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Liver Transplantation for Propionic Acidemia: A multi-center linked database analysis

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Abstract:

Objectives: Propionic Acidemia (PA) is a rare inborn error of metabolism resulting from deficiency in the enzyme necessary for catabolism of branched-chain amino acids, some odd chain fatty acids and cholesterol. Despite optimal medical management, PA often leads to acute and progressive neurological injury. Reports on liver transplantation (LT) as a cellular therapy are limited and varied. The objective of this study was to examine the largest collection of patients who underwent LT for PA.

Methods: Examining the Scientific Registry of Transplant Recipients and the Pediatric Health Information System administrative billing databases, we performed a multicenter, retrospective analysis of LT over a 16-year period. During this period, 4849 pediatric LT were performed out of which 23 were done for PA at 10 different centers.

Results: The majority of recipients were 5 years of age or younger and had status 1b exception points at the time of transplant. The 1-, 3-, and 5- year graft survival for PA LT recipients was 84.6% and the 1-, 3, and 5- year patient survival was 89.5%. There was no significant difference in graft or patient survival between PA and non-PA LT recipients. Despite historical data to the contrary, we did not find an increased incidence of hepatic arterial thrombosis in patients undergoing LT for PA. Patients in the PA LT group, however, had a significantly higher post-operative rate of readmission compared to the non-PA LT group (90.5% vs. 72.8%, p=0.021).

Conclusions: LT for children with PA is a viable treatment option with acceptable outcomes.

Keywords: graft survival, metabolic disorders, hyperammonemia

What is Known:

-Propionic academia (PA) is a rare inborn error of metabolism that often leads to neurological injury despite best medical management.

-Liver transplantation (LT) can be utilized as cellular therapy, but reports are limited.

What is New:

-Utilizing large national transplant and billing databases, this multicenter, retrospective analysis includes 23 patients who underwent LT for PA, the largest study to date.

-Contrary to prior single center reports, PA LT recipients can achieve similar patient and graft survival compared to non-PA LT recipients, with PA LT patients at relatively greater risk for readmission in the first year following transplant.

Introduction:

Propionic acidemia (PA) is a rare inborn error of metabolism resulting from deficiency of propionyl CoA carboxylase (PCC), an enzyme necessary for the catabolism of the amino acids valine, methionine, isoleucine and threonine as well as the metabolism of cholesterol and certain odd chain fatty acids(1). PA is an autosomal recessive disorder with an increased prevalence in populations with consanguinity or founder mutations. Secondary hyperammonemia, arising from inhibition of hepatic urea cycle enzymes, results in acute and progressive neurologic injury with devastating consequences. PA symptom onset is variable, but the classic, severe form presents in the first several days of life, often before newborn screening reports elevated 3-carbon acylcarnitine levels. Metabolic decompensation with hyperammonemia can be mitigated, though not completely prevented, through protein restriction, metabolic formula depleted of offending amino acids, ammonia scavenging medications, carglumic acid, and oral antibiotics that reduce propionate production by gut anaerobic bacteria.

Unfortunately, the catabolic state that frequently accompanies common pediatric illnesses can result in catastrophic hyperammonemia, even despite infusion of 10% dextrose to reduce the muscle amino acid breakdown that supports gluconeogenesis. Although PCC is expressed within the nervous system, heart, pancreas, and kidneys, the liver is the primary site for amino acid metabolism and PCC activity(2). As such, liver transplantation has been successfully used as a cellular therapy for PA by providing the recipient with a large amount of functioning PCC enzyme. Liver transplantation decreases the frequency of clinically significant hyperammonemia episodes and progression of neurologic injury, and allows for liberalization of dietary restrictions. However, the benefits of liver transplantation must be weighed against the risks of morbidity and mortality associated with the surgical procedure and subsequent life-long immunosuppression. Due to the rarity of liver transplantation for PA all data on long-term patient and graft survival are limited to small or single center series of patients spanning several decades(1, 3-7), during which the surgical and immunosuppressive management of liver transplant recipients has significantly evolved(8). Here we report the largest multi-center, modern series of patients treated for PA with liver transplantation.

