Heart Transplant and Hepato-Renal Dysfunction: The Model of End-Stage Liver Disease Excluding International Normalized Ratio as a Predictor of Postoperative Outcomes

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ABSTRACT

Introduction. Preoperative liver and renal dysfunction remain surgical risk factors for both postoperative morbidity and mortality. The Model of End-Stage Liver Disease Excluding INR (international normalized ratio), or MELD-XI, score calculation may help as a predictor in patients with advanced heart failure. We analyzed the impact of progressive elevated MELD-XI values among recipients of heart transplant at our institution.

Methods. The data of a total of 425 consecutive adult patients who underwent heart transplantation, between January 2000 and August 2018, have been reviewed and divided into 3 cohorts according to preoperative MELD-XI calculations (MELD-XI < 11; MELD-XI 11-18; and MELD-XI > 18). Early and late outcomes have been analyzed.

Results. Patients with a MELD-XI score > 18 had a more critical clinical condition preoperatively and had a higher risk of early mortality (hazard ratio [HR] 1.45 [1.11-1.67], $P < .001$). They showed high risk for postoperative dialysis (HR 2.8 [1.5-5.3], $P < .001$), rethoracothomy for bleeding (HR 2.1 [1.2-4.1], $P = .001$), prolonged time of mechanical ventilation, time of intensive care unit stay (HR 2.2 [1.3-3.8], $P = .005$), and graft failure requiring mechanical circulatory support (HR 1.9 [1.1-3.3], $P = .003$). After risk adjustment per MELD-XI cohort, ischemic dilated cardiomyopathy, redo operation, and cold ischemic time > 240 minutes resulted in being the strongest predictors of early mortality ($P < .001$). The 5-year and 10-year survival for MELD-XI > 18 cohort was 63% and 47% vs 72% and 59% in the control group (MELD-XI < 18) (log-rank, $P < .001$).

Conclusions. Patients with an elevated preoperative MELD-XI profile presented more comorbidities and significantly lower survival. This suggests the MELD-XI score may provide further insight into appropriate recipient and eventual donor selection. Renal insufficiency and congestive hepatopathy should be properly optimized before heart transplantation.

THE gold standard treatment for refractory end-stage heart failure remains heart transplantation (Htx) [1-3]. Unfortunately, Htx volume is limited by the current shortage of donors; therefore, the potential recipient population on the active waiting list is going to increase over time. In a clinical panorama of both marginal donors and recipients, this limitation is magnified since many grafts are discarded due to strict selection criteria and the concern for regulatory reprimand to less-than-optimal posttransplant outcomes [1-3]. In this scenario, the process of organ

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allocation becomes essential, therefore clinically stratifying the potential recipient population to improve the outcomes.

One of the risk scores proposed to predict postoperative morbidity and mortality in patients undergoing orthotopic Htx is the Model for End-Stage Liver Disease Excluding INR (international normalized ratio), or MELD-XI, score which focuses on 2 single variables (serum bilirubin and serum creatinine) thus defining the degree of liver and renal dysfunction [4-10]. MELD-XI score is an evolution of Model for End-Stage Liver Disease (MELD) score assessment which, instead, focuses on the INR value, serum bilirubin, and serum creatinine [11-21] and has been widely used to list and define priority of patients with end-stage liver disease. MELD-XI calculation have been developed for patients while being on oral anticoagulant therapy [10] to exclude the influence of vitamin K antagonists' maintenance [4-10].

The aim of this study has been to evaluate the clinical effects of a progressive elevated preoperative MELD-XI calculations among recipients of Htx at our institution.

METHODS

We retrospectively reviewed and analyzed a consecutive cohort of adult patients with history of Htx between January 2000 and August 2018 at St. Orsola-Malpighi University Hospital, in Bologna. We excluded patients aged < 18 years old and with a history of multiple organ transplants or patients who underwent > 1 transplant procedure. Our population consisted of 425 patients, who were divided into 3 cohorts according to preoperatory MELD-XI calculations [MELD-XI score < 11, n = 100 (23.5%), MELD-XI score 11-18, n = 245 (57.6%), MELD-XI score >18, n = 80 (18.8%)].

MELD-XI score was individually calculated for each patient by usage of the following equation: MELD-XI = 5.11 × LN (serum bilirubin) ± 11.76 × LN (serum creatinine) ± 9.44, where LN is natural logarithm [4-10]. Serum creatinine and bilirubin values used for preoperative MELD-XI calculation were the last laboratory results before the admission in the operating room for the transplantation procedure.

