ORIGINAL ARTICLE

Case Control Study

Portal hypertension in polycystic liver disease patients does not affect wait-list or immediate post-liver transplantation outcomes

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Abstract

AIM

To establish the impact of portal hypertension (PH) on wait-list/post-transplant outcomes in patients with polycystic liver disease (PCLD) listed for liver transplantation.

METHODS

A retrospective single-centre case controlled study of consecutive patients listed for liver transplantation over 12 years was performed from our centre. PH in the PCLD cohort was defined by the one or more of following parameters: (1) presence of radiological or endoscopic documented varices from our own centre or the referral centre; (2) splenomegaly (> 11 cm) on radiology in

absence of splenic cysts accounting for increased imaging size; (3) thrombocytopenia (platelets < 150 × 10^9/L); or (4) ascites without radiological evidence of hepatic venous outflow obstruction from a single cyst.

RESULTS

Forty-seven PCLD patients (F: M = 42: 5) were listed for liver transplantation (LT) (single organ, *n* = 35; combined liver-kidney transplantation, *n* = 12) with 19 patients (40.4%) having PH. When comparing the PH group with non-PH group, the mean listing age (PH group, 50.6 (6.4); non-PH group, 47.1 (7.4) years; *P* = 0.101), median listing MELD (PH group, 12; non-PH group, 11; *P* = 0.422) median listing UKELD score (PH group, 48; non-PH group, 46; *P* = 0.344) and need for renal replacement therapy (*P* = 0.317) were similar. In the patients who underwent LT alone, there was no difference in the duration of ICU stay (PH, 3 d; non-PH, 2 d; *P* = 0.188), hospital stay length (PH, 9 d; non-PH, 10 d; *P* = 0.973), or frequency of renal replacement therapy (PH, 2/8; non-PH, 1/14; *P* = 0.121) in the immediate post-transplantation period.

CONCLUSION

Clinically apparent portal hypertension in patients with PCLD listed for liver transplantation does not appear to have a major impact on wait-list or peri-transplant morbidity.

Key words: Polycystic liver disease; Portal hypertension; Liver transplantation

Core tip: Clinically apparent portal hypertension is common in patients with polycystic liver disease, however it appears that this finding does not affect wait list or post-transplantation outcomes in the short-term.

INTRODUCTION

Polycystic liver disease (PCLD) is an autosomal dominant condition that has 2 forms - either occurring in isolated form or combined with cysts in extra-hepatic organs[1,2]. Of those patients who have PCLD associated with extra-hepatic cysts, 80%-90% have renal cysts and can develop progressive renal impairment ultimately leading to end-stage renal failure (ESRF). In those with only polycystic kidney disease (PCKD) at initial diagnosis, 30% can thereafter develop liver cysts within 30 years of diagnosis[3]. Genetic mutations have been identified in patients with PCLD with downstream protein processing defects leading to proliferation in cyst-lining epithelia, fluid secretion into cysts, extracellular membrane re-modelling around cysts and finally neovascularization of the cysts[4-8]. Eighty percent of patients can remain asymptomatic or present with mild abnormalities in liver function blood tests[9], whereas some patients can become symptomatic with enlargement of cysts and their mass/pressure effects on adjacent organs. Liver cysts can become infected with a mortality of 2%[10] or even in rare cases rupture with severe pain, haemodynamic instability and/or rarely death.

Treatment options for PCLD can include medical therapies, interventional radiology, surgical fenestration/resection or liver transplantation (LT), whilst renal replacement therapy (RRT) or renal transplantation can be performed for PCKD-associated ESRF in those with PCLD. Transplantation remains an effective curative treatment for PCLD and is indicated if disabling symptoms leading to decreased performance status or quality of life[11]. In the United states, LT for PCLD falls into the Model for End-stage Liver Disease (MELD) exception guidelines[12] whilst United Kingdom guidelines (NHSBT 2009:4.1.2.3) state that a LT can be performed in the PCLD setting if "intractable symptoms due to mass of liver or pain unresponsive to cystectomy, or severe complications secondary to portal hypertension"[13].