Methods:

This study utilized data from the Scientific Registry of Transplant Recipients (SRTR, Hennepin Healthcare Research Institute, Minneapolis, MN) and the Pediatric Health Information System (PHIS, Children's Hospital Association, Lenexa, KS) administrative billing database. The SRTR data system includes data from all donors, wait-listed candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. The

SRTR database includes data from every organ transplant and waitlist addition within the U.S. since October 1987. The PHIS database collects clinical and resource utilization data for hospital encounters from >50 tertiary children's hospitals including inpatient hospitalizations, observation, ambulatory surgery, and emergency department encounters. The PHIS database records International Classification of Diseases (ICD) 9 and 10 codes as well as detailed billing and charge data for each encounter. The SRTR and PHIS databases were linked at the patient level using indirect identifiers (hospital, sex, date of birth, and date of transplant), the results of which have been previously described(9).

All pediatric (age<21) liver transplant recipients were identified from the linked database (2002-2018) for inclusion. The presence of PA was determined by the presence of ICD-10 code E71.121 at any encounter. The characteristics of liver transplant recipients with PA were assessed using standard descriptive statistics and compared to patients without PA. The Fisher's exact test was used for categorical variables and the Wilcoxon rank sum test was used for continuous variables, as appropriate. The Kaplan Meier method was used to assess post-transplant patient and graft survival, censoring at death, re-transplant, or last known follow-up. Survival curves were compared using the log-rank test.

All readmissions within the first-year post-transplant were collected and described. Freedom from readmission was assessed using the Kaplan-Meier method and compared between patients with and without PA using the log rank test. Indications for readmission were assessed using the primary diagnosis associated with each admission encounter and reported using standard descriptive statistics.

All statistical analyses were performed in SAS version 9.4 (SAS Institute; Cary, NC) or STATA version 15 (StataCorp LLC; College Station, TX). This project was approved by PHIS, SRTR, and the Vanderbilt University Institutional Review Board.

Results:

A total of 4849 liver transplant recipients were included from the linked database. Of this group 23 (0.5%) patients carried a diagnosis of PA and underwent liver transplantation at 10 different centers. (Figure 1). The median number of admissions within 1 year prior to liver transplant in the PA group was 3 (IQR 2-6) and median number of days admitted within 1 year prior to liver transplant was 37 (IQR 22-70). Two out of the 23 PA patients (8.7%) had an ICD diagnosis code for heart failure prior to or during the liver transplant admission. Demographics of patients with and without PA are presented in Table 1. The majority of recipients with PA were male (60.9%) and of Caucasian or Hispanic ethnicity (78.3%). Three quarters of recipients were 5 years of age or younger and none required mechanical ventilation at the time of transplantation. When compared to non-PA recipients, children transplanted for PA had a lower laboratory PELD/MELD score at transplant (-8 vs 14, $p<0.001$) and were less frequently hospitalized at the

time of transplant (13% vs 39%, p=0.034). The majority of PA recipients (74%) had a Status 1b exception at the time of transplantation. Serum creatinine and estimated GFR did not vary significantly between PA and non-PA liver transplant recipients at the time of transplant. Finally, there was no difference in age stratified waiting time between PA and non-PA liver transplant recipients.

A deceased donor liver allograft was utilized in 20 (87%) of the PA liver transplants. Living donor liver transplantation did not significantly differ between PA and non-PA recipients (13% vs. 11.4%, p=0.741). 22 out of 23 (95.7%) PA transplant recipients survived to hospital discharge. The median post-transplant length of stay (20 days vs. 16 days, p=0.182) and total length of stay (21 days vs. 21 days, p=0.683) did not vary significantly between PA and non-PA liver transplant recipients. There were no post-operative hepatic artery thromboses (HAT) during the transplant admission or follow-up in the PA liver transplant recipients compared to a 1.5% incidence of HAT during the transplant admission and 0.6% incidence of HAT during follow-up for non-PA transplant recipients.

The 1-, 3-, and 5- year graft survival for PA liver transplant recipients was 84.6% reflecting three graft failures (all within the first year) in 23 liver transplants (Figure 2a). The 1-, 3, and 5- year patient survival for PA liver transplant recipients was 89.5%, with all deaths occurring in the first post-transplant year (Figure 2b). One recipient underwent liver re-transplantation for a graft failure that occurred within the first 6 months post-transplant. There was no difference in either graft (log rank p=0.445) or patient (log rank p=0.304) survival between PA and non-PA liver transplant recipients.

