Portopulmonary Hypertension: An Effect of Vasomodulation and Mortality Post-Transplant

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Abstract: *Introduction*: Portopulmonary hypertension (PPH) complicates the perioperative conditions in patients who anticipate orthotopic liver transplant (OLT). PPH is rare-occurring in only 6% of those referred for OLT. There is decrease in survival with the moderate to severe PPH subgroup with OLT. Overall only a third live to 5 years time after transplant. Treatment of PPH with vasomodulative therapies before transplantation has increased survival both pre- and post-transplant. The purpose of this study is to report the mortality, prevalence of vasomodulator therapy in PPH before and after OLT depending on group severity.

Methods: This is a retrospective cohort study conducted from our liver transplant database over the course of 15 years. Patients were selected if they were diagnosed with PPH and received OLT. There pulmonary pressures were recorded preoperatively thereby categorizing patients into severity stages. Patient age, ethnicity, gender, BMI, and concurrent comorbidities were also included. The outcomes were overall and group-specific survival, and vasomodulator therapy types used.

Results: The most common cause of liver failure in both groups was Hepatitis C and alcohol-induced cirrhosis. Overall mortality was 50%. There was an increase in use of sildenafil and epoprostenol post-transplant in the PPH group. Forty-percent of transplanted patients lived to more than 1200 day end-point. Patients in moderate to severe had a sustained survival rate from years 1-5 post-transplant.

Conclusions: Patients with pulmonary vascular disease have a complicated liver transplant course specifically with moderate to severe PPH. This retrospective study suggests that in the setting of PPH and liver transplant, mortality is greatly improved after OLT with long-term treatment with vasomodulators, specifically those with moderate-severe disease.

Keywords: Portopulmonary hypertension, Liver transplant, vasodilator.

INTRODUCTION

There are two distinct pulmonary vascular conditions which complicate chronic liver failure patients and some candidates for liver transplants. These are hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPH).

PPH is a vascular condition whereby arterial vasoconstriction as a result of vascular remodeling increases the pulmonary vascular resistance [1]. The gold standard for diagnosis of PPH is right heart catheterization (RHC) measurement of the mean pulmonary artery pressure (mPAP). PPH is further divided into “mild” (mPAP 25-34mmHg), “moderate” (mPAP 35-44mmHg), and “severe” (mPAP > 45mmHg). This stratification permits the identification of those with severe disease and thereby excluding them from transplant. PPH is a rare disease and has been reported in only 2-8% of candidates referred for OLT who have moderate-severe PPH [2,3].

Patients who undergo liver transplant with PPH have higher mortality than those with HPS. PPH patients have an overall mortality after post-transplant of 36% [4] and only a third of these patients will survive to 5-years post-OLT [5,6]. The subset of those with moderate to severe PPH has a higher risk of death post-operatively, up to 90% have died [4]. Many authors have effectively demonstrated the use of vasomodulating agents in the setting of moderate-severe PPH before and after OLT [7]. Small case reports and retrospective studies have presented various outcomes with use of sildenafil, ambrisentan, iloprost, epoprostenol, bosentan, and trepostinil, [8-11]. With improved hemodynamics before OLT, this specific subgroup of PPH patients may now qualify for transplant, which otherwise, would prohibit them from receiving a new liver [12].

We hypothesize that treatment of PPH with vasomodulators before and after OLT portends a superior survival rate than previously reported in the literature in similar patients. The aim of our study is to assess the duration of survival afforded to these patients long after their liver transplant

PATIENTS AND METHODS

Study Population

The study was conducted at Tampa General Hospital, Tampa, FL, as a retrospective cohort study.

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Patient with end stage liver disease who underwent OLT between December 1996 and June 2011 were identified. Their charts were evaluated during the pre- and post-liver transplant period. These subjects were then followed until December 2012 when the study concluded. One thousand patient charts were reviewed. Twenty patients with PPH were identified.

Study Design

PPH was diagnosed by either echocardiographic demonstration of systolic pulmonary artery pressure (sPAP) or right heart catheterization (RHC) mean pulmonary artery pressure (mPAP) greater than 25 mmHg. If both values were found on the same individual *via* either modality, the RHC values prevailed. The patients were then categorized as having PPH that is “mild” (mPAP 25-34mmHg), “moderate” (mPAP 35-44mmHg), or “severe” (mPAP > 45mmHg).