Statistic Analysis

Continuous variables are presented as mean ± SD and categorical data as percentages and frequency distribution. The Kruskall-Wallis test was used to compare continuous variables, and χ^2 tests were used for the comparison of categorical variables. Survival probabilities were estimated by the Kaplan-Meier method, and the log-rank test was used to compare survival curves. Univariate and multivariable Cox proportional hazards models were applied to define the ability of MELD-XI in predicting clinical outcomes. For all analyses, $P \leq .05$ was considered statistically significant. Data were analyzed using statistical software SPSS, version 20 (SPSS, Inc, Chicago, IL, United States).

RESULTS

A total of 425 patients underwent Htx during the study period (Table 1). Overall mean MELD-XI score was 14.4 ± 4.1. Mean age was 52.6 ± 11.6 years; 80.2% (n = 341) were men; and mean ischemic time was 193.5 ± 48.1 minutes. The most frequent etiologies of recipient refractory heart failure were end-stage ischemic dilative cardiomyopathy (39.1%) and idiopathic dilative cardiomyopathy (37.4%). Part of the patient population (24.2%) was already hospitalized before Htx surgery due to need of intravenous inotropic therapy, intra-aortic balloon pump support (7.3%), or extracorporeal membrane oxygenation system support (8%). Mechanical ventilation rate before Htx was 9.2%. The overall patient population was split into 3 cohorts according to arbitrary institutionally defined MELD-XI score values and all baseline characteristics are reported in Table 1.

Clinical status and end-organ function were preoperatively worst in the MELD-XI > 18 cohort. Waiting-list time was recorded to be even longer for the same cohort of patients, suggesting a severe deterioration.

Regarding to primary outcomes (Table 1), in-hospital mortality was significantly higher in the MELD-XI > 18 cohort than in the MELD-XI 11-18 and MELD < 11 cohorts (27.5% vs 10.2% and 7%, respectively) (HR 1.45 [1.11-1.67], $P < .001$).

After Cox regression analysis (Table 2), patients with MELD-XI score > 18 showed a greater risk for dialysis (HR 2.8, $P = .001$), prolonged mechanical ventilation > 48 hours (HR 2.2, $P = .005$), nitric oxide administration (HR 1.9, $P = .017$), and intravenous noradrenaline infusion > 24 hours (HR 1.9, $P = .018$) than patients belonging to a lower MELD-XI score. Moreover, they showed a higher risk of developing early graft failure represented by a post-transplantation inotropic score > 10 (HR 3.2, $P = .003$) and need of extracorporeal membrane oxygenation support (HR 4.7, $P = .001$) with consequent higher need of red blood cell transfusions (HR 3.1, $P = .001$) and rethoracotomy procedures for bleeding (HR 6.6, $P = .003$), thus leading to a prolonged intensive care unit (ICU) stay (HR 3.8, $P = .040$). After risk adjustment for the MELD-XI > 18 cohort (Table 3), ischemic dilative cardiomyopathy etiology directly correlated to a greater risk of postoperative renal failure requiring dialysis ($P = .008$), redo operation correlated to prolonged mechanical ventilation > 48 hours, high time of ICU stay and surgery for postoperative bleeding ($P = .039$), and cold ischemic time > 240 minutes was correlated to a post-transplantation inotropic score > 10 and early graft failure requiring mechanical circulatory support ($P = .045$).

Moreover, we observed a significant difference in long-term survival among the 3 MELD-XI cohorts according to the Kaplan-Meier method as being 5-year (63%) and 10-year (47%) MELD-XI > 18 survival vs 72% and 59% in the MELD-XI < 18 control group, respectively (log-rank, $P < .001$) (Fig 1).

DISCUSSION

In this single-center retrospective study, we tried to evaluate and weigh the role of MELD-XI score grading in terms of prediction of postoperative outcomes in patients undergoing Htx surgery. We showed that patients with severe

Table 1. Preoperative, Intraoperative, and Postoperative Heart Transplant Population by MELD-XI Cohort Characteristics and Outcomes

