



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/207272/>

Version: Published Version

Article:

Gittus, M., Moore, J. and Ong, A.C.M. (2024) Liver transplant recipients with polycystic liver disease have longer waiting times but better long-term clinical outcomes than those with liver disease due to other causes: a retrospective cross-sectional study. PLOS ONE, 19 (1). e0294717. ISSN: 1932-6203

<https://doi.org/10.1371/journal.pone.0294717>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

RESEARCH ARTICLE

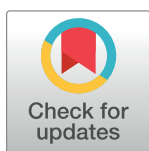
Liver transplant recipients with polycystic liver disease have longer waiting times but better long-term clinical outcomes than those with liver disease due to other causes: A retrospective cross-sectional study

Matt Gittus^{1*}, Joanna Moore^{2‡}, Albert C. M. Ong^{1‡}

1 Academic Nephrology Unit, Division of Clinical Medicine, Faculty of Health, Sheffield Teaching Hospitals Trust, University of Sheffield and Sheffield Kidney Institute, Sheffield, United Kingdom, **2** Liver Transplant Unit, Leeds Teaching Hospitals Trust, Leeds, United Kingdom

‡ JM and ACMO are joint senior authors on this work.

* m.gittus@sheffield.ac.uk



OPEN ACCESS

Citation: Gittus M, Moore J, Ong ACM (2024) Liver transplant recipients with polycystic liver disease have longer waiting times but better long-term clinical outcomes than those with liver disease due to other causes: A retrospective cross-sectional study. PLoS ONE 19(1): e0294717. <https://doi.org/10.1371/journal.pone.0294717>

Editor: Yuri Longatto Boteon, Hospital Israelita Albert Einstein, BRAZIL

Received: June 12, 2023

Accepted: November 6, 2023

Published: January 2, 2024

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0294717>

Copyright: © 2024 Gittus et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data underlying the results presented in the study are available

Abstract

Introduction

Liver transplantation is the only curative option for patients with polycystic liver disease (PLD). In the United Kingdom, these patients are listed on the variant syndrome list due to their preserved liver function reflected in the United Kingdom End-stage Liver Disease (UKELD) score. The transplantation and survival rates for this patient group in the UK have not been previously reported.

Methods

A retrospective cross-sectional analysis of patients receiving liver transplantation between 2010 and 2017 was performed using the NHS blood and transplantation database. This database contains the demographic, clinical parameters, indication for transplantation and follow-up of all patients in UK-based transplant centres. Basic statistics was performed using SPSS version 27.

Results

5412 recipients received elective liver allografts in the study period. 1.6% (100) of recipients had PLD as their primary indication for transplantation with 60 receiving liver only allografts and 40 receiving combined liver-kidney allografts. PLD patients had a >3-fold longer mean waiting time for transplantation compared to non-PLD patients, 508 days v 154 days respectively. PLD patients receiving combined liver-kidney allografts had a longer waiting time than those receiving a liver only allograft, 610 days v 438 days respectively. There were comparable patient survival rates for people with PLD and non-PLD primary indications at 30 days (94.0% vs 97.6%) and 1 year (92.0% vs 93.2%) but improved survival rates at 5 years (81.3% vs 76.5%). There were also comparable allograft survival rates for people with

from NHS Blood and Transplant (statistical.enquiries@nhsbt.nhs.uk).

Funding: The author(s) received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: ADPKD, Polycystic Kidney Disease; CLD, Chronic Liver Disease; HCC, Hepatocellular Carcinoma; MELD, Model for End-stage Liver Disease; NHSBT, National Health Service Blood and Transplant; ODT, Organ Donation and Transplantation; PLD, Polycystic Liver Disease; UK, United Kingdom; UKELD, United Kingdom Model for End-Stage Liver Disease; VS, Variant Syndrome.

PLD and non-PLD primary indications at 30 days (93.9% vs 95.3%) and 1 year (91.9% vs 91.2%) but improved survival rates at 5 years (82.5% vs 77.3%). Transplant centre-level analysis identified variation in the proportion of liver transplantations for people with PLD as their primary listed indication.

Conclusions

Patients with PLD wait significantly longer for liver transplantation compared to other indications. However, transplanted PLD patients demonstrate better longer-term patient and liver allograft survival rates compared to transplanted non-PLD patients. The unexpected variation between individual UK centres transplanting for PLD deserves further study.

Introduction

Polycystic Liver Disease (PLD) is the most common extrarenal feature of Autosomal Dominant Polycystic Kidney Disease (ADPKD) but may occur in isolation due to other rare gene variants [1–3]. The prevalence of PLD is estimated to be 1:100,000–1:1,000,000. It is usually asymptomatic but often identified when ADPKD is diagnosed. In contrast, patients with isolated Autosomal Dominant Polycystic Liver Disease (ADPLD) often remain undiagnosed [4–7] or under-diagnosed [8]. Advanced disease may lead to abdominal pain, cyst infection, dyspnoea, anorexia and reduced quality of life [9]. The majority of these symptoms correlate with the increase in total liver volume leading to compression of adjacent tissues despite the preservation of liver function [5]. There is a striking gender imbalance with a female-to-male ratio of 6:1 despite the autosomal dominant inheritance pattern of both ADPKD and ADPLD. Females also tend to develop a more severe phenotype with higher average liver volumes and younger age of presentation [7, 10–14]. This is likely to relate to the known effects of oestrogen on liver cyst growth [15].

Liver transplantation remains the only curative option for patients with PLD, being reserved for highly symptomatic patients to relieve symptom burden and improve quality of life [16–19]. Liver function is preserved in PLD and there is no increased risk of hepatocellular carcinoma [20]. Thus, most patients would not fulfil the common criteria for transplantation listing secondary to chronic liver disease (CLD), which requires a United Kingdom model for End-stage Liver Disease (UKELD) score ≥ 49 , or the presence of hepatocellular carcinoma. Patients with chronic liver disease whose UKELD score is < 49 are referred to as having a “variant syndrome” (VS). The PLD ‘variant syndrome’ indications for transplantation according to NHS Blood and Transplant (NHSBT) liver selection criteria and recipient registration include “intractable symptoms due to mass of liver or pain unresponsive to cystectomy, or severe complications secondary to portal hypertension” [21]. Swenson et al reported significant symptomatic relief and improvement in quality of life after transplant at their US-based transplant centre [22].

Prior to 2018, liver allografts were allocated on a regional basis in the UK with the “local” transplant centre receiving the first offer followed by allocation to other centres by blood group compatibility, size match and greatest need [23]. In 2018, the UK changed from a regional to a national allocation scheme: specifically, this involved the DBD (donation after brain death) liver allograft being offered to a named patient. The policy change was implemented to reduce waiting list mortality. Part of this change included a proportional offering of a 90% probability of selecting the Chronic Liver Disease/Hepatocellular carcinoma (CLD/HCC) list and a 10% probability of selecting the variant syndrome list based on their relative prevalence on the waiting list. This ensured that patients with variant syndromes would have

an earlier opportunity to receive a liver transplant. In addition, patients were also ranked according to their length of time on the waiting list [21, 24].

