의학박사 학위논문

경증 및 중등도 폐고혈압이 생체 간이식의 임상 경과에 미치는 영향

Clinical Impact of Mild to Moderate Pulmonary Hypertension in Living-Donor Liver Transplantation

울산대학교 대학원

의학과

이승아

경증 및 중등도 폐고혈압이
생체 간이식의 임상 경과에 미치는 영향

지도교수 송종민

이 논문을 의학 박사 학위 논문으로 제출함

2020년 08 월

울산대학교대학원
의학과
이승아

이 승 아의 의학박사 학위 논문을 인준함

심사위원 김 대 희 (인)

심사위원 송 종 민 (인)

심사위원 이 재 승 (인)

심사위원 김 기 훈 (인)

심사위원 김 형 관 (인)

울 산 대 학 교 대 학 원

2020 년 08 월

국문요약

간경화 환자에게 중증의 폐동맥 고혈압이 동반되어 있을 경우 간이식은 금기로 알려져 있다. 그러나 경증 및 중등도의 폐동맥 고혈압이 동반된 환자에게 생체 간이식을 할 경우 그 임상 경과 및 예후에 대해서는 아직 밝혀진 바가 없다. 따라서 본 연구는 경증 및 중등도의 폐고혈압이 생체 간이식의 이식 성공률에 미치는 영향을 살펴보고, 간이식 전 폐고혈압을 예측할 수 있는 위험인자에는 어떤 것이 있는지 살펴보고자 한다.

2007년부터 2016년까지 서울아산병원에서 생체 간이식을 받은 1307명의 환자 (평균 연령 52세, 남성 71%)를 대상으로, 수술 전 후 폐동맥압 측정하였으며, 폐고혈압은 평균 폐동맥압 25mmHg 이상인 경우로 정의하였다. 생체 간이식 후 1년 간 이식 간의 생존 여부를 연구의 1차 종료점으로 설정하였고, 연구의 2차 종료점은 수술 후 합병증 발생 (수술 후 30일 내 사망, 30일 내 이식 간부전, 재이식, 중환자실 재실 기간, 기계 호흡 이용 기간, 심폐 순환보조장치 사용, 지속적 신대체 요법의 적용)으로 설정하였다.

전체 코호트에서 Model for End-stage Liver Disease-Sodium (MELD-Na) 점수의 중앙값은 19점 이었고 (1-3 사분 범위, 14-27), 100명의 환자에서 폐고혈압이 발견되었다. 94명의 환자는 경증 폐고혈압 (평균 폐고혈압 25~35 mmHg) 에 해당되었으며, 6명의 환자는 중등도의 폐고혈압 (평균 폐고혈압 35~45 mmHg)에 해당하였다. 전체 코호트에서 1년간 이식 간부전은 94명 (7.2%)에서 발생하였으며, 폐동맥 고혈압을 갖은 환자들은 그렇지 않은 환자들에 비해 낮은 1년 이식 간 생존 (86% 대 93.4%, log-rank P=0.005) 및 낮은 1년 생존률 (87% 대 93.6%, Log-rank P=0.011) 과 관련 있었다. 평균 폐동맥압은 1년 이식 간부전 (odds 비 1.05, 95% confidence interval 1.03-1.08, P=0.005) 및 입원 합병증 (odds 비 1.10, 95% confidence interval 1.08-1.12, $p<0.001$)의 높은 위험과 관련 있었다. 임상 지표에 더해 평균 폐동맥압을 고려하였을 때, 수술 후 입원 합병증이나 1년 이식 간부전의 예측력은 더욱 향상되는 것으로 확인되었다. 수술 전 평가 지표 중, 삼첨판막 역류 최대속도, 우심방 압력 상승, 빈혈, brain natriuretic peptide, MELD-Na score를 고려했을 때, 폐동맥 고혈압을 예측할 확률이 높아졌다. (Area under curve: 0.843)

경증 및 중등도 폐동맥 고혈압은 생체 간이식 후 입원 합병증 및 1년 이식 간 생존의 위험을 높이는 예후 인자로 확인되었으며, 특히 사망률에도 영향을 끼친다. 수술 중 측정한 평균 폐동맥압은 생체 간이식 후 초기 임상경과를 예측하는데 도움을 준다.

Table of Contents

I. Introduction

In patients with liver cirrhosis, pulmonary hypertension (PHT), the evidence of circulatory volume excess or increased pulmonary vascular resistance, occurs owing to hyperdynamic cardiac output status, sodium retention, or portopulmonary hypertension.[1] Among the major causes of PHT, portopulmonary hypertension is associated with poor clinical outcomes in patients awaiting liver transplantation (LT), which can be the only effective treatment option. However, if severe, transplantation should be avoided because of the unacceptable mortality rate.[2-4] Therefore, the current guideline suggests that severe PHT should be considered as an absolute contraindication to LT, and transplantation in the setting of moderate PHT has been associated with an increased risk of perioperative morbidity and mortality.[5] However, the prognosis of mild to moderate PHT in LT is not well established.[6-8] Nowadays, as the number of adult living-donor liver transplantation (LDLT) is growing owing to improved surgical techniques and perioperative critical care management, awareness of the prognostic value of mild to moderate PHT in candidate patients for LDLT is needed for clinical decision making. However, no data have demonstrated the clinical impact of PHT in LDLT. Therefore, we aimed to evaluate the clinical value of mild to moderate PHT in predicting the early outcomes of patients who underwent LDLT.

II. Methods

Study population

A total of 2,170 patients underwent LDLT for liver cirrhosis between 2007 and 2016 in our institution. After excluding 863 patients who had liver cirrhosis with Child-Turcotte-Pugh class A or a Model for End-stage Liver Disease-Sodium (MELD-Na) score of <10 units (822 patients)

and had a significant decrease in left ventricular contractility of <55% (37 patients) or a significant valvular heart disease (4 patients), 1,307 eligible patients were included in our study cohort. All the clinical and surgical data stored in the patients' electronic medical records were retrospectively collected. Clinical data, including age, sex, weight, height, medical history, laboratory tests, and MELD-Na score, and echocardiographic data, including estimated right atrial pressure and maximal velocity of tricuspid regurgitation, were obtained at the time of preoperative evaluation. MELD and MELD-Na scores were calculated in accordance with the current Organ Procurement and Transplantation Network guidelines. [9] The MELD score was calculated using the following equation: $0.957 \times \text{Log}_e(\text{Creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{Bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$, rounded to the nearest tenth decimal place and multiplied by 10. The MELD-Na score was calculated using the following equation: $\text{MELD-Na} = \text{MELD} + 1.32 \times (137 - \text{Sodium mmol/L}) - [0.033 \times \text{MELD} \times (137 - \text{Sodium mmol/L})]$. The data on surgical procedures and operative times were collected from the surgical records. Information on hemodynamic parameters and postoperative events was obtained from vital sheets of anesthetic records and medical records, respectively. Most patients (99.3%) completed the 1-year clinical follow-up in our institute, and the remaining 9 patients' (0.7%) data on the vital status, dates, and causes of death were obtained from the Korean National Statistical Office. The local institutional review board approved the study and waived the requirement of informed consent owing to the retrospective observational nature of the study.

