Model for End-Stage Liver Disease (MELD) Score Among Patients Qualified For Lung Transplantation With End-Stage Lung Diseases With Particular Consideration of Median Pulmonary Artery Pressure

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ABSTRACT

Background. Model for End-Stage Liver Disease (MELD) score is used to assess the severity of chronic liver disease. It is implemented in transplantology in the process of qualification for urgent liver transplant. The aim of our study was to assess the liver function of patients qualified for lung transplant using MELD score, taking under consideration mean pulmonary artery pressure as an important risk factor of death.

Methods. The study group consisted of 123 patients qualified for lung transplant in Silesian Center for Heart Diseases between 2004 and 2017. Data relevant for MELD score calculations and medial pulmonary artery pressure were acquired from medical records.

Results. The average MELD score among patients qualified for lung transplant was 8.24 points, and mean pulmonary pressure (mPAP) was 35.02 mm Hg. Patients with idiopathic pulmonary artery hypertension acquired the highest MELD and highest mPAP results (13.1 points and 57.7 mm Hg, respectively). Patients with idiopathic pulmonary fibrosis presented higher mean MELD-Na score among those with pulmonary arterial hypertension than those without pulmonary arterial hypertension (36.59 mm Hg; 7.74 points vs 18 mm Hg; 6.5 points). There is strong positive correlation between MELD-Na and mPAP among patients who underwent lung transplant because of idiopathic pulmonary fibrosis.

Conclusions. This is the first study in the worldwide literature assessing MELD-Na as a predictor of survival among patients qualified for lung transplant and those who already are recipients. Further studies regarding this issue are required as authors will explore this issue in the future.

MODEL for End-Stage Liver Disease (MELD) score is used all over the world to assess the severity of chronic liver disease, particularly in the process of qualification for liver transplant [1]. Moreover, the MELD score was examined to be an outcome predictor in patients with advanced heart failure referred for cardiac transplant evaluation [2]. There are also several studies on liver failure effects on mean pulmonary artery pressure (mPAP) [3–5]. The aim of our study was to assess liver function among patients qualified for lung transplant because of end-stage lung disease, especially among those with pulmonary arterial hypertension (PAH). To evaluate this, we used the MELD-Na score. It is calculated using bilirubin, creatinine, sodium, and international normalized ratio of prothrombin time levels. The minimum score is 4 and maximum is 40. A score of 10 and above is an indicator of higher probability of liver-related death, whereas

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Table 1. Clinical and Demographic Features of Patients Qualified for Lung Transplant Among Those Who Died While Waiting for Procedure and Those Who Underwent Lung Transplant

	No Transplant (n = 102)	Transplant (n = 57)	*P* Value
Clinical and Demographic Features of Patients at Qualification to Lung Transplant			
Recipient age at qualification, y	51.66 (9.86)	48.73 (11.65)	.09
Diagnosis, %			
COPD	21.57	52.63	
IPF	37.25	14.03	
IPAH	11.76	17.54	
Other*	29.42	15.8	
MELD-Na score	8.11 (2.52)	8.49 (3.41)	.42
FEV_1, %	46.78 (17.32)	36.81 (22.48)	.01
FVC, %	50.63 (19.68)	54.75 (19.78)	.33
6MWT distance, mile	200.76 (146.99)	229.99 (146.11)	.24
Borg's scale	4.49 (1.95)	4.6 (1.98)	.76
SpO_2 before 6MWT, %	89.62 (6.46)	91.18 (4.11)	.11
SpO_2 after 6MWT, %	75.74 (11.62)	80.98 (9.85)	.006
Ht, %	44.16 (5.29)	43.58 (5.11)	.51
Hg, g/dL	11.29 (2.98)	11.91 (3.28)	.22
RBC, millions/dL	4.98 (1.2)	4.93 (0.56)	.77
WBC, thousands/dL	9.38 (2.87)	9.18 (4.11)	.73
PLT, thousands/dL	227.76 (75.55)	223.8 (73.73)	.75
NT-proBNP, pg/mL	1443,72 (2825.44)	706.95 (1633.56)	.11
LVEF, %	54.39 (5.48)	54.96 (8.01)	.61
Clinical Features of Patients After Lung Transplant (assessed only for transplant recipients)			
FEV_1, %		62.17 (27.96)	
FVC, %		80.53 (20.86)	
Ht, %		35.3 (4.2)	
Hb, g/dL		7.2 (0.94)	
RBC, millions/dL		3.86 (0.55)	
WBC, thousands/dL		6.62 (2.19)	
PLT, thousands/dL		216.73 (58.91)	
LVEF, %		53 (1.96)	

Values are given as mean (SD).

