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Predicting Survival in Patients Receiving Continuous Flow Left Ventricular Assist Devices

The HeartMate II Risk Score

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Objectives The aim of this study was to derive and validate a model to predict survival in candidates for HeartMate II (HMII) (Thoratec, Pleasanton, California) left ventricular assist device (LVAD) support.

Background LVAD mortality risk prediction is important for candidate selection and communicating expectations to patients and clinicians. With the evolution of LVAD support, prior risk prediction models have become less valid.

Methods Patients enrolled into the HMII bridge to transplantation and destination therapy trials (N = 1,122) were randomly divided into derivation (DC) (n = 583) and validation cohorts (VC) (n = 539). Pre-operative candidate predictors of 90-day mortality were examined in the DC with logistic regression, from which the HMII Risk Score (HMRS) was derived. The HMRS was then applied to the VC.

Results There were 149 (13%) deaths within 90 days. In the DC, mortality (n = 80) was higher in older patients (odds ratio [OR]: 1.3, 95% confidence interval [CI]: 1.1 to 1.7 per 10 years), those with greater hypoalbuminemia (OR: 0.49, 95% CI: 0.31 to 0.76 per mg/dl of albumin), renal dysfunction (OR: 2.1, 95% CI: 1.4 to 3.2 per mg/dl creatinine), coagulopathy (OR: 3.1, 95% CI: 1.7 to 5.8 per international normalized ratio unit), and in those receiving LVAD support at less experienced centers (OR: 2.2, 95% CI: 1.2 to 4.4 for <15 trial patients). Mortality in the DC low, medium, and high HMRS groups was 4%, 16%, and 29%, respectively ($p < 0.001$). In the VC, corresponding mortality was 8%, 11%, and 25%, respectively ($p < 0.001$). HMRS discrimination was good (area under the receiver-operating characteristic curve: 0.71, 95% CI: 0.66 to 0.75).

Conclusions The HMRS might be useful for mortality risk stratification in HMII candidates and may serve as an additional tool in the patient selection process. (J Am Coll Cardiol 2013;61:313–21) © 2013 by the American College of Cardiology Foundation

Left ventricular assist device (LVAD) support is increasingly being used for patients with refractory heart failure as either a bridge to transplantation (BTT) or destination therapy (DT). Through June 2012, over 4,000 LVAD implants have been reported to the U.S. INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) (1), and it is estimated that 30,000 to 100,000 individuals annually in the United States could potentially benefit from LVAD support. With so many patients potentially in need of a device that carries (simultaneously) associated medical and societal benefits and burdens, careful patient selection is paramount.

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In a young and evolving field such as mechanical circulatory support (MCS), risk modeling for the purposes of LVAD patient selection and patient and family education is in a constant state of revision. Increasing clinical experience,

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Abbreviations and Acronyms

AUC = area under the receiver-operating characteristic curve
BTT = bridge to transplant
DT = destination therapy
DTRS = destination therapy risk score
HMII = HeartMate II
HMRS = HeartMate II risk score
IABP = intra-aortic balloon pump
INR = international normalized ratio
LVAD = left ventricular assist device
MCS = mechanical circulatory support
MELD = model for end-stage liver disease
RA = right atrium/atrial

refinements in device technology, and information gleaned from studies on patient selection (2–4), as well as pre- and post-operative management strategies have led to improvements in patient survival from 52% at 1 year on pulsatile LVAD support (5) to >85% for BTT patients (6), and 73% for DT patients (7) supported with continuous flow LVAD technology. At present, the destination therapy risk score (DTRS) and INTERMACS profiles are the most widely used LVAD risk prediction tools (2). Derived in the pulsatile LVAD era, the DTRS was recently shown to provide poor discrimination for BTT patients and only modest discrimination for DT patients supported with continuous flow LVADs (8). However, the utility of both tools for assessing LVAD candidate risk in the contemporary LVAD era is in question, and a reassessment and revision of LVAD candidate risk prediction is warranted.

The primary objective of this analysis was to develop and validate a risk model for predicting LVAD candidate outcome in the "continuous flow era" of MCS. The second objective was to identify predictors of longer-term survival, independent of LVAD operative success.

Methods

Patient cohort. Patients enrolled between March 2005 and January 2010 into either the HeartMate II (HMII) (Thoratec, Pleasanton, California) BTT or DT clinical trials who received a HMII LVAD (N = 1,122) were selected for this study. Both HMII trials were prospective multicenter studies designed to assess the morbidity and mortality of subjects with end-stage heart failure undergoing implantable LVADs for long-term MCS. Details of the design, methods, and results of both the BTT (9,10) and DT trials (11) have been previously reported. Patients receiving the HMII for compassionate use or as an exchange for a previous HeartMate XVE were excluded. All patients provided written informed consent before study participation, and local institutional review board approval was provided by all enrolling centers.

Statistical analysis. DESCRIPTIVE STATISTICS. Data analysis was performed with SAS (version 9.2, Cary, North Carolina). Continuous data were evaluated for normality, and accordingly, between-group comparisons with Student *t* or Mann-Whitney testing were performed. Categorical data were compared with Fisher exact test.