Measurement of intraoperative pulmonary artery pressure

Anesthesia induction and hemodynamic monitoring were performed in accordance with our institutional standards.[10] Briefly, we maintained anesthesia using sevoflurane or desflurane with a mixture of 50% O_2 and 50% air and continuous infusion of fentanyl. Arterial pressure

was monitored using radial or femoral arterial catheters. For advanced hemodynamic monitoring, a pulmonary arterial catheter was inserted and connected to a Vigilance device (Vigilance II, Edwards Lifesciences, Irvine, CA, USA). The intraoperative blood pressure, heart rate, pulmonary artery pressure, and cardiac output were initially measured 10 to 15 minutes after induction of general anesthesia. Hemodynamic monitoring was continued until the end of anesthesia, and data were recorded at 15-minute intervals. Patients with PHT were identified on the basis of elevated mean pulmonary artery pressures of ≥25 mmHg at the first measurement before skin incision.

Study endpoints

The primary end point was graft failure within 1 year after LDLT. Graft failure was defined as retransplantation or death from any cause. The secondary end points were in-hospital adverse events, which is a composite of 30-day mortality; allograft dysfunction requiring retransplantation; intensive care unit stay for >30 days; prolonged ventilator care of >2 weeks; and newly applied mechanical circulatory support or continuous renal replacement therapy after transplantation.

Statistical analysis

For the categorical variables, data are reported as numbers with percentages and compared using the chi-square test. On the basis of their distribution, continuous variables are expressed as mean and standard deviation analyzed using a *t* test or median values, and the first and third interquartile ranges were compared using the Wilcoxon rank-sum test. The estimated probability of PHT was calculated on the basis of the regression coefficient of multivariable logistic regression. Adverse events after transplantation were also compared using the chi-square test and presented as counts or percentages. For prediction of the study end points,

clinical, echocardiographic, and hemodynamic variables were investigated using logistic regression models. The multivariable model was determined considering statistical significance, multicollinearity, and clinical knowledge. The primary end point is also expressed as a Kaplan–Meier curve and analyzed using the log-rank test. The improvement in risk prediction performance resulting from the addition of PHT to the clinical variables was quantified using the Harrell C-statistics, continuous net reclassification index (NRI), integrated discrimination improvement (IDI), and likelihood ratio test. The NRI and IDI values were estimated with their 95% confidence intervals (CIs). All reported *p*-values were two-sided, and a *p* value of <0.05 was considered statistically significant. R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analyses.

III. Results

Baseline and operative characteristics

The patients' ages at transplantation ranged from 18 to 73 years (mean, 52.0 years), and 928 patients (71.0%) were men. Hepatitis B virus infection was the predominant etiology of liver cirrhosis in 56.9% of the cohort, and hepatocellular carcinoma was found in 455 patients (34.8%). The mean pulmonary artery pressures ranged from 3 to 42 mmHg in the entire cohort. The preoperative clinical characteristics of patients with or without PHT are compared in Table 1. One hundred patients had confirmed PHT (7.7%), which was mild (25–34 mmHg) in 94 (7.2%) and moderate (35–44 mmHg) in 6 (0.5%). The patients with PHT had advanced liver cirrhosis with a higher proportion of Child-Turcotte-Pugh class C, more elevated MELD-Na scores, higher total bilirubin levels and prothrombin times, and lower albumin and hemoglobin levels than those without PHT. Although the ejection fraction was similar, patients with PHT

were more likely to have higher brain natriuretic peptide (BNP) levels and maximal velocity of tricuspid regurgitation than those without PHT.

Table 1. Baseline Characteristics

Variables	Overall cohort (n=1,307)	mPAP <25 mmHg (n=1,207)	mPAP ≥25 mmHg (n=100)	p value
Age, years	52.0 ± 8.4	52.0 ± 8.3	51.9 ± 9.6	0.915
Male, n (%)	928 (71.0)	864 (71.6)	64 (64.0)	0.136
Body mass index (kg/m^2)	23.7 ± 3.3	23.7 ± 3.3	24.1 ± 3.6	0.195
Etiology of end-stage liver disease, n (%)				0.023
Alcohol	221 (16.9)	197 (16.3)	24 (24.0)	
Hepatitis A	8 (0.6)	7 (0.6)	1 (1.0)	
Hepatitis B	779 (59.6)	738 (56.5)	41 (41.0)	
Hepatitis C	92 (7.0)	83 (6.9)	9 (9.0)	
Autoimmune	20 (1.5)	18 (1.5)	2 (2.0)	
Toxin & drug	41 (3.1)	36 (3.0)	5 (5.0)	
Cryptogenic	63 (4.8)	55 (4.6)	8 (8.0)	
Others	83 (6.4)	73 (6.0)	10 (10.0)	
Hepatocellular carcinoma, n (%)	455 (34.8)	434 (36.0)	21 (21.0)	0.003
CTP class, n (%)				0.006
Class B	746 (57.1)	702 (58.2)	44 (44.0)	
Class C	561 (42.9)	505 (41.8)	56 (56.0)	
MELD-Na score	21.0±8.4	20.7±8.3	24.7±8.9	<0.001
Hypertension, n (%)	148 (11.3)	139 (11.5)	9 (9.0)	0.549
Diabetes, n (%)	296 (22.6)	279 (23.1)	17 (17.0)	0.201
Lung disease, n (%)	16 (1.2)	14 (1.2)	2 (2.0)	0.463

