = 1$). A total of 7 centers in 5 countries used different forms of MELD exception systems that were applied to their 10 patients. Most (97%) received grafts from deceased donors and 1 from a live donor. Of the patients, 5 (13%) received a combined liver-kidney transplant. One patient had an auxiliary transplant (ie, 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 9 (24%) had died. The 1-year and 5-year overall patient survival rates were 92% and 82%, similar to ELTR survival data on patients who received transplants for other metabolic diseases and all patients who received transplants from 2002 to 2019 (Fig. 1). Severe neurological impairment was associated with an increased mortality rate. Patients with any motor paresis or who were wheelchair dependent, bedridden, or suffered severe neuropathic pain at the time of LT ($n = 10$) had a 5-year survival rate of 83% compared with 94% in patients ($n = 19$) with moderate or no neuropathy ($P = 0.04$) (Fig. 2A). Pretransplant renal impairment tended to increase mortality after LT. Patients with a GFR <60 mL at the pre-LT assessment ($n = 14$) who did not receive a combined liver-kidney transplant had a 5-year survival rate of 71% compared with 81% for patients ($n = 18$) with GFR > 60 mL/minute ($P = 0.16$; Fig. 2B). All 5 patients who received combined liver-kidney transplants were alive at last follow-up. Two patients were retransplanted. The causes of death for the 9 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 patients who received transplants. Minor complications (Clavien-Dindo grade I-II), such as acute rejection, cytomegalovirus viremia, other

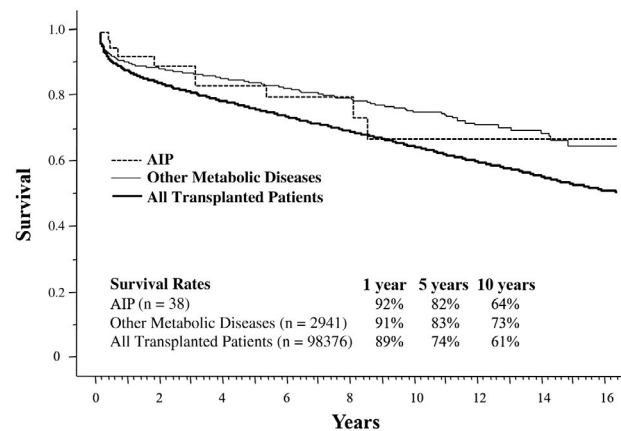


FIG. 1. Kaplan-Meier curve plot of overall patient survival for the patients with AIP ($n = 38$), patients who received transplants for other metabolic diseases ($n = 2941$), and all patients who received transplants during the ELTR collaboration ($n = 98,376$) from 2002 to 2019.

infections, cholangitis, and deep venous thrombosis, were recorded in 26% of the patients who received transplants. Major complications (Clavien-Dindo grade III-IV), such as bile duct leakage or obstruction, wound tissue rupture, human herpes virus-6 infection with multiorgan failure, and late bleeding requiring surgical intervention, were recorded in 35%. Hepatic artery thrombosis (HAT) occurred in 4 patients (11%), all women. One patient had early HAT within 1 month after LT, was retransplanted, and recovered. One patient (exact time for HAT missing) was retransplanted after 4.5 months but died 18 months later from cerebral hemorrhage. A third patient developed HAT after about 1 month and was listed for re-LT but deteriorated and died. A fourth patient developed HAT after 3 years and recovered without retransplantation.

