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Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: Use of the Model of End-stage Liver Disease (MELD) and MELD eXcluding INR (MELD-XI) scoring system

Jonathan A. Yang, MD, MPH,[a] Tomoko S. Kato, MD, PhD,[b] Brittney P. Shulman, BS,[a] Hiroo Takayama, MD, PhD,[a] Maryjane Farr, MD,[b] Ulrich P. Jorde, MD,[b] Donna M. Mancini, MD,[b] Yoshifumi Naka, MD, PhD,[a] and P. Christian Schulze, MD, PhD[b]

From the [a]Division of Cardiothoracic Surgery, Department of Surgery and the [b]Division of Cardiology, Department of Medicine, Columbia University Medical Center, New York, NY

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BACKGROUND: Liver dysfunction increases post-surgical morbidity and mortality. The Model of End-stage Liver Disease (MELD) estimates liver function but can be inaccurate in patients receiving oral anti-coagulation. We evaluated the effect of liver dysfunction on outcomes after ventricular assist device (VAD) implantation and the dynamic changes in liver dysfunction that occur during VAD support.

METHODS: We retrospectively analyzed 255 patients (147 with pulsatile devices and 108 with continuous-flow devices) who received a long-term VAD between 2000 and 2010. Liver dysfunction was estimated by MELD and MELD-eXcluding INR (MELD-XI), with patients grouped by a score of ≥ 17 or < 17. Primary outcomes were on-VAD, after transplant, and overall survival.

RESULTS: MELD and MELD-XI correlated highly ($R \geq 0.901$, $p < 0.0001$) in patients not on oral anti-coagulation. Patients with MELD or MELD-XI < 17 had improved on-VAD and overall survival ($p < 0.05$) with a higher predictive power for MELD-XI. During VAD support, cholestasis initially worsened but eventually improved. Patients with pre-VAD liver dysfunction who survived to transplant had lower post-transplant survival ($p = 0.0193$). However, if MELD-XI normalized during VAD support, post-transplant survival improved and was similar to that of patients with low MELD-XI scores.

CONCLUSIONS: MELD-XI is a viable alternative for assessing liver dysfunction in heart failure patients on oral anti-coagulation. Liver dysfunction is associated with worse survival. However, if MELD-XI improves during VAD support, post-transplant survival is similar to those without prior liver dysfunction, suggesting an important prognostic role. We also found evidence of a transient cholestatic state after LVAD implantation that deserves further examination.

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Liver dysfunction due to end-stage heart failure (HF) is often referred to as cardiac or congestive hepatopathy.[1] The underlying pathophysiology is related to poor end-organ perfusion leading to ischemic parenchymal changes with hepatocellular necrosis, especially in cases of acute decompensation. Second, passive hepatic venous congestion develops in the setting of right heart dysfunction with increased right atrial pressures.[1,2] Cholestatic changes are the hallmark of chronic congestive hepatopathy, with serum

Reprint requests: P. Christian Schulze, MD, PhD, Assistant Professor of Medicine, Columbia University Medical Center, Center for Advanced Cardiac Care, Department of Medicine, Division of Cardiology, 622 W 168 St, PH 10, Rm 203, New York, NY 10032. Telephone: 212-305-6916. Fax: 212-342-5355.

E-mail address: pcs2121@mail.cumc.columbia.edu

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bilirubin and alkaline phosphatase concentrations often elevated.[3] Although early stages are reversible, long-term congestive hepatopathy leads to irreversible damage to the liver parenchyma and cirrhosis with associated transaminitis.[4] The management is focused on treating the underlying cardiac abnormalities, and hepatic function has been shown to benefit from orthotopic heart transplantation (OHT), with normalization of liver function assays by 6 months after transplant.[5]

Although individual laboratory assays can provide some insight on a patient's liver function, the composite Model for End-Stage Liver Disease (MELD) is a more robust score of liver dysfunction. It was first developed to predict death in patients undergoing transjugular intrahepatic portosystemic shunt procedures[6,7] and has since been verified as a measure of liver dysfunction, providing an objective score based on a patient's creatinine, total bilirubin, and international normalized ratio (INR). In 2002, the United Network for Organ Sharing (UNOS) adopted this system for prioritizing liver transplant candidates based on disease severity.[8,9] Elevated MELD scores also predict post-operative death in cirrhotic patients undergoing major digestive, orthopedic, and cardiovascular operations.[10] For patients with a MELD score of < 8, 30-day mortality was 5.7% compared with $> 50\%$ for patients with MELD of > 20.

Left ventricular assist devices (LVADs) are increasingly used to treat patients with end-stage HF, leading to improvements in survival and quality of life as a bridge to transplant (BTT) or destination therapy (DT).[11] A recent study by Matthews et al[12] demonstrated that liver dysfunction (defined as a MELD > 17) before LVAD implantation predicts increased perioperative blood product use and 6-month survival. However, no study has analyzed the effect of dynamics in liver dysfunction on outcomes after LVAD insertion. LVAD support should lead to improvements in cardiac hepatopathy, yet no study has reported the specific factors associated with this potential relationship or its effect on survival. One reason has been the lack of a good measure of liver function in HF patients during LVAD support, which often requires oral anti-coagulation with warfarin. Because warfarin increases INR, which is a major component of the MELD score, MELD becomes an inaccurate gauge of liver dysfunction.

As an alternative to the traditional MELD system, the MELD-XI (MELD eXcluding INR) score was developed by Heuman et al.[13] It is calculated from creatinine and total bilirubin only. MELD-XI was validated in a population of $> 7{,}000$ patients with liver cirrhosis and highly correlated with MELD in patients not on oral anti-coagulation, with both scores predicting survival similarly. Given that INR is not used in its calculation, MELD-XI will remain accurate even if a patient receives oral anti-coagulation. Therefore, it is potentially a more effective method of estimating liver dysfunction in patients on LVAD support requiring concomitant oral anti-coagulation.