Age, sex, ethnicity, body mass index (BMI), comorbid conditions, and etiology of liver disease were obtained for each patient. The primary outcome was time until death while on vasomodulator therapy after transplant. Secondary outcomes included length of stay in ICU, cause of death, days until death post-transplant and total survival days were recorded. Survival was measured in days beginning immediately post-OLT. The cause of death is also presented.

Patient demographics are described according to means, medians and standard deviations. Outcome variables included range of data. Overall survival was estimated using the Kaplan–Meier methodology. Cox-Regression statistic was utilized to test the relationship between time to death and all the covariates.

RESULTS

The characteristics of the patients in the PPH cohort are listed on Table **1**. The majority of the patients were Caucasian men. Systemic hypertension was the most common comorbidity (PPH 40%) followed by diabetes mellitus. Hepatitis C was the most common etiology of liver disease.

Table **2** outlines the end-points of the study. Fifty percent of patients died after OLT. More men died as compared to women after transplant. Pulmonary, cardiac and vascular complications were the most common causes of death. The median survival was 357 days. Thirty percent died within 180 days, while forty percent of the patients lived to greater than 1200 days before succumbing to death. The 1- and 3- year overall survival was 80 and 70% respectively. The five-year survival was predicted at 60% (Figure **1**).

Table **3** summarizes the pre-transplant hemodynamics and vasomodulator treatment. There were an equal number of subjects within each severity group. Table **4** represents post-transplant time to death within each severity group and vasomodulator therapy. As expected the median time until death in the moderate group was longer (1667 days) compared to those with severe PPH (216.5 days). One patient in the mild severity group died of cardiopulmonary complications at day 36 post-transplant. Interestingly, epoprostenol is the most administered vasomodulator treatment in those with PPH in the pre-transplant period, comprising of 40% of the pharmacological agents used. After transplant, the need for Epoprostenol increased to 45%.

Figure **2** represents time until death by the degree of severity of PPH. Patients with severe-stage PPH had experienced a plateau effect with regards to survival rate from the first year after transplant until the 6.7-year mark. Patients in the moderate group had sustained lack of decline in death rate from year 3 onwards until end of study at 13 years.

DISCUSSION

There are few studies that demonstrate that augmenting and prolonging vasodilator therapy in patients with PPH in the post-liver transplant period has improved mortality. Our results suggest that with escalation of vasomodulator treatment for an extended duration of time in the post-transplant imparts improved mortality especially for those who have moderate-severe disease. This is in contrast to the grim survival rates as reported in recent literature [3,5,6].

The overall death rate for PPH patients who received liver transplant is 50%. Our overall 5-year survival is predicted at 60%, both of which is an improvement when compared to other cohort studies [3,5,6]. Interestingly, 40% of PPH patients lived to greater than 1200 days. This is in contrast the published data that less than a third of PPH patients survive to more than 3 years [11]. There was an increased use of epoprostenol and sildenafil after transplant was noted. Perhaps the use of vasomodulators in the post-OLT state to more aggressively reduce pulmonary pressures for longer than 1 year, imparts a delay until death, especially for those with moderate-severe PAP pressures. A large

Table 1: PPH Patient Characteristics

	Total# n=20 (%)	Median	Mean (SE)	CI (95%)
Age (years):		50	49 (1.88)	+/- 3.95
≤40	1 (5)			
41-50	10 (50)			
51-60	8 (4)			
>61	1 (5)			
Gender:				
Males	14 (70)			
Females	6 (30)			
Ethnicity:				
Caucasian	18 (90)			
Hispanic	2 (10)			
Blacks	0			
Asians				
BMI:		31	30.14 (1.31)	+/- 2.78
Comorbidities:				
Congestive Heart Failure	0			
COPD	0			
Systemic Hypertension	8 (40)			
Cardiomyopathy	0			
Stroke/Seizure	0			
Diabetes Mellitus	5 (25)			
Coronary Artery Dis	1 (5)			
Gastric Reflux	1 (5)			
Dyslipidemia	0			
Renal Disease	3 (15)			
Other cancers	1 (5)			
Thyroid disorders	4 (20)			
Sleep Apnea	2 (10)			
CMV infection	2 (10)			
Ulcerative Colitis	0			
Bacterial Pneumonias	0			
Autoimmune/				
Vasculitis/CTD	1 (5)			
Liver Etiology For Transplant:				
Hepatocellular Carcinoma	1 (5)			
Alcohol/Laennec	8 (40)			
Hepatitis C	7 (35)			
Cryptogenic	5 (25)			
Hepatitis C + Alcohol	4 (20)			
Autoimmune+Cryptogenic	1 (5)			
Alpha1Antitrypsin Defic	2 (10)			

(Table 1). Continued.