Renal replacement therapy, n (%)	74 (5.7)	65 (5.4)	9 (9.0)	0.133
Hemoglobin (g/dL)	10.2 ± 1.8	10.3 ± 1.8	9.6 ± 2.0	0.001
Platelet ($\times 10^3/\mu L$)	38 [54, 77]	54 [38, 77]	46 [32, 78]	0.146
AST (IU/L)	54 [38, 83]	53 [38, 82]	56 [35, 90]	0.123
ALT (IU/L)	30 [20, 50]	30 [19, 49]	30 [17, 56]	0.175
Total bilirubin (mg/dL)	3.7 [2.0, 14.6]	3.3 [2.0, 9.9]	6.6 [2.9, 25.3]	<0.001
Albumin (g/dL)	2.8 ± 0.6	2.7 ± 0.6	2.9 ± 0.6	0.005
Prothrombin time (INR)	1.8 ± 0.7	1.8 ± 0.7	2.1 ± 0.9	<0.001
Creatinine (mg/dL)	0.76 [0.60, 1.00]	0.74 [0.60, 0.97]	0.90 [0.63, 1.26]	0.032
Sodium (mmol/dL)	135.7 ± 5.9	135.7 ± 5.8	135.7 ± 6.8	0.985
BNP (pg/mL)	57 [29,112]	55 [28, 104]	137 [46, 316]	<0.001
CRP (mg/dL)	0.58 [0.23, 1.36]	0.57 [0.23, 1.36]	0.61 [0.24, 1.43]	0.535
Preoperative echocardiography				
Peak velocity of tricuspid regurgitation (m/s)	2.4±0.3	2.4±0.3	2.6±0.4	<0.001
Left ventricular ejection fraction (%)	65.0±4.3	65.0±4.3	65.2±4.3	0.650
Intraoperative cardiac catheterization				
Systolic pulmonary artery systolic pressure (mmHg)	24.0 ± 6.6	23.0 ± 5.3	36.9 ± 7.0	<0.001
Diastolic pulmonary artery systolic pressure (mmHg)	11.4 ± 4.2	10.7 ± 3.6	19.2 ± 3.4	<0.001
Mean pulmonary artery systolic pressure (mmHg)	16.7 ± 5.1	15.8 ± 4.0	27.9 ± 3.3	<0.001
Total operating time (min)	807 [735, 892]	809 [734, 893]	797 [739, 878]	0.765

BNP, brain natriuretic peptide; CRP, C-reactive protein; CTP, Child-Turcotte-Pugh; INR international normalized ratio; MELD-Na, Model For End-Stage Liver Disease Sodium, mPAP, mean pulmonary artery pressure

Pulmonary hypertension and clinical outcomes

The in-hospital events and 1-year clinical outcomes are summarized in Table 2. The entire cohort had 14 cases of operative mortality (1.1%). Within 30 days, 13 deaths (1.1%) and 4 graft failures (0.3%) occurred in patients without PHT, and 1 death (1.0%) and 2 graft failures (2%) occurred in patients with PHT. The length of mechanical ventilator care was longer in the PHT group than in the non-PHT group. Patients with PHT were more likely to apply continuous renal replacement therapy after LT and had a longer intensive care unit stay (median, 4 vs. 5 days, mean 7 vs. 15 days; p = 0.004). The composite outcomes of in-hospital events occurred in 22 patients (22%) with PHT and 117 patients (9.7%) without PHT.

During the 1-year follow-up, 90 deaths (6.9%) and 17 retransplantations (1.3%) occurred in the overall cohort. Graft failure occurred in 14 patients (14%) in the PHT group and 90 patients (6.6%) in the non-PHT group. Detailed clinical events in the PHT group are summarized in Table 3. PHT was associated with a lower 1-year graft survival (86% vs. 93%, log-rank *p*=0.005) and 1-year survival rates (87% vs. 94%, log-rank *p*=0.011; Figure 1). After multivariable adjustment for the potential explanatory factors of the study end points, mean pulmonary artery pressure was identified as an independent risk factor of 1-year graft failure (adjusted odds ratio, 1.05; 95% CI, 1.01–1.10; *p*=0.014) and in-hospital adverse events (adjusted odds ratio, 1.05; 95% CI, 1.01–1.09; *p*=0.008). The independent risk factors, except mean pulmonary artery pressure, included age, C-reactive protein level, and MELD-Na score for 1-year graft failure and older age, male sex, and lower body mass index, C-reactive protein level, and MELD-Na score for in-hospital adverse events (Table 4).

During the median 6.2 years of follow-up, no statistically significant difference in long-term patient survival rate was found between the study groups. The Kaplan–Meier estimate of 5-year survival rate was 83.8% for the PHT group and 88.9% for the non-PHT group (hazard

ratio, 1.55; 95% CI, 0.94–2.57; p = 0.09).

Table 2. Clinical outcomes

Outcome	Overall cohorts (n=1,307)	mPAP <25 mmHg (n=1,207)	mPAP ≥25 mmHg (n=100)	P Value
In-hospital adverse events				
30-day death (%)	14 (1.1)	13 (1.1)	1 (1.0)	0.943
30-day re-transplantation (%)	6 (0.5)	4 (0.3)	2 (2.0)	0.018
30-day graft failure (%)	17 (1.3)	14 (1.2)	3 (3.0)	0.119
Prolonged ICU care (%)	58 (4.4)	47 (3.9)	11 (11.0)	0.001
ICU length of stay, median [Q1, Q3]	4 [2, 6]	4 [2, 6]	5 [3, 15]	0.004
Prolonged ventilator care (%)	96 (7.3)	75 (6.2)	21 (21.0)	<0.001
Length of time on mechanical ventilator, median [Q1, Q3]	1 [1, 3]	1 [1, 3]	4 [1, 11]	0.026
Newly applied ECMO (%)	21 (1.6)	19 (1.6)	2 (2.0)	0.745
Newly applied CRRT (%)	46 (3.5)	38 (3.1)	8 (8.0)	0.011
Composite of in-hospital adverse events	137 (10.6)	117 (9.7)	22 (22.0)	<0.001
One-year clinical outcomes				
One-year death (%)	90 (6.9)	77 (6.4)	13 (13.0)	0.012
One-year re-transplantation (%)	17 (1.3)	11 (0.9)	6 (6.0)	<0.001
One-year graft failure (%)	94 (7.2)	90 (6.6)	14 (14.0)	0.006

CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; 1Q, the first quartile; 3Q, the third quartile

Figure 1. Kaplan-Meier curves for (A) 1-year graft survival and (B) 1-year patient survival stratified according to the presence or absence of pulmonary hypertension. The results of the analysis for (A) 1-year graft survival and (B) 1-year patient survival are shown. The hazard ratios are for the group of patients with pulmonary hypertension (PHT) as compared with those without PHT.