	Total (N = 425)	MELD < 11 (n = 100)	MELD 11-18 (n = 245)	MELD > 18 (n = 80)	*P*
Recipient Characteristics					
Sex male (%)	341 (80.2)	66 (66)	207 (84.4)	68 (85)	ns
Age (y), mean ± SD	52.6 ± 11.6	49.4 ± 11.7	53.8 ± 11.1	52.6 ± 12.3	ns
BMI (kg/m^2), mean ± SD	24.4 ± 3.6	23.3 ± 3.8	24.7 ± 3.6	24.8 ± 3.2	ns
BSA (m^2), mean ± SD	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	ns
DCMP etiology					
Ischemic (%)	166 (39.1)	25 (25)	110 (44.8)	31 (38.7)	ns
Idiopathic (%)	159 (37.4)	34 (34)	93 (37.9)	32 (40)	ns
Valvular (%)	42 (9.9)	12 (12)	20 (8.1)	10 (12.5)	ns
Restrictive (%)	32 (7.5)	14 (14)	13 (5.3)	5 (6.2)	ns
Hypertrophic (%)	21 (4.9)	9 (9)	10 (4.1)	2 (2.5)	ns
Myocarditis (%)	5 (1.2)	3 (3)	2 (0.8)	NA	ns
WL time (d), mean ± SD	303.9 ± 350.6	218.7 ± 182.3	303.6 ± 288.6	344.7 ± 385.6	.03
PVR (WU), mean ± SD	2.3 ± 1.5	2.3 ± 1.7	2.2 ± 1.6	2.4 ± 1.4	ns
Diabetes n (%)	92 (21.6)	13 (13)	69 (28.1)	10 (12.5)	.05
Hypertension n (%)	68 (16)	8 (8)	23 (9.3)	37 (46.2)	.03
Arterial vasculopathy n (%)	30 (7.1)	8 (8)	10 (4.1)	12 (15)	.02
Redo operation n (%)	136 (32)	26 (26)	85 (34.6)	25 (31.2)	ns
Inotropes n (%)	103 (24.2)	18 (18)	27 (11.1)	58 (72.5)	.001
IABP n (%)	31 (7.3)	7 (7)	7 (2.8)	17 (21.2)	.002
ECMO n (%)	34 (8)	4 (4)	8 (3.2)	22 (27.5)	.001
Mechanical ventilation n (%)	39 (9.2)	9 (9)	11 (4.4)	19 (23.7)	.03
Creatinine (mg/dL), mean ± SD	1.5 ± 1.1	0.9 ± 0.2	1.4 ± 0.3	1.9 ± 2.1	.003
Bilirubin (mg/dL), mean ± SD	1.0 ± 0.9	0.7 ± 0.3	1.6 ± 0.7	2.3 ± 1.6	.002
Donor Characteristics					
Sex male (%)	297 (69.8)	45 (45)	184 (75.1)	58 (72.5)	ns
Age (y), mean ± SD	39.6 ± 11.3	38.3 ± 12.1	41.2 ± 10.5	40.1 ± 12.4	ns
Surgical Variables					
Ischemic time (min), mean ± SD	193.5 ± 48.1	187.6 ± 43.3	195.5 ± 48.5	194.5 ± 51.7	ns
Ischemic time > 240 min n (%)	68 (16)	10 (10)	45 (18.3)	13 (16.2)	ns
CPB time (min), mean ± SD	125 ± 60.6	125 ± 59	122 ± 63	128 ± 60	ns
Outcomes					
EGF n (%)	73 (17.2)	10 (10)	22 (8.9)	41 (51.2)	.001
ECMO n (%)	30 (7.05)	4 (4)	8 (3.2)	18 (22.5)	.004
Inotropic score > 10 n (%)	161 (37.8)	28 (28)	64 (26.1)	59 (73.5)	.02
Noradrenaline> 24h n (%)	120 (28.2)	16 (16)	46 (18.7)	58 (72.5)	.01
Mechanical ventilation > 48h n (%)	97 (22.8)	19 (19)	31 (12.6)	47 (58.7)	.02
NO n (%)	104 (24.4)	28 (28)	22 (8.9)	54 (67.5)	.02
CVVH n (%)	55 (12.9)	10 (10)	18 (7.3)	27 (33.7)	.05
Permanent dialysis n (%)	31 (7.3)	6 (6)	8 (3.2)	17 (21.2)	.04
Re-Htx n (%)	3 (0.7)	-	3 (1.2)	NA	-
Rethoracotomy for bleeding n (%)	56 (13.2)	6 (6)	19 (7.7)	31 (38.7)	.001
RBC (units), mean ± SD	7.4 ± 12.3	6.6 ± 9.3	6.5 ± 9.6	11.4 ± 20.3	.01
FFP (units), mean ± SD	5.4 ± 8.6	4.2 ± 5.7	5.2 ± 8.8	7.3 ± 10.6	ns
PLT (units), mean ± SD	0.7 ± 2.3	0.4 ± 1.5	0.7 ± 2.4	1.2 ± 3.0	ns
ICU stay (d), mean ± SD	8.7 ± 13.4	7.0 ± 16.1	8.3 ± 10.2	11.9 ± 18.5	.04
ICU stay ≥ 10 (d), mean ± SD	83 (19.6)	10 (10)	28 (11.4)	45 (56.2)	.003
Hospital stay (d), mean ± SD	29.9 ± 21.9	26.8 ± 26.6	28.5 ± 19.4	37.6 ± 22.8	.04
In-hospital mortality n (%)	119 (28)	7 (7)	25 (10.2)	22 (27.5)	.003