Portal Vein Thrombus	9
Hepatocelluar carcinoma	
+Primary Biliary	
cirrhosis	
+Portal Vein	
thrombus	1 (5)

**BMI= Body Mass Index, COPD = Chronic Obstructive Lung Disease, SE = Standard Error, CI = Confidence Interval.

Table 2: PPH Outcomes

	Total# (%)	Median	Mean(SD)	CI (95%)
Deaths:	10 (50)			
Gender of those Deaths:				
Males	8 (80)			
Females	2 (20)			
Ethnicity of those Deaths:				
Caucasian	9 (90)			
Hispanic	1 (10)			
Age at time of death:		51	49.2 (3.18)	+/- 7.20
Days in ICU/Vent of those Deaths:		3	7.8 (3.84)	+/- 8.68
Total LOS Post-LTx of those Deaths (days):		11	18 (6.67)	+/- 15.09
Overall				
Days until Death from Date of transplant:		357.5	991.4 (378.35)	+/- 855.89
<30	1 (10)			
31-180	3 (30)			
181-250	0			
251-1200	2 (20)			
>1201	4 (40)			
Mild PPH days until death:		4 (40)	1667	1372.75 (969.7)
Moderate PPH days until death:		2 (20)	258	258 (181.0)
Severe PPH days until death:		4 (40)	216.5	976.7 (1670.4)
Cause of Death:				
Cardiopulmonary Arrest	1 (10)			
Cardiac Failure	2 (20)			
Renal Failure	1 (10)			
Infection/sepsis	1 (10)			
Respiratory	3 (30)			
HCV Recurrence	0			
Vascular complications	2 (20)			
Embolic Event	0			

**LOS= Length of Stay, ICU = Intensive Care Unit, LTx = Liver transplant, SE = Standard Error, CI = Confidence Interval.

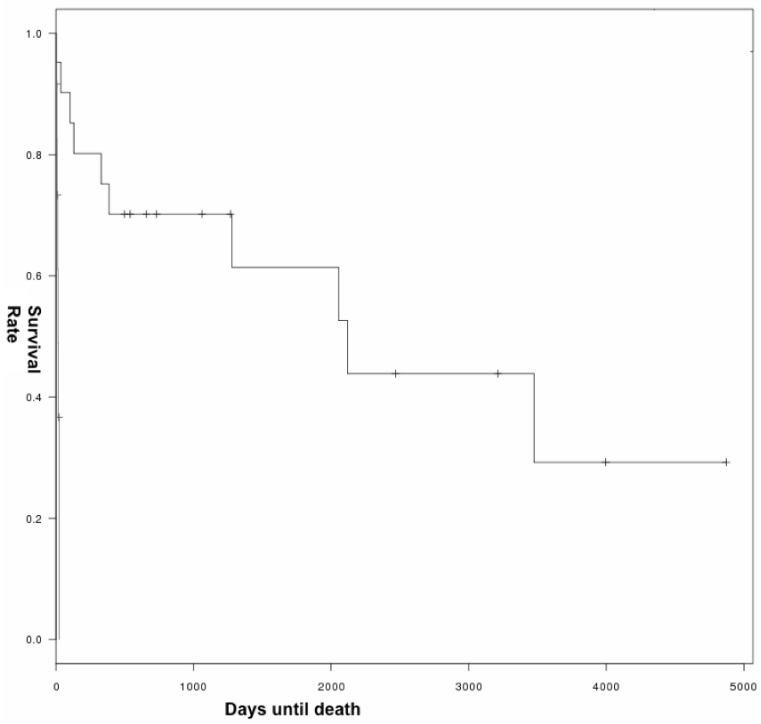

Figure 1: Kaplan-Meier - Overall Survival.