The primary objective of this study was to compare the waiting times and outcomes of patients with PLD and those with other indications for liver transplantation prior to the change in the allocation model for the UK. A secondary objective was to identify any variation in liver transplantation rates for patients with PLD between UK based transplant centres.

Materials and methods

A retrospective cross-sectional study was performed from the NHSBT Liver Transplant dataset of all patients undergoing primary liver transplantation in the UK between 01/01/2010 to 31/12/2017. This data is collected by the UK Transplant Registry through the DonorPath application software and electronic/paper forms. Data is submitted by NHSBT and hospital staff provide transplant follow-up information. All patient identifiers were irreversibly removed by NHSBT prior to access to the dataset and data subjects were not identifiable. Variables included the year of transplantation, CLD/HCC or VS category, cause of liver disease, waiting time, transplant centre, recipient details (gender, age and ethnicity), creatinine at the time of listing, UKELD, Model for End-stage Liver Disease (MELD) score and survival. Survival rates were informed by patient death (patient survival), allograft failure (allograft survival) or either combined (transplant failure). Before and during data analysis, the researchers were blinded to the participant's diagnosis and the transplanting centre in order to reduce bias. Data extraction occurred on 16/09/2021. A checklist has been undertaken and included according to the recommendations of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) in the [S1 Checklist](#).

Eligibility criteria

- Age $\geq$ 18 years
- Recipient of a liver allograft, liver only or combined liver-kidney, between 01/01/2010 and 31/12/2017
- Transplantation at a UK-based transplant centre
- Not transplanted for a super-urgent indication

The primary liver disease diagnosis is reported by the referring transplant centre. Diagnosis of PLD may be based on genetic analysis or the identification of multiple liver cysts on liver imaging (Reynolds criteria) [4].

Statistical analysis was performed using SPSS 2020 and Kaplan-Meier survival analysis. Quantitative variables were analysed in their continuous form with no categorisation performed. Any data subjects with incomplete demographic, primary disease, list type or survival data were excluded. We compared recipient characteristics using the Chi² test for categorical variables and the independent t-test for continuous variables. Sub-group analysis was performed using ANOVA to assess the difference between liver only and liver-kidney allografts. Ethical approval was not sought as the data provided was fully anonymised and routinely collected by NHSBT: Organ Donation and Transplantation (ODT).

Results

Study participants

All study participants included in the data analysis are summarised in [Fig 1](#). 5412 recipients received elective liver allografts between 2010 and 2017 in UK transplant centres. Their

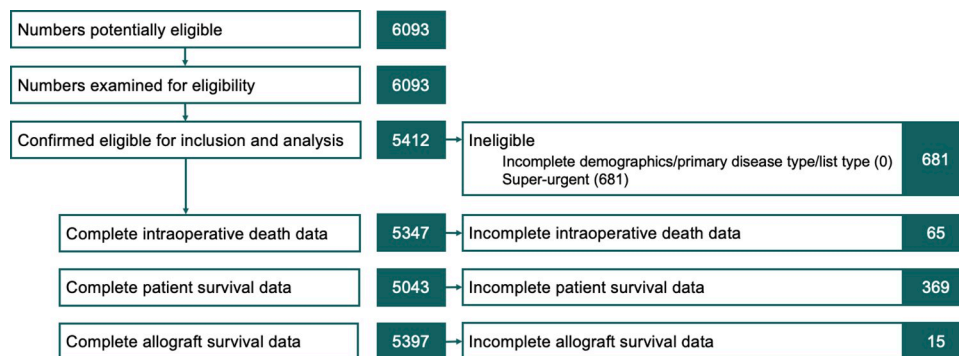


Fig 1. Flowchart of study participants included in data analysis.

<https://doi.org/10.1371/journal.pone.0294717.g001>

characteristics are summarised in Table 1. 5321 (98.3%) received a liver allograft alone and the remaining 91 (1.7%) received a combined liver-kidney allograft.

100 patients (1.6%) underwent transplantation with PLD as the primary indication from the elective transplantation list. There was a clear predominance of female patients in the PLD group (78.0%) and male patients in the non-PLD group (65.7%). Despite a similar mean age at transplantation (52.1 v 52.7 years), the non-PLD group was more evenly distributed across the age groups compared to the majority of recipients being in the 48–57 age group for the PLD group (Fig 2). There was a predominance of Caucasian recipients in all categories (S1 Table). Patients with PLD had a higher baseline listing creatinine compared to recipients transplanted for non-PLD indications.

Waiting time

Patients with PLD not meeting the criteria for the CLD/HCC indication, those listed variant syndrome pathway, had the longest waiting time for liver transplantation when compared to

Table 1. Liver allograft recipient characteristics.

List type	Non-PLD			PLD			Chi-square
	CLD/HCC	VS	Total	CLD/HCC	VS	Total	
Number of transplants	4988	324	5312	26	74	100	-
Liver only	4948 (99.2%)	313 (96.6%)	5261 (99.0%)	14 (53.8%)	46 (62.2%)	60 (60.0%)	<0.001
Liver-Kidney	40 (0.8%)	11 (3.4%)	54 (1.0%)	12 (46.2%)	28 (37.8%)	40 (40.0%)	
Gender (%)	M:3313 (66.4%) F:1674 (33.6%) NR:1 (0.0%)	M:177 (54.6%) F:147 (45.4%)	M:3490 (65.7%) F:1821 (34.3%) NR:1 (0.0%)	M:5 (19.2%) F:21 (80.8%)	M:17 (23.0%) F:57 (77.0%)	M:22 (22.0%) F:78 (78.0%)	<0.001
Mean age (SD)	52.7 (11.8)	49.4 (13.3)	52.7 (11.8)	52.7 (5.1)	51.9 (8.7)	52.1 (7.9)	
Mean UKELD (SD)	55.1 (5.6)	51.0 (5.8)	55.1 (5.6)	49.2 (3.5)	48.0 (3.1)	48.4 (3.3)	<0.001
Mean MELD (SD)	17.0 (6.9)	14.1 (6.6)	17.0 (6.9)	17.8 (5.9)	15.3 (6.8)	16.0 (6.7)	<0.001
Mean Cr umol/l (SD)	87.7 (52.5)	101.8 (109.0)	89.1 (59.0)	264.0 (184.7)	217.5 (187.4)	316.3 (885.6)	<0.0001

PLD–Polycystic liver disease, VS–Variant syndrome pathway, CLD–chronic liver disease pathway, M–Male, F–Female, NR–Not Reported, SD–standard deviation