PA transplant recipients were significantly more likely to be re-admitted to the transplant hospital within the first-year post-transplant compared to non-PA transplant recipients (90.5% vs. 72.8%, p=0.021) (Figure 3). There were 62 readmissions that occurred within the first year in 20 patients transplanted for PA. The median time to readmission was 17 days [IQR 4 - 65 days] and the median number of readmissions was 3 [IQR 1 - 4]. The most common primary diagnosis for readmission was complication of liver transplantation (18.3%) followed by viral infection (11.7%), acute renal failure (6.7%), bacteremia (6.7%), cholangitis (5%), sepsis (3.3%), gastrointestinal hemorrhage (3.3%), hyperkalemia (3.3%), and rejection (3.3%).

Discussion:

PA is an organic acidemia affecting 1 in 220,000 newborns(10) resulting in accumulated neurological, cardiac, pancreatic, and bone marrow cellular injury due to repetitive metabolic crises and secondary hyperammonemia. It is frequently diagnosed within the first week of life. Nearly half of all cases from a recent United States study were identified through newborn screening, with half of these being critically ill at initial metabolic consultation(11) . Although there is variability in disease severity, only a small minority of patients with PA remain

asymptomatic(12). Despite improvement in life expectancy with modern dietary management, long-term outcomes remain unfavorable with demonstrable progressive neurocognitive impairment in most patients by adolescence(13-15).

Liver transplantation, which should be considered in all patients with frequent metabolic decompensations or when medical stabilization is difficult to attain(16), has been reported as a successful cellular therapy for PA(3) and prevents further metabolic crises in the majority of recipients(4, 6, 17). Although successful liver transplantation does not arrest localized tissue production of propionic acid, as demonstrated through the quantification of propionylcarnitine in cerebrospinal fluid post-operatively, the prevention of systemic and life-threatening metabolic acidosis and hyperammonemia can improve neurocognitive disability (6, 7, 17, 18). Liver transplantation has been associated with reversal or stabilization of PA-associated dilated cardiomyopathy and QT interval prolongation in reported cases (17, 19-21). The potential benefits of liver transplantation must be carefully weighed against the morbidity and mortality associated with liver transplantation. Treatment strategies are continually evolving, and the progress of novel approaches such as systemic messenger RNA therapy should be monitored closely but are not yet available clinically(22).

Due to the very low incidence of PA, no single center has been able to amass a significant experience in the treatment of this disease with liver transplantation. As a result, there are a limited number of reports of liver transplantation for PA with significantly divergent outcomes. The early experience with liver transplantation for PA resulted in poor patient and graft survival. In a review of the OPTN database from 2006, Barshes et al identified 11 patients who underwent liver transplantation for PA between 1988 and 2005 with a Kaplan-Meier 1-year patient survival of 72.2% and a 1-year graft survival of 56.3%(1). A series from the United Kingdom in 2011 of 5 patients who underwent liver transplantation for PA between 1987 and 2008 reported 100% patient survival and 83% graft survival at a median follow-up of 7.3 years(4). A subsequent two-center combined series by Charbit-Henrion et al described 12 patients who underwent 17 liver transplants for PA from 1984 to 2005 with a resultant 58% 1-year patient mortality rate(5). Half of the patients had pre-transplant renal dysfunction and HAT occurred in 6 grafts. Finally, the most recent series by Quintero et al of 6 patients transplanted for PA between 2012 and 2016 in Spain also described the occurrence of HAT in 2 grafts(6). Based on the historical variation in outcomes it is important to report contemporary outcome data pertaining to liver transplantation for PA. Such reports are especially important given the secular trend towards increased numbers of liver transplants done for children with metabolic liver disease, earlier referral of patients in better pre-transplant condition, and improvements in peri- and post-operative transplant surgery care.

Our analysis has inherent limitations. Our unique linkage between PHIS and SRTR facilitated identification of liver transplant recipients with PA using ICD codes. However, miscoding can occur, and it is not possible to retrospectively confirm the diagnoses using the linked database. However, the PA population identified appears consistent with the expected demographics of

this group. Therefore, we believe that our analysis accurately identifies the population of interest. Additionally, the specific identification of PA was only made possible with the introduction of ICD-10 (started in the 4th quarter of 2015). Therefore, identification of patients with PA from an earlier era (using ICD-9) was not possible unless subsequent hospital encounters occurred following the introduction of ICD-10. This may bias our analysis towards the more recent era of patients during which candidate selection criteria have changed. It is also possible that patients with PA from an earlier era were included in the control group, as these patients may not have been identified using our methodology. However, given the relative rarity of PA as an indication for liver transplantation, we believe that this is unlikely to impact the results of our analysis.