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 3 categories at follow-up

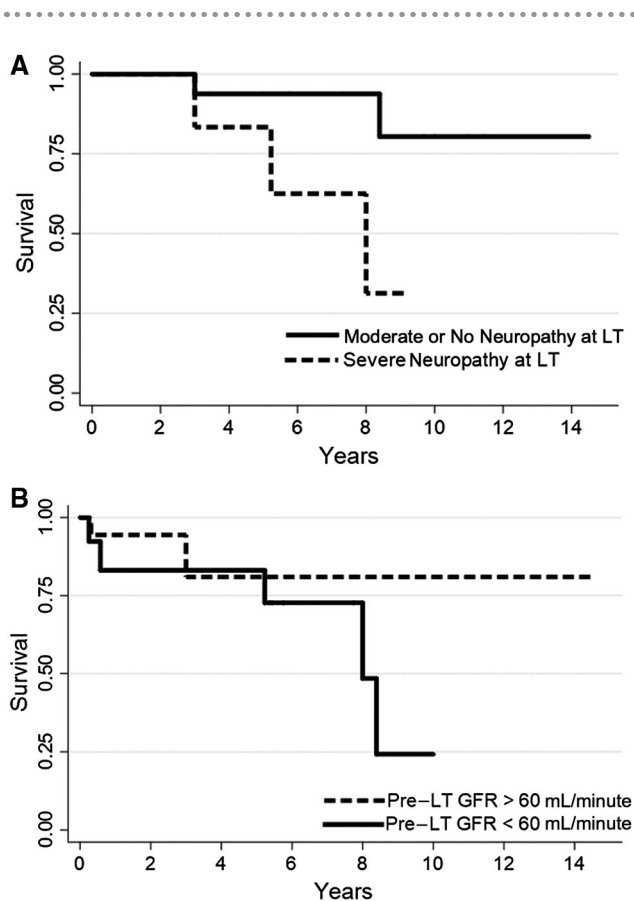


FIG. 2. (A) Kaplan-Meier curve plots of overall survival for patients with severe neuropathy (any motor paresis, wheelchair dependent, bedridden, or severe neuropathic pain; $n = 10$) and moderate or no neuropathy at LT ($n = 19$; $P = 0.04$). (B) Kaplan-Meier curve plots of overall survival for patients receiving only LT with GFR > 60 mL/minute ($n = 18$) and GFR < 60 mL/minute ($n = 14$) pre-LT ($P = 0.16$).

after LT compared with the pre-LT assessments (Fig. 3A-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).

RENAL IMPAIRMENT

At pretransplant assessment, 4 patients (11%) had GFR > 90 mL/minute, 14 (38%) had a GFR 60 to 90 mL/minute, 12 (32%) had a GFR 30 to 60 mL/minute, and 7 (19%) had a GFR < 30 mL/minute. Four of the patients with GFR < 30 mL/minute 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 cyclosporine ($n = 1$, 3%). The median GFR before LT in patients who did not receive a combined liver-kidney transplant was 62 mL/minute, decreased to 52 mL/minute at the 1-year follow-up, and was 46 mL/minute at the most recent follow-up.

Post-LT GFR varied in patients with a pre-LT GFR < 60 mL/minute who received only LT and had complete GFR information ($n = 12$). Although 7 had stable GFR (defined as less than 30% decline from pre-LT GFR) or improved GFR, 5 had more than a 30% decline in GFR after LT (Fig. 4). All 3 patients with CKD stage 4 (GFR < 30 mL/minute) at LT had a further worsening in renal function after LT with more than 30% decline in GFR at the latest follow-up. The 5 patients who received combined liver-kidney transplantations were all alive with a median GFR of 63 mL/minute (range, 36-73) at latest follow-up.

EXPLANTED LIVERS

Data were collected on 25 explanted livers (Table 4). The most common finding was increased iron deposits (72%), presumably from pre-LT heme therapy. Fibrosis stage 2 was found in 20%, only 1 (4%) had stage 3 fibrosis, and no liver was cirrhotic (stage 4). The explanted livers from the 2 patients who received transplants for HCC showed no advanced fibrosis or cirrhosis. HCC was not found in any other explanted livers.

Discussion

In this largest case series to date, we report on the characteristics and outcomes of 38 LTs done for AIP in 12 European countries from 2002 to 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, whereas renal impairment in most patients does not. At least 3 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 (4 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

TABLE 2. Causes of Death

Case No.	Time From LT	Background	Cause of Death
1	3 months	Ventilator dependent for months before LT; GFR 34 mL/minute	Sepsis and multiorgan failure
2	4 months	No data	No data
3	7 months	"Very poor vascular condition" before LT; GFR 45 mL/minute before LT	Pulmonary infection
4	2 years		Hepatic artery thrombosis, retransplantation, died from cerebral hemorrhage
5	3 years		Hepatic artery thrombosis
6	3 years	Auxiliary LT	Recurrent AIP attacks, cardiac and renal impairment after LT
7	5 years		Patient ended immunosuppression therapy
8	8 years	GFR 54 mL/minute before LT	Sepsis, renal failure
9	8 years	GFR 28 mL/minute before LT	Complications from chronic renal failure

high mortality risk. The economic burden on the health care 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 LT is considered for severe AIP with recurrent attacks.

