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ORIGINAL ARTICLE

Excellent survival after liver transplantation for isolated polycystic liver disease: an European Liver Transplant Registry study

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Summary

Patients with end-stage isolated polycystic liver disease (PCLD) suffer from incapacitating symptoms because of very large liver volumes. Liver transplantation (LT) is the only curative option. This study assesses the feasibility of LT in PCLD. We used the European Liver Transplant Registry (ELTR) database to extract demographics and outcomes of 58 PCLD patients. We used Kaplan–Meier survival analysis for survival rates. Severe abdominal pain (75%) was the most prominent symptom, while portal hypertension (35%) was the most common complication in PCLD. The explantation of the polycystic liver was extremely difficult in 38% of patients, because of presence of adhesions from prior therapy (17%). Karnofsky score following LT was 90%. The 1- and 5-year graft survival rate was 94.3% and 87.5%, while patient survival rate was 94.8% and 92.3%, respectively. Survival rates after LT for PCLD are good.

Introduction

Isolated polycystic liver disease (PCLD) is characterized by the presence of numerous cysts scattered throughout the liver parenchyma without the presence of polycystic kidneys. This last item leads to the difference between PCLD and autosomal dominant polycystic kidney disease (ADPKD) [1]. The majority of patients with a polycystic liver suffers from ADPKD [2]. PCLD is a much more rare disease [1]. Although polycystic livers are a feature of both ADPKD and PCLD, the genetic background of these two disorders is clearly different, because a distinct set of genes has been implicated [3].

Symptoms, such as abdominal pain, abdominal distension, postprandial fullness, and dyspnea, are dependent on the volume of the polycystic liver, and develop because of mass effect of the large liver [3]. The polycystic liver retains its normal physiologic features even in advanced stage synthesis, and excretion is preserved at all times. The most severe complications, such as portal

hypertension and inferior caval vein syndrome occur rarely, but are notoriously difficult to treat [1,4].

In view of the rarity of PCLD, its therapeutic algorithm is under debate [3]. Aspiration-sclerotherapy, open or laparoscopic fenestration, and partial liver resection are possible therapeutic options [2,5,6]. The main limitation of these techniques is that they are only appropriate in a very small proportion of patients, and offer only temporary relief of symptoms [3,4,6–8]. More recently, liver transplantation (LT) has surfaced as a last resort alternative in patients with massive polycystic livers. In this respect, there are several important issues that need to be addressed. The experience with LT for polycystic liver is limited to a handful of cases precluding an adequate overview of the procedure-related morbidity and mortality [9–20]. In addition, long-term follow-up data on patient and graft survival are missing. Furthermore, several studies report about LT in ADPKD, but studies on PCLD are conspicuously lacking. To address these issues, we assessed the outcome of LT in PCLD from the European Liver Transplantation Registry (ELTR).

Patients and methods

The ELTR database contains data on a total of 534 patients who underwent LT with main or associated diagnosis 'polycystic liver', between November 1985 and June 2007. We extracted demographic and outcome parameters from this database.

Basis for selection

As we were interested in the outcome of LT for the indication PCLD, we introduced a stepwise search strategy. This strategy was aimed to specifically select patients who underwent a LT exclusively because of PCLD.

We excluded 193 patients because these patients underwent a combined liver–kidney transplantation. We also excluded 42 patients in whom the presence of polycystic liver was not the main indication for transplantation.

We went on to collect additional data for the remaining 299 patients. To this end, we used a standardized questionnaire, which was sent to 75 European LT centers. The questionnaire included items that focused on diagnosis, e.g., PCLD or ADPKD; family history; data on the pretransplant period (including symptoms, complications, laboratory results, and prior therapies); data on the peritransplant period (including indication of LT, with the following three options: mechanical difficulties (defined as expansion of the liver volume to such an extent that it compromised function or location of adjacent organs), invalidation (defined as impaired in daily life and quality of life), and complications resulting directly from the polycystic liver, such as portal hypertension); further peritransplant data included surgical aspects of transplant procedure and weight of the excised liver); data about the postoperative period (including length of admission, postoperative complications) and quality of life after LT using the Karnofsky score.