The current analysis represents the largest report of liver transplantation in patients with PA in the recent era. While PA remains an uncommon indication for liver transplantation, we demonstrate that these patients can achieve similar patient and graft survival compared to non-PA liver transplant recipients. Additionally, we did not detect the increased risk of vascular thrombosis that is described in previous series. PA patients are at relatively greater risk for readmission in the first year following transplant. It is unclear whether the increased risk for readmission is primarily related to their liver transplantation or metabolic disease. However, the increased rates of readmission in this group do not appear to influence patient or graft survival. Patients with PA should be referred early for evaluation and consideration for liver transplant. Based on the most recent Organ Procurement and Transplantation Network (OPTN) data, liver transplantation appears to be a viable therapeutic strategy for patients with PA, with acceptable long-term outcomes.

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Figure 1: Distribution of Liver Transplant Recipients with PA at 10 different centers.

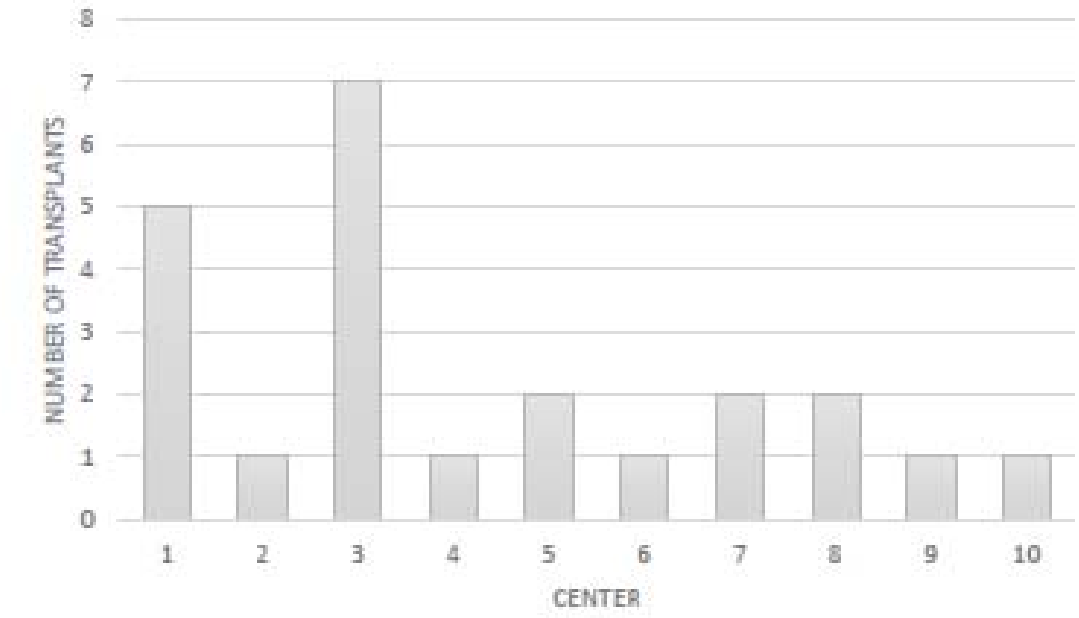
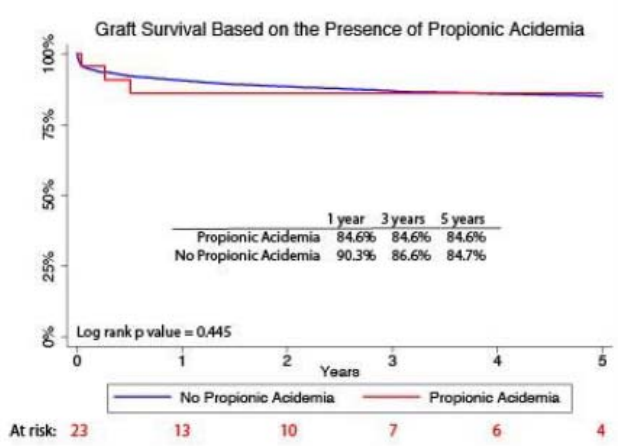


Figure 2: (a) 1-, 3-, and 5- year graft survival for PA liver transplant recipients and non-PA liver transplant recipients. (b) The 1-, 3, and 5- year patient survival for PA liver transplant recipients and non-PA liver transplant recipients.



