ORIGINAL ARTICLE

Clinical impact of mild to moderate pulmonary hypertension in living-donor liver transplantation

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SUMMARY

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. The study cohort retrospectively included 1307 patients with liver cirrhosis who underwent LDLT. PHT was defined as a mean pulmonary artery pressure (PAP) of ≥25 mmHg, measured intraoperatively just before surgery. The primary endpoint was graft failure within 1 year after LDLT, including retransplantation or death from any cause. The secondary endpoints were in-hospital adverse events. In the overall cohort, the median Model for End-stage Liver Disease-Sodium (MELD-Na) score was 19, and 100 patients (7.7%) showed PHT. 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%, $P = 0.005$) and survival rates (87% vs. 93.6%, $P = 0.011$). Mean PAP was associated with a high risk of in-hospital adverse events and 1-year graft failure. Adding the mean PAP to the clinical risk model improved the risk prediction. In conclusion, mild to moderate PHT was associated with higher risks of 1-year graft failure and in-hospital events, including mortality after LDLT in patients with liver cirrhosis. Intraoperative mean PAP can help predict the early clinical outcomes after LDLT.

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Key words
graft survival, liver transplantation, living donor, prognosis, pulmonary hypertension

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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, the benefit and safety of LT in such patients remain an important open question.

In patients with severe PHT, transplantation should be avoided because of the unacceptable mortality rate [2–4]. The current guideline also indicates that severe PHT should be considered as an absolute contraindication to LT, and transplantation in the setting of

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moderate PHT has been associated with an increased risk of perioperative morbidity and mortality [5]. However, the prognostic data for graft or overall survival after LT in patients with mild to moderate PHT are not yet available [6–8]. Moreover, 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. No data are demonstrating the clinical impact of PHT on in-hospital adverse events and graft survival in LDLT. Thus, we aimed to evaluate the clinical value of mild to moderate PHT in predicting the early outcomes of patients who underwent LDLT.

Patients and methods

Study population

When a severe PHT is suspected on echocardiography, right heart catheterization is recommended in our institution. A mean PAP ≥45 mmHg on catheterization is regarded as a contraindication of LDLT. For the patients who are suggestive of mild to moderate PHT, treatment strategies, including right heart catheterization and PHT-specific medications before surgery, have been at attending surgeons' or physicians' discretions. A total of 2170 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 significant valvular heart disease (four patients), 1307 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 a diameter of the inferior vena cava (IVC), the inspiratory collapse of IVC, and maximal velocity of tricuspid regurgitation were obtained at the time of preoperative evaluation. IVC plethora was defined as a blunted respiratory response (proximal IVC diameter by <50%) of a dilated IVC (>21 mm). MELD and MELD-Na scores were calculated in accordance with the current Organ Procurement and Transplantation Network guidelines [9,10]. 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: MELD-Na = MELD + 1.32 × (137 − Sodium mmol/l) − [0.033 × MELD × (137 − 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 nine 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 [11]. 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 10–15 min after induction of general anesthesia. Hemodynamic monitoring was continued until the end of anesthesia and recorded at 15-min 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 endpoint was graft failure within one year after LDLT. Graft failure was defined as retransplantation or death from any cause. The secondary endpoints 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 for >2 weeks; and newly applied mechanical circulatory support or continuous renal replacement therapy after LDLT.

Statistical analyses

For the categorical variables, data are reported as numbers with percentages and compared using the chi-square test. Based on their distribution, continuous variables are expressed as mean and standard deviation compared using a *t*-test, or as median values and interquartile ranges compared using the Wilcoxon rank-sum test. The estimated probability of PHT was calculated on the basis of the regression coefficient of univariate logistic regression. For the prediction of the study endpoints, 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 endpoint 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, integrated discrimination improvement, and likelihood ratio test. The net reclassification index and integrated discrimination improvement values were estimated with their 95% confidence intervals (CIs). The continuous net reclassification index, which does not depend on the arbitrary choice of categories, was graphically depicted for the correctness of reclassification of subjects based on their predicted probability of adverse events. 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.

Results

Baseline and operative characteristics

The age of the patients at LDLT ranged from 18 to 73 years (mean, 52.0 years), and 928 patients (71.0%) were men. Hepatitis B viral infection was the predominant etiology of liver cirrhosis accounting for 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 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 hemoglobin levels than those without PHT. Although the left ventricular 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.