Abbreviations: BMI, body mass index; BSA, body surface area; CPB, cardiopulmonary bypass; CVVH, continuous veno-venous hemofiltration; DCMP, dilative cardiomyopathy; ECMO, extracorporeal membrane oxygenation; EGF, early graft failure; FFP, fresh frozen plasma; Htx, heart transplantation; IABP, intra-aortic balloon pump; ICU, intensive care unit; INR, international normalized ratio; MELD-XI Model for End-Stage Liver Disease Excluding INR; NO, nitric oxide; ns, not significant; PLT, platelet; PVR, pulmonary vascular resistance; RBC, red blood cell; WL, waiting list; WU, Woods units.

presurgical hepato-renal dysfunction, herein defined by a MELD-XI score calculation > 18, may have the worst outcomes after surgery, if compared with lower MELD-XI transplant categories.

Advanced heart failure is a clinical status characterized by multiple organ dysfunction secondary to an impaired cardiac function [5-10,15-21]. Hepatic congestion and liver dysfunction may develop in response to chronically

Table 2. Progressive Risk for MELD-XI > 18 Heart Transplant Cohort

Adverse Event	*P*	Hazard Ratio	95% CI
Dialysis	.001	2.8	1.51-5.34
Mechanical ventilation > 48 h	.005	2.2	1.32-3.84
NO administration	.017	1.9	1.12-3.38
Inotropic score post-Htx > 10	.003	3.2	1.31-3.75
Noradrenaline infusion > 24 h	.018	1.9	1.23-4.26
Rethoracotomy for bleeding	.03	6.6	1.73-55.33
RBC transfusions	.001	3.1	1.27-4.14
ICU stay	.040	3.8	1.15-3.46
ECMO post-Htx	.001	4.7	8.31-20.42

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; Htx, heart transplantation; ICU, intensive care unit; INR, international normalized ratio; MELD-XI Model for End-Stage Liver Disease Excluding INR; NO, nitric oxide; RBC, red blood cell.

increased central venous pressure. Liver function abnormalities are most commonly seen in patients with heart failure with a cardiac index of $\leq$1.5 L/min/m^2 [15-20]. Abnormal liver function has been linked to increased short- and long-term morbidity and mortality in patients undergoing both cardiac and noncardiac surgery [4-21]. Although a number of scoring systems have been established to assess risk and performance measures for cardiac transplantation, these scores fail to adequately address liver abnormalities. Both the Child-Turcotte-Pugh classification and the MELD score have been used as prognostic tool platforms before cardiac and noncardiac surgery procedures but mostly focusing on patients with hepatic cirrhosis [4,11-14]. Chokshi et al [18] assessed baseline serum levels of hepatic function laboratory tests and MELD score calculations, thus monitoring the results up to 5 years after Htx. In the same study, a modified MELD score calculation was proposed to exclude the effects of an anticoagulation treatment by focusing on albumin levels. Their analyses showed the significant correlation between liver dysfunction and poor postoperative early and late outcomes in patients undergoing orthotopic Htx.

MELD-XI was, again, conceived to overcome INR modifications due to anticoagulation treatment maintenance [4-10]. Patients with higher MELD-XI scores are more often in a worse clinical condition before the transplant. They have more often a biventricular dysfunction with a severe degree of pulmonary hypertension explaining the greater necessity of prolonged mechanical ventilation and

Table 3. Risk Adjustment for Adverse Events in MELD-XI > 18 Heart Transplant Cohort

Adverse Events	Variables	*P*
Dialysis	iDCMP etiology	.008
Mechanical ventilation > 48 h + ICU stay + rethoracotomy for bleeding	Redo operation	.039
Post-Htx inotropic score > 10 + EGF requiring MCS	Cold ischemic time > 240 min	.045

Abbreviations: EGF, early graft failure; Htx, heart transplantation; ICU, intensive care unit; iDCMP, ischemic dilative cardiomyopathy; INR, international normalized ratio; MCS, mechanical circulatory support; MELD-XI Model for End-Stage Liver Disease Excluding INR.