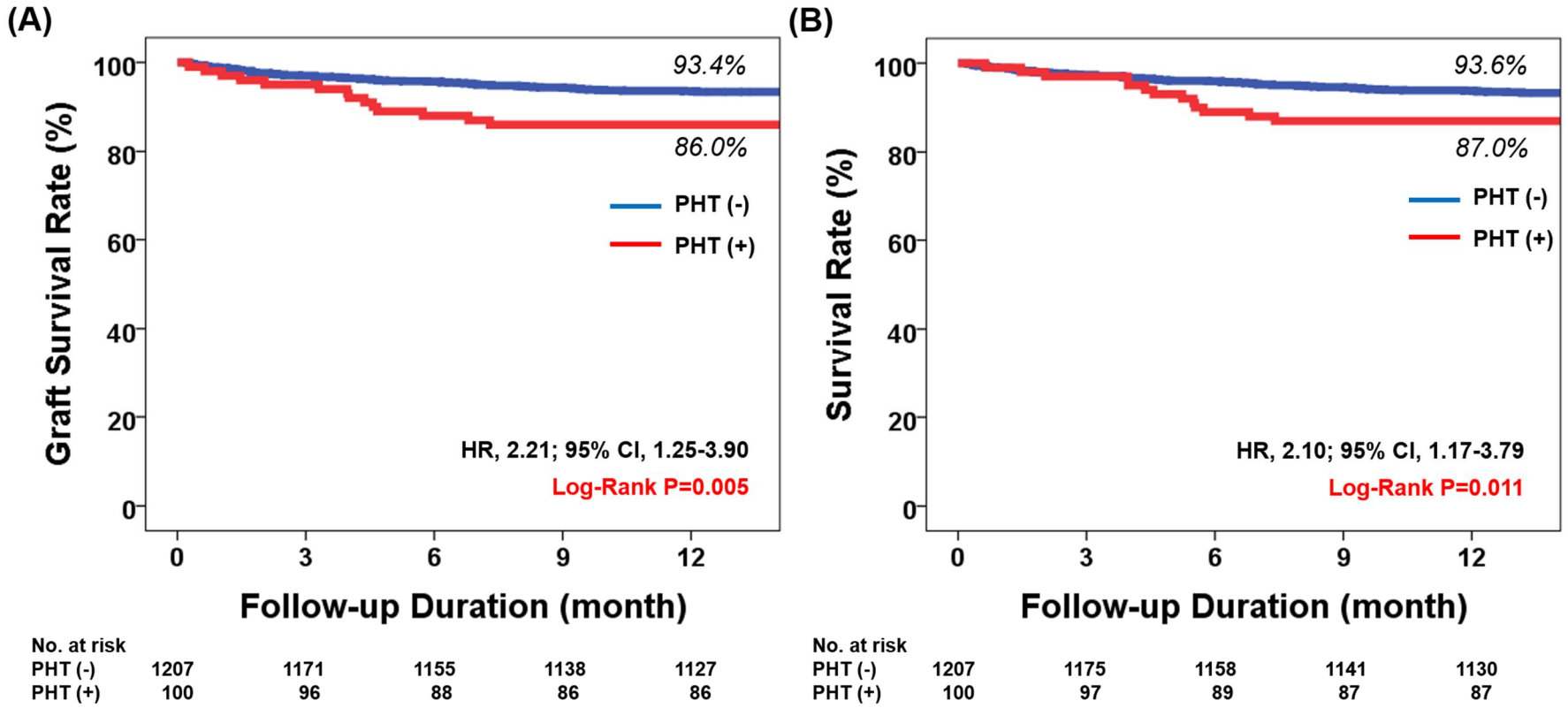


Table 3. Preoperative pulmonary hemodynamics and clinical events in pulmonary hypertensive patients who experienced graft failure within 1-year after transplantation

Patient's No.	Age/Sex	MELD-Na score	BNP (pg/mL)	TR Vmax (m/s)	PASP (mmHg)	PADP (mmHg)	Mean PAP (mmHg)	Death or retransplantation	Reason for death or retransplantation
1	67/F	30	N/A	2.5	35	15	26	POD 137, death	Graft failure
2	44/M	41	N/A	3.2	37	20	26	POD 99, re-TPL	Graft rejection
3	67/M	21	54	2.9	40	20	30	POD 172, death	Pneumonia
4	58/F	28	496	2.9	32	25	28	POD 44, death	Pneumonia
5	39/F	33	11	2.3	35	17	25	POD 120, re-TPL	Bile duct obstruction
6	47/F	40	2670	3.2	54	25	39	POD 8, re-TPL	Outflow obstruction
7	27/F	41	387	3.3	43	25	37	POD 219, re-TPL	Bile duct obstruction
8	58/M	25	141	2.1	35	22	29	POD 119, death	CMV infection
9	61/M	21	294	2.3	40	18	29	POD 61, death	Pneumonia
10	68/F	37	215	2.6	35	14	25	POD 140, re-TPL	Graft rejection
11	54/M	22	19	1.9	33	20	27	POD 131, death	Graft failure
12	52/F	20	52	3.1	37	14	26	POD 19, death	Intraoperative arrest
13	69/M	35	270	2.3	32	18	25	POD 31, re-TPL	Outflow obstruction
14	62/F	32	149	2.4	37	21	28	POD 204, death	Pneumonia

BNP, brain natriuretic peptide; CMV, cytomegalovirus; MELD-Na, Model for End-Stage Liver Disease Sodium; PADP, pulmonary artery diastolic pressure, PAP, pulmonary artery pressure; PASP, pulmonary artery systolic pressure; POD, post-operative date; re-TPL, re-transplantation; TR Vmax, Maximal velocity of tricuspid regurgitation

Table 4. Logistic regression analysis of the primary and secondary end points

	Univariate Analysis			Model 2			Model 3		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
In-hospital Adverse Events									
Age	1.019	1.00-1.04	0.101	1.044	1.02-1.07	<0.001	1.046	1.02-1.07	<0.001
Male	1.537	1.06-2.21	0.021	1.641	1.08-2.47	0.019	1.529	1.00-2.32	0.047
Body mass index	0.931	0.88-0.98	0.012	0.931	0.88-0.99	0.024	0.924	0.87-0.98	0.012
Diabetes	1.071	0.70-1.60	0.745						
Hypertension	1.021	0.57-1.72	0.941						
Log-CRP	1.547	1.32-1.82	<0.001	1.240	1.03-1.50	0.025	1.498	1.02-1.49	0.027
Log-BNP	1.609	1.37-1.89	<0.001						
Left ventricular ejection fraction	1.015	0.97-1.06	0.465						
MELD-Na score	1.100	1.08-1.12	<0.001	1.096	1.07-1.12	<0.001	1.124	1.07-1.12	<0.001
Mean pulmonary artery pressure	1.067	1.03-1.10	<0.001				1.051	1.01-1.09	0.008
1-year Graft Failure									
Age	1.025	1.00-1.05	0.070	1.029	1.00-1.06	0.046	1.030	1.00-1.06	0.035
Male	1.042	0.65-1.63	0.861						
Body mass index	0.959	0.90-1.02	0.214						
Diabetes	1.259	0.77-2.00	0.343						