DERIVATION AND VALIDATION OF THE HMII RISK SCORE. HMII patients enrolled into both trials were consolidated and then randomly divided into derivation (n = 583) and validation (n = 539) cohorts. The derivation cohort was used to develop a model for calculation of a patient-specific risk estimate, termed the HeartMate II Risk Score (HMRS), for predicting LVAD candidate 90-day mortality. Unadjusted predictors of mortality were identified from logistic regression comparisons of baseline clinical (patient demographic data, body mass index, heart failure etiology, pre-operative vasopressor and inotrope use), pre-operative laboratory (white blood count, hematocrit, platelet count, serum sodium, blood urea nitrogen, creatinine, total bilirubin, albumin, protein, alanine and aspartate aminotransferase, international normalization ratio [regardless of warfarin use]), and cardiopulmonary hemodynamic data (right atrial [RA] pressure, pulmonary artery pressures, cardiac index, pulmonary vascular resistance). Hemodynamic and laboratory measures were obtained ≤48 h before LVAD implant.

Clinically relevant risk correlates from prior LVAD risk modeling studies (age, sex, DT indication, pre-operative ventilator and/or intra-aortic balloon pump (IABP) support, pre-operative vasodilator, vasopressor and/or inotrope support, platelet count, total bilirubin, aspartate aminotransferase, blood urea nitrogen, serum creatinine, hematocrit, international normalized ratio [INR], albumin, mean pulmonary artery pressure, RA pressure, and right ventricular stroke work index, and implanting center LVAD study volume) (1–3,12,13) were then manually entered into stepwise multivariable logistic analysis (exit criteria $p \geq 0.05$). Correlated variables (e.g., RA pressure and right ventricular stroke work index) were not entered simultaneously, and only 8 to 10 variables were entered at one time to avoid model "overfitting." Center volume was defined as the volume of LVADs implanted by the center of study during the entire HeartMate BTT or DT study period. To determine center volume thresholds, patients were first dichotomized at the 10th, 15th, 20th, and 25th percentiles on the basis of the total volume of HMIIs implanted at the study center. The dichotomization threshold was selected as the smallest percentile value for center volume at which statistically significant differences in survival were observed. This was also the center volume demonstrated to be of importance by Lietz et al. (13). Model discrimination and calibration was evaluated with the area under the receiver-operating characteristic curve (AUC) and Hosmer-Lemeshow goodness of fit tests, respectively.

The continuous HMRS was first dichotomized into deciles of risk in order to derive the low, medium, and high HRMS categories. The deciles were then examined and consolidated into 3 risk categories (low [<10% mortality], medium [10% to 20% mortality], and high risk [>20% mortality]) offering clinically relevant risk estimates of 90-day mortality with good discrimination. LVAD survival on the basis of HMRS category was assessed in the derivation and validation cohorts by evaluating the proportion of patients alive at 90 days post-LVAD implant

(censoring for transplant or device explant for ventricular recovery). Survival differences between the 3 groups were compared with the Pearson chi-square test. When significant differences between groups were observed, post hoc comparisons were performed with the Fisher exact test. To avoid bias in model development, the validation cohort was only analyzed after the risk model was derived.

COMPARISON OF HMRS WITH DTRS AND MODEL FOR END-STAGE LIVER DISEASE. The HMRS was compared with pre-operative DTRS (8) and the United Network for Organ Sharing–modified model for end-stage liver disease (MELD) scores that has recently been shown to be predictive of survival in LVAD patients (3). Receiver-operating characteristic curves for predicting 90-day survival on the basis of HMRS, DTRS, and MELD were generated for the total study cohort. The AUCs were calculated and compared between HMRS and DTRS as well as HMRS and MELD with the methodology described by DeLong et al. in SAS (14).

Predictors of long-term survival. Long-term survival on the basis of HMRS category was estimated with Kaplan-Meier methods, and survival was compared with log-rank testing. Cox proportional hazards modeling was then used to identify correlates of long-term survival in patients who survived the initial 90-day post-operative period.

Results

Characteristics of the derivation and validation cohorts. The derivation and validation cohorts were similar with regard to baseline demographic data, pre-operative hemodynamic status, laboratory values, and medication use (Table 1). Median LVAD support durations were 347 and 332 days in the derivation cohort and validation cohort, respectively ($p = 0.84$), and Kaplan-Meier survivals were similar ($p = 0.84$) (Fig. 1).

Correlates of mortality after LVAD implant. There were 80 deaths (14%) in the derivation cohort (n = 583) during the 90-day post-operative period. Expired patients tended to be older, had greater degrees of hypoalbuminemia, coagulopathy (higher INR), and poorer renal function (higher creatinine) (see Table 2; complete listing available in the Online Table). Pre-operative warfarin was used in only 39 patients and was not correlated with survival, suggesting that a higher INR was a risk factor for mortality irrespective

Table 1 Baseline Characteristics of Patients Randomized Into the Derivation and Validation Cohorts