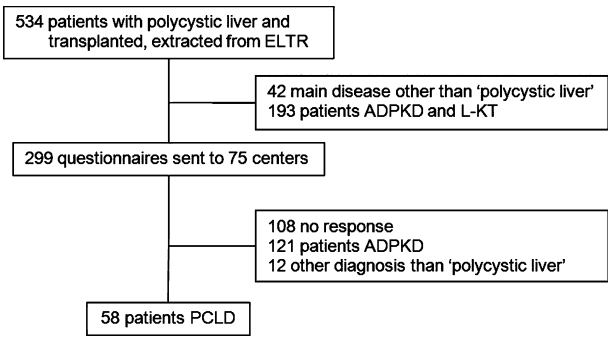

Figure 1 Patient selection.

A total of 49 centers responded and returned questionnaires on a total of 191 patients. We further excluded 121 patients with ADPKD and 12 patients who received another diagnosis, such as cystic fibrosis ($n = 2$), hepatic hemangioma ($n = 1$), hepatic cellular carcinoma ($n = 1$), Caroli's disease ($n = 2$) hereditary amyloidosis ($n = 1$), and polyadenomatosis ($n = 1$), or were unknown in the center ($n = 4$). The final data set contains 58 patients with PCLD (Fig. 1).

Statistical analysis

Laboratory results were calculated in relation to the upper limit of normal (ULN) of each individual LT center. Descriptive statistics are given as total number and percentage for categorical variables. Continuous variables are given as median with interquartile range (IQR) distribution. Kaplan–Meier analysis was used to estimate the post-transplant patient and graft survival rate. All statistical analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographics of the PCLD cohort

Fifty-eight PCLD patients (10 men, 48 women) were transplanted in 25 LT centers from 11 European countries. Table 1 depicts the demographic characteristics of the cohort. The median age at the time of diagnosis was 39.8 years (IQR 35–47), and 52.3 years (IQR 44–56) at time of LT.

Symptoms

Severe abdominal pain (38 patients; 75%), abdominal distension (39 patients; 75%), and dyspnea (27 patients; 53%) were among the most common symptoms. There were 28 (55%) patients who had developed one or more complications from their polycystic liver, with portal hypertension as the most common clinical sequel (19 (35%) patients).

Table 1. Baseline characteristics of patients transplanted for PCLD.

	Total (n = 58)
Age at diagnosis* (years)	39.8 (34.6–46.9)
Age at LT* (years)	52.3 (43.6–56.4)
Gender, M/F	10/48
Symptoms	
Abdominal pain†	38/51 (75)
Abdominal distension†	39/52 (75)
Dyspnea†	27/51 (53)
Postprandial fullness†	21/45 (47)
Weight loss†	22/51 (43)
Anorexia†	13/48 (27)
Nausea†	8/47 (17)
Vomiting†	4/47 (9)
Any complication†	28/51 (55)
Cyst infection†	9/55 (16)
Cyst hemorrhage†	4/52 (8)
Cyst rupture†	3/53 (6)
Portal hypertension†	19/55 (35)
Ascites†	18/54 (33)
Varices†	4/53 (8)
IVC syndrome†	3/54 (6)
Laboratory results	
Creatinine*, times ULN	1.00 (1.00–1.00)
AST*, times ULN	1.00 (1.00–1.19)
ALT*, times ULN	1.00 (1.00–1.17)
Alkaline phophatase*, times ULN	1.50 (1.00–2.45)
γ glutamyl transferase*, times ULN	3.08 (1.26–6.07)
Bilirubin*, times ULN	1.00 (1.00–1.07)
Albumin*, times LLN	1.00 (1.00–1.00)
INR*	1.10 (1.00–1.18)
Prior therapy†	33/57 (58)
Aspiration†	14/33 (42)
Aspiration-sclerotherapy†	12/33 (36)
Open fenestration†	12/33 (36)
Laparoscopic fenestration†	7/33 (21)
Partial liver resection†	7/33 (21)

Data for creatinine, aspartate transferase (AST), alanine transferase (AST), alkaline phosphatase (AP), γ glumatyl transferase (GGT), bilirubine, albumin, and INR were normalized and calculated as times of the upper limit of normal (ULN).
LT, liver transplantation; IVC, inferior caval vein
*Data are median (IQR).
†n/N (%) Denominators depend on the number of provided answers for a specific question in the questionnaire.