In this study, we aimed to validate the MELD-XI and MELD scoring systems in HF patients undergoing LVAD placement. We also followed serum markers of cholestasis, hepatic injury, and other relevant conditions during LVAD support and analyzed the role that changes in liver dysfunction assessed by MELD-XI may play in predicting survival after OHT.

Methods

Approval for this study was obtained from the Institutional Review Board at Columbia University Medical Center.

Patient selection

All patients who received a long-term VAD between January 1, 2000, and September 7, 2010, at Columbia University Medical Center were included. Given that 85% of these patients received a pulsatile or continuous-flow HeartMate (HM) or HeartMate II (HMII; Thoratec, Pleasanton, CA), we restricted our study cohort to those who received these devices. Sub-analysis was performed for patients who were supported by continuous-flow devices. The study excluded patients who were on temporary mechanical circulatory support before long-term VAD and those whose preoperative laboratory values were not available.

Data collection

Patient data were obtained from hospital medical records. Preoperative laboratory values were defined as the last set of results immediately before VAD implantation. Primary outcomes included overall survival, on-VAD survival, and survival after OHT in those who received an allograft. Post-operative laboratory values were assessed at 30 days, 3 months, and 6 months for those who had a VAD for at least that length of time and immediately before transplant if they underwent OHT. Post-operative right HF (RHF) was defined as requirement of nitric oxide inhalation > 48 hours, inotropic support > 14 days, and/or a right VAD (RVAD) after LVAD.

MELD and MELD-XI definition

We used the UNOS modification of the MELD score,[8] which uses the formula MELD $= 3.78 \times \text{Ln (bilirubin)} + 11.2 \times \text{Ln (INR)} + 9.57 \times \text{Ln (creatinine)} + 6.43$. Any variable with a value < 1 is assigned a value of 1 to avoid negative scores; thus, the minimum possible MELD score is 6.43. MELD-XI is defined by the formula MELD-XI $= 5.11 \times \text{Ln (bilirubin)} + 11.76 \times \text{Ln (creatinine)} + 9.44$.[13] Again, variables with values of < 1 were given the value of 1, with a minimum possible MELD-XI score of 9.44.[13] According to the MELD and MELD-XI score before VAD surgery, patients were dichotomized into those with values ≥ 17 and those with values < 17, as previously described.[12]

Statistical analysis

Statistical analyses were performed using Stata 11 software (StataCorp, College Station, TX). Statistical significance was determined based on a pre-established $\alpha = 0.05$. Associations between categoric data were tested using chi-square and Fisher's exact tests. Continuous data were com-

Table 1 Clinical Characteristics of Patients Undergoing Ventricular Assist Device Placement

Variables[a]	MELD <17	MELD ≥17	*p*-value	MELD-XI <17	MELD-XI ≥17	*p*-value
	(*n* = 176)	(*n* = 79)		(*n* = 157)	(*n* = 98)	
Age, years	53.1 ± 14.8	57.3 ± 11.2	0.028	52.6 ± 15.0	57.4 ± 11.3	0.006
Sex						0.011
Female	37 (21.0)	12 (15.2)	0.274	38 (24.2)	11 (11.2)	
Male	139 (79.0)	67 (84.8)		119 (75.8)	87 (88.8)	
Body mass index, kg/m^2	27.2 ± 6.0	26.4 ± 4.3	0.293	27.1 ± 5.9	26.6 ± 4.9	0.504
Diabetes	55/165 (33.3)	28/72 (38.9)	0.410	42/146 (28.8)	41/91 (45.1)	0.011
Coronary artery disease	73/165 (44.2)	31/71 (43.7)	0.934	62/146 (42.5)	42/90 (46.7)	0.528
COPD	9/162 (5.6)	5/71 (7.0)	0.765	7/144 (4.9)	7/89 (7.9)	0.348
Pre-op LVEF, %	17.6 ± 6.4	18.6 ± 8.3	0.359	18.2 ± 6.7	17.5 ± 7.5	0.544
Ventilation	22/140 (15.7)	11/60 (18.3)	0.647	22/123 (17.9)	11/77 (14.3)	0.504
History of hepatitis	1/102 (1.0)	1/48 (2.1)	0.539	2/95 (2.1)	0/55 (0)	0.532
History of cancer	20/161 (12.4)	6/70 (8.6)	0.395	17/142 (12.0)	9/89 (10.1)	0.663
BTT (vs DT)	140/176 (79.6)	67/77 (87.0)	0.156	127/156 (81.4)	80/97 (82.5)	0.831

BTT, bridge to transplant; COPD, chronic obstructive pulmonary disease; DT, destination therapy; LVEF, left ventricular ejection fraction; MELD, Model of End-stage Liver Disease (MELD); MELD-XI, Model of End-stage Liver Disease eXcluding INR.

[a]Continuous variables are expressed as mean ± standard deviation and categoric variables as number (%).

pared using Student's *t*-tests. Survival was compared using Kaplan-Meier analysis and log-rank tests. A Cox-proportional hazards model was used to test the significance of the individual variables as predictors of survival. The relation between MELD and MELD-XI scores was investigated by Pearson's correlation analysis.

Results

Patient cohort

We captured data for 264 adults who underwent primary long-term VAD placement between January 2000 and September 2010, including 158 (60%) pulsatile HM and 106 (40%) HMII recipients. Of these, the initial LVAD goal was BTT in 215 (81.44%), DT in 46 (17.42%), and bridge to decision in 3 (1.14%; Table 1). Owing to incomplete medical records that prevented calculation of the pre-VAD MELD, 9 patients were excluded, leaving 255 in the study. Sub-analysis of survival after continuous-flow LVAD implantation included 104 patients.