	Derivation Cohort (n = 583)	Validation Cohort (n = 539)	p Value
Demographic data			
Age, yrs	58.9 ± 13.3	58.2 ± 14.2	0.57
Female	133 (23%)	117 (22%)	0.67
Ischemic etiology	315 (54%)	283 (53%)	0.61
NYHA functional class			0.12
IIIb	158 (27%)	124 (23%)	
IV	425 (73%)	415 (77%)	
Length of support, days*	347 (111–656)	332 (117–727)	0.84
Concomitant procedure	235 (40%)	228 (42%)	0.51
Bypass time, min	107 ± 63	109 ± 58	0.25
Caucasian race	433 (74%)	391 (73%)	0.54
LVAD indication			0.28
Destination therapy	338 (58%)	295 (55%)	
Bridge to transplant	245 (42%)	244 (45%)	
Implant after May 5, 2007	331 (57%)	309 (57%)	0.86
Center volume ≥15	508 (87%)	485 (90%)	0.16
Laboratory values			
Sodium, mg/dl	134.3 ± 4.7	134.4 ± 4.7	0.88
Creatinine, mg/dl	1.47 ± 0.55	1.46 ± 0.54	0.89
Aspartate aminotransferase, IU/l	54 ± 137	64 ± 190	0.97
Total bilirubin, mg/dl	1.22 ± 0.80	1.24 ± 0.90	0.60
Hematocrit, %	34.8 ± 5.6	34.9 ± 5.6	0.45
Albumin, g/dl	3.44 ± 0.58	3.52 ± 1.21	0.14
Platelets, K/m^3	212 ± 87	221 ± 86	0.02
INR	1.31 ± 0.33	1.36 ± 0.60	0.82
Medications			
Intravenous inotrope	495 (85%)	426 (79%)	0.01
Intravenous vasodilator	155 (27%)	157 (29%)	0.35

Values are n (%), mean ± SD, or median (25th–75th percentile).

CI = confidence interval; HR = hazard ratio; INR = international normalized ratio; LVAD = left ventricular assist device; NYHA = New York Heart Association functional class.

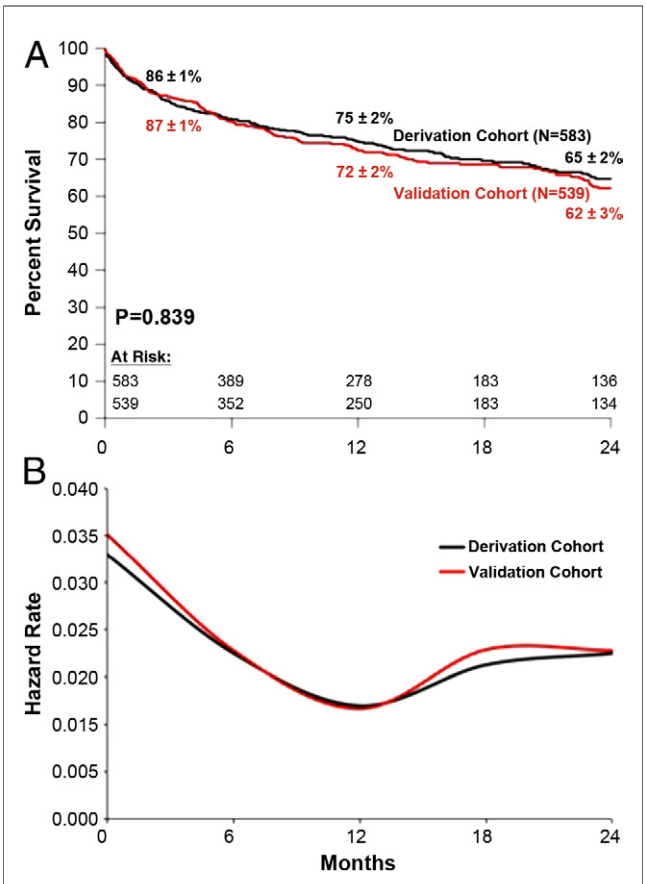

Figure 1 **Survival and Hazard Rate for the Derivation and Validation Cohorts**

A comparison of Kaplan-Meier survival **(A)** and hazard rates **(B)** for the two HeartMate II (Thoratec, Pleasanton, California) cohorts is shown.

of warfarin use. Center volume was significantly related to 90-day survival. Centers that had implanted 15 or more HMIIs during the trial periods (89% of centers) had significantly better outcomes than centers that implanted <15 patients over the course of the trial.

On multivariable analysis, age, serum creatinine, albumin, INR, and LVAD implanting center volume correlated with overall survival during LVAD support (Table 3). Pre-operative IABP and ventilator support and vasoactive medication requirements were not associated with worse outcome. LVAD indication (BTT vs. DT) was also not predictive of outcome in the multivariable model (see footnote of Table 3 for covariates entered into the model).

The HMRS and post-operative outcomes in derivation cohort. With logistic regression estimates for 90-day survival, a patient pre-operative HMRS was derived as shown in Table 3. The median (25th to 75th percentile) HMRS for the derivation cohort was 1.75 (1.18 to 2.36). Survivors had lower HMRS scores (1.68 [1.13 to 2.19]) than patients who died (2.37 [1.95 to 3.09], $p < 0.001$). The HMRS AUC (95% confidence interval [CI]) was 0.77 (95% CI: 0.72 to 0.82), and the Hosmer-Lemeshow goodness of fit test chi-square was 9.97 ($p = 0.27$), suggesting good discrimination and calibration, respectively.

The HMRS score cutoffs for the 3 risk groups were: low risk (HRMS <1.58), medium risk (1.58 ≤HMRS ≤2.48), and high risk (HMRS >2.48). Ninety-day mortality in these 3 groups was 4%, 16%, and 29%, respectively ($p < 0.001$) (Fig. 2). Pair-wise comparisons showed that both the high- and medium-risk groups had significantly worse outcome than the low-risk group ($p < 0.001$).