Laboratory values

All reported laboratory results were within the normal range except for alkaline phosphatase (AP) and γ glutamyl transferase (GGT) [AP median 1.50 ULN (IQR 1.00–2.45); GGT median 3.08 ULN (IQR 1.26–6.07)].

Prior treatment

Thirty-four (59%) patients had prior therapy, such as aspiration with (14 patients) or without (15 patients) injection of a sclerosant. Twenty patients underwent cyst fenestration via laparotomy (13 patients) or laparoscopy (seven patients), whereas seven patients were subjected to partial liver resection.

Peritransplant period

Primary reasons for LT in PCLD patients were mechanical difficulties (for example, inability to sit or sleep because of a sizable liver) in 35 patients (60%), invalidation in 14 patients (24%), and pain in 11 patients (19%). Transplant teams decided to perform LT in seven patients (12%) because of the severity of complications such as portal hypertension and cyst infection. Median operation time was 6.6 h (IQR 4.8–8.3). Median blood loss with the procedure was 1520 ml (IQR 500–4500). Median weight of the explanted liver was 5890 g (IQR 3019–9858). Furthermore, explantation of the polycystic liver was considered extremely difficult in 22/58 patients (38%) in most part of adhesions because of prior therapy (n = 10; 17%), grossly enlarged liver (n = 7; 12%), or miscellaneous causes (n = 3; 5%). Inability to explantation led to premature termination of the LT procedure in one patient.

Postoperative complications were more frequent than intra-operative complications (46% vs. 17%) (Table 2). Median stay at the intensive care unit was 5 days (IQR 2–9), while total hospital admission length was 23 days (IQR 13–35).

Table 2. Operative complications.

Intra-operative complications	n/N (%)	Postoperative complications	n/N (%)
Vascular	6/58 (10)	Rejection	8/56 (14)
Venous tear	2/58 (3)	Vascular	8/56 (14)
Revascularisation problem	2/58 (3)	Infection	6/56 (11)
Bleeding	2/58 (3)	Nonfunctional graft	1/56 (2)
Hepatic vein thrombosis	1/58 (2)	Death	1/56 (2)
Death	1/58 (2)	Other	14/56 (25)
Other	3/58 (5)	Total	26/56 (46)
Total	10/58 (17)		

Survival after LT in PCLD

Two patients (3.6%) died during admission, one patient during the LT procedure, and one patient 7 days after LT as a result of sepsis. Median survival time in this study was 6.0 years (IQR 2.5–11.8). The 1- and 5-year patient survivals are 94.8% and 92.3%. Two patients were retransplantated: one patient after 7 days because of primary liver dysfunction and the second patient after 2.2 years because of artery thrombosis and anastomotic biliary stenosis. Graft survival was 94.3% at 1 year and 87.5% at 5 years.

Four patients died at follow-up between 4.7 and 12.4 years after LT. One patient died 5.9 years post-transplantation because of metastasized malignancy with unknown primary tumor, a second patient died after 8.7 years with chronic graft rejection and long-term assisted ventilation. For the remaining two patients, reason of death is unknown (death at 4.7 years and 12.4 years post-transplantation). We next investigated whether the patient characteristics differed between those who had died and the survivors. Both groups were comparable except that the deceased patients were older at time of diagnosis and at time of LT: 48.0 years (IQR 36.4–63.5) vs. 39.2 years (IQR 34.0–45.9) and 57.4 years (IQR 51.6–60.5) vs. 51.9 years (IQR 42.7–55.2), respectively.

The median Karnofsky score for the surviving patients was 90%, which indicates that they are capable of normal activity, with only few symptoms or signs of disease.