PHT 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 LDLT 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 S1. 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 $P = 0.011$; Fig. 1). After multivariable adjustment for the potential explanatory factors of the study endpoints, 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 old age, male sex, and lower body mass index, C-reactive protein level, and MELD-Na score for in-hospital adverse events (Table 3).

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Table 1. Patients' baseline characteristics

Variables	Overall cohort (n = 1307)	Non-PHT (n = 1207)	PHT (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 (%)				
Alcohol	221 (16.9)	197 (16.3)	24 (24.0)	0.023
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 and 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 (%)				
B	746 (57.1)	702 (58.2)	44 (44.0)	0.006
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

ALT, alanine aminotransferase; AST, aspartate aminotransferase; 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; PHT, pulmonary hypertension.

Incremental prognostic value of PHT

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 (Model 1) was 0.733, which significantly increased to 0.757 with the addition of clinical variables (Model 2; P for improvement <0.001). A similar magnitude of the effect was observed after clinical variables and mean pulmonary artery pressure was added to the MELD-Na score (C-statistics of 0.764 for Model 3; P for improvement <0.001). No significant

Table 2. Patients' outcomes

Variables	Overall cohort (n = 1307)	Non-PHT (n = 1207)	PHT (n = 100)	P value
In-hospital adverse events				
30-day death (%)	14 (1.1)	13 (1.1)	1 (1.0)	0.943
30-day retransplantation (%)	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
Days of ICU 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
Days 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 retransplantation (%)	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; PHT, pulmonary hypertension; 1Q, first quartile; 3Q, third quartile.

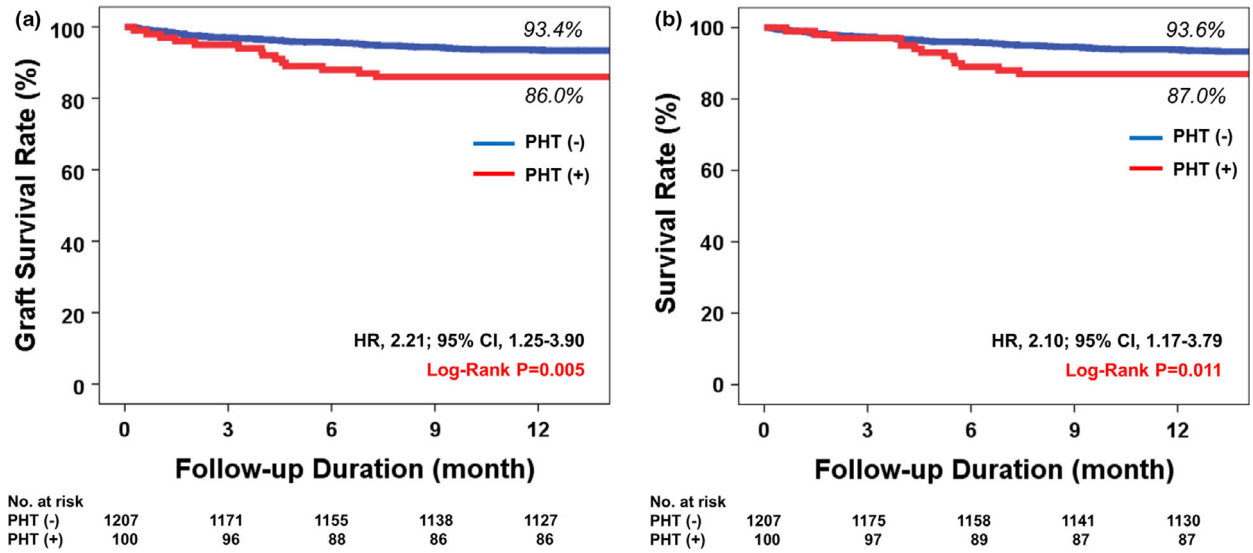

Figure 1 Kaplan–Meier curves of patients with and without pulmonary hypertension. The results of the analysis for (a) 1-year graft survival and (b) 1-year patient survival are shown. The hazard ratios are for the group of patients with pulmonary hypertension (PHT) as compared with those without PHT

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 was 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 added to the MELD-Na score, we observed the overall improvements in the net risk stratification for in-hospital events and 1-year graft failure (Table 4). As a result of the risk reclassification analyses, adding mean pulmonary artery pressure to the clinical variables (Model

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Table 3. Logistic regression analysis of the clinical endpoints

	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 (Model 1)	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 (Model 1)	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; CI, confidence interval; CRP, C-reactive protein; MELD-Na, Model for End-stage Liver Disease-Sodium; OR, odds ratio.