Validation of the HMRS. The median (25th to 75th percentile) HMRS in the validation cohort was 1.71 (1.10 to 2.31) and was similar to that of the derivation cohort ($p = 0.27$). Like the derivation cohort, survivors in the validation cohort had significantly lower HMRS than deaths (HMRS: 1.66 [25th, 75th percentile: 1.05 to 2.25] vs. HMRS: 2.11 [1.47 to 2.74], $p < 0.001$). The 90-day mortality for the low-, medium-, and high-risk HMRS groups was 8%, 11%, and 25%, respectively ($p < 0.001$) (Fig. 2). Patients in the validation cohort high-risk HRMS group also had significantly worse outcome than both low- ($p < 0.001$) and medium-risk ($p = 0.002$) groups. However, comparison of outcome for patients within the low- versus medium-risk group did not reach statistical significance ($p = 0.25$). The Hosmer-Lemeshow chi-square in the validation cohort was 1.04 ($p = 0.31$).

HMRS versus DTRS and MELD and by device indication. Receiver-operating characteristic curves representing the ability of the HMRS, DTRS, and MELD scores to predict 90-day mortality in the total HMII sample (derivation + validation) are shown in Figure 3. Table 4 lists the model AUCs in various patient samples (the total cohort, the derivation/validation cohorts, and the BTT/DT cohorts). The HMRS provided significantly higher risk discrimination than the DTRS when evaluated in the total HMII sample ($p < 0.001$). When evaluated by device intent (BTT vs. DT), the HMRS was also more discriminative than the DTRS ($p < 0.05$). The HMRS had a numerically higher AUC than the MELD, but statistically significant differences were only noted in the derivation cohort and the entire HMII sample.

Long-term survival after LVAD implant. Figure 4 shows the Kaplan-Meier survival curves for the total HMII sample stratified by HMRS categories. Survivals at 1 year in the low-, medium-, and high-risk groups were 83 ± 2%, 72 ± 2%, and 58 ± 3%, respectively ($p < 0.001$) (Table 5). Pair-wise comparisons revealed that there were significant differences between the low- versus medium- ($p < 0.001$), low- versus high- ($p < 0.001$), and medium- versus high-risk ($p < 0.001$) groups, suggesting that the HMRS also provides discrimination of risk several months after LVAD implant. As shown in Figure 5, HMRS risk discrimination is maintained regardless of initial device indication (i.e., BTT or DT).

Conditional survival. When conditioned on surviving 90 days postoperative, the only statistically significant pre-operative predictors of long-term mortality in the derivation

Table 2 Univariable Correlates of 90-Day Mortality in the Derivation Cohort

	Alive (n = 503)	Dead (n = 80)	p Value*	OR (95% CI)
Demographic data				
Age, yrs	58.1 ± 13.7	63.6 ± 9.6	<0.001	1.45 (1.17–1.80)/10 yrs
Female	122 (92%)	11 (8%)	0.041	0.50 (0.26–0.97)
Male	381 (85%)	69 (15%)		
Ischemic cardiomyopathy	261 (83%)	54 (17%)	0.010	1.93 (1.17–3.17)
Nonischemic cardiomyopathy	242 (90%)	26 (10%)		
Preoperative ventilator support	23 (85%)	4 (15%)	0.87	
No ventilator support	480 (86%)	76 (14%)		
Preoperative IABP	154 (87%)	23 (15%)	0.73	
No IABP	349 (86%)	57 (14%)		
Race				
Caucasian (vs. rest)	366 (84%)	67 (16%)	0.040	1.93 (1.2–2.5)
Black (vs. rest)	96 (90%)	11 (10%)	0.26	
Other (vs. rest)	41 (95%)	2 (5%)	0.091	0.29 (0.07–1.22)
LVAD indication				
Destination therapy	283 (84%)	55 (16%)	0.037	1.71 (1.03–2.83)
Bridge to transplant	220 (90%)	25 (10%)		
Implant era				
After May 5, 2007	285 (86%)	46 (14%)	0.89	
Before May 5, 2007	218 (87%)	34 (13%)		
Center volume, n				
<15	59 (79%)	16 (21%)	0.043	1.88 (1.02–3.47)
≥15	444 (87%)	64 (13%)		
Hemodynamic status				
Right atrial pressure, mm Hg	12.2 ± 6.3	14.9 ± 7.3	0.001	1.06 (1.03–1.10)
PA systolic, mm Hg	51.7 ± 13.8	53.6 ± 13.2	0.26	
Wedge pressure, mm Hg	24.3 ± 8.5	25.9 ± 8.1	0.16	
Cardiac index, l/min/m^2	2.01 ± 0.60	2.15 ± 0.63	0.066	1.43 (0.98–2.08)
RVSWi, mm Hg ml/m^2	544 ± 282	527 ± 299	0.64	
Laboratory values				
Sodium, mg/dl	134 ± 5	134 ± 5	0.60	
Creatinine, mg/dl	1.44 ± 0.54	1.70 ± 0.56	<0.001	2.20 (1.48–3.27)
Blood urea nitrogen, mg/dl	27 (19–40)	34 (23–47)	0.024	1.01 (1.00–1.02)
Aspartate aminotransferase, IU/l	30 (23–44)	28 (22–39)	0.13	
Total bilirubin, mg/dl	1.2 ± 0.8	1.3 ± 0.7	0.58	
Albumin, g/dl	3.47 ± 0.58	3.23 ± 0.56	0.001	0.49 (0.32–0.75)
Hematocrit, %	35.0 ± 5.6	33.0 ± 5.0	0.003	0.93 (0.89–0.98)
Platelets, K/mm^3	214 ± 88	199 ± 79	0.160	
INR	1.29 ± 0.31	1.46 ± 0.41	<0.001	3.36 (1.84–6.14)
Intravenous medications				
Inotropes	424 (86%)	71 (14%)	0.30	
No inotropes	79 (90%)	9 (10%)		
Vasodilator	134 (86%)	21 (14%)	0.94	
No vasodilator	369 (86%)	59 (14%)		
Vasopressor	22 (81%)	5 (19%)	0.46	
No vasopressor	481 (87%)	75 (13%)		