Table 3: PRE-OLT Hemodynamics and Vasomodulator Treatment

	Total # (%)	Median	Mean (SE)	Range
Overall sPAP or mPAP (mmHg):		36	39.1 (3.02)	22-80
Overall ECHO EF (%):		65.5	68.6 (2.09)	55-82
Mild PPH:	6 (30)	30.5	29.6 (1.17)	25-32
Moderate PPH:	6 (30)	37.5	38.83 (1.70)	35-44
Severe PPH:	6 (30)	50.5	54.5 (5.26)	45-80
Vasomodulator Agent:				
Sildenafil	4 (20)			
Epoprostenol	8 (40)			
Nitric Oxide	5 (25)			
Milrinone	1 (5)			
Bosentan	0			
Ambristentan	1 (5)			
CCB	2 (10)			

Mayo clinic study revealed that 9 of the 11 transplanted patients required vasomodulating medications for up to 1 year, and their 5-year survival was 67% [13]. Krowka *et al.* had demonstrated that 5 of their 23 surviving patients required prostacyclin for up to 30 months post-transplant with reduced overall mortality to 36% [4]. While certainly beneficial as a “bridge” to OLT in PPH, vasomodulators may prove effective in prolonging survival post-transplant especially in those with moderate to severe disease. Our practice now is to identify PPH patients before transplant and to treat them before transplant to get the mPAP to the mild level. Then, transplantation takes place.

Limitations include the retrospective nature of this study which does not permit adequate assessment of several uncertainties. Firstly, we could not decipher which vasomodulating agent was optimal for each

Table 4: POST-OLT Survival and Vasomodulator Treatment

	Total # (%)	Median days until death
Mild PPH:		1667
1-year survival: 0.88		
3-year survival: 0.88		
5-year survival: 0.05		
Moderate PPH:		258
1-year survival: 0.80		
3-year survival: 0.74		
5-year survival: 0.74		
Severe PPH:		216.5
1-year survival: 0.70		
3-year survival: 0.70		
5-year survival: 0.70		
Vasomodulator Agent:		
Sildenafil:	13 (65)	
Epoprostenol:	9 (45)	
Nitric Oxide:	1 (5)	
Milrinone:	0	
Bosentan:	2 (10)	
Ambristentan:	0	
CCB:	1 (5)	

**EF = Ejection Fraction, sPAP = Systolic Pulmonary Artery Pressure, CCB = Calcium Channel Blocker, SE = Standard Error, CI = Confidence Interval.

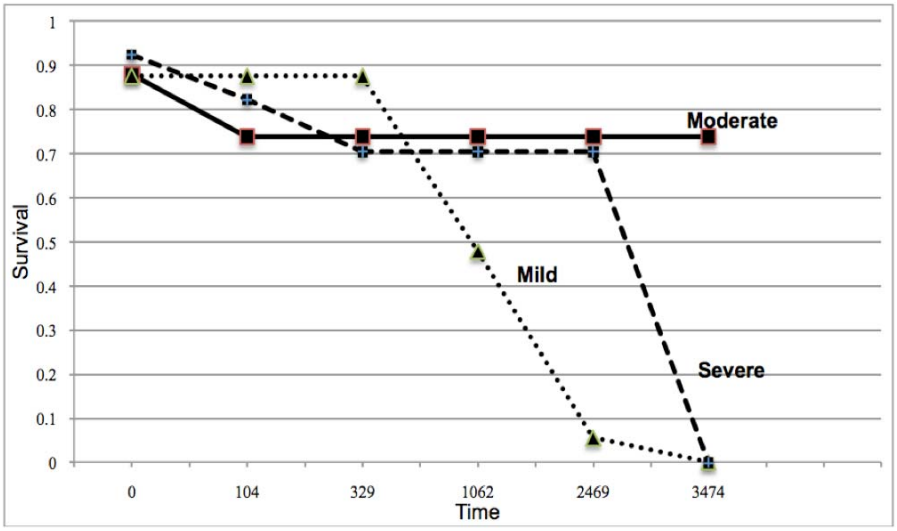

Figure 2: Cox-Regression Survival analysis of the varying degrees of PPH.

subset PPH severity (mild, moderate, severe) that would produce the optimal survival time post-transplant. Secondly, was the improved survival an after-effect of the pre-transplant treatment of PPH with vasomodulators or due to the medications themselves after transplant?

Thirdly, was the lack of consistent right heart catheterization measurements of hemodynamics after liver transplant for which to trend the pulmonary pressures during treatment. Fourthly, the duration of treatment of each vasodilator regimen was not found in the patient charts either in the pre- or post-transplant

phase. This could have been helpful in determining any associations between duration of certain therapies with survival.

CONCLUSION

Patients with pulmonary vascular disease have a complicated post liver transplant course specifically those with moderate to severe PPH. This retrospective study suggests that in the setting of PPH and liver transplant, mortality is greatly improved if not sustained survival rate after OLT with long-term treatment with vasomodulators. This conclusion is emphasized for those with moderate-severe PPH.

CONFLICTS OF INTERESTS/UNDISCLOSED FUNDING

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