<https://doi.org/10.1371/journal.pone.0294717.t001>

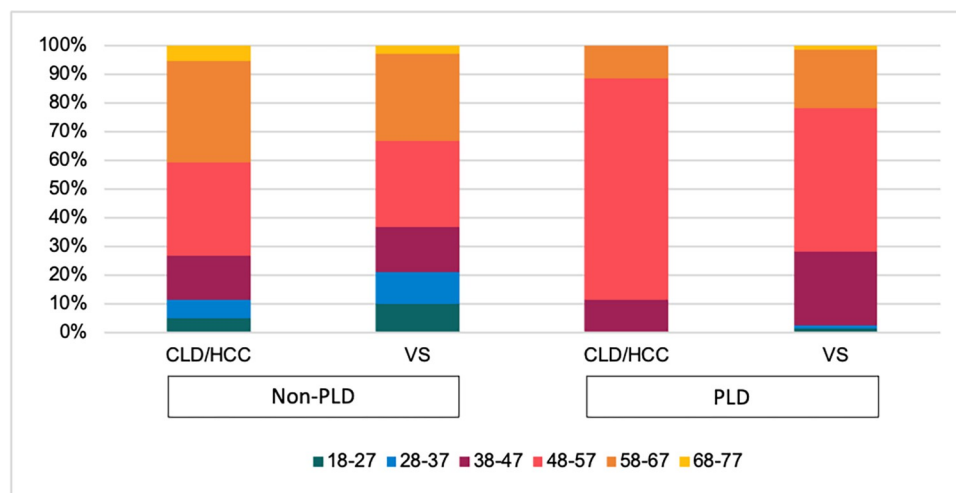


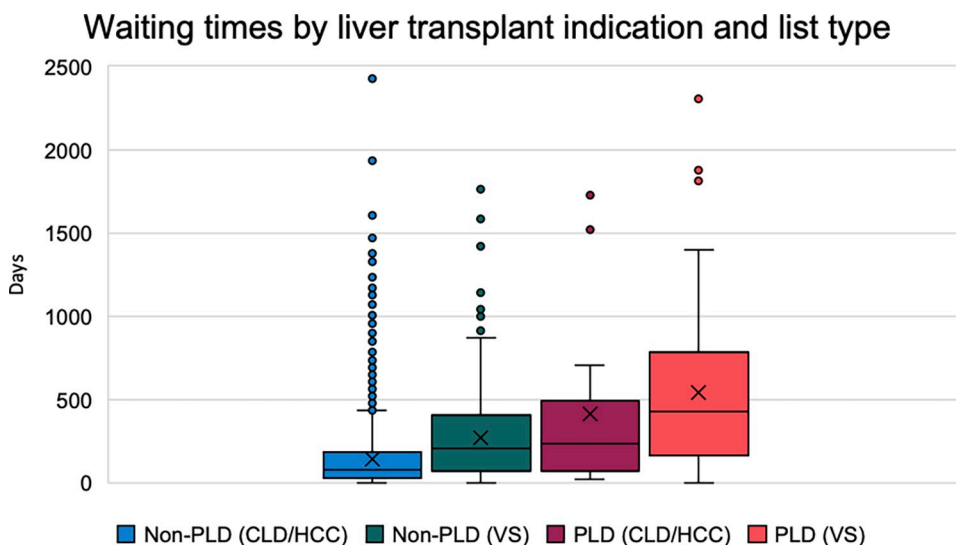
Fig 2. Liver graft recipient age distribution for indication and transplant list type.

<https://doi.org/10.1371/journal.pone.0294717.g002>

non-PLD CLD/HCC, PLD CLD/HCC and other variant syndrome conditions (Fig 3). Overall transplant recipients with PLD indications had a mean waiting time for transplantation from listing of 508 days compared to 154 days for non-PLD indications.

Patient and allograft survival

Overall, there was a low intraoperative mortality rate among liver allograft recipients with a total of 22 episodes over the study period (S2 Table). Patients with PLD undergoing



	Non-PLD		PLD	
List type	CLD/HCC	VS	CLD/HCC	VS
Mean (SD) days	146.2 (188.7)	276.1 (276.1)	413.7 (499.7)	541.5 (493.8)
Combined	153.7 (197.2)		507.6 (496.0)	

Fig 3. Box and whisker plot of waiting time by elective liver transplant indication.

<https://doi.org/10.1371/journal.pone.0294717.g003>

Table 2. Patient survival outcomes by transplantation indication and list type.

		Patient survival		
		30 days	1 year	5 years
Non-PLD	Total non-PLD (both)	4826/4943 (97.6%)	4544/4875 (93.2%)	2546/3329 (76.5%)
	Liver only	4784/4900 (97.6%)	4504/4832 (93.2%)	2527/3304 (76.5%)
	Liver-kidney	42/43 (97.7%)	40/43 (93.0%)	19/25 (76.0%)
	CLD/HCC (both)	4528/4637 (97.6%)	4272/4583 (93.2%)	2399/3134 (76.5%)
	Liver only	4497/4605 (97.7%)	4241/4551 (93.2%)	2384/3116 (76.5%)
	Liver-kidney	31/32 (96.9%)	31/32 (96.9%)	15/18 (83.3%)
	VS (both)	298/306 (97.4%)	272/292 (93.2%)	147/195 (75.4%)
	Liver only	287/295 (97.3%)	263/281 (93.6%)	143/188 (76.1%)
PLD	Liver-kidney	11/11 (100.0%)	9/11 (81.8%)	4/7 (57.1%)
	Total PLD (both)	94/100 (94.0%)	92/100 (92.0%)	52/64 (81.3%)
	Liver only	54/60 (90.0%)	52/60 (86.7%)	32/41 (78.0%)
	Liver-kidney	39/39 (100.0%)	39/39 (100.0%)	20/23 (87.0%)
	CLD/HCC (both)	25/26 (96.2%)	25/26 (96.2%)	13/14 (92.9%)
	Liver only	13/14 (92.9%)	13/14 (92.9%)	6/7 (85.7%)
	Liver-kidney	11/11 (100.0%)	11/11 (100.0%)	7/7 (100.0%)
	VS (both)	69/74 (93.2%)	67/74 (90.5%)	39/50 (78.0%)
	Liver only	41/46 (89.1%)	39/46 (84.8%)	26/34 (76.5%)
	Liver-kidney	28/28 (100.0%)	28/28 (100.0%)	13/16 (81.3%)

<https://doi.org/10.1371/journal.pone.0294717.t002>

transplantation had comparable patient survival rates at 30 days and 1 year but higher survival rates at 5 years compared to those transplanted for non-PLD indications: 81.3% versus 76.5% (Tables 2 & 3, Fig 4). Comparable allograft survival rates were demonstrated at 30 days and 1 year but patients transplanted for PLD indications had higher 5-year allograft survival rates: 82.5% versus 77.3% (Tables 4 & 5, Fig 5).

Patients with PLD transplanted from the CLD/HCC list, compared to their counterparts transplanted from the VS list, had a higher patient survival rate at 30 days with 96.2% (95% CI 0.89–1.04) v 93.2% (95% CI 0.88–0.99); 1 year with 96.2% (95% CI 0.89–1.04) v 90.5% (95% CI 0.84–0.97); and 5 years with 92.9% (95% CI 0.89–1.04) vs 78.0% (95% CI 0.75–0.93). Similar findings were demonstrated for allograft survival.