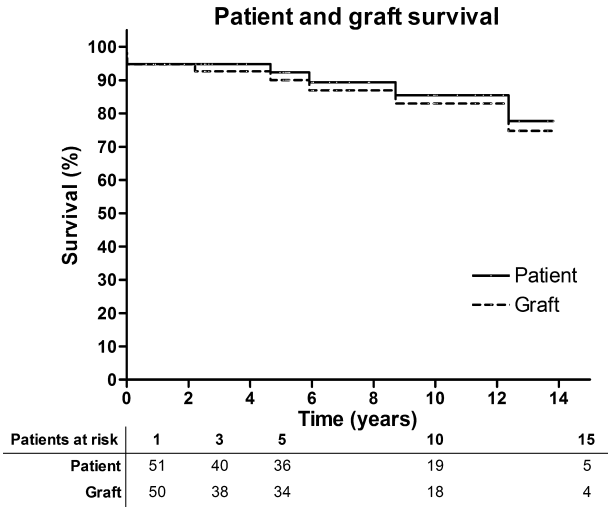

Figure 2 Patient and graft survival. In one patient, the transplantation procedure was prematurely terminated. This patient is included in the survival analysis as an intra-operative dead. Patient survival: 94.8% (1 year), 92.3% (5 years). Graft survival: 94.3% (1 year), 87.5% (5 years).

Discussion

This study demonstrates that LT for PCLD leads to excellent patient and graft survival.

We evaluated LT in a large cohort of PCLD patients and demonstrated an excellent 1- and 5-year patient and graft survivals (Fig. 2). Comparison of the LT results for polycystic liver compared with other indications suggests that these patients run a favorable course. The collective survival data from the ELTR database, which comprises patients with a wide spectrum of liver diseases, shows a 5-year patient survival of 75% for all indications compared with 92% of that in PCLD [21].

There are a number of smaller LT series retained in the literature. The demographic features of included patients and peri-operative data are in line with our series, with the exception that PCLD patients have been rarely included [9–20,22,23]. Only a few studies report patient and graft survival rates of LT in patients with polycystic liver. One study of 36 patients (15 patients of whom underwent combined liver–kidney transplantation) found a 1-year patient survival rate of 86% including both ADPKD and PCLD [23].

We found substantially higher survival rates compared with the ELTR report in 2003 [24]. The main difference between these studies is that we excluded all patients with ADPKD. It is possible that combined liver–kidney transplantation results in poorer survival than LT alone, but with the dataset from this study, it is not possible to address this issue.

The most important problem encountered during LT was the explantation of the polycystic liver, mostly because of adhesions from previous surgical procedures. Extensive adhesions might preclude successful execution of the procedure and others report on similar issues [10,13,15]. These experiences suggest that reluctance to subject polycystic liver patients who are potential LT candidates to other invasive liver volume reducing procedures, is warranted.

The place of LT in treatment of PCLD is subject to ethical discussion, as the polycystic liver has a normal synthesis capacity, and the disorder appears not to be associated with excess mortality. Is it justified to allocate a liver to a patient with PCLD during a shortage of donor organs? Do we want to give otherwise healthy patients life-long immunosuppression, while also exposing them to a higher risk of infections and malignancies? In an effort to address this issue, Kirchner *et al.* evaluated the outcome and quality of life in patients with polycystic livers after LT or combined liver–kidney transplantation [23]. Transplantation improved actual health status,

symptoms, and quality of life to a level comparable with that of an age-matched general population which accords with our data. This improvement of quality of life after transplantation supports the choice of LT as a therapeutic option in PCLD.

Are there any medical options left? Several clinical trials performed in the last 2 years indicate that somatostatin analogs when given for 6–12 months in patients with AD-PKD and PCLD decrease total polcystic liver volume, attenuate polycystic kidney volume, and improve perception of health. However, the effect size (ca 5% decrease of total liver volume after 6–12 months) is probably too low to be of benefit for patients who are listed for transplantation [25–27].