Hypertension	1.282	0.67-2.29	0.427						
Log-CRP	1.552	1.29-1.88	<0.001	1.392	1.13-1.72	0.002	1.396	1.13-1.72	0.002
Log-BNP	1.219	1.00-1.47	0.043						
Left ventricular ejection fraction	1.015	0.97-1.07	0.542						
MELD-Na score	1.053	1.03-1.08	<0.001	1.038	1.01-1.07	0.008	1.032	1.00-1.06	0.028
Mean pulmonary artery pressure	1.065	1.03-1.11	0.001				1.054	1.01-1.10	0.014

BNP, brain natriuretic peptide; CRP, C-reactive protein; MELD-Na, Model for End-Stage Liver Disease Sodium.

Incremental prognostic value of pulmonary hypertension

To assess the value of intraoperative mean pulmonary artery pressure in surgical risk prediction, risk discrimination and reclassification analyses were performed. In the receiver operating characteristic (ROC) analysis for in-hospital adverse events, the C-statistic for the model with MELD-Na score alone was 0.733, which significantly increased to 0.757 (Model 2) with the addition of clinical variables (Model 2; *p* for improvement <0.001). A similar magnitude of effect was observed after clinical variables and mean pulmonary artery pressure were added to the MELD-Na score (C-statistics of 0.764 for Model 3; *p* for improvement <0.001). No significant increment in C-statistics was observed when the mean pulmonary artery pressure was added to the clinical risk model (C-statistics for Model 2 vs. Model 3; *p*=0.329). In the ROC analysis for 1-year graft failure, the C-statistics for the model with NELD-Na score alone was 0.625, which significantly increased to 0.667 when the clinical variables were added (Model 2, *p* for improvement <0.001) and 0.682 after the clinical variables and mean pulmonary artery pressured were added (Model 3, *p* for improvement <0.001). However, the addition of mean pulmonary artery pressure to the clinical model did not significantly change the C-statistics (Model 2 vs. Model 3; *p*=0.521).

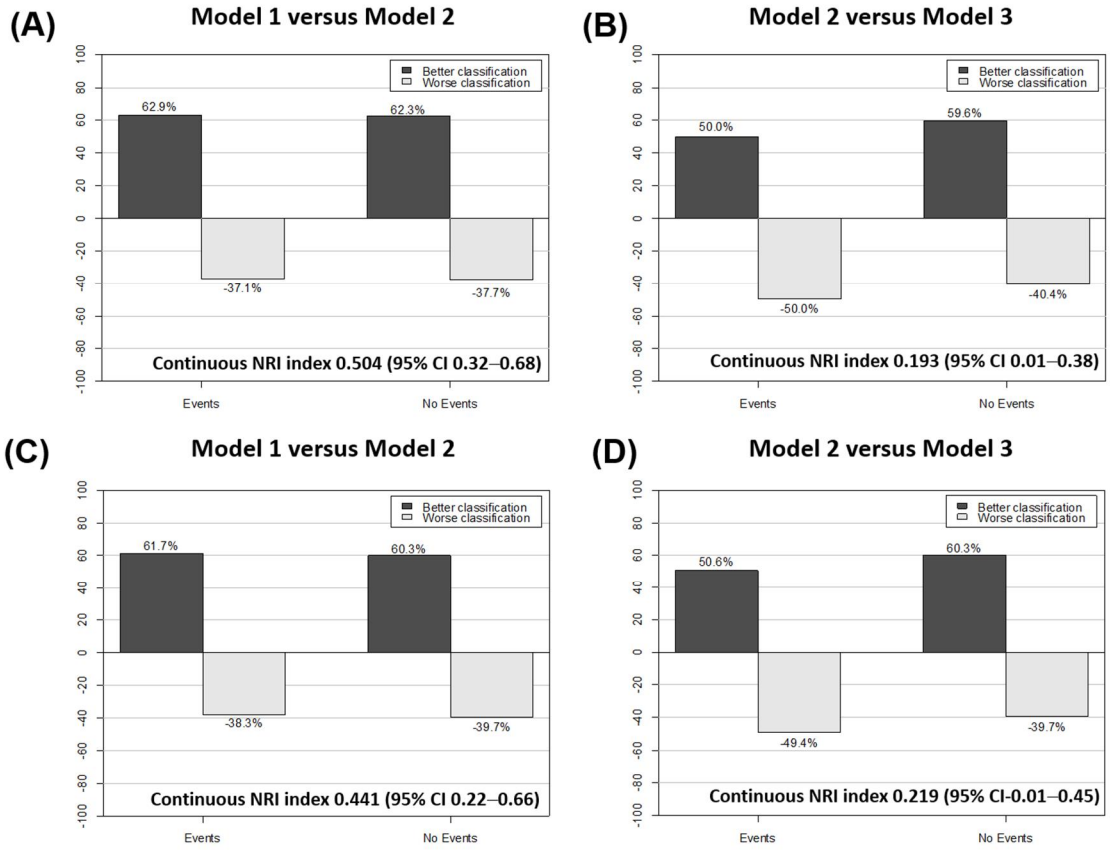
When examining the reclassification properties of the clinical factors and mean pulmonary artery pressure that were greater than the MELD-Na score, we observed the overall improvements in the net risk stratification for in-hospital events and 1-year graft failure (Table 5). As a result of the risk reclassification analyses, adding mean pulmonary artery pressure to the clinical variables (Model 2 vs. Model 3) improved the risk prediction for in-hospital adverse events and 1-year graft failure after LDLT. The improvement was largely driven by a downward reclassification of non-events (Figure 2).