Values are mean ± SD, n (%), or median (25th–75th percentile). *For comparison of alive versus dead at 90 days.
CI = confidence interval; INR = international normalized ratio; IABP = intra-aortic balloon pump; LVAD = left ventricular assist device; OR = odds ratio; PA = pulmonary artery; RVSWi = right ventricular stroke work index.

cohort were patient age (hazard ratio: 1.3 [95% CI: 1.1 to 1.5]/10 years, p = 0.003) and center implant volume <15 (hazard ratio: 1.6 [95% CI: 1.0 to 2.6]). Upon adjustment for age and center volume, mortality in BTT versus DT patients who survived the 90-day post-operative period was similar (hazard ratio: 1.1 [95% CI: 0.7 to 1.7] p = 0.74). Likewise, when the entire HMII sample was analyzed, conditional survival was similar in BTT and DT patients (Fig. 6).

Discussion

In this study, we developed and prospectively validated the first model for assessing patient risk in the era of continuous

Table 3 Multivariable Predictors of 90-Day Mortality in Derivation Cohort and Formula for Calculating HMRS

Parameter	Estimate	SE	OR (95% CI)	p Value
Age (per 10 yrs)	0.274	0.12	1.32 (1.05–1.65)	0.018
Albumin (per g/dl)	−0.723	0.23	0.49 (0.31–0.76)	0.002
Creatinine (per mg/dl)	0.740	0.22	2.10 (1.37–3.21)	<0.001
INR (per unit)	1.136	0.32	3.11 (1.66–5.84)	<0.001
Center volume <15	0.807	0.34	2.24 (1.15–4.37)	0.018

Multivariable predictors ($p < 0.05$) of 90-day mortality in the derivation cohort and the formula for calculating the HeartMate II Risk Score (HMRS). Calculation of HMRS: HMRS = (0.0274 × [age in years]) − (0.723 × [albumin g/dl]) + (0.74 × [creatinine mg/dl]) + (1.136 × [INR]) + (0.807 × [center LVAD volume <15*]). *Enter value of 1 if total center LVAD volume is <15 and 0 if ≥15. Other variables entered into multivariable analysis (all $p > 0.05$ in final model): sex, LVAD indication, pre-operative inotrope, vasopressor and/or vasodilator use, pre-operative ventilator support and/or IABP support, RVSWi, hematocrit, platelets, aspartate aminotransferase, total bilirubin, and implant era. Model fit was inferior when blood urea nitrogen was entered in place of creatinine into the aforementioned model. Likewise, entering right atrial pressure and/or mean pulmonary artery pressure in place of RVSWi did not improve modeling.

Abbreviations as in Tables 1 and 2.

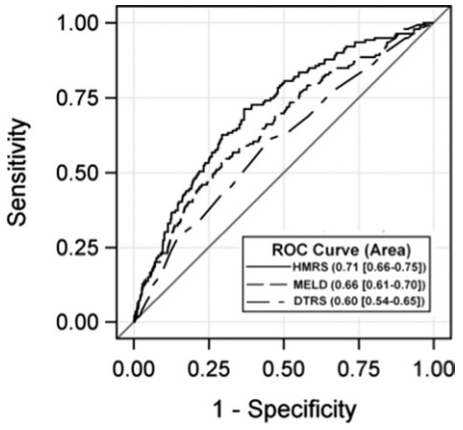

Figure 3 ROC Curves for Predicting 90-Day Mortality

Receiver-operating characteristics (ROC) curves for predicting 90-day mortality in the entire HeartMate II patient sample using the HeartMate II Risk Score (HMRS), model for end-stage liver disease (MELD), and destination therapy risk score (DTRS) are displayed. Area [95% confidence interval] is shown. The ROC p values: HMRS versus MELD, $p = 0.022$; and HMRS versus DTRS, $p < 0.001$.

flow LVAD support using a large multicenter clinical trial dataset. The HMRS components—age, serum albumin, creatinine, INR, and implant center LVAD experience—highlight important pre-operative determinants of survival after LVAD implantation in patients for whom LVAD support is being considered. Benefits of the HMRS include its ease of calculation (4 variables) with relatively noninvasive, routinely obtained, and reproducible clinical data points. Furthermore, because device indication (i.e., BTT vs. DT) is often difficult to predict in the pre-operative period, the HMRS allows risk prediction in undifferentiated LVAD candidates.