Since December 2006, the allocation of liver grafts in Europe is based on the Model for End-stage Liver Disease (MELD). As PCLD patients do not have a renal or liver impairment, the MELD score will be low. Indeed, the calculated median MELD score in our PCLD cohort was 6 (data not shown). This suggests that the MELD score does not accurately select those PCLD patients who benefit most from LT. There has been an attempt to design criteria for patients with a polycystic liver which should be met for them to be listed [28]. These criteria include: a massive polycystic liver and complication of polycystic liver which is likely to resolve after LT; not a candidate for, or failed to respond to, nontransplant interventions for relief of symptoms; clinically significant manifestations of liver disease that can be attributed to massive polycystic liver: cachexia, ascites, portal hypertension, hepatic venous outflow obstruction, biliary obstruction, cholestasis, recurrent cyst infection; severe malnutrition; serum albumin <2.2 mg/dl; lean body mass, reflected by decreased midarm circumference, measured in the nondominant arm midway between acromion and the olecranon process: <23.1 cm in female patients and <23.8 cm in male patients. Patients who meet these criteria should be granted a MELD score exception: patients with and without renal insufficiency (glomerular filtration rate or creatinine clearance <30 ml/min) may receive a MELD score of 15 and 20, respectively. The score may be increased by an additional 3 points every 3 months upon reapplication. The midarm circumference measured in the nondominant arm has been added as an additional criterion for MELD score exception, probably as it might reflect malnourishment. We have analyzed a set of 13 female patients with severe PCLD (median liver volume of 4648 ml) and found that the median midarm circumference of the nondominant arm was 27 cm, higher than the maximum threshold of 23.1 cm that is required for MELD exception (unpublished data). This suggests that the utility of this parameter is rather limited [12,13,15,29,30]. Unfortunately, it is very difficult to define exact selection criteria for LT for polycystic livers. The ideal way to compose a list of the best selection criteria is to execute a study in which patients will be randomly selected to either receive or not receive a transplant liver and with the primary end point being survival. It is possible that the patients with a transplant will have a lower survival rate, but gain a better quality of life. However, such a hypothetical randomized trial would be ethically unacceptable.

In our view, the only objective measurement of disease in polycystic livers is total liver volume, and a minimum threshold (for example, 5000 ml) would clarify the issue. The minimum threshold is not strict and we just give this as an example, as our experience shows that the majority of patients with polycystic livers smaller than 5000 ml still have a good quality of life and become more handicapped as the liver gets larger. In addition, the hepatic anatomy, the severity of symptoms, and the presence of complications, together with the general health status, should be considered in the selection of LT [31].

There are several limitations inherent to this study. We cannot exclude selection bias. We excluded 108 patients on the basis that we were not able to retrieve additional clinical information from these transplant centers. It is possible that this has introduced systematic selection bias, as we cannot exclude that centers with worse or better results did not respond. However, the sample we collected from 49 other centers coming from 11 different countries is representative for the ELTR region, limiting the possibility of systematic selection bias.

Another limitation is that the observation period was between 1985 and 2007. We now know that results from LT in terms of patient and graft survival have improved over time [21]. On the contrary, the relatively good survival data from our cohort study suggest that the space for improvement is limited. In addition, there was no temporal effect of patient and graft survival observed in our cohort.

Third, we pooled results from multiple LT centers that have different surgical and therapeutic protocols, including immunosuppressive therapy. Indeed, this suggests that the success of LT in PCLD is independent from the treatment center, which helps in interpreting the general applicability of this procedure.

Lastly, the indication for LT was based on the opinion of the transplant team. This may have introduced bias. As indicated, the criteria for LT in PCLD are rather arbitrary and might be interpreted differently among transplant centers.

Despite the listed limitations, LT for patients with PCLD is associated with good patient and graft survival, and should be provided as a therapeutic measure in carefully selected cases.

Authorship

LK: participated in research design, in the writing of the paper, in the performance of the research, and in data analysis. FN: participated in research design, performed research, and participated in the writing of the paper. RA: participated in the performance of the research. RJP: participated in research design, and in the performance of the research. PF: participated in the performance of the research. TB: participated in the performance of the research. PK: participated in the performance of the research. HJM: participated in research design, and in the performance of the research. JPHD: participated in research design, in the writing of the paper, in the performance of the research, and in data analysis.

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