6MWT, 6-minute walk test; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in first second; FVC, forced vital capacity; Hb, hemoglobin; Ht, hematocrit; IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; LVEF, left ventricular ejection fraction; MELD-Na score, Model for End-Stage Liver Disease calculated with sodium score; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PLT, platelet; RBC, right blood cell; SpO2, oxygen saturation; WBC, white blood cell.

*Rare lung diseases not qualified elsewhere (see text).

a score of 25 and above is a recommendation for an urgent liver transplant. The aim of the study was to assess MELD-Na score among patients qualified for lung transplant. An additional objective was to check whether there is a correlation between MELD-Na and mPAP.

METHODS

The study group primarily consisted of 123 patients qualified for lung transplant in Silesian Center for Heart Diseases between 2004 and 2017. The study included only patients with right heart catheterization. The basic clinical data and the routinely measured laboratory parameters were collected by reviewing the patients' records. MELD-Na score was calculated for every patient individually using the MELD formula updated in 2016 (Table1) [6].

The study group consisted of 35.8% patients with idiopathic pulmonary fibrosis (IPF), 26.8% patients with chronic obstructive pulmonary disease (COPD), 20.3% patients with idiopathic pulmonary arterial hypertension (IPAH), and 17.1% patients with other diseases, such as sarcoidosis, extrinsic allergic alveolitis, cystic fibrosis, histiocytosis, and bronchiectasis (Table 1).

Statistical Analysis

All statistical analyses were performed in Statistica 13.3 (TIBCO Software, Palo Alto, Calif, United States). Basic descriptive statistics were analyzed with Shapiro-Wilk tests as well as correlation analysis using Spearman ρ coefficient, Kaplan-Meier survival analysis with Gehan-Wilcoxon test, and Cox regression analysis. A *P* value less than .05 was deemed statistically significant.

RESULTS

The average MELD-Na score among patients qualified for lung transplant was 8.24 (SD, 3) points, and mPAP was 35.02 (SD, 16) mm Hg. Patients with PAH obtained higher mean MELD score (9.05 [SD, 4] points) than those without PAH (6.45 [SD, 2] points). Mean PAP among patients with

Table 2. Correlation Between MELD-Na Score and mPAP

Analyzed Group	Spearman ρ	Statistical Significance
IPAH, transplant recipients	−0.74	.014
IPF, transplant recipients	0.71	.047
Other,* transplant recipients	0.11	.523
Patients who died without transplant	0.34	< .001

Abbreviations: IPAH, idiopathic pulmonary arterial hypertension; IPF, idiopathic pulmonary fibrosis; MELD-Na, Model for End-Stage Liver Disease calculated with sodium score; mPAP, mean pulmonary artery pressure.
*Rare lung diseases not qualified elsewhere (see text).

PAH and without PAH was 42.3 (SD, 14) mm Hg and 18.9 (SD, 4) mm Hg, respectively.

Those patients with IPAH acquired the highest MELD and highest mPAP results (13.1 [SD, 5] points and 57.7 [SD, 14] mm Hg, respectively).

Patients with COPD presented the lowest overall mPAP and MELD-Na score (26.1 [SD, 12] mm Hg; 6.61 [SD, 2] points). Patients with this underlying disease presented higher mean MELD-Na score among those with PAH (7 [SD, 2] points; 35.93 [SD, 12] mm Hg) than those without PAH (6.32 [SD, 1] points; 18.84 [SD, 4] mm Hg).

Patients with IPF presented higher mean mPAP and higher MELD-Na score than those with COPD (31.67 [SD, 12] mm Hg; 7.41 [SD, 2] points). Patients with this underlying disease presented higher mean MELD-Na score among those with PAH (7.74 [SD, 2] points; 36.59 [SD, 10] mm Hg) than those without PAH (6.5 [SD, 2] points; 18 [SD, 3] mm Hg).

As stated above the main objective of the study was to assess whether there is a correlation between MELD-Na score and mPAP among patients qualified for lung transplant. The study group was divided into 2 smaller ones based on outcome of the qualification process. The first one consisted of the transplant recipients. The second one contained those who died while waiting for lung transplant.

In both groups, the distribution of key variables (MELD and mPAP) and most of the other ones do not meet the criteria of matching to the normal distribution; hence, nonparametric tests were performed in this study.

Correlation analysis using Spearman ρ coefficient was performed. Detailed results are presented in Table 2. It is worth mentioning that 1. there is strong positive correlation between MELD-Na and mPAP among patients who underwent lung transplant because of IPF, 2. similar yet not as strong correlation was noticed among lung transplant candidates who died on the waiting list, and 3. strong negative correlation between aforementioned parameters was observed in the group of lung recipients who received transplants because of IPAH.

As the following correlations were observed, it was decided to perform survival analysis by using Cox regression to estimate what factors could be the predictors of death in 2 groups. The first one consisted of those who died while waiting for lung transplant. The second one contained the transplant recipients. The statistical model developed for the aforementioned analysis contained several factors. Results for the first and second group are presented in Table 3 and Table 4, respectively.