2 vs. Model 3) improved the risk prediction for in-hospital adverse events and 1-year graft failure after LDLT, and the improvement was driven mainly by a better reclassification of non-events (Fig. 2). These data indicated that adding mean pulmonary artery pressure stratifies the risk of adverse events more accurately than clinical variables alone.

Preoperative noninvasive predictors of PHT

The five variables, including the presence of IVC plethora, 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 (Fig. 3). For identifying the preoperative noninvasive predictors of PHT, clinical and echocardiographic variables were evaluated using a simple logistic regression analysis (Table 5). The predictive power of each variable was evaluated, and the areas under the curve (AUC) of all the variables were <0.80, ranging from 0.603 to 0.743. When combined with the five 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 TR Vmax is the maximal velocity of tricuspid regurgitation and Hb is hemoglobin.

Discussion

The present study demonstrated that (i) the presence of mild to moderate PHT was associated with early adverse events, including 1-year graft failure and in-hospital events; (ii) the addition of mean pulmonary artery pressure to the clinical risk factors improved the reclassification of early surgical risks after LDLT; and (iii) preoperative anemia, high MELD-Na score, elevated BNP level, IVC plethora, 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.

Liver transplantation is a potentially life-saving therapeutic intervention for patients with advanced liver cirrhosis. As some patients with severe portopulmonary

Table 4. Risk reclassification analyses for the study end points

	Model 1 vs. Model 2	Model 1 vs. Model 3	Model 2 vs. Model 3
In-hospital events			
C-statistics	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 to 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

CRP, C-reactive protein; IDI, integrated discrimination index; MELD-Na, Model for End-stage Liver Disease-Sodium; NRI, net reclassification index.

Model 1: MELD-Na score. Model 2: MELD-Na score + clinical variables (In-hospital events: age, sex, body mass index, log-CRP; 1-year graft failure: age, log-CRP). Model 3: MELD-Na score + clinical variables + mean pulmonary artery pressure.