There were 860 reported episodes of liver allograft failure, excluding recipient death as the cause of failure (Table 6). Recurrent disease and vascular complications were the most commonly reported single cause of allograft failure in people with non-PLD indications for liver transplantation at 13.9% and 15.9% respectively. Acute vascular occlusion was the most commonly reported single cause of allograft failure in people with PLD indications for liver transplantation at 27.3% (3 patients).

Table 3. Patient survival probability by transplantation indication and list type.

		Patient survival probability (95% CI)		
		30 days	1 year	5 years
Non-PLD	CLD/HCC	0.976 (0.97–0.98)	0.933 (0.93–0.94)	0.828 (0.82–0.84)
	VS	0.974 (0.96–0.99)	0.934 (0.91–0.96)	0.818 (0.77–0.87)
PLD	CLD/HCC	0.962 (0.89–1.04)	0.962 (0.89–1.04)	0.962 (0.89–1.04)
	VS	0.932 (0.88–0.99)	0.905 (0.84–0.97)	0.838 (0.75–0.93)

Log rank (Mantel-Cox): Chi-square 4.385, df 3, P = 0.223

<https://doi.org/10.1371/journal.pone.0294717.t003>

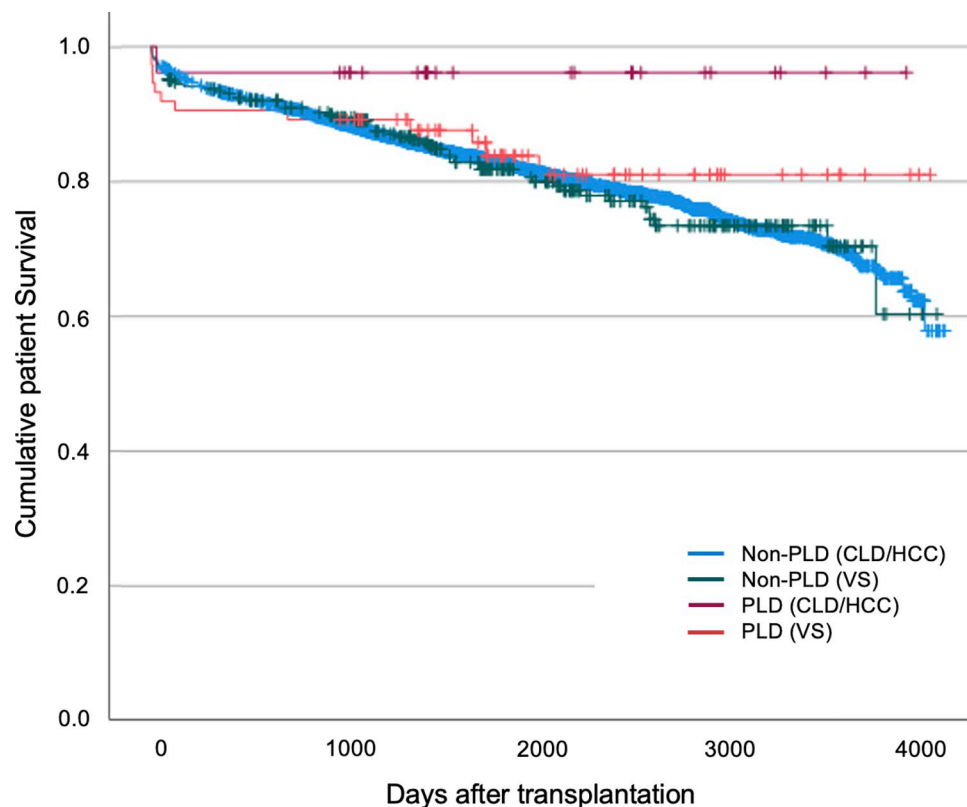


Fig 4. Kaplan Meier survival curve for patient survival following elective transplantation.

<https://doi.org/10.1371/journal.pone.0294717.g004>

Table 4. Allograft survival outcomes by transplantation indication and list type.

		Allograft survival		
		30 days	1 year	5 years
Non-PLD	Total non-PLD (both)	5003/5249 (95.3%)	4630/5079 (91.2%)	2521/3261 (77.3%)
	Liver only	4956/5201 (95.3%)	4586/5033 (91.1%)	2498/3234 (77.2%)
	Liver-kidney	47/48 (97.9%)	44/46 (95.7%)	22/26 (84.6%)
	CLD/HCC (both)	4698/4931 (95.3%)	4355/4781 (91.1%)	2381/3080 (77.3%)
	Liver only	4662/4894 (95.3%)	4319/4744 (91.0%)	2361/3057 (77.2%)
	Liver-kidney	36/37 (97.3%)	36/37 (97.3%)	19/22 (86.4%)
	VS (both)	305/318 (95.9%)	275/298 (92.3%)	140/181 (77.3%)
	Liver only	294/307 (95.8%)	267/289 (92.4%)	137/177 (77.4%)
	Liver-kidney	11/11 (100.0%)	8/9 (88.9%)	3/4 (75.0%)
PLD	Total PLD (both)	93/99 (93.9%)	91/99 (91.9%)	52/63 (82.5%)
	Liver only	53/59 (89.8%)	51/59 (86.4%)	32/41 (78.0%)
	Liver-kidney	39/39 (100.0%)	29/29 (100.0%)	20/22 (90.9%)
	CLD/HCC (both)	25/26 (96.2%)	25/26 (96.2%)	13/14 (92.9%)
	Liver only	13/14 (92.9%)	13/14 (92.9%)	6/7 (85.7%)
	Liver-kidney	11/11 (100.0%)	11/11 (100.0%)	7/7 (100.0%)
	VS (both)	68/73 (93.2%)	66/73 (90.4%)	39/49 (79.6%)
	Liver only	40/45 (88.9%)	38/45 (84.4%)	26/34 (76.5%)
	Liver-kidney	28/28 (100.0%)	28/28 (100.0%)	13/15 (86.7%)

<https://doi.org/10.1371/journal.pone.0294717.t004>

Table 5. Allograft survival probability by transplantation indication and list type.

		Allograft survival probability (95% CI)		
		30 days	1 year	5 years
Non-PLD	CLD/HCC	0.953 (0.89–1.01)	0.913 (0.83–0.99)	0.847 (0.75–0.95)
	VS	0.959 (0.93–0.98)	0.927 (0.90–0.96)	0.858 (0.82–0.90)
PLD	CLD/HCC	0.962 (0.89–1.04)	0.962 (0.89–1.04)	0.962 (0.89–1.04)
	VS	0.932 (0.88–0.99)	0.905 (0.84–0.97)	0.857 (0.77–0.94)

Log rank (Mantel-Cox): Chi-square 3.866, df 3, P = 0.276

<https://doi.org/10.1371/journal.pone.0294717.t005>

Sub-group analysis of liver alone vs liver-kidney transplantation

A higher proportion of patients awaiting liver transplantation for PLD received a combined liver-kidney transplant compared to patients transplanted for other indications (Table 1).