Table 5. Risk reclassification analyses for the study endpoints

	Model 1 vs. Model 2		Model 1 vs. Model 3		Model 2 vs. Model 3	
	MELD-Na	MELD-Na + clinical factors	MELD-Na	MELD-Na + clinical factors + mPAP	MELD-Na + clinical factors	MELD-Na + clinical factors + mPAP
In-hospital events						
C-statistic	0.733	0.757	0.733	0.764	0.757	0.764
Continuous NRI	0.504 (0.32-0.68; p < 0.001)		0.517 (0.34-0.70; p < 0.001)		0.193 (0.01-0.38; p = 0.042)	
IDI	0.033 (0.02-0.05; p < 0.001)		0.043 (0.03-0.06; p < 0.001)		0.010 (0.00-0.02; p = 0.019)	
Likelihood ratio, p value	< 0.001		< 0.001		0.009	
1-year graft failure						
C-statistics	0.625	0.667	0.625	0.682	0.667	0.682
Continuous NRI	0.441 (0.22-0.66; p < 0.001)		0.466 (0.25-0.68; p < 0.001)		0.219 (-0.01-0.45; p = 0.057)	
IDI	0.013 (0.01-0.02; p = 0.001)		0.021 (0.01-0.03; p <0.001)		0.008 (0.00-0.01; p = 0.030)	
Likelihood ratio, p value	0.001		<0.001		0.016	

IDI, integrated discrimination index; MELD-Na, Model for End-Stage Liver Disease Sodium; mPAP, mean pulmonary artery pressure; NRI, net reclassification index.

Figure 2. Reclassification rates when sequentially adding clinical factors and mean pulmonary artery pressure to the Model for Liver Disease Sodium (MELD-Na) scores of patients with and without events. (A) and (B) In-hospital adverse events, (C) and (D) One-year graft failure.



Clinical predictors of the presence of pulmonary hypertension

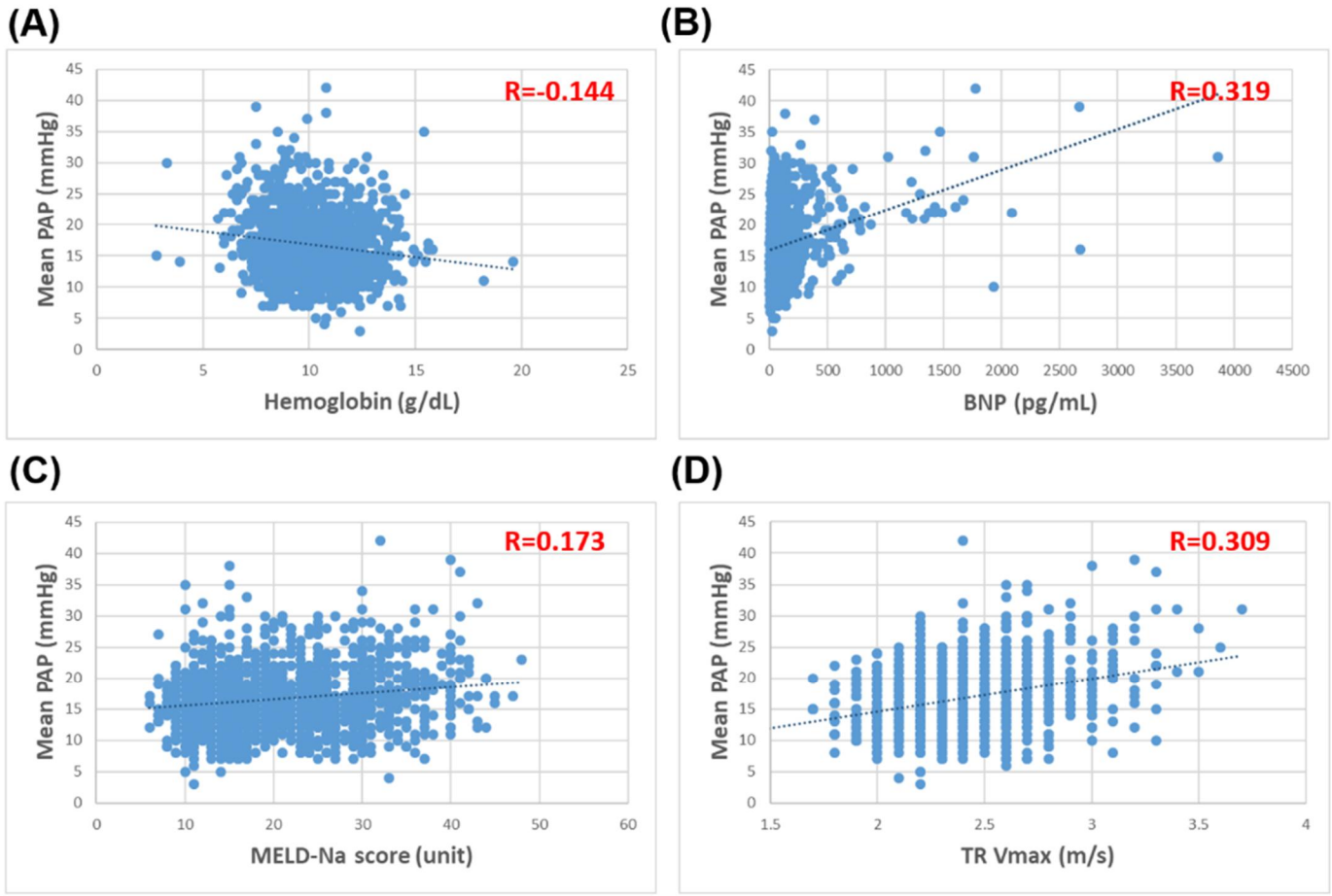
For identifying the predictors of PHT, clinical and echocardiographic variables were evaluated using a simple logistic regression analysis (Table 6). The 5 variables, including high right atrial pressure, the maximal velocity of tricuspid regurgitation, BNP level, hemoglobin level, and MELD-Na score, were associated with PHT in the univariate analysis and showed a weak correlation (Figure 3). The predictive power of each variable for PHT is summarized in Table 6. The areas under the curve (AUC) of all the variables were <0.80. When combined with the 5 variables, the model was found to be robust for predicting PHT (AUC, 0.843; 95% CI, 0.802–0.883). The equation for the estimated probability of PHT was as follows: $1/[1 + \exp\{-(-8.287 + 5.250 \times \text{IVC plethora} + 2.443 \times \text{TR Vmax} - 0.116 \times \text{Hb} + 0.001 \times \text{BNP} + 0.021 \times \text{MELD-Na score})\}]$, where IVC is the inferior vena cava, TR Vmax is the maximal velocity of tricuspid regurgitation, and Hb is hemoglobin.