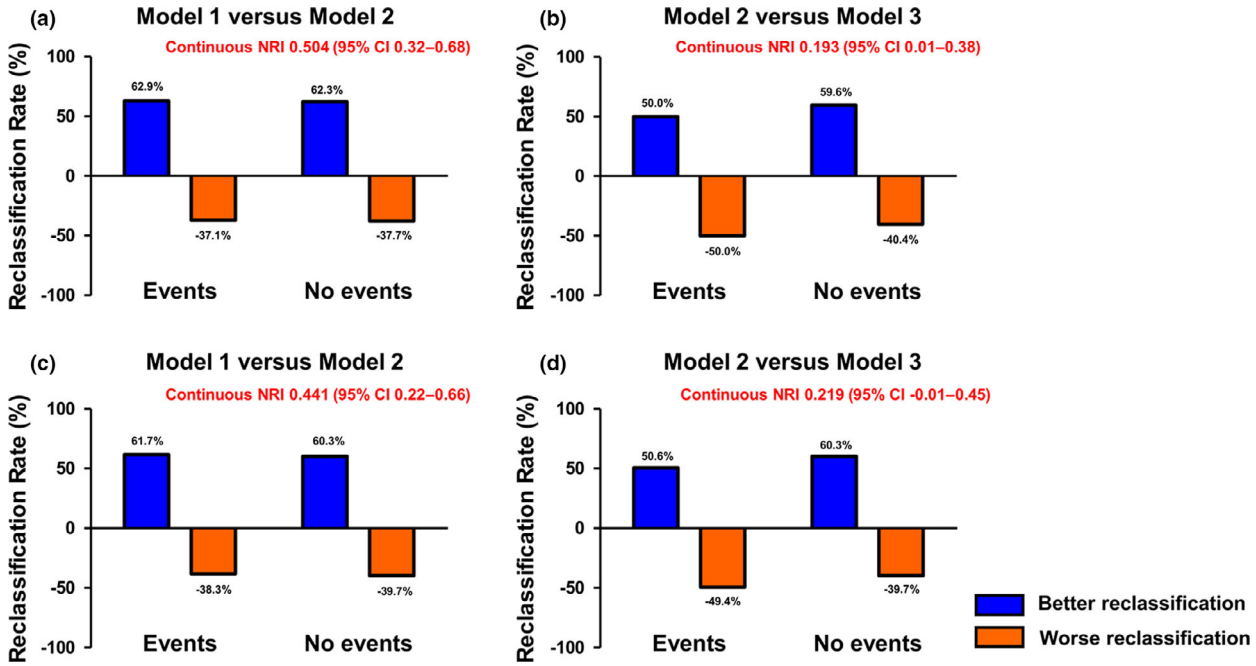

Figure 2 Net reclassification index. Graphical illustration of the net reclassification index (NRI) based on the logistic regression model for predicting in-hospital events (a and b) and one-year graft failure (c and d), when sequentially adding clinical factors (Model 2) and mean pulmonary artery pressure (Model 3) to the Model for Liver Disease-Sodium (MELD-Na) scores (Model 1)

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

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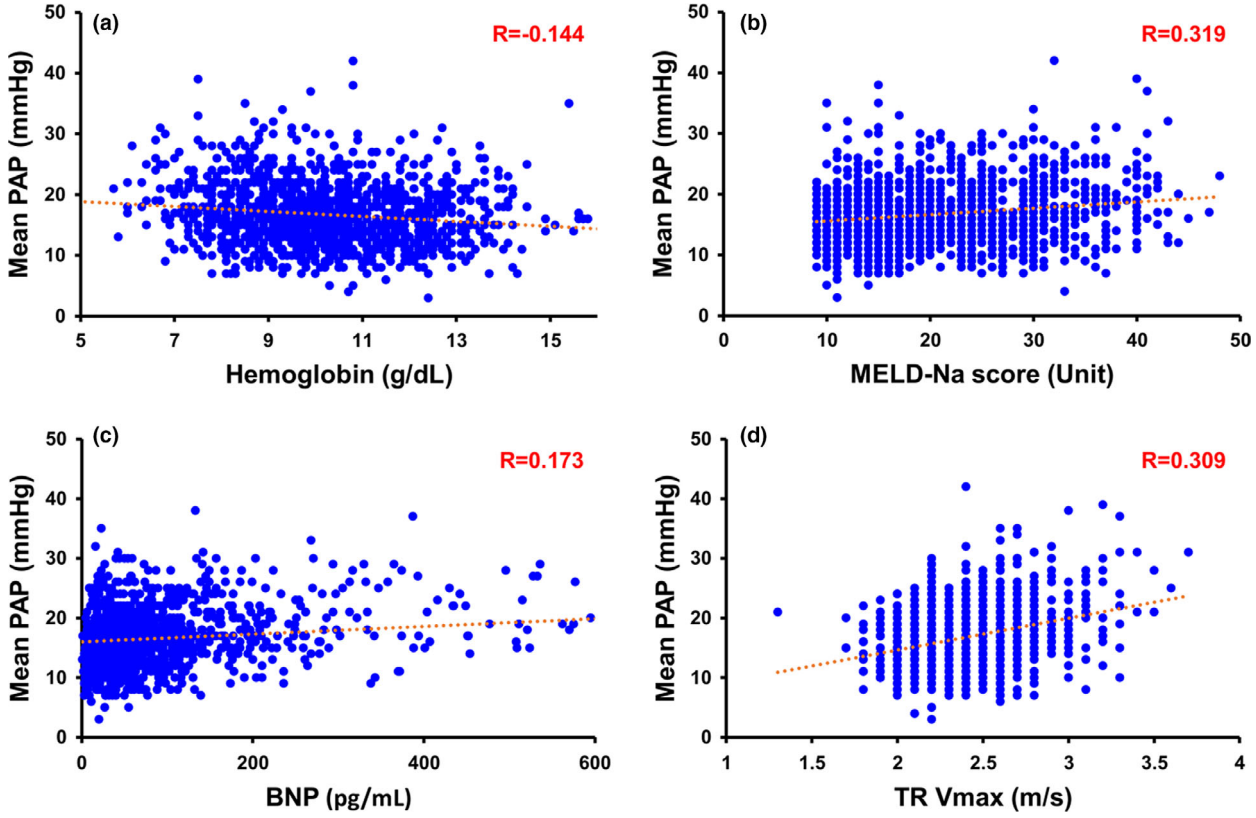

Figure 3 Linear regression analysis of mean pulmonary artery pressure and clinical variables. Weak correlations were observed between mean pulmonary artery pressure (PAP) and (a) hemoglobin level, (b) brain natriuretic peptide (BNP) level, (c) Model for Liver Disease-Sodium (MELD-Na) score, and (d) the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

Table 5. Operating characteristics of the clinical parameters for the diagnosis of pulmonary hypertension.