The 1-year and 5-year survival rates of 92% and 82%, respectively, are comparable with patients who received transplants for other metabolic diseases and with all patients who received transplants during the same time period (Fig. 1). Compared with other LT indications, the median age of 37 in this cohort is, however, low, and higher survival rates would be desirable. The identification of risk factors for worse outcomes 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 on average, and that the majority of patients had developed AIP-related comorbidities. This suggests that LT generally is considered late in the disease course and highlights the importance of the 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 the following 3 factors that deserve attention:

1. At least 2 patients were in poor clinical condition at the time of LT, and 1 patient was ventilator dependent as a result of 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 4 patients (11%) with HAT in this study, which led to retransplantation in 2 patients and death in 1 patient. The HAT rate of 11% is low compared with the previously reported 40% but higher than an expected rate of 3% to 9% in general LT.⁽²⁹⁾ Two of the previously reported cases of HAT⁽²³⁾ are, however, not included in this study as a result of nonresponse from the transplant center, suggesting a real HAT rate of more than 11%. The occurrence of both early and very late HAT suggests that 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 sex.^(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 patients with AIP who receive transplants. 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 have been scarce. Half of the patients in this cohort (50%) had CKD stage 3 or worse at LT. The trends in GFR after LT varied considerably between patients. The median GFR was 62 mL/minute at pre-LT assessment, 52 mL/minute 1-year post LT, and 46 mL/minute at last follow-up. A progressive decline in GFR, particularly in the first year after LT, is not uncommon, and post-LT