Development of portal hypertension (PH) in PCLD can be a significant concern in advanced disease manifested by splenomegaly, ascites [without necessarily signs of hepatic venous outflow obstruction (HVOO)] or variceal formation. PH in the context of PCLD was described in 35% of patients from a European cohort[14] and often can be notoriously difficult to treat[15], however the clinical course and outcome of such patients once listed for LT has not yet been clearly identified. The aim of this study was thus to establish the impact of clinically apparent PH on wait-list and immediate post-transplantation outcomes specifically in patients with PCLD listed for LT.

MATERIALS AND METHODS

A single centre retrospective study was performed in a LT centre (Queen Elizabeth Hospital, Birmingham, United Kingdom). The study protocol was approved by the Queen Elizabeth Hospital local clinical audit committee (Reference CAB:04870-12). Patients with PCLD listed consecutively over a 12-year period (January 2000 and December 2012) were included. All PCLD referred to our centre or undergoing follow-up (irrespective of transplantation or not) were identified from a pre-existing transplant database which included all parameters of listed patient's illness, liver function, and if applicable listing criteria and operation/intensive

	Single organ liver (n = 15 with portal HBP)	Combined liver/kidney (n = 4 with portal HBP)	*P* value
Ascites	8	3	0.582
Varices[1]	1	0	0.745
Splenomegaly[2]	7	2	0.585
Thrombocytopenia[3]	3	2	0.379

Table 1 Comparison of features of portal hypertension between the groups requiring single liver transplant and those requiring combined liver/kidney transplant (note some patients had > 1 manifestation)

[1]Confirmed endoscopically or radiologically on CT; [2]Confirmed on imaging without evidence of splenic cysts; [3]Platelet count < 150 × 10⁹. HBP: Hypertension.

care unit (ICU) spell details (including data on blood product usage and follow-up). Details on nutritional status except listing weight were not routinely available.

The decision to start patients on RRT whilst on the waiting list was made by the local Nephrology team and decision to perform combined liver/kidney transplantation was made together by the Hepatology and Nephrology teams at a multi-disciplinary transplantation listing meeting. Patients were listed for LT based on symptoms after vigorous multi-professional assessment process. Validated symptom questionnaires were not used as part of this study, rather cases were discussed on an individual basis by the clinical team during the transplantation assessment process. Symptoms were normally secondary to liver cysts causing intractable pain, poor quality of life, malnutrition, recurrent liver cyst infection, or those symptoms secondary to the development of PH. The transplant assessment process involved standard radiological assessment by the surgical team *via* Ultrasound (US), computed tomography (CT) and/or magnetic resonance imaging (MRI). Liver volumetric measurement data was not performed during this time period.

PH in the PCLD cohort was defined by the one or more of following parameters: (1) presence of radiological or endoscopic documented varices from our own centre or the referral centre; (2) splenomegaly (> 11 cm) on US, CT or MRI in absence of radiological splenic cysts accounting for increased imaging size; (3) thrombocytopenia (platelets < 150 × 10⁹/L); or (4) ascites without radiological evidence of HVOO from a single cyst. Patients were assessed and listed for a combined kidney/liver transplant if they had concomitant ESRF with the main measurement of renal function being the estimated glomerular filtration rate (eGFR), determined using the Modification of Diet in Renal Disease Study 4-variable equation[16]. This was then confirmed with an isotopic GFR where required or recommended by the nephrology team. Chronic kidney disease (CKD) was defined as eGFR

< 60 mL/min/1.73 m² on at least 2 occasions and sustained[17].

Normally distributed continuous variables and non-parametric continuous variables were compared using the Student's *t*-test and Mann-Whitney test, respectively. χ^2 analysis or Fisher's exact test were used for comparison of categorical data. Patient survival after transplantation was estimated using Kaplan-Meier plots with log-rank test for differences. Patients were censored at time of last known follow-up. Data was analysed using the SPSS 21 package (SPSS Inc, Chicago, IL, United States). All values are expressed as mean and standard deviation, median and inter-quartile range (IQR) and number and percent (%) as appropriate. *P* < 0.05 was considered statistically significant at all times.