Baseline characteristics

Most pre-operative characteristics were similar between the 2 groups, except that the 79 patients with MELD ≥ 17 and the 98 with MELD-XI ≥ 17 were older (Table 1). Also, patients with elevated MELD-XI were more likely to be men (88.8% vs 75.8%, $p = 0.011$) and diabetic (45.1% vs 28.8%, $p = 0.011$). As expected, pre-operative creatinine and bilirubin levels were significantly greater for patients with elevated scores. INR was similar between MELD-XI groups but significantly higher (1.62 vs 1.25, $p < 0.0001$) in the MELD ≥ 17 group, as was expected. In addition, aspartate aminotransferase and alanine aminotransferase levels were generally higher and albumin levels generally lower in the elevated MELD and MELD-XI groups (Table 2). MELD and MELD-XI values highly correlated, especially after excluding patients on oral anticoagulation within 5 days before VAD placement ($R = 0.901$, $p < 0.0001$).

Survival differences based on pre-VAD liver dysfunction scores

During LVAD support, 48 patients died, with survival of 82.4% at 6 months and 75.8% at 1 year. On-VAD survival was defined as survival to OHT, VAD explant (eg, for ventricular recovery) with survival for at least 30 days, or survival with device in place to the last date of follow-up. Patients with lower MELD or MELD-XI scores had better survival after VAD implantation. When dichotomized by MELD, patients with pre-VAD scores < 17 had higher 18-month (73.5% vs 63.2%, $p = 0.0050$; Figure 1A) and long-term on-VAD survival ($p = 0.0069$). Patients with a MELD-XI < 17 also had higher 18-month (77.2% vs 59.8%, $p = 0.0220$; Figure 1B) and long-term ($p = 0.0437$) on-VAD survival. Patients with high MELD-XI scores had a 30-day post-VAD mortality of 8.0%. Most of these deaths occurred during the early post-operative period due to multiorgan system failure, typically associated with sepsis or pre-existing organ failure such as post-cardiotomy shock as indication for VAD.

In addition to an on-VAD survival advantage, patients with a MELD or MELD-XI < 17 before LVAD implantation also had an overall survival advantage (Figure 1C and D). OHT rates were similar between groups and thus did not account for this survival difference (Table 3). The duration of BTT VAD support was also similar across groups.

In a sub-set of 104 patients with continuous-flow devices, 71 patients had a MELD-XI < 17 before LVAD surgery and the remaining 33 showed a MELD XI ≥ 17. The analysis of patients who were supported by continuous-

Table 2 Baseline Laboratory Values in Patients Undergoing Ventricular Assist Device Placement

Variable[a]	MELD <17	MELD ≥17	*p*-value	MELD-XI <17	MELD-XI ≥17	*p*-value
Albumin, mg/dl	3.56 ± 0.54	3.38 ± 0.52	0.016	3.53 ± 0.55	3.45 ± 0.53	0.242
Total protein, mg/dl	6.5 ± 1.2	6.4 ± 1.2	0.608	6.4 ± 1.2	6.5 ± 1.2	0.445
AST, IU/liter	48 ± 78	135 ± 318	0.0007	61 ± 160	97 ± 234	0.156
ALT, IU/liter	65 ± 177	143 ± 350	0.018	70 ± 182	121 ± 321	0.106
Alkaline phosphatase, IU/liter	92 ± 52	101 ± 55	0.183	92 ± 52	100 ± 55	0.219
Bilirubin, mg/dl						
Total	1.42 ± 0.98	2.36 ± 1.34	<0.0001	1.31 ± 0.73	2.36 ± 1.46	<0.0001
Direct	0.48 ± 0.52	0.94 ± 0.67	<0.0001	0.43 ± 0.35	0.93 ± 0.78	<0.0001
White blood cell count, $10^3/\mu l$	8.9 ± 3.3	10.2 ± 4.2	0.011	8.9 ± 3.3	10.0 ± 4.1	0.026
Hemoglobin, g/dl	11.3 ± 1.9	10.9 ± 1.8	0.136	11.2 ± 1.9	11.0 ± 1.9	0.442
Hematocrit, %	34.2 ± 5.3	33.0 ± 5.4	0.081	34.1 ± 5.2	33.5 ± 5.6	0.371
Platelet count, $10^3/\mu l$	200 ± 77	191 ± 97	0.422	202 ± 80	191 ± 89	0.304
International normalized ratio	1.25 ± 0.20	1.62 ± 0.57	<0.0001	1.34 ± 0.41	1.42 ± 0.38	0.141
Blood urea nitrogen, mg/dl	33 ± 16	50 ± 23	<0.0001	30 ± 13	51 ± 22	<0.0001
Creatinine, mg/dl	1.34 ± 0.40	2.14 ± 0.70	<0.0001	1.26 ± 0.33	2.12 ± 0.64	<0.0001
Sodium, mg/dl	134 ± 5	131 ± 6	0.0005	134 ± 5	131 ± 6	<0.0001
Potassium, mg/dl	4.1 ± 0.5	4.2 ± 0.5	0.321	4.1 ± 0.5	4.2 ± 0.5	0.195

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MELD, Model of End-stage Liver Disease (MELD); MELD-XI, Model of End-stage Liver Disease eXcluding INR.

[a]Data are shown as mean ± standard deviation.

flow devices also revealed that on-VAD survival and overall survival were better in patients with MELD XI < 17 (log-rank $p = 0.0279$) than in patients with MELD-XI ≥ 17 ($p = 0.0398$, Figure 2A and B).

Impact of MELD-XI on survival

Given that those with MELD-XI < 17 and ≥ 17 had significantly different creatinine levels, we performed a Cox proportional hazard analysis on creatinine alone and MELD-XI as predictors of survival. Cox regression showed creatinine and MELD-XI were both predictive of survival, but multivariable analysis was not feasible due to colinearity. After grouping patients by high preoperative creatinine (> 1.5 mg/dl) and high MELD-XI (≥ 17), multivariable analysis confirmed high MELD-XI was a predictive variable (hazard ratio, 1.84; 95% confidence interval, 1.081–3.135; $p = 0.025$) but not high creatinine levels (hazard ratio, 1.2; 95% confidence interval, 0.716–2.081; $p = 0.464$). A Cox proportional hazard ratio analysis based on MELD and MELD-XI scores, using the values as continuous variables (Table 4), showed MELD and MELD-XI scores were significantly associated with on-VAD survival and overall survival; however, the MELD score showed only a trend of association with 2-year on VAD survival.