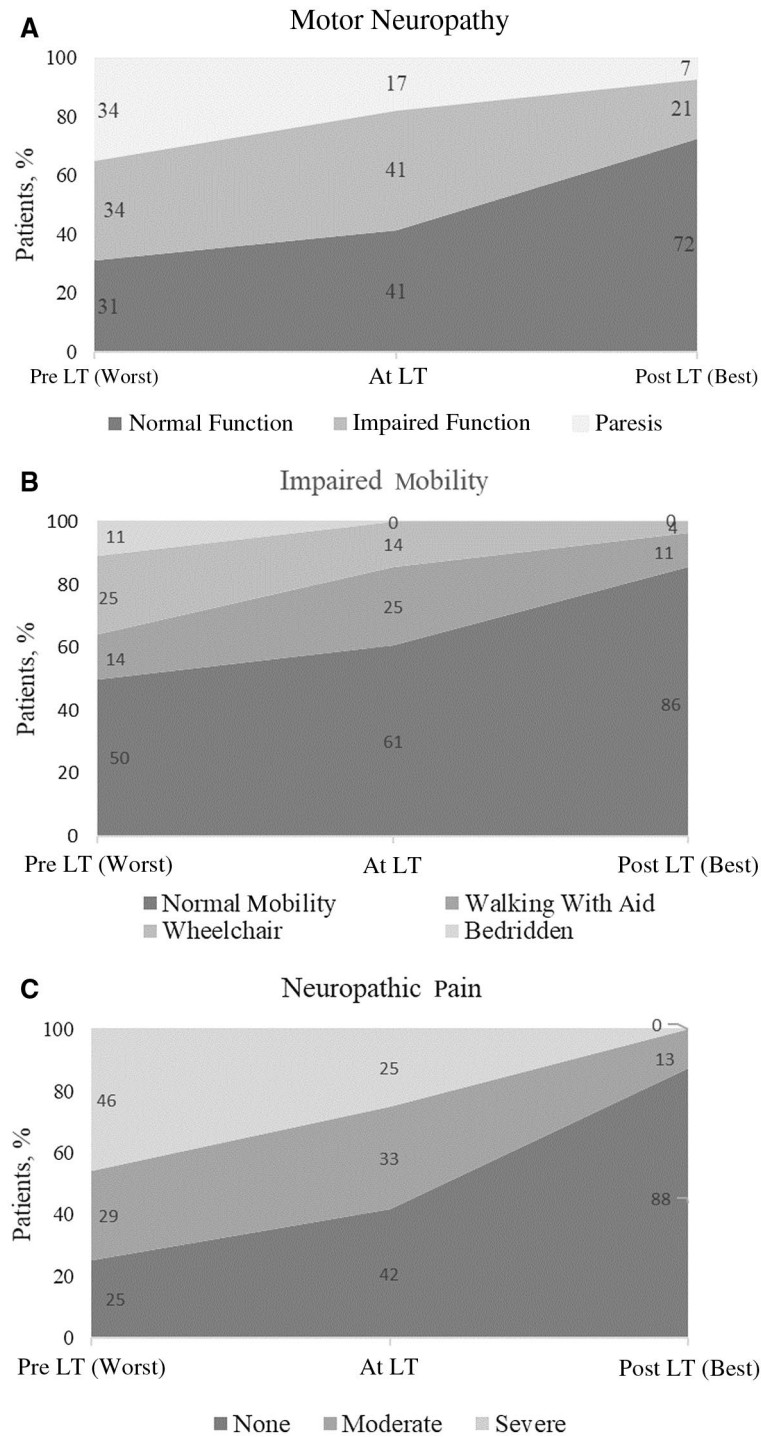


FIG. 3. Rates (percentages) of 3 categories of neuropathic symptoms before LT at the time of transplantation and at latest recorded follow-up. Numbers are patients with sufficient data to be included in the analysis: (A) motor neuropathy (n = 29), (B) impaired mobility (n = 28), and (C) neuropathic pain (n = 24).

TABLE 3. Pretransplantation Clinical Features Associated With Persistent Neuropathy After LT

Variable	n	Persistent Neuropathy	Neuropathy Absent	Difference	Chi-Square Test	P Value
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
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 a 2-sample *t* test for the means. Grade of paresis and mobility impairment at LT was compared by chi-square association test.

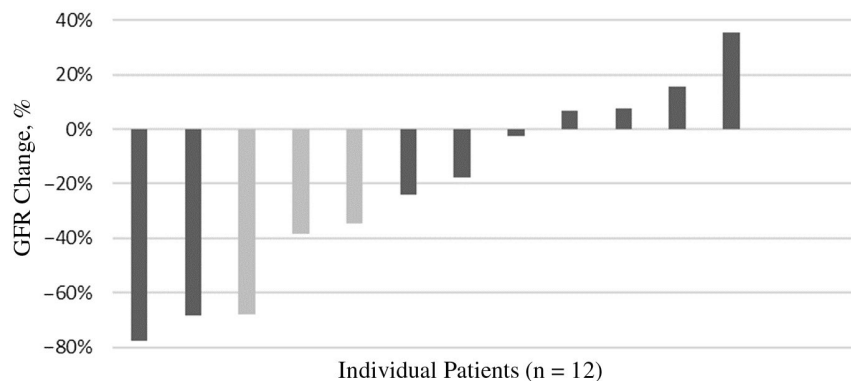


FIG. 4. Percent change in GFR from before to most recent value after LT for 12 patients with pretransplant GFR 30 to 60 mL/minute (black bars, n = 9) or <30 mL/minute (gray bars, n = 3).

TABLE 4. Liver Histology: Explanted Livers (n = 25)

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

*Fibrosis stages according to the metavir staging system.

renal impairment is an independent risk factor for morbidity and mortality.^(26,32) Almost half of the patients with a pre-LT GFR < 60 mL/minute but no patients with GFR < 30 mL/minute 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 5 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 the evaluation for LT. In patients approaching severely impaired renal function (GFR < 30 mL/minute), a combined liver-kidney transplant should be thoroughly considered because 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 were lower after LT (Fig. 3A-C). 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.

Patients with AIP have an increased risk of developing primary liver cancer, most commonly 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 AIP-related primary liver cancers are diagnosed in females without significant fibrosis.⁽³⁵⁾ In the 2 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 a total of 25 patients in this study. In line with 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 European Medicines Agency and US Food and Drug Administration for the treatment of AIP.⁽¹²⁾ Givosiran may reduce the frequency of attacks in many patients, but LT will remain an option when this and other treatment options are ineffective.