RESULTS

Patient demographics and portal hypertension manifestations

A total of 75 patients were identified with PCLD attending our centre during the 12-year period. Of this overall cohort 32 patients (42.5%) had signs in keeping with clinically apparent PH. Of the overall cohort (n = 75), 47 patients (62.7%) were listed for LT (35 patients listed for single organ and 12 patients listed for combined liver/kidney). Of the 35 patients listed for single organ liver transplantation 15 had PH (42.9%) and of the 12 listed for combined liver/kidney transplant 4 had PH (33.3%) (*P* = 0.410). There were no differences in how PH was manifested between the groups (Table 1) irrespective if receiving a single organ liver transplant or combined liver/kidney transplant.

When comparing the PH group and those without (non-PH group - Table 2), at listing, baseline characteristics were similar between the groups. Characteristics were similar with regards to age (PH 50.6 years, non-PH 47.1 years, *P* = 0.101) and gender (*P* = 0.683). The patients' liver synthetic function was similar between the PH group and non-PH groups (Bilirubin *P* = 0.965, INR *P* = 0.173) and United Kingdom Model for End-Stage Liver Disease (UKELD) (PH 48, non-PH 46, *P* = 0.344)/MELD scores (*P* = 0.344/PH 12, non-PH 11, *P* =0.422) were similar between the groups. 84.2% of patients with PH had CKD stage III-V compared to 67.9% of patients without (*P* = 0.179). 19.2% and 7.1% of PH and non-PH patients were dialysis dependent respectively (*P* = 0.317).

Outcomes on the list

Thirty-four patients were transplanted by the time of data analysis (72.3%). Two patients with PH died prior to transplantation (sepsis and progressive liver disease) and 1 patient without PH (progressive liver disease). Of the remaining 10 patients not transplanted at time of data analysis, 9 were still active on the waiting list and 1 patient had been removed from the

Table 2 Comparison of patient demographics between patients with and without portal hypertension

Listing parameter	Portal hypertension (*n* = 19)	Non-portal hypertension (*n* = 28)	*P* value
Age (yr)	50.6 (6.4)	47.1 (7.4)	0.101
Female gender	17 (89.5)	25 (89.3)	0.683
Bilirubin (μmol/L)	8 (6-11)	8 (6-12)	0.965
INR	1.1 (1.0-1.2)	1.1 (1.0-1.1)	0.173
Creatinine (mmol/L)	106 (104-436)	119 (92-201)	0.508
Platelet count (× 10⁹)	177 (147-242)	234 (198-242)	0.012
Sodium (mmol/l)	139 (137-143)	140 (138-142)	0.483
MELD score	12 (9-21)	11 (8-16)	0.422
UKELD score	48 (44-50)	46 (45-48)	0.344
Chronic kidney disease[1]	16 (84.2)	19 (67.9)	0.179
Dialysis dependant	3 (15.8)	2 (7.1)	0.317

[1]Chronic kidney disease defined as stage Ⅲ-Ⅴ[17]. INR: International normalized ratio; MELD: Model For End-stage Liver Disease; UKELD: United Kingdom Model for End-Stage Liver Disease.

Table 3 Intensive care unit requirements and hospital stay between the portal hypertensive and non-portal hypertensive groups in patients receiving a single organ liver transplant

	Portal hypertensive group (*n* = 8)	Non-portal hypertensive group (*n* = 14)	*P* value
Intra-operative			
RCC(units)	3 (1-4)	4 (2-7)	0.238
FFP(units)	10 (1-18)	8 (7-14)	0.973
Plts (units)	0	3 (0-10)	0.145
ICU stay (d)	3 (3-4)	2 (2-4)	0.188
Hospital stay (d)	9 (7-13)	10 (7-12)	0.973
RRT in ICU immediately post-op	2/8 (25%)	0/14 (0)	0.121

FFP: Fresh frozen plasma; ICU: Intensive care unit; Plts: Platelets; RCC: Red cell concentrate; RRT: Renal replacement therapy.