Benefits of a new LVAD risk model. Current models for predicting LVAD candidate survival after surgery were largely derived from patients implanted with older-generation pulsatile devices (2,4,12). At present, the DTRS is the most commonly applied LVAD risk prediction tool (2). The DTRS was derived from patients in the HeartMate XVE post-REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) experience (2) and was originally intended to estimate patient risk for 90-day in-hospital mortality after LVAD implant. The DTRS is limited by its complexity (9 variables with a requirement for pulmonary catheter measurement), the categorization of continuous variables,

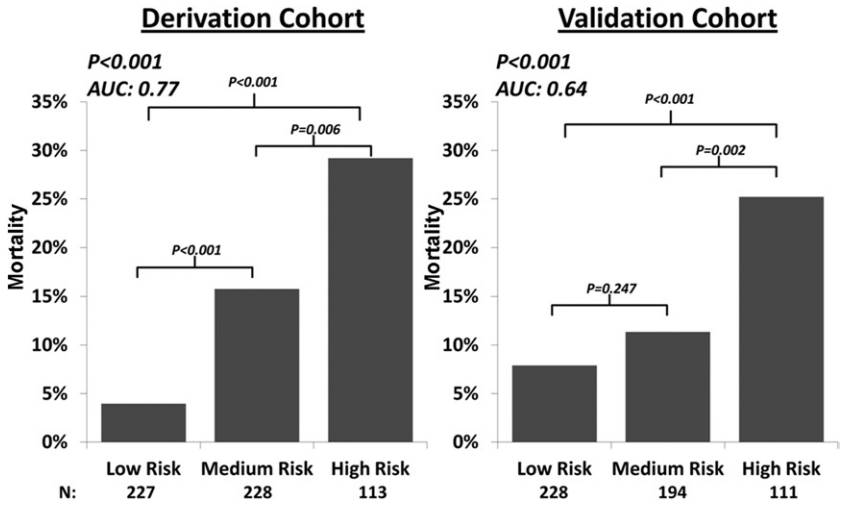

Figure 2 90-Day Mortality on the Basis of HMRS

Ninety-day mortalities for the validation and derivation cohorts are shown, stratified by HeartMate II Risk Score (HMRS) group.
AUC = area under receiver-operating characteristic curve.

Table 4 Comparisons of AUCs Between Different Risk Models Used to Predict 90-Day Mortality

	AUC (95% CI)				
	All Patients (N = 1,122)	Derivation Cohort (n = 583)	Validation Cohort (n = 539)	BTT Cohort (n = 489)	DT Cohort (n = 633)
HMRS	0.71 (0.66–0.75)	0.77 (0.72–0.82)	0.64 (0.56–0.71)	0.71 (0.63–0.80)	0.68 (0.63–0.74)
MELD	0.66 (0.61–0.70)*	0.70 (0.64–0.76)*	0.61 (0.53–0.71)	0.67 (0.59–0.76)	0.64 (0.58–0.70)
DTRS	0.60 (0.54–0.65)†	0.60 (0.53–0.67)†	0.59 (0.51–0.67)	0.56 (0.47–0.65)†	0.61 (0.55–0.67)*
DTRS‡	0.57 (0.52–0.63)	—	—	0.54 (0.45–0.64)	0.58 (0.52–0.57)

*$p < 0.05$; †$p < 0.001$ compared with HMRS; ‡area under the receiver-operating curve (AUC) reported in the paper by Teuteberg et al. (8) for predicting 90-day in-hospital mortality.
BTT = bridge to transplant; CI = confidence interval; DT = destination therapy; DTRS = destination therapy risk score; HMRS = HeartMate II risk score; MELD = model for end-stage liver disease.

and derivation from a patient cohort supported with a now-antiquated pump that was associated with a significantly higher morbidity and mortality than that of continuous flow technology. Furthermore, the DTRS excluded BTT candidates in model development and did not include validation with multicenter data. When the DTRS was applied to the HMII BTT and DT clinical trial data by Teuteberg et al. (8), the DTRS was poorly discriminative of in-hospital 90-day survival (AUC = 0.59). A single-center analysis by Schaffer et al. (15) also identified similar deficiencies in the DTRS for predicting outcome in candidates for continuous flow LVAD support. By contrast, we have shown that the HMRS offers improved risk discrimination compared with the DTRS, regardless of device indication (DT or BTT).

The INTERMACS levels have been shown to provide useful categorization of patient risk solely on the basis of subjective descriptions of clinical status (16,17). Boyle et al. (16) in a 3-center study demonstrated that patients presenting with INTERMACS Level 1 and Levels 2 to 3 had survival rates of 51% and 69% at 36 months post-LVAD, respectively, compared with 95% in Profiles 4 to 7. Although INTERMACS Level 1 (cardiogenic shock) used to comprise 44% of LVAD implants (18), findings of poor outcomes in these patients along with an improvement in MCS technology have led to a shift to slightly earlier implantation strategies, such that INTERMACS Level 1 now only comprises 14% of patient profiles at implant (1). Levels 4 to 7 are highly subjective in assignment, are not assigned with concrete patient-level data, and have never been shown to demonstrate graded mortality risk. The INTERMACS profiles were not included in the HMII clinical trials herein and could not be included in this analysis. However, the objective nature of the HMRS might offer risk stratification within and across INTERMACS profiles. In this analysis, we included important correlates of INTERMACS Level 1 status, including pre-operative vasopressor, inotrope, IABP, and ventilator use. That these data did not contribute additional information to the HMRS suggests that preserved end-organ function, however preoperatively achieved, might be the most important predictor of successful LVAD outcome. The HMRS will also take into account the added independent risk of mortality in the elderly that is not captured in INTERMACS.