The model constructed for patients awaiting transplant showed a weak correlation with the risk of death during observation, as evidenced by the value of $R^2 = 0.17$. Hematocrit and red blood counts were significantly associated with the risk of death. An increase in hematocrit of 1 percentage point resulted in a decrease in the risk of death of 1.117 × (1.014-1.230). In turn, an increase in the number of erythrocytes by 1 million/dL increased the risk of death by 1.612 × (1.055-2.462). The other predictors included in the analysis were not significantly associated with the risk of death of patients awaiting transplant. Detailed results are presented in Table 3.

For patients after transplant the analysis showed a very strong correlation with the risk of death during observation, as evidenced by the value of $R^2 = 0.87$. Several factors were included in the analysis. The MELD score, mPAP, N-terminal prohormone of brain natriuretic peptide level, and red blood cell count were the only independent variables significantly associated with the risk of death.

An increase in MELD score of 1 point increased the risk of death by 1.778 × (1.082-2.922). An increase in mPAP by

Table 3. Coefficients of Regression Analysis Predicting Survival of Patients Awaiting Lung Transplant

Variables	β	SE	*t*	*P* Value	RR	LL	UL
MELD-Na score	−0.09	0.12	0.56	.454	0.916	0.727	1.153
mPAP, mm Hg	−0.01	0.02	0.31	.580	0.990	0.955	1.026
Age at qualification, y	−0.01	0.02	0.27	.605	0.988	0.942	1.036
BMI at qualification	0.08	0.07	1.27	.259	1.084	0.942	1.247
Ht, %	−0.11	0.05	5.06	.025	0.895	0.813	0.986
Hb, g/dL	0.06	0.07	0.89	.344	1.066	0.934	1.215
RBC, millions/dL	0.48	0.22	4.88	.027	1.612	1.055	2.463
WBC, thousands/dL	0.00	0.06	0.00	.967	0.997	0.880	1.130
PLT, thousands/dL	0.00	0.00	0.24	.627	1.001	0.996	1.006
NT-proBNP, pg/mL	0.00	0.00	1.91	.167	1.000	1.000	1.000
LVEF, %	0.02	0.03	0.48	.488	1.021	0.963	1.083

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Hb, hemoglobin; Ht, hematocrit; LL, lower limit of 95% CI for relative risk; LVEF, left ventricular ejection fraction; MELD-Na, Model for End-Stage Liver Disease calculated with sodium score; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PLT, platelet; RBC, red blood cell; RR, relative risk; SE, standard error; UL, upper limit of 95% CI for relative risk; WBC, white blood cell.

Table 4. Coefficients of Regression Analysis Predicting Survival of Patients After Transplant

Variables	β	SE	*t*	*P* Value	RR	LL	UL
MELD- Na score	0.58	0.25	5.15	.023	1.778	1.082	2.922
mPAP, mm Hg	−0.26	0.12	4.58	.032	0.772	0.609	0.979
Age at qualification, y	0.09	0.05	2.52	.113	1.090	0.980	1.213
BMI at qualification	0.08	0.16	0.24	.625	1.079	0.796	1.463
Ht, %	−0.23	0.18	1.51	.218	0.798	0.557	1.143
Hb, g/dL	0.07	0.20	0.13	.715	1.077	0.723	1.604
RBC, millions/dL	3.28	1.62	4.12	.042	26.709	1.118	637.946
WBC, thousands/dL	−0.25	0.19	1.79	.181	0.778	0.539	1.124
PLT, thousands/dL	0.00	0.01	0.26	.609	1.003	0.992	1.014
NT-proBNP, pg/mL	0.00	0.00	4.50	.034	1.000	1.000	1.001
LVEF, %	0.06	0.09	0.42	.517	1.057	0.894	1.249

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Hb, hemoglobin; Ht, hematocrit; LL, lower limit of 95% CI for relative risk; LVEF, left ventricular ejection fraction; MELD-Na, Model for End-Stage Liver Disease calculated with sodium score; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PLT, platelet; RBC, red blood cell; RR, relative risk; SE, standard error; UL, upper limit of 95% CI for relative risk; WBC, white blood cell.

1 mm Hg resulted in a decrease in the risk of death of 1.296 × (1.022-1.642). An increase in N-terminal prohormone of brain natriuretic peptide level of 1 pg/mL increased the risk of death by 1.00044 × (1.00033-1.00080), and increase in the number of erythrocytes by 1 million/dL increased the risk of death by 26.709 × (1.118-637.95). The other predictors included in the analysis were not significantly associated with the risk of death among lung transplant recipients. Data are presented in Table 4.