Patients with PLD who were transplanted for VS indications had the longest waiting time for both liver allografts alone and combined liver-kidney transplantation (Fig 6).

In this study period, no patients receiving combined liver-kidney allografts were reported to have died intraoperatively (S2 Table). Survival rates for patients receiving liver only allografts and combined liver-kidney allografts are presented in Tables 2 and 4.

Variation between transplant centres

There was an unexpected but statistically significant variation in the proportion of liver transplantations performed for PLD indications between the 6 liver transplant centres in the United

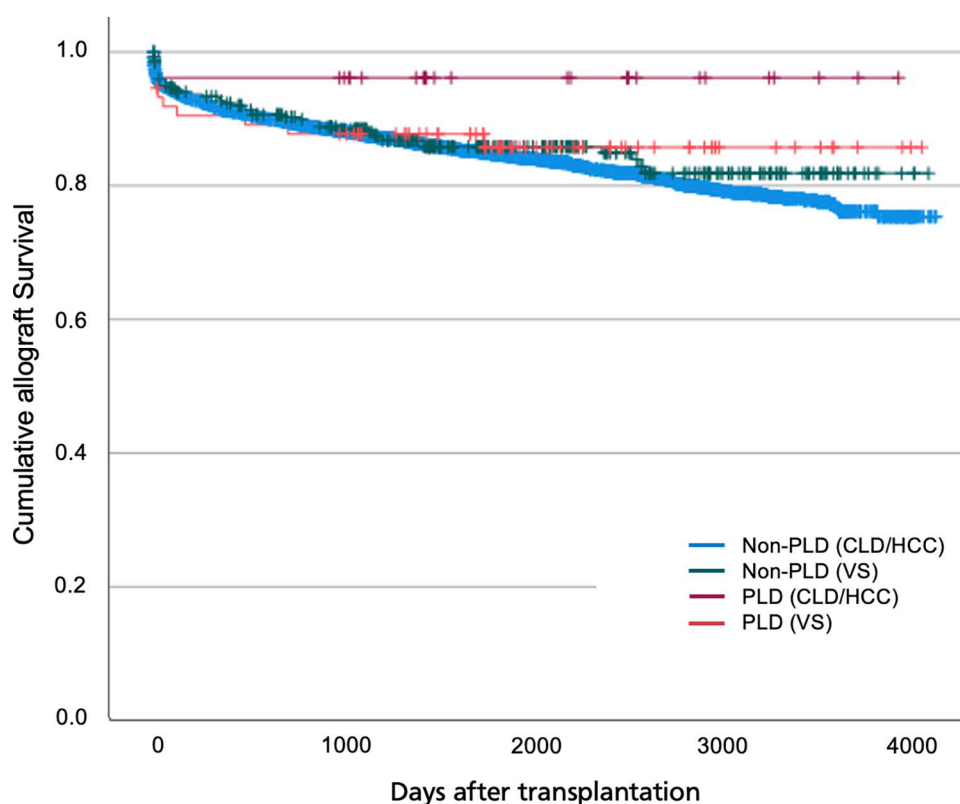


Fig 5. Kaplan Meier survival curve for allograft survival following elective transplantation.

<https://doi.org/10.1371/journal.pone.0294717.g005>

Table 6. Summary of allograft failure by PLD diagnosis and transplantation pathway.

List type	Non-PLD			PLD			Overall
	CLD/HCC	VS	Total	CLD/HCC	VS	Total	
Graft still functioning	3803 (76.2%)	247 (76.2%)	4050 (76.2%)	25 (96.2%)	60 (81.1%)	85 (85.0%)	4135 (76.4%)
Recipient death	434 (8.7%)	34 (10.5%)	468 (8.8%)	0 (0.0%)	4 (5.4%)	4 (4.0%)	472 (8.7%)
Primary non-functioning	80 (10.0%)	3 (0.9%)	83 (1.6%)	0 (0.0%)	2 (2.7%)	2 (2.0%)	85 (1.6%)
Recurrent disease	113 (2.3%)	5 (1.5%)	118 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	118 (2.2%)
All rejection	76 (1.5%)	4 (1.2%)	80 (1.5%)	0 (0.0%)	1 (1.4%)	1 (1.0%)	81 (1.5%)
Acute Rejection	16 (0.3%)	0 (0.0%)	16 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (0.3%)
Chronic Rejection	54 (1.1%)	4 (1.2%)	58 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	58 (1.1%)
Ductopenic rejection	6 (0.1%)	0 (0.0%)	6 (0.1%)	0 (0.0%)	1 (1.4%)	1 (1.0%)	7 (0.1%)
All vascular	123 (2.5%)	12 (3.7%)	135 (2.5%)	1 (3.8%)	2 (2.7%)	3 (3.0%)	138 (2.5%)
Acute vascular occlusion	78 (1.6%)	9 (2.8%)	87 (1.6%)	1 (3.8%)	2 (2.7%)	3 (3.0%)	90 (1.7%)
Vascular occlusion	34 (0.7%)	2 (0.6%)	36 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	36 (0.7%)
Non-thrombotic infarction	11 (0.2%)	1 (0.3%)	12 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (0.2%)
Biliary complications	100 (2.0%)	5 (1.5%)	105 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	105 (1.9%)
Other	167 (3.3%)	8 (2.5%)	175 (3.3%)	0 (0.0%)	3 (4.1%)	3 (3.0%)	178 (3.3%)
Unknown	92 (1.8%)	6 (1.9%)	98 (1.8%)	0 (0.0%)	2 (2.7%)	2 (2.0%)	100 (1.8%)
Total	4988	324	5312	26	74	100	5412

<https://doi.org/10.1371/journal.pone.0294717.t006>

Kingdom (UK) which ranged from 0.3% to 2.7% of all liver transplants performed at each centre ($P < 0.0001$), Table 7. Similarly, there was a statistically significant variation in the proportion of liver transplants being performed from the VS list ranging from 0.3% to 10.1% of the liver transplant performed at that centre ($P < 0.0001$), Table 8. Conversely, there was less variation in the proportion of liver-kidney transplants performed at different centres, ranging from 0.9% to 2.6% ($P = 0.1$), Table 7.