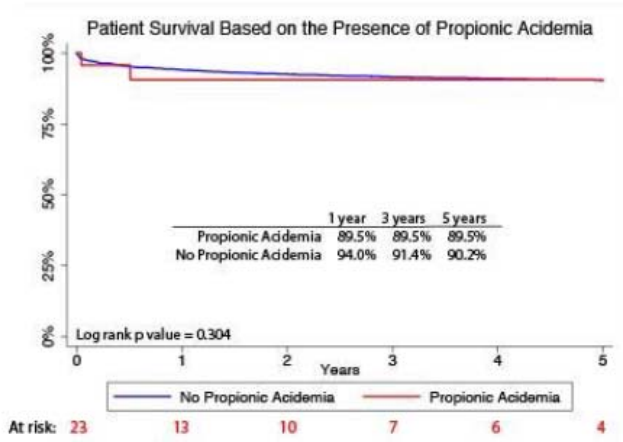


Figure 3: Readmissions with first year post-liver transplant in PA liver transplant recipients and non-PA liver transplant recipients.

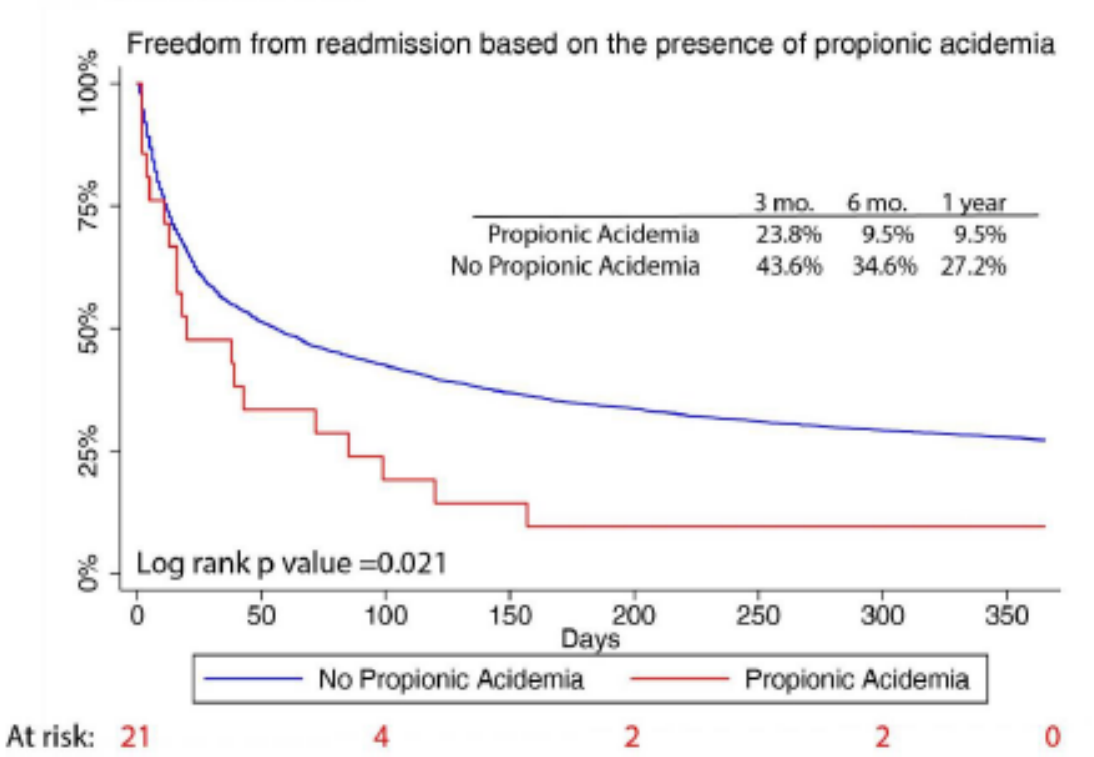


Table 1. Demographics of PA liver transplant recipients and non-PA liver transplant recipients.