Table 6. Operating characteristics of the clinical parameters for the diagnosis of pulmonary hypertension

Independent Variable	Odds ratio (95% CI)	Area under the curves (95% CI)	Cut-off value	Specificity (%)	Sensitivity (%)
MELD-Na score, per 1 point	1.05 (1.03-1.08)	0.635 (0.578-0.692)	19 units	50.2	73.0
BNP, per 1 pg/mL	1.85 (1.55-2.23)	0.677 (0.614-0.740)	133 pg/mL	82.2	52.1
Hemoglobin, per 1 g/dL	0.81 (0.72-0.91)	0.603 (0.541-0.665)	9.2 g/dL	72.7	49.0
IVC plethora	190.3 (55.13-1198.0)	0.619 (0.577-0.661)	Presence	99.8	24.0
TR Vmax, per 1 m/s	6.56 (3.46-12.5)	0.743 (0.695-0.790)	2.4 m/s	54.1	85.0

BNP, brain natriuretic peptide; CI, confidence interval; IVC, inferior vena cava; MELD-Na, Model For End-Stage Liver Disease Sodium; TR Vmax, Maximal velocity of tricuspid regurgitation

Figure 3. Linear regression analysis of mean pulmonary artery pressure (PAP) and clinical variables. Weak correlations were observed between mean PAP and (A) hemoglobin level, (B) brain natriuretic peptide (BNP) level, (C) Model for Liver Disease Sodium (MELD-Na) score, and (D) the maximal velocity of tricuspid regurgitation (TR Vmax).



IV. Discussion

The present study demonstrated that (1) the presence of mild to moderate PHT was associated with early adverse events, including in-hospital events and 1-year graft failure; (2) the addition of mean pulmonary artery pressure to the clinical risk factors improved the reclassification of early surgical risks after LDLT; and (3) preoperative anemia, high MELD score, elevated BNP level, high right atrial pressure, and elevated maximal velocity of tricuspid regurgitation were associated with PHT in patients with advanced liver cirrhosis. To our knowledge, this is the first study to demonstrate the clinical impact of mild to moderate PHT in patients with liver cirrhosis who underwent LDLT.

LT is a potentially life-saving therapeutic intervention for patients with advanced liver cirrhosis. As some patients with severe portopulmonary hypertension have been reported to die of right ventricular failure immediately after transplantation, the presence of PHT in advanced liver cirrhosis began to draw attention.[2-4] Several studies have demonstrated the clinical outcomes of patients with PHT who underwent deceased-donor liver transplantation (DDLT). National data showed lower patient (85%) and graft survival rates (82% in 1 year and 78% in 3 years) in 78 patients with portopulmonary hypertension treated with DDLT than in patients without portopulmonary hypertension.[8] Recently, a meta-analysis demonstrated that 1-year survival rate was lower in patients with portopulmonary hypertension after DDLT than in those without portopulmonary hypertension, while graft survival rate was not significantly different between the two groups.[6] However, these two studies were not limited to patients with mild to moderate PHT. As severe PHT is regarded as a contraindication of LT,[5] the data of patients with mild to moderate PHT can provide more clinically useful information. A previous study that involved 102 patients with mild to moderate PHT among 1,263 patients who underwent DDLT revealed that patients with PHT showed lower 1-year graft survival rate (79% vs. 87%), prolonged post-

transplant ventilator use, and longer hospital stay than did patients without PHT.[7] However, 1-year survival rate did not show statistical difference between the two groups (82% vs. 88%). Recently, the clinical outcome of LDLT has improved in a high-volume transplantation center,[11, 12] and our institute also achieved 5,000 cases of LDLT in 2018, with favorable in-hospital outcomes.[13] Some case reports demonstrated successful LDLT in patients with moderate to severe PHT by administering intravenous prostacyclin after LDLT.[14, 15] Patients with portopulmonary hypertension have also been reported to be appropriate candidates for LDLT after careful considerations,[16] and LDLT can be performed safely after appropriate preoperative medical management in patients with mild PHT.[17] Therefore, the risk and outcomes after LDLT in patients with PHT remains to be fully elucidated. In our present study, patients with mild to moderate PHT treated with LDLT demonstrated lower 1-year graft and patient survival rates than did those without PHT. Although the values of the two prognostic parameters for patients with PHT in our study were slightly better than those in previous studies, the clinical outcomes of these patients were worse than those of patients without PHT after LDLT. The former patients were more likely to receive a 30-day retransplantation, prolonged mechanical ventilator care, and newly applied continuous renal replacement therapy. As we have demonstrated in the present study, the addition of mean pulmonary artery pressure to the clinical risk factors such as high age, inflammatory marker, and MELD-Na score improved the discrimination and reclassification of early surgical risk after LDLT. Therefore, our data suggest that the detection of PHT before LDLT planning has clinical importance in the prediction of the prognosis of patients and in deciding preventive measures before surgery.

Echocardiography can be a noninvasive tool for PHT screening before LT. However, many studies showed that echocardiography performs poorly in detecting patients with mild to moderate PHT.[18-21] A subclinical high pressure gradient of tricuspid regurgitation was also

reported to be an important marker for predicting worse survival after LDLT.[15, 22] Our present study demonstrated that the maximal velocity of tricuspid regurgitation significantly correlated with mean pulmonary artery pressure, but the predictive power of PHT was not satisfactory. However, when the maximal velocity of tricuspid regurgitation was combined with other parameters such as inferior vena cava plethora, hemoglobin level, BNP level, and MELD-Na score, the ability to predict PHT was improved. Although we measured pulmonary artery pressure in the operating room just before operation, our data may still help identify patients with PHT in advance with a high probability.

Study limitation

This study has several limitations. First, this was a single-center retrospective observational study and therefore had inherent limitations. Second, the exact etiology of PHT was not fully evaluated because we could not measure pulmonary vascular resistance or pulmonary artery wedge pressure. However, the patients who were included in this study had advanced liver cirrhosis requiring LT; therefore, most patients could be regarded as having portopulmonary hypertension. Finally, pulmonary artery pressure was measured intraoperatively under general anesthesia in our study, and our data could not be extrapolated to cardiac catheterization data without general anesthesia.

V. Conclusion

Mild to moderate PHT is associated with higher risks of in-hospital events and 1-year graft failure, including mortality after LDLT in patients with liver cirrhosis. The mean pulmonary artery pressure measured intraoperatively can help predict the early clinical outcomes after LDLT.

Reference

1. Bozbas SS and Bozbas H. Portopulmonary hypertension in liver transplant candidates. *World Journal of Gastroenterology*. 2016;22:2024-2029.

2. Kuo PC, Plotkin JS, Gaine S, Schroeder RA, Rustgi VK, Rubin LJ and Johnson LB. Portopulmonary hypertension and the liver transplant candidate. *Transplantation*. 1999;67:1087-93.

3. Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C, Pardo M, Jr., Marotta P, Uemoto S, Stoffel MP and Benson JT. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transplantation*. 2004;10:174-82.

4. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C and Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver Transplantation and Surgery*. 1997;3:494-500.

5. Krowka MJ, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MA, Sitbon O and Sokol RJ. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. *Transplantation*. 2016;100:1440-52.