Discussion

Patients with PLD wait 3 times longer for liver transplantation than those with non-PLD CLD/HCC and other variant syndromes. This is independent of whether they are listed for CLD/HCC or VS indications. During the time period studied, only 1.5% of transplantations were for combined liver-kidney allografts. Longer waiting times can lead to advanced age,

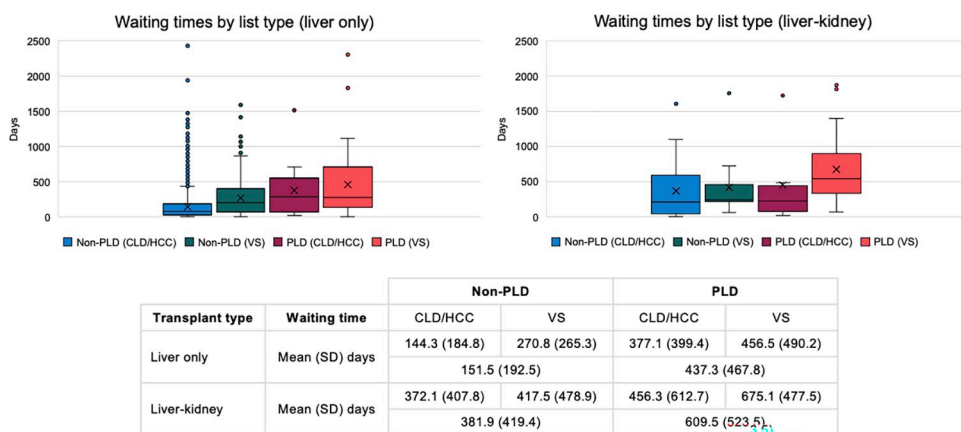


Fig 6. Waiting time of elective liver and liver-kidney transplant allografts by indication and list type.

<https://doi.org/10.1371/journal.pone.0294717.g006>

Table 7. Elective liver transplantation (PLD vs Non-PLD) by centre.

Centre	Allograft type	Non-PLD			PLD			Overall
		CLD/HCC	VS	Total	CLD/HCC	VS	Total	
A	Both	334 (99.1%)	0 (0.0%)	334 (99.1%)	2 (0.6%)	1 (0.3%)	3 (0.9%)	337 (100.0%)
	Liver only	331 (98.2%)	0 (0.0%)	331 (98.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	331 (98.2%)
	Liver-kidney	3 (0.9%)	0 (0.0%)	3 (0.9%)	2 (0.6%)	1 (0.3%)	3 (0.9%)	6 (1.8%)
B	Both	880 (89.4%)	87 (8.8%)	967 (98.3%)	5 (0.5%)	12 (1.2%)	17 (1.7%)	984 (100.0%)
	Liver only	866 (88.0%)	84 (8.5%)	950 (96.5%)	2 (0.2%)	6 (0.6%)	8 (0.8%)	958 (97.4%)
	Liver-kidney	14 (1.4%)	3 (0.3%)	17 (1.7%)	3 (0.3%)	6 (0.6%)	9 (0.9%)	26 (2.6%)
C	Both	824 (95.0%)	40 (4.6%)	864 (99.7%)	0 (0.0%)	3 (0.3%)	3 (0.3%)	867 (100.0%)
	Liver only	820 (94.6%)	37 (4.3%)	857 (98.8%)	0 (0.0%)	2 (0.2%)	2 (0.2%)	859 (99.1%)
	Liver-kidney	4 (0.5%)	3 (0.3%)	7 (0.8%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	8 (0.9%)
D	Both	770 (94.2%)	33 (4.0%)	803 (98.3%)	5 (0.6%)	9 (1.1%)	14 (1.7%)	817 (100.0%)
	Liver only	767 (93.9%)	33 (4.0%)	800 (97.9%)	3 (0.4%)	3 (0.4%)	6 (0.7%)	806 (98.7%)
	Liver-kidney	3 (0.4%)	0 (0.0%)	3 (0.4%)	2 (0.2%)	6 (0.7%)	8 (1.0%)	11 (1.3%)
E	Both	1438 (90.1%)	117 (7.3%)	1555 (97.4%)	7 (0.4%)	34 (2.1%)	41 (2.6%)	1596 (100.0%)
	Liver only	1426 (89.3%)	114 (7.1%)	1540 (96.5%)	5 (0.3%)	25 (1.6%)	30 (1.9%)	1570 (98.4%)
	Liver-kidney	12 (0.8%)	3 (0.2%)	15 (0.9%)	2 (0.1%)	9 (0.6%)	11 (0.7%)	26 (1.6%)
F	Both	742 (91.5%)	47 (5.8%)	789 (97.3%)	7 (0.9%)	15 (1.8%)	22 (2.7%)	811 (100.0%)
	Liver only	738 (91.0%)	45 (5.5%)	783 (96.5%)	4 (0.5%)	10 (1.2%)	14 (1.7%)	797 (98.3%)
	Liver-kidney	4 (0.5%)	2 (0.2%)	6 (0.7%)	3 (0.4%)	5 (0.6%)	8 (1.0%)	14 (1.7%)
Total	Both	4988 (92.2%)	324 (6.0%)	5312 (98.2%)	26 (0.5%)	74 (1.4%)	100 (1.8%)	5412 (100.0%)
	Liver only	4948 (91.4%)	313 (5.8%)	5261 (97.2%)	14 (0.3%)	46 (0.8%)	60 (1.1%)	5321 (98.3%)
	Liver-kidney	40 (0.7%)	11 (0.2%)	51 (0.9%)	12 (0.2%)	28 (0.5%)	40 (0.7%)	91 (1.7%)

<https://doi.org/10.1371/journal.pone.0294717.t007>

malnutrition and increased frailty which could lead to patients dying on the waiting list, becoming unsuitable for transplantation and experiencing a worse quality of life [25, 26]. Our study demonstrates that there are comparable survival rates, patient and allograft, for patients with PLD and non-PLD indications for transplantation at 30 days and 1 year. However, transplant recipients with PLD have higher 5-year survival rates.

Our study also demonstrates a difference between patients with PLD transplanted from the two different list types, CLD/HCC and VS. PLD patients who received a liver allograft from the CLD/HCC list had greater patient, allograft and transplant survival rates at 30 days, 1 year and 5 years. One potential explanation could be the shorter waiting time for the patients transplanted from the CLD/HCC list.

The current ranking of patients on the waiting list for variant syndrome indications is based solely on time on the waiting list. This does not take into consideration the impact on functional life, intractable pain and severely diminished quality of life [27]. Lang et al reported symptomatic relief in all patients following transplantation [28]. Furthermore, Kirchner et al

Table 8. Elective liver transplantation (CLD/HCC vs VS) by centre.

List type	Centre						
	A	B	C	D	E	F	Total
CLD/HCC	336 (99.7%)	885 (89.9%)	824 (95.0%)	775 (94.9%)	1445 (90.5%)	749 (92.4%)	5014 (92.6%)
VS	1 (0.3%)	99 (10.1%)	43 (5.0%)	42 (5.1%)	151 (9.5%)	62 (7.6%)	398 (7.4%)
Total	337	984	867	817	1596	811	5412
% of UK transplants (2010–2017)	6.2%	18.2%	16.0%	15.1%	29.5%	15.0%	100.0%

<https://doi.org/10.1371/journal.pone.0294717.t008>

demonstrated an improved quality of life following transplantation with 91% of their patients reporting feeling “much better” or “better” based on the Short Form Health Survey, SF-36 [9]. Several authors have recommended that patients should not wait until the onset of end-stage complications of PLD before being offered the option of transplantation [22, 28, 29]. According to current indications, patients in the UK with PLD are waiting until their symptoms are “intractable”.