Table 4 Intensive care unit requirements and hospital stay between the portal hypertensive and non-portal hypertensive groups in patients receiving a combined liver/kidney transplant

	Portal hypertensive group (*n* = 4)	Non-portal hypertensive group (*n* = 8)	*P* value
Intra-operative			
RCC (units)	13 (4-19)	9 (3-19)	0.933
FFP (units)	15 (7-23)	14 (5-18)	0.683
Plts (units)	10 (3-10)	10 (0-20)	0.683
ICU stay (d)	5 (3-7)	7 (3-41)	0.368
Hospital stay (d)	16 (12-18)	15 (12-49)	0.808
RRT in ICU immediately post-op	3/4 (75%)	3/8 (37.5%)	0.273

FFP: Fresh frozen plasma; ICU: Intensive care unit; Plts: Platelets; RCC: Red cell concentrate; RRT: Renal replacement therapy.

waiting list (as had declined a transplant after being listed). The median time from listing to transplantation for PH patients was 72 d (IQR 34-524) and for non-PH patients was 139 d (IQR 48-390) (*P* = 0.466).

In the single organ LT patients (*n* = 22), the median time from listing to transplantation for patients with PH was 49 d (IQR 16-426) compared to 139 d (IQR 53-345) (*P* = 0.188) for patients in the non-PH group. In the combined liver/kidney transplant patients (*n* = 12), the median time from listing to transplantation for PH patients was 289 d (IQR 58-551) and for those in the non-PH group 210 d (IQR 16-579) (*P* = 0.933). Overall, when the length of time of the list was compared, there were no significant differences found in the median time on the list between the PH group (*n* = 12) [72 d (IQR 34-524)] and the non-PH group (*n* = 22) [139 d (IQR 48-390), *P* = 0.466]. On follow up 3 patients died on waiting list (2 with PH).

ICU spells/requirements and hospital stays
In the patients who underwent LT alone, there was no difference in the duration of ICU (PH group 3 d; non-

PH group 2 d, *P* = 0.188) and hospital stay (PH group 9 d; non-PH group 10 d, *P* = 0.973). There was no difference in frequency of RRT (PH group 2/8; non-PH group 1/14, *P* = 0.121) with similar observations made in the patients who underwent combined liver-kidney transplantation (data not shown). There were no differences found (in the single organ liver transplant or the combined liver/kidney group) when transfusion requirements were assessed between the PH groups and the non-PH groups (Tables 3 and 4). The duration of ICU spells post-transplantation were similar [3 d in PH group *vs* 2 d in non-PH group (*P* = 0.188)]. Also overall hospital stays were similar between the groups (9 d in PH group *vs* 10 d in non-PH group, *P* = 0.973).

DISCUSSION
Patients with PCLD can have variable courses of their disease with the majority of patients remaining asymptomatic. As the liver cysts grow, patients can start to develop symptoms due to local mass effect such as: right upper quadrant pain, early satiety and post-prandial fullness (due to pressure effects on adjacent stomach). Patient can also develop shortness of breath (due to liver volume burden), and direct compression of the portal vein/inferior vena cava. Symptoms also may be due to complications of the cysts such as haemorrhage, infection or rupture. Treatment can be broadly divided into medical, radiological and surgical. Medical treatments include somatostatin analogues which reduce the secretion of fluid into the cysts and inhibit cholangiocyte proliferation[18-22] and have been shown to be effective in reducing liver volume when compared to placebo and effective in improving symptoms[23-25]. Radiological treatments can include interventional radiological arterial embolization or injection sclerotherapy of cysts, whilst surgical techniques include cysts fenestration, resection or transplantation. The choice of surgical technique often is dependent on factors such as: symptoms, cyst characteristics, volume of normal liver parenchyma and

also patency of hepatic/portal veins - with the surgeons often using Schnelldorfer *et al*[26] or Gigot *et al*[27]'s classification to aid with decisions. LT remains an effective curative treatment for patients with PCLD with indications varying but indicated if decreased performance status or quality of life[11,28] then LT can be offered. LT has been shown to improve domains of quality of life in a series of 36 patients[29] with 11% of patients in this study having PH. Recent Australian national guidelines[30] summarised that treatment of liver cysts should be directed at reducing liver volume when the patients were highly symptomatic, with options including sclerotherapy, fenestration, segmental resection and transplantation (Level 1D evidence).