Independent variable	Odds ratio (95% CI)	Area under the curves (95% CI)	Cutoff value	Specificity (%)	Sensitivity (%)
MELD-Na score, per point	1.05 (1.03–1.08)	0.635 (0.578–0.692)	19 units	50.2	73.0
BNP, per pg/ml	1.85 (1.55–2.23)	0.677 (0.614–0.740)	133 pg/ml	82.2	52.1
Hemoglobin, per 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 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

[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 1263 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 [12,13], and our institute also achieved 5000 cases of LDLT in 2018, with favorable in-hospital outcomes [14]. Some case reports demonstrated successful LDLT in patients with moderate to severe PHT by administering intravenous prostacyclin after LDLT [15,16]. Patients with portopulmonary hypertension have also been reported to be appropriate candidates for LDLT after careful considerations [17], and LDLT can be performed safely after appropriate preoperative medical management in patients with mild PHT [18]. Therefore, the risk and outcomes after LDLT in patients with PHT remain 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. We found that the patient and graft survival rates of the two groups started to diverge from around 3 months after LDLT as shown in Fig. 1, and this is compatible with a previous report presenting that the patients with mild to moderate PHT had a lower 1-year graft survival after DDLT than the patients without PHT while did not show a significant difference in early graft function [7]. As we have demonstrated in the present study, the addition of mean pulmonary artery pressure to the clinical risk factors such as old age, an 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. One hundred patients had PHT (7.7%), which was mild in 94 (7.2%) and moderate in 6 (0.5%). The 1-year graft failure rates in the mild and moderate PHT group were 12.8% and 33.3%, respectively, and there was no significant difference ($P = 0.144$). However, the number of patients with moderate PHT was too small, and a further study is needed to evaluate the difference in clinical outcomes between mild and moderate PHT patients.

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 [19–22]. A subclinical high-pressure gradient of tricuspid regurgitation was also reported to be an important marker for predicting worse survival after LDLT [16,23]. 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 IVC 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 limitations

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. Some patients with PHT included in the present study might have been in a hyperdynamic state with high cardiac output. However, only two patients, out of fourteen who experienced graft failure for one year, had high cardiac output status (Table S1). Since most LDLT candidates underwent intensive preoperative care, including intravascular volume control, portopulmonary hypertension might be regarded as the cause of PHT in most patients. Third, PHT and some causes of deaths did not seem to be directly linked. We could not clearly elucidate these pathophysiological causal relationships. However, in-hospital adverse events such as prolonged ICU care, prolonged ventilator care, and continuous renal replacement therapy application were more common in PHT patients than those in other patients, and this might result in development of fatal multi-organ complications such as bile duct obstruction, CMV infection, and pneumonia. Forth, our results regarding incremental prognostic value of PHT and preoperative noninvasive predictors of PHT should be validated using independent cohorts in the future. Finally, pulmonary artery pressure was measured intraoperatively under general anesthesia in our study, and our data could not simply be extrapolated to cardiac catheterization data without general anesthesia.

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Conclusion

Mild to moderate PHT is associated with higher risks of 1-year graft failure and in-hospital events, 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.

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Authorship

S-AL, J-MS: Participated in research design. S-AL, JH, S-YP, J-MS: Acquisition, analysis or interpretation of data. S-AL, JSL, D-HK, J-MS: Participated in the writing of the paper. Y-IY, G-WS, K-HK, D-BM, J-GS, G-SH, S-GL: Participated in the performance of the research. All authors: Critical revision of the manuscript for important intellectual content. S-YP: Statistical analysis. G-SH, S-GL, J-MS: Supervision.

Conflict of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Preoperative pulmonary hemodynamics and clinical events in pulmonary hypertensive patients who experienced graft failure within 1-year after transplantation.

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