Based on these and previous results, we recommend that the evaluation for LT should be considered at an early stage in all patients with AIP suffering from recurrent attacks with insufficient responses to available therapies. The evaluation should include the 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. An LT unit, preferably with experience in AIP, should be involved in the evaluation. Combined liver-kidney transplantation 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) and 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 LT 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 sent to the identified transplant and porphyria centers were intentionally designed to encourage high compliance and response rates and reduce issues of missing data. Accordingly, the amount and level of detail in the collected data were less than what would be desirable. Data were not available for 4 (10%) patients who received transplants. Of these, 2 patients had HAT, as commented previously, and the 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.

In conclusion, this study confirms that LT offers a 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 outcomes. Patients with AIP with recurrent attacks and 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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REFERENCES

- Elder G, Harper P, Badminton M, Sandberg S, Deybach JC. The incidence of inherited porphyrias in Europe. *J Inher Metab Dis* 2013;36:849–857.
- Neeleman RA, Wagenmakers M, Koole-Lesuis RH, Mijnhout GS, Wilson JHP, Friesema ECH, et al. Medical and financial burden of acute intermittent porphyria. *J Inher Metab Dis* 2018;41:809–817.
- Puy H, Gouya L, Deybach JC. Porphyrias. *Lancet* 2010;375:924–937.
- Lenglet H, Schmitt C, Grange T, Manceau H, Karboul N, Bouchet-Crivat F, et al. From a dominant to an oligogenic model of inheritance with environmental modifiers in acute intermittent porphyria. *Hum Mol Genet* 2018;27:1164–1173.
- Chen B, Solis-Villa C, Hakenberg J, Qiao W, Srinivasan RR, Yasuda M, et al. Acute intermittent porphyria: predicted pathogenicity of *HMBS* variants indicates extremely low penetrance of the autosomal dominant disease. *Hum Mutat* 2016;37:1215–1222.
- Gouya L, Ventura P, Balwani M, Bissell DM, Rees DC, Stölzel U, et al. EXPLORE: a prospective, multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. *Hepatology* 2020;71:1546–1558.
- Wikberg A, Jansson L, Lithner F. Women's experience of suffering repeated severe attacks of acute intermittent porphyria. *J Adv Nurs* 2000;32:1348–1355.
- Stein P, Badminton M, Barth J, Rees D, Stewart MF. Best practice guidelines on clinical management of acute attacks of porphyria and their complications. *Ann Clin Biochem* 2013;50(Pt 3):217–223.
- Marsden JT, Guppy S, Stein P, Cox TM, Badminton M, Gardiner T, et al. Audit of the use of regular haem arginate infusions in patients with acute porphyria to prevent recurrent symptoms. *JIMD Rep* 2015;22:57–65.
- Willandt B, Langendonk JG, Biermann K, Meersseman W, D'Heygere F, George C, et al. Liver fibrosis associated with iron accumulation due to long-term heme-arginate treatment in acute intermittent porphyria: a case series. *JIMD Rep* 2016;25:77–81.
- Innala E, Backstrom T, Bixo M, Andersson C. Evaluation of gonadotropin-releasing hormone agonist treatment for prevention of menstrual-related attacks in acute porphyria. *Acta Obstet Gynecol Scand* 2010;89:95–100.
- Balwani M, Sardh E, Ventura P, Peiró PA, Rees DC, Stölzel U, et al. Phase 3 trial of RNAi therapeutic Givosiran for acute intermittent porphyria. *N Engl J Med* 2020;382:2289–2301.
- Pallet N, Mami I, Schmitt C, Karim Z, Francois A, Rabant M, et al. High prevalence of and potential mechanisms for chronic kidney disease in patients with acute intermittent porphyria. *Kidney Int* 2015;88:386–395.