		Propionic Acidemia		
		No	**Yes**	**p-value**
		N=4826 (99.5%)	N=23 (0.5%)	
Race				
	Caucasian	2716 (56.3%)	10 (43.5%)	0.013
	African-American	660 (13.7%)	0 (0%)	
	Hispanic	1019 (21.1%)	8 (34.8%)	
	Other	431 (8.9%)	5 (21.7%)	
Age Group				
	<1yr	1316 (27.3%)	5 (21.7%)	0.712
	1-5 yrs	1823 (37.8%)	12 (52.2%)	
	6-10 yrs	674 (14%)	3 (13%)	
	11-17 yrs	962 (19.9%)	3 (13%)	
	18-21 yrs	51 (1.1%)	0 (0%)	
Male sex		2385 (49.4%)	14 (60.9%)	0.302
On ventilator at Tx		467 (9.7%)	0 (0%)	0.161
Donor type				
	Cadaveric	4275 (88.6%)	20 (87%)	0.741
	Living	551 (11.4%)	3 (13%)	
MELD/PELD Score		14 (3 - 24)	-8 (-9 - -5)	<0.001
Location at transplant				
	Outpatient	2909 (61%)	20 (87%)	0.034
	Inpatient	826 (17.3%)	2 (8.7%)	
	In ICU	1036 (21.7%)	1 (4.4%)	
Weight (kg)		13 (8.1 - 28.4)	12.8 (11.1 - 23.3)	0.538
	<1yr	7 (6 - 7.9)	10.4 (9.6 - 11.6)	<0.001
	1-5 yrs	11.9 (9.7 - 14.9)	12.8 (11.1 - 13.6)	0.563
	6-10 yrs	25.6 (21.7 - 30.7)	23.7 (21.1 - 31)	0.772
	11-17 yrs	50.6 (41.1 - 63.3)	39.4 (37 - 40.5)	0.086
	18-21 yrs	62 (52.2 - 70.8)	-	-
Serum creatinine (mg/dL)		0.3 (0.2 - 0.5)	0.3 (0.21 - 0.39)	0.214
	<1yr	0.2 (0.2 - 0.3)	0.22 (0.21 - 0.28)	0.662
	1-5 yrs	0.3 (0.2 - 0.36)	0.28 (.2 - 0.32)	0.705
	6-10 yrs	0.4 (0.3 - 0.6)	.39 (0.3 - 0.6)	0.748
	11-17 yrs	0.6 (0.5 - 0.9)	0.4 (0.3 - 0.7)	0.161

	18-21 yrs	0.6 (0.5 - 0.8)	-	-
Estimated GFR*		123 (89 - 157)	128 (113 - 159)	0.305
	<1yr	123 (86 - 145)	128 (112 - 143)	0.489
	1-5 yrs	134 (97 - 172)	127 (114 - 168)	0.954
	6-10 yrs	127 (92 - 163)	126 (80 - 175)	0.999
	11-17 yrs	110 (76 - 137)	142 (82 - 195)	0.279
	18-21 yrs	113 (76 - 133)	-	-
Waitlist time (days)		57 (14 - 167)	81 (37 - 130)	0.312
	<1yr	39 (13 - 78)	48 (37 - 81)	0.401
	1-5 yrs	74 (18 - 215)	89 (41 - 138)	0.863
	6-10 yrs	66 (12 - 222)	78 (68 - 121)	0.733
	11-17 yrs	72 (11 - 243)	139 (17 - 238)	0.72
	18-21 yrs	739 (385 - 1214)	-	-
Total LOS		21 (13 - 36)	21 (17 - 31)	0.683
Pre-tx LOS		1 (0 - 6)	1 (1 - 1)	0.251
Post-tx LOS		16 (11 - 28)	20 (15 - 31)	0.182
Portal vein thrombosis				
	During tx admission	19 (0.4%)	0 (0%)	1
	During follow-up	14 (0.3%)	0 (0%)	1
Hepatic artery thrombosis				
	During tx admission	74 (1.5%)	0 (0%)	1
	During follow-up	27 (0.6%)	0 (0%)	1
Number of readmits (1yr)		2 (0 - 3)	2.5 (1 - 4.25)	0.073
Data reported as N(%) or median (IQR)				
p-values from the Fisher's exact test or the Wilcoxon rank sum test				
* Estimated GFR from the Schwartz formula				