PH in chronic liver disease is the established key event leading to such complications such as ascites and variceal formation. PH results from mechanical obstruction due to fibrosis or regenerative nodules resulting in increased resistance to flow. In PCLD this may be the case secondary to flow distortion due to large cysts and thus their compressive effects leading to increased intrahepatic resistance. In cirrhosis and PH a hyperdynamic circulation develops in response to changes in haemodynamics, manifested as high cardiac output with low systematic vascular resistance and arterial hypotension[31]. In our centre portal pressure measurements are not routinely performed and could be deemed a criticism of this retrospective study however the technique to gain the hepatic venous pressure gradient (HVPG) measurement can indeed be difficult in patients with PCLD due to distorted anatomy[32] with lack of reporting of such measurements in other PCLD studies where PH has been assessed[14]. Varices in non-PCLD patients are more likely to develop if the HVPG is > 10 mmHg[33] however the role of HVPG measurements in the PCLD patient cohort requires further clarification in future studies. In young patients with PCLD who have early signs of PH, congenital hepatic fibrosis should also be considered as a potential cause of PH[34].

In our study we sought to explore if any differences in outcome in PCLD patients with PH once listed for LT to those who did not. To our knowledge our study is the 1st paper to analyse such subgroups in this manner in patients listed LT. The overall number of patients in such studies in PCLD has not been large and indeed those with PH described. In a review of 9 studies in patients with PCLD[35-43] a median of 8 patients (range 3-17) was found - this compares to 47 patients listed for LT in our single-centre study. Mortality rates in the series studied ranged from 0%-50% on follow up and the number of patients with PH however was not clear. In one such multicenter study[14], 58 patients were pooled together from 75 centres via the European Liver and Intestinal Association (ELITA) - with 35% patients having PH (compared to 42.9% of patients listed for LT in our study - a single centre). By analysing in such a manner, we have established to seek if there was any difference in patients who had clinically apparent PH as

a consequence of PCLD on their outcome once listed for transplantation. Ascites in the context of HVOO can be exudative due to high permeability of the dilated sinusoidal walls to proteins[44]. Patients with HVOO can also however present with transudative ascites, abdominal pain and hepatomegaly in 90%-96% of cases[34]. By taking established markers of clinically apparent PH and applying it to the PCLD cohort, we attempted to stratify the patients and assess for any differences in outcome once listed for LT. The 2 groups appeared to be well matched patient groups at time of listing between the PH and non-PH groups especially when assessing their liver synthetic function (Table 2), again suggesting clearly the mechanism in developing PH in this cohort is different to those patients with cirrhosis who can develop PH and synthetic liver dysfunction with progressive disease. Patients with PCLD often have preserved liver function as reflected by low UKELD and MELD scores - thus PCLD patients fall within MELD[12] exception guidelines and also the variant syndrome United Kingdom listing criteria[13]. When comparing the groups who had single LT compared to those having a combined kidney/ liver transplant there appeared to be no significant differences in the type/manifestation of clinically apparent PH that these 2 groups had. The advent of PH importantly did not appear to affect the immediate post-transplantation course of the patients, with similar requirement for blood product use between the groups and similar post-operative ICU and hospital stays. PH in the context of transplantation for cirrhosis does often cause a need for blood product requirement with tendency to bleed from the high pressure portal circulation or the coagulopathy associated with cirrhosis. This however did not appear the case in this cohort.