- Pischik E, Kauppinen R. Neurological manifestations of acute intermittent porphyria. *Cell Mol Biol (Noisy-le-grand)* 2009;55:72–83.
- Baravelli CM, Sandberg S, Aarsand AK, Nilsen RM, Tollanes MC. Acute hepatic porphyria and cancer risk: a nationwide cohort study. *J Intern Med* 2017;282:229–240.
- Sardh E, Wahlin S, Bjornstedt M, Harper P, Andersson DE. High risk of primary liver cancer in a cohort of 179 patients with acute hepatic porphyria. *J Inher Metab Dis* 2013;36:1063–1071.
- Schmitt C, Lenglet H, Yu A, Delaby C, Benecke A, Lefebvre T, et al. Recurrent attacks of acute hepatic porphyria: major role of the chronic inflammatory response in the liver. *J Intern Med* 2018;284:78–91.
- Baravelli CM, Aarsand AK, Sandberg S, Tollanes MC. Sick leave, disability, and mortality in acute hepatic porphyria: a nationwide cohort study. *Orphanet J Rare Dis* 2020;15:56.
- Soonawalla ZF, Orug T, Badminton MN, Elder GH, Rhodes JM, Bramhall SR, et al. Liver transplantation as a cure for acute intermittent porphyria. *Lancet* 2004;363:705–706.
- Dar FS, Asai K, Haque AR, Cherian T, Rela M, Heaton N. Liver transplantation for acute intermittent porphyria: a viable treatment? *Hepatobiliary Pancreat Dis Int* 2010;9:93–96.
- Stojeba N, Meyer C, Jeanpierre C, Perrot F, Hirth C, Pottcher T, et al. Recovery from a variegate porphyria by a liver transplantation. *Liver Transpl* 2004;10:935–938.
- Yasuda M, Erwin AL, Liu LU, Balwani M, Chen B, Kadirvel S, et al. Liver transplantation for acute intermittent porphyria: biochemical and pathologic studies of the explanted liver. *Mol Med* 2015;21:487–495.
- Dowman JK, Gunson BK, Mirza DF, Bramhall SR, Badminton MN, Newsome PN, et al. Liver transplantation for acute intermittent porphyria is complicated by a high rate of hepatic artery thrombosis. *Liver Transpl* 2012;18:195–200.
- Wahlin S, Harper P, Sardh E, Andersson C, Andersson DE, Ericzon BG. Combined liver and kidney transplantation in acute intermittent porphyria. *Transpl Int* 2010;23:e18–e21.
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–213.
- Kang GW, Lee IH, Ahn KS, Kim JD, Kwak SG, Choi DL. One-year follow-up of the changes in renal function after liver transplantation in patients without chronic kidney disease. *Transpl Proc* 2016;48:1190–1193.
- Adam R, Karam V, Cailliez V, O'Grady JG, Mirza D, Cherqui D, et al. 2018 Annual report of the European Liver Transplant Registry (ELTR)—50-year evolution of liver transplantation. *Transpl Int* 2018;31:1293–1317.
- Frei P, Minder EI, Corti N, Muellhaupt B, Geier A, Adams H, et al. Liver transplantation because of acute liver failure due to heme arginate overdose in a patient with acute intermittent porphyria. *Case Rep Gastroenterol* 2012;6:190–196.
- Silva MA, Jambulingam PS, Gunson BK, Mayer D, Buckels JA, Mirza DF, et al. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. *Liver Transpl* 2006;12:146–151.
- Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant* 2009;9:746–757.
- Ikegami T, Hashikura Y, Nakazawa Y, Urata K, Mita A, Ohno Y, et al. Risk factors contributing to hepatic artery thrombosis following living-donor liver transplantation. *J Hepatobiliary Pancreat Surg* 2006;13:105–109.
- Pawarode A, Fine DM, Thuluvath PJ. Independent risk factors and natural history of renal dysfunction in liver transplant recipients. *Liver Transpl* 2003;9:741–747.
- Marsden JT, Chowdhury P, Wang J, Deacon A, Dutt N, Peters TJ, et al. Acute intermittent porphyria and chronic renal failure. *Clin Nephrol* 2008;69:339–346.
- Pallet N, Karras A, Thervet E, Gouya L, Karim Z, Puy H. Porphyria and kidney diseases. *Clin Kidney J* 2018;11:191–197.
- Peoc'h K, Manceau H, Karim Z, Wahlin S, Gouya L, Puy H, et al. Hepatocellular carcinoma in acute hepatic porphyrias: a Damocles sword. *Mol Genet Metab* 2019;128:236–241.