Improvement of laboratory values on VAD support

Laboratory values generally improved during VAD support. We followed the trends of these values from pre-VAD implantation to 30 days of VAD support to late VAD support (Table 5). "Late VAD" values were defined as at time of OHT or, for those who did not undergo transplant, at 6 months of VAD support. The mean duration to transplant for patients after VAD implantation was 180 days (median, 124.5 days) and was not significantly different between those with MELD-XI ≥ 17 and < 17 (162.6 vs 183.6 days, $p = 0.35$).

Renal function improved overall, with concentrations of blood urea nitrogen, creatinine, and sodium all normalizing. Transaminases, albumin, and total protein improved on average as well.

INR was difficult to use as a gauge of synthetic function because some patients received oral anti-coagulation during VAD support. Given the differences in post-operative anti-coagulation requirements, the trend in INR differed based on device. For pulsatile HM recipients, post-operative long-term anti-coagulation was generally not required, and there was no significant change in INR (1.42 ± 0.46 vs 1.34 ± 0.46, $p = 0.256$). INR rose for HMII recipients, who typically received oral anti-coagulation (1.28 ± 0.30 vs 1.82 ± 0.6, $p < 0.0001$).

Cholestasis during VAD support

There was evidence that cholestasis worsened during early VAD support. Mean alkaline phosphatase levels increased significantly during the first 30 days of VAD support (94.6 to 156.9 IU/liter, $p < 0.0001$), during which 85.7% of patients had an increased level. Although levels decreased during further VAD support (late VAD mean: 120.5 IU/liter; $p = 0.022$), they did not return to pre-VAD levels. Hyperbilirubinemia also worsened during the first 30 days of VAD support, with mean total bilirubin levels increasing from 1.7 to 2.2 mg/dl, although the mean value did normalize subsequently (late VAD mean: 1.0 mg/dl; $p < 0.0001$). Direct bilirubin had a similar trend. This data suggests that

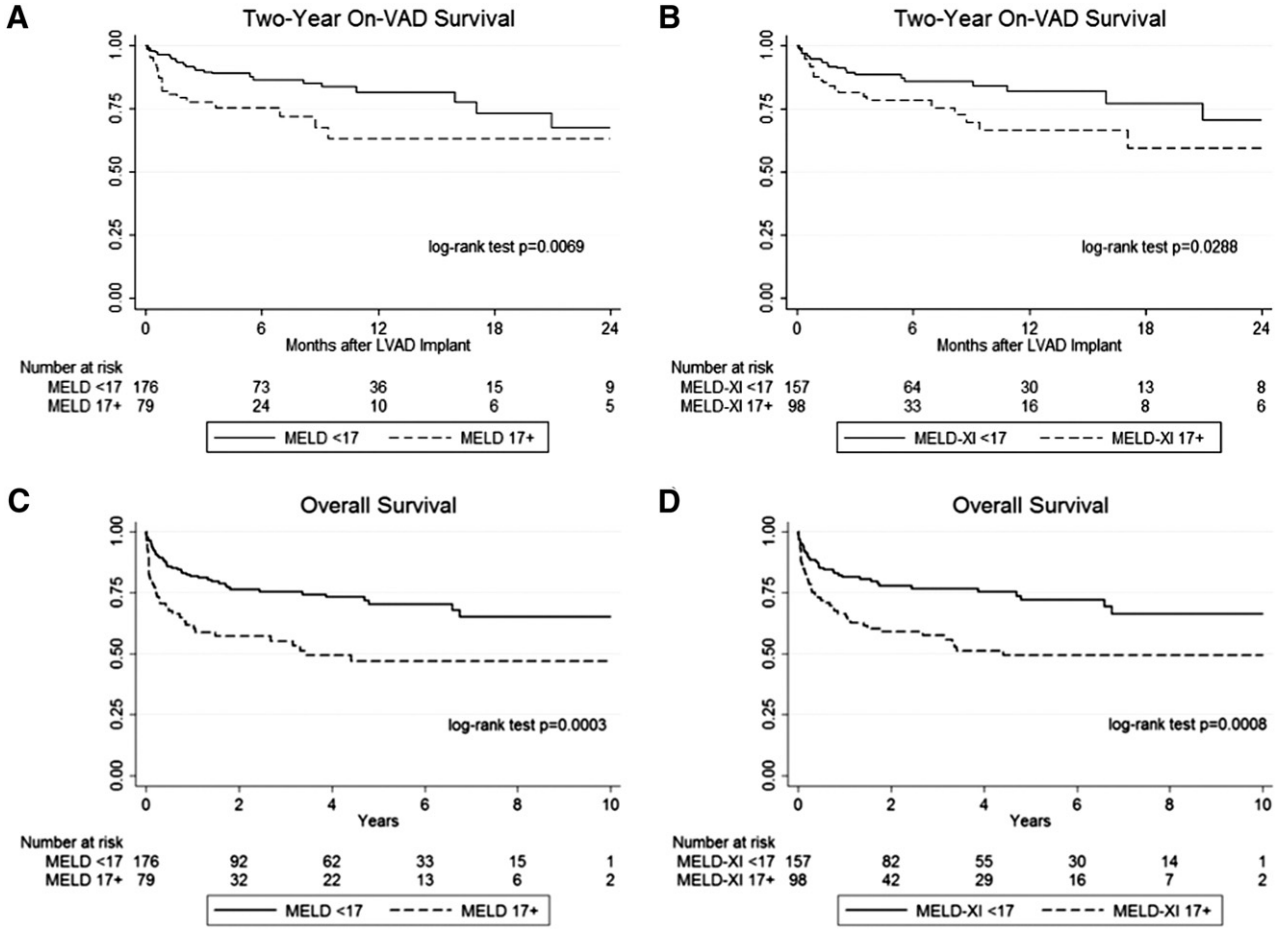

Figure 1 Survival based on the degree of liver dysfunction assessed by Model of End-stage Liver Disease (MELD) and MELD-eXcluding INR (MELD-XI), scores at the time of ventricular assist device (VAD) implantation. Survival at 2 years on-VAD based on (A) MELD and (B) MELD-XI scores shows significantly worse outcomes for patients with a score ≥ 17 compared with patients with scores < 17. Overall survival based on (C) MELD and (D) MELD-XI scores demonstrates a more pronounced survival difference between patients with a score < 17 vs ≥ 17.