6. Huang B, Shi Y, Liu J, Schroder PM, Deng S, Chen M, Li J, Ma Y and Deng R. The early outcomes of candidates with portopulmonary hypertension after liver transplantation. *BMC Gastroenterology*. 2018;18:79.

7. Mangus RS, Kinsella SB, Marshall GR, Fridell JA, Wilkes KR and Tector AJ. Mild to moderate pulmonary hypertension in liver transplantation. *Journal of Surgical Research*. 2013;184:1150-1156.

8. Salgia RJ, Goodrich NP, Simpson H, Merion RM and Sharma P. Outcomes of Liver

Transplantation for Porto-Pulmonary Hypertension in Model for End-Stage Liver Disease Era. *Digestive Diseases and Sciences*. 2014;59:1976-1982.

9. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT and Therneau TM. A revised model for end-stage liver disease optimizes prediction of mortality among patients awaiting liver transplantation. *Gastroenterology*. 2011;140:1952-1960.

10. Kim Y, Shin W, Song J, Jun I, Kim H, Seong S, Huh I and Hwang G. Effect of right ventricular dysfunction on dynamic preload indices to predict a decrease in cardiac output after inferior vena cava clamping during liver transplantation. *Transplantation proceedings*. 2010;42:2585-2589.

11. Abu-Gazala S and Olthoff KM. Current Status of Living Donor Liver Transplantation in the United States. *Annual Review of Medicine*. 2019;70:225-238.

12. Olthoff KM, Abecassis MM, Emond JC, Kam I, Merion RM, Gillespie BW, Tong L and Group tA-t-ALDLTCS. Outcomes of adult living donor liver transplantation: Comparison of the adult-to-adult living donor liver transplantation cohort study and the national experience. *Liver Transplantation*. 2011;17:789-797.

13. Lee S-G, Song G-W and Yoon Y-I. An Exceptional Series: 5000 Living Donor Liver Transplantations at Asan Medical Center, Seoul, Korea. *Transplantation*. 2019;103:1739-1741.

14. Uchiyama H, Soejima Y, Taketomi A, Yoshizumi T, Harada N, Ijichi H, Yonemura Y and Maehara Y. Successful adult-to-adult living donor liver transplantation in a patient with moderate to severe portopulmonary hypertension. *Liver Transplantation*. 2006;12:481-4.

15. Sugimachi K, Soejima Y, Morita K, Ueda S, Fukuhara T, Nagata S, Ikegami T, Taketomi A and Maehara Y. Rapid normalization of portopulmonary hypertension after living donor liver transplantation. *Transplantation Proceedings*. 2009;41:1976-8.

16. Ogawa E, Hori T, Doi H, Segawa H and Uemoto S. Living-donor liver transplantation for moderate or severe porto-pulmonary hypertension accompanied by pulmonary arterial hypertension: a single-centre experience over 2 decades in Japan. *Journal of Hepato-Biliary-Pancreatic Sciences*. 2012;19:638-49.

17. Bandara M, Gordon FD, Sarwar A, Knauft ME, Pomfret EA, Freeman RB and Wirth JA. Successful outcomes following living donor liver transplantation for portopulmonary hypertension. *Liver Transplantation*. 2010;16:983-9.

18. D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Correra A, Bossone E, Sarubbi B, Calabro R, Russo MG and Naeije R. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. *International journal of cardiology*. 2013;168:4058-62.

19. Kim WR, Krowka MJ, Plevak DJ, Lee J, Rettke SR, Frantz RP and Wiesner RH. Accuracy of Doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. *Liver Transplantation*. 2000;6:453-8.

20. Cotton CL, Gandhi S, Vaitkus PT, Massad MG, Benedetti E, Mrtek RG and Wiley TE. Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates. *Liver Transplantation*. 2002;8:1051-4.

21. Krowka MJ, Swanson KL, Frantz RP, McGoon MD and Wiesner RH. Portopulmonary hypertension: Results from a 10-year screening algorithm. *Hepatology*. 2006;44:1502-10.

22. Saragai Y, Takaki A, Umeda Y, Matsusaki T, Yasunaka T, Oyama A, Kaku R, Nakamura K, Yoshida R, Nobuoka D, Kuise T, Takagi K, Adachi T, Wada N, Takeuchi Y, Koike K, Ikeda F, Onishi H, Shiraha H, Nakamura S, Morimatsu H, Ito H, Fujiwara T, Yagi T and Okada H. A subclinical high tricuspid regurgitation pressure gradient independent of the

mean pulmonary artery pressure is a risk factor for the survival after living donor liver transplantation. *BMC Gastroenterology*. 2018;18:62.

Abstract

Severe pulmonary hypertension (PHT) is a contraindication to liver transplantation (LT); however, the prognostic implication of mild to moderate PHT in living-donor LT (LDLT) is unknown. This study aimed to evaluate the clinical value of mild to moderate PHT in predicting early outcomes after LDLT. The study cohort retrospectively included 1,307 patients with liver cirrhosis (mean age: 52.0±8.4 years; 71% men) who underwent LDLT between 2007 and 2016. PHT was defined as a mean pulmonary artery pressure (PAP) of ≥25 mmHg, measured just before surgery. The primary end point was graft failure within 1 year after LDLT, including re-transplantation or death from any cause. The secondary end points were in-hospital adverse events. In the overall cohort, the median Model for End-stage Liver Disease-Sodium (MELD-Na) score was 19 (interquartile range, 14–27), and 100 patients (7.7%) showed PHT, mild in 94 and moderate in 6. During 1-year follow-up, graft failure occurred in 94 patients (7.2%). Patients with PHT had lower 1-year graft survival (86% vs. 93.4%, log-rank *p*=0.005) and survival rates (87% vs. 93.6%, log-rank p=0.011). Mean PAP was associated with a high risk of in-hospital adverse events (odds ratio [OR], 1.10; 95% confidence interval [CI], 1.08–1.12; p<0.001) and 1-year graft failure (OR, 1.05; 95% CI, 1.03–1.08; p<0.001). Adding the mean PAP to the clinical risk model improved the risk prediction of in-hospital adverse events and 1-year graft failure. Elevated right atrial pressure, the maximal velocity of tricuspid regurgitation, anemia, elevated brain natriuretic peptide level, and MELD-Na score were predictive variables of PHT (area under the curve, 0.843). Mild to moderate PHT was associated with higher risks of in-hospital events and 1-year graft failure, including mortality after LDLT in patients with liver cirrhosis. Intraoperative mean PAP can help predict the early clinical outcomes after LDLT.

Keywords: pulmonary hypertension; liver transplantation; prognosis