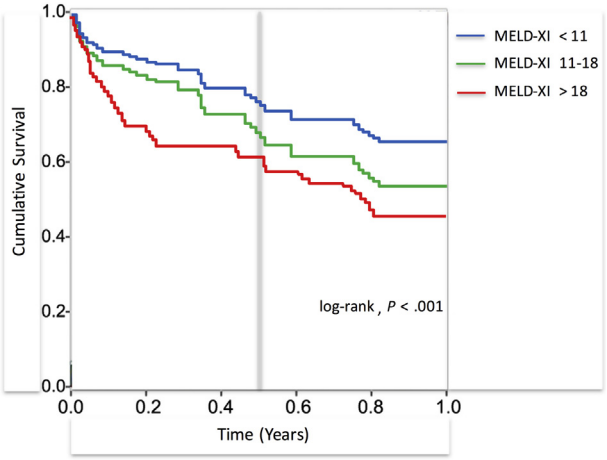

Figure 1. Kaplan-Meier survival analysis of Model for End-Stage Liver Disease Excluding INR (MELD-XI) cohorts.

nitric oxide administration. Higher preoperative levels of creatinine reflect a variable degree of renal impairment, which leads to a more frequent need for dialysis after surgery. The presence of hepatic dysfunction causes an augmented risk of postoperative bleeding, explaining the greater need for red blood cell transfusions and the greater frequency of resternotomy for bleeding [19]. All these findings can explain the longer ICU and in-hospital stay, as well as the mortality rates [5-9, 18-21], higher for patients with higher MELD-XI score levels even in the pediatric population [8]. Liver dysfunction is so important in defining high-risk heart transplant candidates that Farr et al [21] proposed to use liver biopsy in addition to MELD-XI to improve risk stratification of patients with advanced heart failure and suspected irreversible liver dysfunction.

Yang et al [9] studied the adoption of the MELD-XI score calculation in patients receiving long-term ventricular assist device (VAD) support. They observed improved VAD outcomes in the case of MELD-XI < 17 population ($P < .05$). Additionally, after MELD-XI improved while on VAD support, post-transplant survival was found to be similar to those without preoperative poor liver dysfunction and higher MELD-XI.

Similarly, Deo et al [6], by analyzing the data of the United Network for Organ Sharing registry with 39,711 patients undergoing Htx, obtained similar results as previously reported. In their study, high MELD-XI scores were associated with higher early (odds ratio = 1.68; 95% confidence interval, 1.36-2.08; $P < .001$) and long-term mortality (adjusted HR = 1.36; 95% confidence interval, 1.25-1.48; $P < .001$). Thereafter, in another contemporary series from the United Network for Organ Sharing registry, Grimm et al [7] reported that MELD-XI score was an independent predictor of post-Htx mortality with higher 30-day and 1-year mortality rates in higher MELD-XI scores.

A recent study by Ortiz-Bautista et al [10], focusing on the clinical utility of MELD-XI in predicting outcomes after

Htx, reported that the ability of MELD-XI to predict 1-year mortality was poor and similar to that of bilirubin, creatinine, and pulmonary vascular resistance due to the small sample size and to the differences surgical strategies, immunosuppression regimens, and center-specific protocols over the study period.

Our studied patient population got a wide variability in post-transplant immunosuppression regimen due to the evolution of drug treatments over a large study period. Even if we did not weight the influence of such an immunosuppressive maintenance, our study results are in line with most of the previously mentioned literature findings, thereby supporting the adoption of MELD-XI calculation in terms of utility in recipients selection for heart transplant and eventual better clinical optimization before surgery.

No clinical trial to date has evaluated the clinical effect of MELD-XI score in clinical decision-making, some reported results are conflicting and some authors advice a liver biopsy together with MELD-XI calculation to get a more robust evaluation of recipients of organ transplant [10]. However, according to high-volume literature reports, a high MELD-XI was demonstrated to negatively affect both routine and transplant cardiac surgery, therefore confirming the negative prognosis of a severe hepato-renal dysfunction.

CONCLUSIONS

Despite some limitations and the small sample size, our institutional retrospective analysis showed how the MELD-XI scoring system may potentially be considered a predictor of postoperative outcomes in recipients of heart transplant. Therefore, our study supports a precautionary and more selective addition of candidates on an active heart transplant waiting list. Despite the absence of well-accepted clinical evidence, patients with a high degree of hepato-renal dysfunction should be carefully evaluated before transplantation and adequately treated, thus better optimizing any potential candidate, in order to preserve positive outcomes.

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