In addition, a series of Kaplan-Meier survival estimations were performed to advance the study of relationship between the MELD score, mPAP, and survival of patients awaiting transplant and after transplant in every diagnosis. The analyses compared patients with low (< 7) and high (> 7) MELD results as well as patients with normal (< 20 mm Hg) and elevated (> 20 mm Hg) mPAP. Cutoff point of MELD and mPAP were assessed by median. Analyses were performed by primary disease (IPAH, IPF, or other). These groups were compared by the Gehan-Wilcoxon test.

It turned out that a statistically significant difference applies only to transplant recipients with a diagnosis other than IPAH and IPF. In this group, significantly better survival was observed in patients with elevated mPAP.

DISCUSSION

Patients may become lung transplant recipients because of primary pulmonary hypertension or other lung diseases with concomitant secondary pulmonary hypertension. As none of them were qualified with severe cirrhotic liver failure, classic MELD results were expected to be low. Authors of this article decided to use MELD-Na as some studies suggest that hyponatremia is considered to be a predictor of death not only among liver transplant candidates with cirrhosis but also among those with ascites [7,8]. This clinical symptom is frequently presented by patients qualified for lung transplant because of primary pulmonary hypertension. The same studies also assessed that MELD-Na is a better predictor of death among patients with initially low MELD [7,8]. Assessment of these MELD-based parameters is useful not only among liver transplantologists. The study by Puentes et al proved its value as a tool of assessment among patients with advanced liver cirrhosis requiring palliative care [9]. The study by Godfrey et al demonstrated that MELD-Na score is the short-term mortality predictor among patients with severe liver disease who are in need of emergency surgery [10]. The higher the MELD-Na score, the worse the survival. This parameter is even useful among surgical patients without cirrhosis as study by Coakley et al describes MELD-Na to be an independent predictor of anastomotic leak in partial rectal resections [11]. Application of MELD or its derivatives was also tested among diseases beyond abdominal cavity. There are studies assessing the usefulness of MELD score and its derivatives among patients qualified for heart transplant. Ortiz-Bautista et al used MELD-XI (MELD's derivative excluding the international normalized ratio of prothrombin time) as a predictor of mortality after adult heart transplant [12]. Their work evaluated this derivative to be scarce as it considers its discrimination ability to be poor. Such finding was contradicted by Deo et al as their study states that hepatorenal dysfunction measured by means of MELD-XI is in fact the predictor of mortality and morbidity among heart transplant recipients [13]. Other studies have combined MELD-XI with other predictors. Szczurek et al conducted the study assessing the prognostic value of Heart Failure Survival Score combined with MELD-XI and Heart Failure Survival Score combined with modified MELD [14]. Their study claims that these 2 parameters may effectively guide the selection of patients for heart transplant and predict 1-year survival among patients with advanced heart failure.

After researching and reviewing all the accessible literature, authors of this study did not find any article assessing the MELD score or/and its derivatives among patients qualified for lung transplant or/and pulmonary graft recipients. This might be the first article pertaining to this topic. However, there are articles describing MELD as one of the risk factors of respiratory failure in the early postoperative period after liver transplant [15]. The study

published by Aydin et al also points out that high MELD score also can be a significant risk factors for mortality among liver transplant recipients with postoperative pulmonary complications [16]. Our study assessed that MELD-Na and mPAP are not predictors of survival among patients awaiting lung transplant because of end-stage primary pulmonary hypertension, COPD, or IPF (Table 3). However, results obtained at qualification can predict the survival of patients after lung transplant. What is more, there is a strong correlation with the risk of death during observation after lung transplant. Our study assessed that risk of death increases with MELD-Na score and mPAP among lung transplant recipients. This finding is consistent among patients with IPF and lung diseases other than IPAH (Table 4). The most surprising finding was that there is a strong negative correlation between MELD-Na and mPAP among patients with the highest values of pulmonary pressure among entire study group (Table 2). As this study is the first pertaining to this issue, the reason for such a result is unclear. The authors are aware of the facts that serum sodium levels (component of MELD-Na equation) may be vulnerable to alterations by diuretic use and intravenous fluid administrations. It is consistent with the treatment of severe forms of IPAH as diuretics in extremely large doses are used as a treatment concomitant to prostanoids, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors. Nevertheless, other factors must be taken into consideration regarding this particular issue.

CONCLUSIONS

This is the first study in the worldwide literature assessing MELD-Na as a predictor of survival among patients qualified for lung transplant and those who already are recipients. MELD-Na and mPAP are the outcome predictors after lung transplant regardless of underlying disease. There is a strong positive correlation between mPAP and MELD-Na among lung transplant recipients who receive transplant because of IPF, but in IPAH lung transplant recipients there is a strong negative correlation between mPAP and MELD-Na. Further studies regarding this issue are required as authors will explore this issue in the future.

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