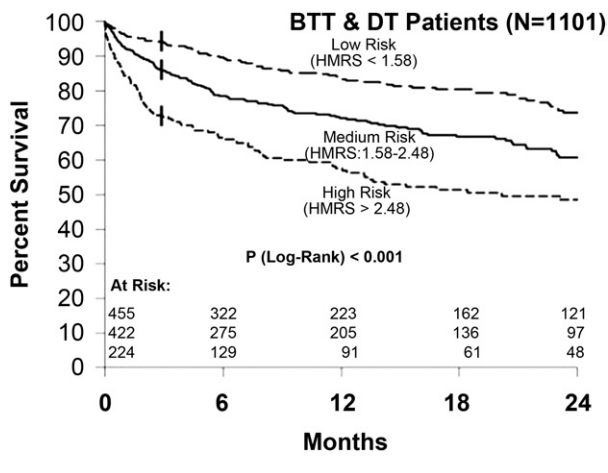

Figure 4 Kaplan-Meier Survival Stratified by HMRS Group

Survival for the entire HeartMate II patient sample is shown on the basis of HeartMate II Risk Score (HMRS) group. The **vertical lines** on the curves correspond to the 90-day time-point at which the risk model was derived. BTT = bridge to transplant; DT = destination therapy.

Finally, MELD scores have also been shown to be predictive of mortality in LVAD candidates, and this model performed quite well in this analysis for predicting mortality in HMII patients (3,19). Although the HMRS and MELD comprise similar variables, the coefficients used for MELD score calculation were derived from patients with multifactorial liver disease and no documented cardiac dysfunction. By contrast, HMRS is derived solely from patients with advanced heart failure and takes into account the impact of age and center experience on surgical outcome. By receiver-operating characteristic curve analysis, the HMRS provided a better discrimination of outcomes compared with MELD or DTRS.

Uses for the HMRS. In a field with a potential for high patient morbidity and mortality, high resource use in "non-thrivers," and a large pool of medically diverse candidates, careful patient selection is critical. The HMRS is not meant to supplant or supersede clinical judgment, nor does it provide recommendation whether or not to proceed with LVAD implant. However, the HMRS can provide additional knowledge of patient risk to help in education and communication with referring cardiologists, patients, fami-

Table 5 Survival on the Basis of HMRS in the Total H MII Sample and in the Derivation and Validation Cohorts After LVAD Implant

	HMRS Threshold	HMRS	90-Day Survival	1-Yr Survival	2-Yr Survival
Derivation cohort (n = 583)					
Overall	—	1.75 (1.18–2.36)	86 ± 1%	75 ± 2%	65 ± 2%
Low risk	<1.58	1.05 (0.75–1.31)	96 ± 1%	87 ± 3%	78 ± 4%
Medium risk	1.58–2.48	1.99 (1.75–2.19)	84 ± 2%	71 ± 3%	59 ± 4%
High risk	>2.48	3.05 (2.75–3.44)	71 ± 4%	59 ± 5%	50 ± 5%
Validation cohort (n = 539)					
Overall	—	1.71 (1.10–2.31)	87 ± 1%	72 ± 2%	62 ± 3%
Low risk	<1.58	1.00 (0.60–1.33)	92 ± 2%	80 ± 3%	69 ± 4%
Medium risk	1.58–2.48	1.94 (1.74–2.20)	88 ± 2%	73 ± 3%	63 ± 4%
High risk	>2.48	2.95 (2.70–3.28)	74 ± 4%	56 ± 5%	47 ± 5%
Total sample (N = 1,122)					
Overall	—	1.73 (1.15–2.34)	86 ± 1%	74 ± 1%	63 ± 2%
Low risk	<1.58	1.03 (0.68–1.32)	94 ± 1%	83 ± 2%	74 ± 3%
Medium risk	1.58–2.48	1.96 (1.74–2.19)	86 ± 2%	72 ± 2%	61 ± 3%
High risk	>2.48	3.01 (2.70–3.35)	73 ± 3%	58 ± 3%	49 ± 4%

Values are median (25th–75th percentile) or mean ± SD.
HMII = HeartMate II; HMRS = HeartMate II risk score; LVAD = left ventricular assist device.