LVAD insertion not only fails to rapidly resolve cholestatic disease but may also exacerbate it initially.

A separate analysis performed for patients with pulsatile devices and those with continuous-flow devices showed mean alkaline phosphatase levels increased significantly during the first 30 days of VAD support, from 88.6 to 159.2 IU/liter ($p = 0.0010$) for the pulsatile group, and from 100.0 to 146.5 IU/liter ($p < 0.0001$) for continuous flow group. However, the decrease in alkaline phosphatase levels during long-term VAD support was only significant in patients with pulsatile devices (late VAD mean: 1290.0 IU/liter; $p < 0.0001$) but not in patients with continuous flow devices (late VAD mean: 107.9 IU/liter; $p = 0.1652$). Hyperbilirubinemia also showed a trend toward worsening during the first 30 days of VAD support, with mean total bilirubin levels increasing from 1.8 to 2.2 mg/dl in the pulsatile VAD group ($p = 0.4885$) and from 1.5 to 2.1 mg/dl in the continuous flow group ($p = 0.2854$), but this normalized subsequently in both groups, with a late VAD mean of 1.1 mg/dl ($p < 0.0001$) for pulsatile VADs and 1.0 mg/dl ($p < 0.0001$) for continuous-flow VADs. These data suggest that LVAD insertion is associated with an early development of hepatic cholestasis, which is evident even after a prolonged interval of VAD support,

Table 3 Initial therapeutic goal of Left Ventricular Assist Device Implantation and Subsequent Rate of Heart Transplantation by MELD and MELD XI Groups in Bridge to Transplant Patients and the Entire Cohort

	MELD <17	MELD ≥17	*p*-value	MELD-XI <17	MELD-XI ≥17	*p*-value
BTT, %	79.4	85.1	0.293	80.9	81.6	0.883
All patients, %	65.7	55.4	0.124	64.3	59.2	0.409

BTT, bridge to transplant; MELD, Model of End-stage Liver Disease (MELD); MELD-XI, Model of End-stage Liver Disease eXcluding INR.

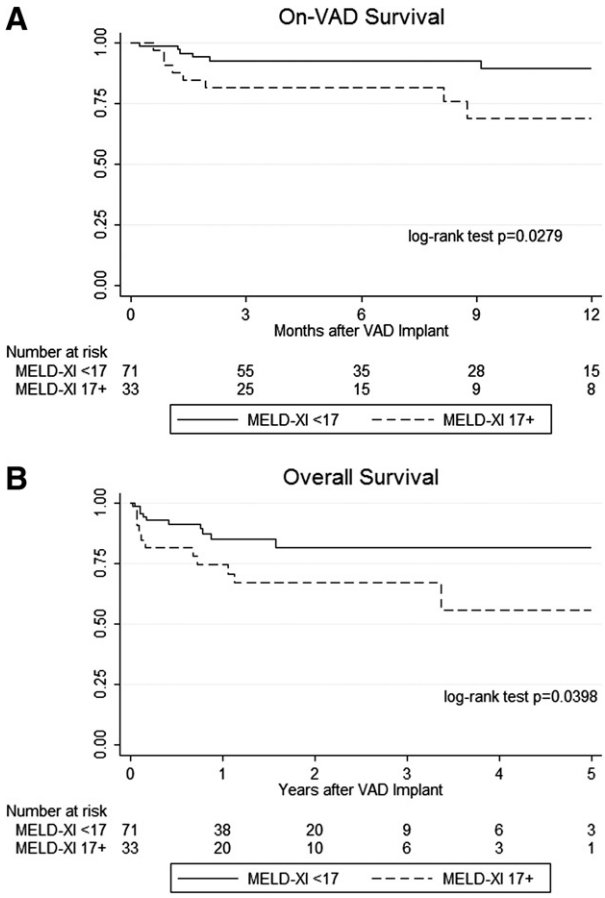

Figure 2 Sub-analysis of survival is shown in patients with continuous-flow ventricular assist devices (VADs) based on the degree of liver dysfunction assessed by Model of End-stage Liver Disease eXcluding INR (MELD-XI) score at the time of VAD implantation. (A) The 12-month on-VAD survival based on MELD-XI scores shows significantly worse outcomes for patients with a score ≥ 17 compared with patients with scores < 17. (B) Overall survival up to 5 years after VAD implantation based on MELD-XI scores demonstrate a significantly worse outcome for patients with a score ≥ 17 compared with patients with scores <17.

whereas other parameters of liver dysfunction improve significantly (Table 5).

RHF after VAD surgery

Because of the incomplete data for the duration of nitric oxide inhalation after VAD support, the data regarding RHF development after VAD surgery was obtained from 230 patients in the present study. Among those, 72 patients (31.3%) developed RHF after VAD surgery and 36 (14.1%) required RVAD implantation. The proportion of patients who developed RHF was not significantly different between patients with MELD scored ≥ 17 vs < 17 (33.9% vs 29.4%, $p = 0.510$) or MELD-XI ≥ 17 vs < 17 (33.7% vs 28.9%, $p = 0.445$). However, when we compared the proportion of patients who eventually underwent OHT, patients who developed RHF on-VAD support were less likely to reach OHT (56.9% vs 72.8%, $p = 0.017$) even when we only analyzed patients with VAD for BTT (64.9% vs 79.6%, $p = 0.033$).