Our results are specific to the UK population of people with PLD receiving a liver transplant within the specific time period. Although organ allocation policies vary between different countries limiting generalisability, this study adds to the existing literature from other countries demonstrating similar outcomes. An increased risk of perioperative mortality reported in the literature is suspected to be due to the increased operative complexity in patients with PLD. This is supported by our dataset where 1% of PLD recipients died intraoperatively compared to 0.4% of non-PLD recipients. This could be made worse by delaying transplantation due to the continued increase in cyst and liver size [26, 30]. Nonetheless, our study demonstrates that patients with PLD have a better patient and liver allograft survival rate following transplantation independent of whether transplanted for CLD/HCC or VS indications. Other single centre studies have reported similar findings (86–96% survival) [31, 32].

The 860 reported episodes of allograft failure represent 15.9% of transplantation episodes within the time period in our study. This is consistent with worldwide reported liver allograft failure rates of 5–22% [33]. Recurrence of primary disease was the most common cause of liver allograft failure amongst patients with non-PLD indications for liver transplantation. As would be expected, there was no evidence of recurrent disease amongst recipients with PLD given that liver transplantation is curative for their genetic condition. Vascular complications were the most common cause of liver allograft failure in recipients with both non-PLD and PLD indications. This is in line with other studies which report vascular complications as a frequent indication for re-transplantation [33–35].

An unexpected finding from our study was the significant variation in the rate of liver transplantation for PLD patients between transplant centres in the UK. This may be explained by the significant variation between centres in the proportion of transplanted allografts from the variant syndrome list. Another reason could be the interpretation of the criteria in the current liver allocation policy used to inform listing practices. The term “intractable” is used to quantify the severity of symptoms that would warrant referral for liver transplantation which is clearly subjective. The criteria also includes “symptom(s) due to (the) mass of liver or pain unresponsive to cystectomy” although cystectomy is not widely implemented in UK clinical practice [36]. Clarifying the precise indications is likely to promote more equitable access to liver transplantation for PLD patients across the UK.

Strengths and limitations

We report transplantation rates prior to the updated listing policy in 2018 for people with and without PLD in UK-based transplant centres. One weakness of this study is that we are unable to comment on the characteristics of patients not listed for transplantation or those on the waiting list. Although there was overall a high level of complete data return, there was incomplete reporting of intraoperative death (87.9% complete), patient death (90.7% complete) and graft failure (99.6% complete).

Recommendations for clinical practice and future research

We recommend further research to assess the impact of the change from regional to national liver allograft allocation since 2018. These findings could further refine the current national

allocation policy, especially for patients with a variant syndrome indication. Patients on the waiting list should be studied longitudinally after listing and outcome data obtained on those assessed for listing but who are then not listed. Finally, the variation in transplantation rates for patients with PLD between different UK centres should be analysed.

Conclusions

Patients with PLD have a longer waiting time to transplantation compared to those with other indications for liver transplantation but better long-term patient and liver allograft survival rates. This is independent of the type of list at registration, chronic liver disease/hepatocellular carcinoma or variant syndrome list. There is significant variation in the numbers of patients with PLD undergoing liver transplantation at different UK-based transplant centres.

Supporting information

S1 Checklist. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist.
(DOCX)

S1 Table. Patient ethnicity by PLD diagnosis and transplantation pathway.
(PNG)

S2 Table. Intraoperative death.
(PNG)

Acknowledgments

National Institute for Health and Care Research, NHS Blood and Transplantation, statistics services and the transplant patients who consented to data collection.

Author Contributions

Conceptualization: Matt Gittus, Joanna Moore, Albert C. M. Ong.

Data curation: Matt Gittus.

Formal analysis: Matt Gittus.

Methodology: Matt Gittus.

Project administration: Matt Gittus.

Supervision: Joanna Moore, Albert C. M. Ong.

Writing – original draft: Matt Gittus.

Writing – review & editing: Matt Gittus, Joanna Moore, Albert C. M. Ong.

References

1. Cornec-Le Gall E, Torres VE, Harris PC. Genetic Complexity of Autosomal Dominant Polycystic Kidney and Liver Diseases. *J Am Soc Nephrol*. 2018; 29(1):13–23. <https://doi.org/10.1681/ASN.2017050483> PMID: [29038287](https://pubmed.ncbi.nlm.nih.gov/29038287/)
2. Patel A, Chapman AB, Mikolajczyk AE. A Practical Approach to Polycystic Liver Disease. *Clin Liver Dis (Hoboken)*. 2019; 14(5):176–9. <https://doi.org/10.1002/cld.864> PMID: [31879559](https://pubmed.ncbi.nlm.nih.gov/31879559/)
3. van de Laarschot LFM, Drenth JPH. Genetics and mechanisms of hepatic cystogenesis. *Biochim Biophys Acta Mol Basis Dis*. 2018; 1864(4 Pt B):1491–7. <https://doi.org/10.1016/j.bbadis.2017.08.003> PMID: [28782656](https://pubmed.ncbi.nlm.nih.gov/28782656/)