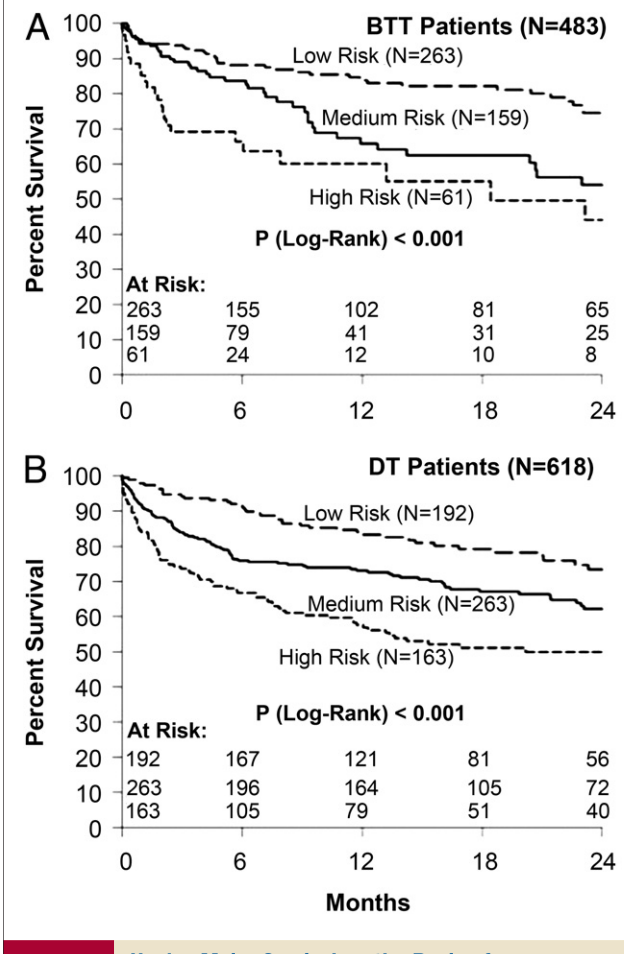

Figure 5 Kaplan-Meier Survival on the Basis of Device Indication Stratified by HMRS Group

Survival of patients on the basis of HMRS grouping is shown for BTT **(A)** and DT **(B)** patients in the total HeartMate II sample. Abbreviations as in Figure 4.

lies, and the clinical LVAD team. The HMRS might highlight important goals for pre-operative optimization and identify a period of optimal patient "fitness" for surgery. All HMRS variables except for age are potentially modifiable. Targeted reduction in patient operative risk through use of pre-operative percutaneous mechanical support technologies; inotropes; and/or diuresis to amend renal (serum creatinine), hepatic/right ventricular dysfunction (INR), and inflammatory/nutritional states (albumin) might afford better outcomes. Users of the HRMS should take into account that INR values used in this study were largely measured in absence of warfarin use.

LVAD risk modeling is also an important tool for the principle of "patient-centered" care. Patient-centered care

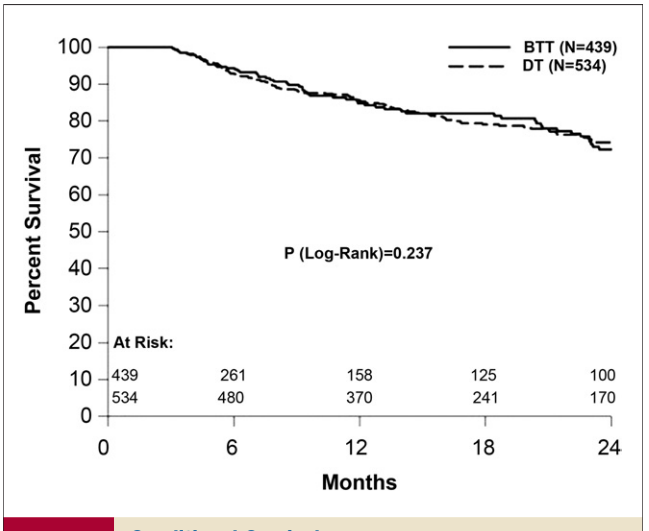

Figure 6 Conditional Survival on the Basis of Device Indication

Kaplan-Meier survival curves for those patients surviving 90 days post-operative are shown for bridge to transplant (BTT) and destination therapy (DT) indications.

requires the process of shared decision making between the patient and the clinician (20). Studies have shown that patients want clinicians to openly discuss risks before surgery (20). Furthermore, patients tend to poorly predict their own survival. In a study of 122 individuals with chronic heart failure, 68% of patients over estimated their survival, and the magnitude of this overestimation was large (by 40%) (21). Presenting survival estimations with patient-level data provides LVAD candidates information beyond that of "average" published LVAD statistics. In elderly patients and those without a realistic option for transplant, such information might play even more critically into the shared decision-making process.

Study limitations. There are several limitations of this study that must be acknowledged. Even though a large cohort was studied for purposes of HMRS derivation with use of internal model validation, the clinical trial patient population herein is not representative of many non-trial patients. Thus, further validation of the HMRS in broader patient populations should be performed. The applicability of the HMRS to patients undergoing implant of other types of continuous flow devices is also not known.

Finally, a secondary aim of this analysis was to also develop a model for predicting long-term survival. Although the HMRS successfully risk stratified patient survivals beyond 12 months of LVAD support, only operative survival, age, and center experience were found to be predictive of long-term success on LVAD therapy. The study did not evaluate post-operative management and the advancement or development of comorbidities during on LVAD outcomes, which should be included in future analyses.

Conclusions

Risk factors for mortality after HMII continuous flow LVAD implant in the contemporary LVAD era were identified with a large patient cohort, and a new risk model (the HMRS) was prospectively developed and validated. The HMRS might be useful for patient, family, and referring provider education, providing patient-level LVAD mortality risk assessment regardless of BTT or DT indication. The HMRS also identifies important pre-operative risk factors that might serve as targets for goal-directed interventions meant to improve LVAD candidate survival.

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Key Words: heart failure ■ left ventricular assist device ■ mortality ■ risk.

APPENDIX

For a supplemental table, please see the online version of this article.