Dynamics in MELD and MELD-XI during VAD support

MELD-XI scores improved on average (15.8 ± 5.6 vs 13.3 ± 3.9, $p < 0.0001$) after LVAD support, with 67% of patients having a decreased MELD-XI score at time of OHT or after 6 months of LVAD support, including 92% of the patients with elevated pre-operative MELD-XI. MELD showed a similar but less dramatic change, improving from 14.7 ± 5.4 to 13.5 ± 4.9 ($p = 0.027$), due to the effect of warfarin treatment on INR. Thus, MELD and MELD-XI were no longer highly correlated ($R = 0.6887$, $p < 0.0001$). We decided to use MELD-XI as our measure of liver dysfunction in subsequent analyses to avoid the influence of oral anti-coagulation.

Survival effect of MELD-XI during VAD support

Because of the significant improvement in the MELD-XI score after 1 month of VAD support, the effect of these MELD-XI scores on overall and on-VAD survival was assessed. Among patients whose VAD was in place for at least 30 days, those who had a MELD-XI < 17 had significantly improved on-VAD survival ($p < 0.0001$) and overall survival ($p = 0.0275$, Figure 3A and B) after 30 days of VAD support. Patients with a MELD-XI ≥ 17 after 30 days of LVAD support had a similar rate of OHT as those with a lower score (57.5% vs 68.7%, $p = 0.174$), so rates of OHT did not explain this overall survival difference.

Survival impact of improvement in MELD-XI during VAD support

The effect of improving MELD-XI during VAD support was assessed for patients successfully bridged to OHT. For the 255 patients in our study, 164 (64.3%) eventually re-

Table 4 Cox Proportional Hazard Models of MELD and MELD-XI as Predictors for Survival[a]

Outcome	HR (95% CI)	*p*-value
1 year on-VAD survival		
MELD	1.058 (1.003–1.117)	0.039
MELD-XI	1.060 (1.003–1.119)	0.038
2 year on-VAD survival		
MELD	1.053 (1.000–1.110)	0.051
MELD-XI	1.058 (1.004–1.116)	0.036
Overall survival		
MELD	1.067(1.026–1.1.8)	0.001
MELD-XI	1.064(1.024–1.105)	0.001

CI, confidence interval; HR, hazard ratio; MELD, Model of End-stage Liver Disease (MELD); MELD-XI, Model of End-stage Liver Disease eXcluding INR; VAD, ventricular assist device.

[a]MELD and MELD-XI were analyzed as continuous variables.

Table 5 Dynamics in Laboratory Values Before and After Ventricular Assist Device Placement

Variables[a]	Pre-VAD	30 days on-VAD	*p*-value[b]	Late on-VAD	*p*-value[c]
Albumin, mg/dl	3.5 ± 0.6	3.4 ± 0.5	0.0001	3.9 ± 0.7	<0.0001
Total protein, mg/dl	6.4 ± 1.3	6.7 ± 1.0	0.0759	7.3 ± 1.1	<0.0001
AST, IU/liter	75 ± 191	34 ± 35	0.0021	40 ± 98	0.0742
ALT, IU/liter	89 ± 245	27 ± 24	0.0003	34 ± 67	0.0057
Alkaline phosphatase, IU/liter	94.6 ± 52.9	156.9 ± 217.9	<0.0001	120.5 ± 88.3	<0.0001
Bilirubin, mg/dl					
Total	1.7 ± 1.2	2.2 ± 6.1	0.4472	1.0 ± 0.9	<0.0001
Direct	0.6 ± 0.6	1.0 ± 3.2	0.3631	0.3 ± 0.5	<0.0001
White blood cell count, $10^3/\mu L$	9.4 ± 3.7	10.1 ± 4.2	0.0254	8.5 ± 3.5	0.0029
Hemoglobin, g/dl	11.2 ± 1.9	10.2 ± 1.5	<0.0001	11.3 ± 1.9	0.5760
Hematocrit, %	33.9 ± 5.4	32.3 ± 4.5	<0.0001	35.1 ± 5.6	0.0508
Platelet count, $10^3/\mu L$	197 ± 84	285 ± 113	<0.0001	230 ± 88	0.0027
International normalized ratio	1.36 ± 0.40	1.67 ± 0.69	<0.0001	1.53 ± 0.56	<0.0001
Pulsatile HM	1.42 ± 0.46	1.38 ± 0.54	0.7254	1.34 ± 0.46	0.2401
HM II	1.28 ± 0.30	1.98 ± 0.70	<0.0001	1.82 ± 0.58	<0.0001
Blood urea nitrogen, mg/dl	38 ± 20	23 ± 15	<0.0001	24 ± 13	<0.0001
Creatinine, mg/dl	1.6 ± 0.6	1.3 ± 0.7	<0.0001	1.3 ± 0.6	<0.0001
Sodium, mg/dl	133 ± 5	137 ± 3	<0.0001	137 ± 3	<0.0001
Potassium, mg/dl	4.2 ± 0.5	4.2 ± 0.5	0.1203	4.3 ± 0.7	0.0547
MELD	14.7 ± 5.4	14.7 ± 5.4	0.7615	13.5 ± 4.9	0.0294
MELD-XI	15.8 ± 5.6	14.0 ± 5.4	<0.0001	13.3 ± 3.9	<0.0001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HM, HeartMate; HMII, HeartMate II; MELD, Model of End-stage Liver Disease (MELD); MELD-XI, Model of End-stage Liver Disease eXcluding INR.

[a]Values are shown as mean ± standard deviation.

[b]*p*-value for comparison pre-VAD vs on-VAD 30 days.