There are shortcomings however of this retrospective study that should be noted with the main one the perceived small numbers of patients over a long-period of time. It could be argued that in PCLD studies large cohorts are not a regular finding but our numbers are comparable if not larger then already published series[35-43]. In a multicentre European study only 58 patients were gained from 75 sites (0.77 per site)[14] thus making our cohort a relatively fair one for a single centre. To answer the question in a more robust manner, larger multicentre databases could be generated or analysed with well defined criteria for clinically apparent PH to replicate our study on a larger setting. Another criticism may be the apparent lack of portal pressure studies not a routine practice in our centre however the difficulties of this have been mentioned previously. Another criticism may be the amalgamation of those patients with ascites along with those with other features as mentioned above of PH. Without HVPG measurements in this group, we think it is difficult to tease out specific mechanisms of ascites formation in this cohort of patients. Where possible, patients protein levels of ascites were checked how-

ever was not always commonplace over the whole 12 years of this study, and patients with ascites due to PCLD can have a mixed picture when analysing protein content as mentioned[34,44]. By grouping these together who have clinically significant ascites (thus impaired quality of life and function) who often required large volume paracentesis (with the potential for introduction of infection) we included them in our cohort as they may have had worse clinical outcomes. However even when this was done, both the PH group and non-PH group had similar outcomes with regards to survival and with operative/post ICU spell parameters. Also irrespective of the actual pathophysiological mechanism of ascites formation, once present and is not managed by conventional therapies, LT assessment would be considered in our centre due to the effects on the patient's quality of life. The study period was conducted before the advent of high resolution volumetric studies in our institution hence we did not comment on liver volumes or those of kidneys retrospectively, and their role in predicting outcome peri- or post-transplantation from our retrospective data set. Also owing to the retrospective nature of the data there was no data available on advanced nutritional aspects of the patients such as actual sarcopenic measurements with CT[45] something that is now practiced in our centre. With either ascites or pure weight-related effect of the liver cysts, weight would not be an accurate measurement for such a cohort thus not commented upon. Data was also not retrospectively available if women (the majority of our cohort) were on the contraceptive oral contraceptive pill (COCP). The presence of PCLD has been shown to be related to the COCP usage in patients with PCKD[46]. Another area to comment is the lack of validated symptom questionnaires in our study to assess improvements with transplantation. Kirchner *et al*[29] showed there was indeed a symptomatic improvement in domains related to health post-LT, however moving forward looking at symptom assessment improvement *via* validated questionnaires between groups with PH and not would be interesting. A final note is caution to the estimated 15-year post-transplantation survivals with no obvious difference found between the groups (P = 0.138). In a recent study from Neijenhuis *et al*[47] a disease specific questionnaire was developed and validated in a European and United States cohort. Moving forward, this questionnaire could be used in prospective studies involving the PH-component of PCLD.

In conclusion, this retrospective single-centre study has shown that clinically apparent PH in patients listed for LT is common, however also our data suggests that PH may not impact on wait-list and peri-/post-operative outcomes in our cohort of patients studied. To our knowledge this is the 1st study to assess a PCLD cohort in such a manner. The advent of PH and the complications in the PCLD cohort should be remembered by physicians and surgeons alike especially when patients are being assessed for liver transplantation, however does not appear clinically apparent PH affects outcome once the decision has been made to transplant such patients, especially in the hands of skilled surgeons.

COMMENTS

Background
The advent of portal hypertension in polycystic liver disease is not well described with regards to its effects on outcomes in patients who have severe disease or are listed for curative liver transplant procedure

Research frontiers
It was hypothesized that patients with polycystic liver disease who are listed for liver transplantation may indeed have worse outcomes if they have established portal hypertension than those without.

Innovations and breakthroughs
This study is the first study in our knowledge to explore the impact of portal hypertension on outcomes in patients with polycystic liver disease providing evidence that the advent of portal hypertension does not affect wait-list or short-term post liver transplantation outcomes.

Applications
This study investigated the advent of portal hypertension of patients listed for liver transplantation with polycystic liver disease. The finding of portal hypertension should always thus be noted and treated appropriately, but does not confer poorer outcomes from the results of our study.

Peer-review
A large retrospective study that you list the many drawbacks but nevertheless it is very interesting data. It is the largest single center study on this topic and it does gain strength from this.

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