4. van Aerts RMM, van de Laarschot LFM, Banales JM, Drenth JPH. Clinical management of polycystic liver disease. *J Hepatol*. 2018; 68(4):827–37. <https://doi.org/10.1016/j.jhep.2017.11.024> PMID: [29175241](#)
5. Cnossen WR, Drenth JP. Polycystic liver disease: an overview of pathogenesis, clinical manifestations and management. *Orphanet J Rare Dis*. 2014; 9:69. <https://doi.org/10.1186/1750-1172-9-69> PMID: [24886261](#)
6. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet*. 2007; 369(9569):1287–301. [https://doi.org/10.1016/S0140-6736\(07\)60601-1](https://doi.org/10.1016/S0140-6736(07)60601-1) PMID: [17434405](#)
7. Van Keimpema L, De Koning DB, Van Hoek B, Van Den Berg AP, Van Oijen MG, De Man RA, et al. Patients with isolated polycystic liver disease referred to liver centres: clinical characterization of 137 cases. *Liver Int*. 2011; 31(1):92–8. <https://doi.org/10.1111/j.1478-3231.2010.02247.x> PMID: [20408955](#)
8. Chandok N. Polycystic liver disease: a clinical review. *Ann Hepatol*. 2012; 11(6):819–26. PMID: [23109444](#)
9. Kirchner GI, Rifai K, Cantz T, Nashan B, Terkamp C, Becker T, et al. Outcome and quality of life in patients with polycystic liver disease after liver or combined liver-kidney transplantation. *Liver Transpl*. 2006; 12(8):1268–77. <https://doi.org/10.1002/lt.20780> PMID: [16741930](#)
10. Brancatelli G, Federle MP, Vilgrain V, Vullierme MP, Marin D, Lagalla R. Fibropolycystic liver disease: CT and MR imaging findings. *Radiographics*. 2005; 25(3):659–70. <https://doi.org/10.1148/rg.253045114> PMID: [15888616](#)
11. Chapman AB. Cystic disease in women: clinical characteristics and medical management. *Adv Ren Replace Ther*. 2003; 10(1):24–30. <https://doi.org/10.1053/jarr.2003.50005> PMID: [12616460](#)
12. Sherstha R, McKinley C, Russ P, Scherzinger A, Bronner T, Showalter R, et al. Postmenopausal estrogen therapy selectively stimulates hepatic enlargement in women with autosomal dominant polycystic kidney disease. *Hepatology*. 1997; 26(5):1282–6. <https://doi.org/10.1002/hep.510260528> PMID: [9362373](#)
13. Bae KT, Zhu F, Chapman AB, Torres VE, Grantham JJ, Guay-Woodford LM, et al. Magnetic resonance imaging evaluation of hepatic cysts in early autosomal-dominant polycystic kidney disease: the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease cohort. *Clin J Am Soc Nephrol*. 2006; 1(1):64–9. <https://doi.org/10.2215/CJN.00080605> PMID: [17699192](#)
14. Qian Q, Li A, King BF, Kamath PS, Lager DJ, Huston J, 3rd, et al. Clinical profile of autosomal dominant polycystic liver disease. *Hepatology*. 2003; 37(1):164–71. <https://doi.org/10.1053/jhep.2003.50006> PMID: [12500201](#)
15. National Organization for Rare Disorders. Polycystic Liver Disease. Rare Disease Database 2018.
16. Kothadia JP, Kreitman K, Shah JM. Polycystic Liver Disease. *StatPearls*. Treasure Island (FL)2022.
17. Drenth JP, Chrispijn M, Nagorney DM, Kamath PS, Torres VE. Medical and surgical treatment options for polycystic liver disease. *Hepatology*. 2010; 52(6):2223–30. <https://doi.org/10.1002/hep.24036> PMID: [21105111](#)
18. Torres VE. Treatment of polycystic liver disease: one size does not fit all. *Am J Kidney Dis*. 2007; 49(6):725–8. <https://doi.org/10.1053/j.ajkd.2007.04.009> PMID: [17533013](#)
19. Salceda JA, Bracco R, Fernandez D. Timing and Treatment Options in Adult Polycystic Liver Disease: A Rare Familiar Case as Example. *Arq Bras Cir Dig*. 2018; 31(4):e1411. <https://doi.org/10.1590/0102-672020180001e1411> PMID: [30539986](#)
20. Kawada M, Hayami N, Suwabe T, Hoshino J, Sumida K, Mise K, et al. Hepatocellular Carcinoma in a Patient with Polycystic Liver Disease. *Intern Med*. 2015; 54(15):1891–6. <https://doi.org/10.2169/internalmedicine.54.3924> PMID: [26234231](#)
21. National Health Service Blood and Transplantation. Liver Transplantation: Selection Criteria and Recipient Registration (POL 195/7). 2018.
22. Swenson K, Seu P, Kinkhabwala M, Maggard M, Martin P, Goss J, et al. Liver transplantation for adult polycystic liver disease. *Hepatology*. 1998; 28(2):412–5. <https://doi.org/10.1002/hep.510280218> PMID: [9696005](#)
23. National Health Service Blood and Transplantation. Liver Transplantation: Selection Criteria and Recipient Registration (POL 195/6). 2017.
24. NHS Blood & Transplant. The transplant benefit score and the national liver offering scheme. 2018.
25. Wu HHL, Woywodt A, Nixon AC. Frailty and the Potential Kidney Transplant Recipient: Time for a More Holistic Assessment? *Kidney360*. 2020; 1(7):685–90. <https://doi.org/10.34067/KID.0001822020> PMID: [35372945](#)

26. Taner B, Willingham DL, Hewitt WR, Grewal HP, Nguyen JH, Hughes CB. Polycystic liver disease and liver transplantation: single-institution experience. *Transplant Proc.* 2009; 41(9):3769–71. <https://doi.org/10.1016/j.transproceed.2009.05.043> PMID: 19917384
27. Starzl TE, Reyes J, Tzakis A, Miele L, Todo S, Gordon R. Liver transplantation for polycystic liver disease. *Arch Surg.* 1990; 125(5):575–7. <https://doi.org/10.1001/archsurg.1990.01410170021003> PMID: 2331212
28. Lang H, von Woellwarth J, Oldhafer KJ, Behrend M, Schlitt HJ, Nashan B, et al. Liver transplantation in patients with polycystic liver disease. *Transplant Proc.* 1997; 29(7):2832–3. [https://doi.org/10.1016/s0041-1345\(97\)00696-9](https://doi.org/10.1016/s0041-1345(97)00696-9) PMID: 9365580
29. Pirenne J, Aerts R, Yoong K, Gunson B, Koshiba T, Fournneau I, et al. Liver transplantation for polycystic liver disease. *Liver Transpl.* 2001; 7(3):238–45. <https://doi.org/10.1053/jlts.2001.22178> PMID: 11244166
30. Gedaly R, Guidry P, Davenport D, Daily M, Ronsenau J, Shah M, et al. Peri-operative challenges and long-term outcomes in liver transplantation for polycystic liver disease. *HPB (Oxford).* 2013; 15(4):302–6. <https://doi.org/10.1111/j.1477-2574.2012.00579.x> PMID: 23458516
31. Alsager M, Neong SF, Gandhi R, Teriaky A, Tang E, Skaro A, et al. Liver transplantation in adult polycystic liver disease: the Ontario experience. *BMC Gastroenterol.* 2021; 21(1):115. <https://doi.org/10.1186/s12876-021-01703-x> PMID: 33750299
32. van Keimpema L, Nevens F, Adam R, Porte RJ, Fikatas P, Becker T, et al. Excellent survival after liver transplantation for isolated polycystic liver disease: an European Liver Transplant Registry study. *Transpl Int.* 2011; 24(12):1239–45. <https://doi.org/10.1111/j.1432-2277.2011.01360.x> PMID: 21955068
33. Morgan J MS, Tripathi D, Perera T. P046 Liver re-transplantation in adults; a single UK centre experience (2009–2020). *Gut.* 2021; 70(3):A34–5.
34. Vivarelli M, Cucchetti A, La Barba G, Bellusci R, De Vivo A, Nardo B, et al. Ischemic arterial complications after liver transplantation in the adult: multivariate analysis of risk factors. *Arch Surg.* 2004; 139(10):1069–74. <https://doi.org/10.1001/archsurg.139.10.1069> PMID: 15492145
35. Pawlak J, Grodzicki M, Leowska E, Malkowski P, Michalowicz B, Nyckowski P, et al. Vascular complications after liver transplantation. *Transplant Proc.* 2003; 35(6):2313–5. [https://doi.org/10.1016/s0041-1345\(03\)00836-4](https://doi.org/10.1016/s0041-1345(03)00836-4) PMID: 14529925
36. NHS Blood and Transfusion. Liver Transplantation: Selection Criteria and Recipient Registration. Policy POL 195/62017.