[c]*p*-value for comparison pre-VAD vs late on-VAD.

ceived an allograft, and those with a pre-VAD MELD-XI ≥ 17 had worse post-OHT survival (log-rank test $p = 0.0193$). Sub-group analysis demonstrated that this was largely due to patients whose MELD-XI remained elevated during VAD support (High/High group), who had worse short-term and long-term post-OHT survival ($p = 0.0182$) than patients with a low MELD-XI throughout (Low/Low group; $p = 0.0295$). However, patients who had an elevated MELD-XI pre-VAD that improved to < 17 by the time of OHT (High/Low group) had near-identical short-term post-OHT survival compared with Low/Low patients ($p = 0.5217$; Figure 4), with similar 10-year post-OHT survival as well (67.2% vs 73.5%, $p = 0.1164$).

Discussion

This study assessed the validity of using MELD-XI as a reliable gauge of liver dysfunction in HF patients undergoing VAD implantation regardless of oral anti-coagulation, which can augment their INR and MELD score. The MELD-XI score has been previously validated with MELD on two cirrhotic cohorts that encompassed > 7,000 patients. Similarly, we demonstrated a high level of correlation between MELD-XI and MELD in our cohort of HF patients who were not receiving oral anti-coagulation in the days preceding their VAD implantation.

This study confirms that pre-VAD MELD is a predictor of survival after VAD implantation, as previously reported by Matthews et al.[12] Patients with MELD scores < 17 had an advantage in both an overall and on-VAD survival compared with those with MELD scores of ≥ 17. We also demonstrated MELD-XI as a similar predictor of both on-VAD and overall survival in this cohort. This provided evidence that MELD-XI not only correlates with MELD but is also a similar predictor of survival. Sub-analysis of patients who received continuous-flow devices alone also revealed that MELD-XI was significantly associated with on-VAD survival as well as overall survival.

We showed that MELD and MELD-XI scores correlated highly before VAD surgery; however, the correlation became weaker during VAD support. A partial explanation is that we enrolled patients with pulsatile and continuous flow VADs and that patients with continuous flow VADs were often treated with oral anti-coagulation, which resulted in increased INR that in turn affected the MELD score but not the MELD-XI score. Therefore, in the modern era with primary use of continuous-flow VADs, the use of the MELD-XI scoring system is more appropriate to assess liver dysfunction of patients during VAD support.

Creatinine represents a major determinant of the MELD-XI score. Indeed, creatinine levels were significantly different between those with high and low MELD-XI scores in our cohort. However, we found that MELD-XI was the only factor highly associated with survival on multivariable analysis; therefore, we speculate that the MELD-XI score is not simply serving as a surrogate for renal dysfunction in this setting. In addition, patients with high

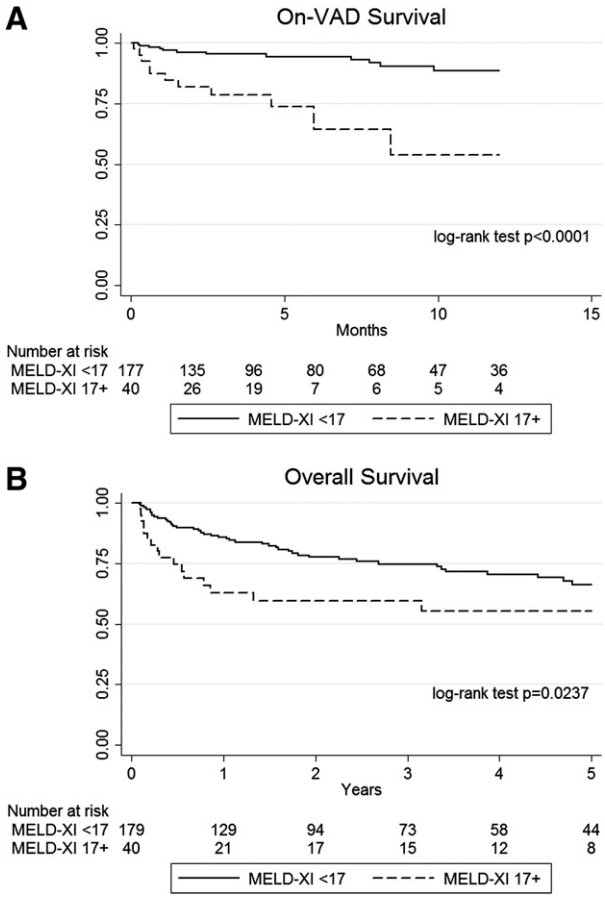

Figure 3 (A) One year on-ventricular assist device (VAD) survival and (B) overall survival are shown based on Model of End-stage Liver Disease eXcluding INR (MELD-XI) score <17 or ≥ 17 at 30 days after left VAD implant. This comparison involved only patients who received LVAD support for at least 30 days, omitting patients who died or underwent OHT before 30 days. Time point zero reflects post-operative Day 30.

MELD scores were possibly in more advanced HF, considering their decreased baseline sodium concentrations, which might have contributed to their higher mortality. Nevertheless, no differences in RV failure were found among the various groups.

MELD and MELD-XI both improved during LVAD support in our study group, suggesting that LV support helped to reverse cardiac hepatopathy when present in our cohort. However, the improvement in MELD-XI was more clinically and statistically significant than that in MELD, largely due to increased INR in patients taking oral anticoagulation while on HMII support and the effect this had on their on-VAD MELD scores. We therefore monitored MELD-XI scores as a more accurate measure of liver dysfunction in patients on VAD support. The mean MELD-XI dropped by nearly 2 points after only 30 days of VAD support and continued to decrease subsequently. In those who received an allograft, a pre-VAD MELD-XI ≥ 17 predicted worse post-OHT survival. However, post-OHT survival improved for those whose MELD-XI decreased $<$ 17 by the time of OHT. During the first 3 months after OHT, the survival of these High/Low MELD-XI patients was nearly identical to that of patients who had a MELD-XI $<$ 17 before VAD implantation. Long-term survival for the High/Low group was likewise similar to that of the Low/Low group. This contrasts with the post-OHT survival curves of the High/High patients, which was significantly worse than the Low/Low group.

These findings suggest that the MELD-XI score can help identify appropriate candidates for OHT. End-stage HF patients with evidence of hepatopathy are reasonable candidates for VAD implantation, especially given that liver function will improve in many of these patients while on VAD support. In fact, if liver function, as defined by MELD-XI, improves sufficiently on VAD support, our results suggest that post-OHT survival is generally similar to patients without liver dysfunction. Post-OHT survival is significantly decreased, however, if a patient's MELD-XI remains persistently elevated before and during VAD support. Thus, MELD-XI before and during VAD support should be considered when evaluating candidates for OHT. A high MELD-XI score after LVAD implantation alone is probably not sufficient to recommend elimination of these patients from the transplant list. However, our findings could be used as a tool for the review of the individual transplant candidacy of these patients after LVAD implantation based on the increased risk associated with OHT.

Ideally, we would have monitored hemodynamic data continuously in patients who had persistently high MELD-XI after LVAD; however, because of the risk for subsequent infection and other complications, we did not perform prolonged and

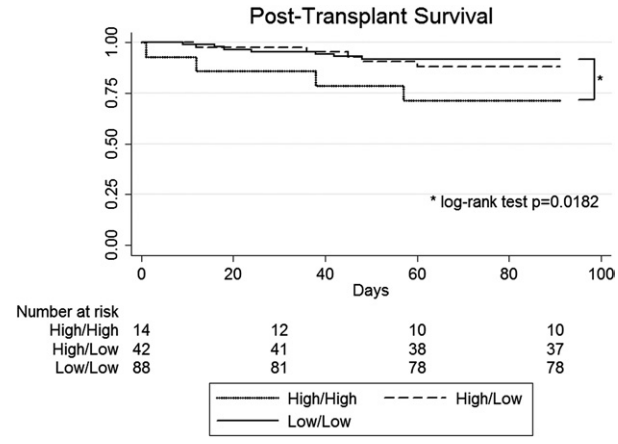

Figure 4 Post-transplant survival of patients based on dynamics in Model of End-stage Liver Disease eXcluding INR (MELD-XI) score during ventricular assist device (VAD) support. The Low/Low patients had a MELD-XI $<$ 17 before and during VAD support. The High/Low patients had a MELD-XI $\geq$ 17 before VAD support that improved to $<$ 17 with VAD support. The High/High patients had an elevated MELD-XI before and during VAD support. Short-term survival after transplant was nearly identical between Low/Low and High/Low groups but significantly worse for High/High patients (p = 0.0182). Longer-term post-transplant survival analysis demonstrated a similar pattern in survival among the 3 groups; however, the small numbers of patients at risk prevented robust comparisons among the 3 groups.

repeated pressure monitoring post-operatively in most patients. Therefore, we could not include more detailed post-operative hemodynamic data for these patients in the present study.

One additional novel finding relates to cholestasis in cardiac hepatopathy patients undergoing VAD implantation. Our results demonstrated a general improvement in most laboratory values, even after only 30 days of VAD support. However, alkaline phosphatase, total bilirubin, and direct bilirubin all increased initially before they decreased. This suggests that an LVAD may exacerbate the cholestatic picture of cardiac hepatopathy, likely when there is concomitant RV dysfunction. An LVAD would increase hepatic perfusion. However, with RV dysfunction, this increase in perfusion could actually worsen hepatic congestion, at least temporarily, and lead to an increase in cholestasis. This effect appears to dissipate over time, possibly due to the gradual improvement in RV function caused by improved LV unloading. Of note, a separate analysis that compared patients with pulsatile vs continuous-flow devices showed the trend of changes in alkaline phosphatase and bilirubin levels over time was similar to the overall population; however, the normalization of alkaline phosphatase levels at the late on-VAD stage was not significant in patients supported by continuous-flow VADs.

We speculate that blood cell injury with subsequent hemolysis and, potentially, differences in intrahepatic blood flow are specifically associated with hemodynamic support through continuous-flow VADs. Future studies focusing on this entity are necessary to elucidate the underlying pathophysiology and its specific impact on clinical outcomes.

Several limitations of this study exist and stem largely from its retrospective nature. Clinical decisions were made in a non-blinded, non-protocoled fashion, possibly instilling bias. Our patients received LVADs over a span of more than 10 years, during which time criteria for selecting patients for a long-term LVAD and for OHT have evolved. Technology has also changed over this time. These changes, in addition to individual clinician variation, add variability to our findings that are difficult to adjust for.

We also did not have complete data on all patients, requiring us to omit some patients. We could not obtain information on blood transfusions in all enrolled patients. Therefore, we could not evaluate the relationship between cholestasis and blood transfusions and possible hemolysis. We also lacked pre-operative and post-operative hemodynamic data in the present study.

Finally, we could not investigate the effect of MELD scores in patients who could not undergo OHT because a number of coexisting factors determined the inability to undergo OHT in these patients, including infection and subsequent neurologic adverse events. Therefore, we could not analyze the specific effect of MELD-XI, and liver dysfunction in general affected the decision to withhold OHT in these patients. However, we anticipate that these omissions were made randomly with no significant impact on our results.

In conclusion, MELD-XI is a valid measure of liver dysfunction that does not rely on INR values and is thus more accurate than standard MELD scores in patients on oral anti-coagulation. MELD and MELD-XI scores, dichotomized as < 17 or ≥ 17 before LVAD insertion, were both predictive of on-VAD, overall, and post-OHT survival. A worsening picture of cholestasis was seen shortly after LVAD insertion but improved over time. In VAD patients with an elevated pre-VAD MELD-XI who receive an OHT, a decrease in score during VAD support to < 17 improved post-OHT survival and can be used to help identify optimal transplant candidates.

Disclosure statement

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