



Risk Prediction Model for Survival of Wait-List Patients on Axial CF-LVAD: A UNOS Database Analysis

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ABSTRACT

Background. Continuous flow left ventricular assist devices (CF-LVADs) have become a viable option for patients with end-stage heart failure as a bridge to transplantation or the destination therapy.

Methods. Adult patients listed for heart transplantation (2010-2015) with an axial CF-LVAD on the wait list were obtained from the UNOS database. The multivariate Cox regression model was used to predict the probability of survival after listing. Patients were divided into derivation (80%) and validation (20%) groups. Receiver operating characteristics curves and area under curves were used to define the strength of the model.

Results. Risk factors on multivariate analyses were diabetes type I (hazard ratio [HR], 2.5; $P = .018$), presence of inotropes (HR, 1.6; $P = .005$), creatinine at listing (HR, 1.2; $P < .001$). No significant differences were observed between the derivation and validation groups for any of the variables. The area under the curve at 3, 6, and 12 months on the wait list was 0.69, 0.65, 0.63, respectively in the training set and 0.71, 0.65, 0.60, respectively in the validation set. Survival analyses showed that patients implanted with Heartmate II before listing had a better survival than those who were implanted after being on the wait list (HR, 0.78; $P = .048$).

Conclusion. To our knowledge, this was the first time a risk prediction model was generated for wait-list survival of Heartmate II patients. A significant difference in survival was noted between patients who received their Heartmate II before being put on a wait list vs those who were implanted while on the list.

ALTHOUGH heart transplantation has been generally acknowledged as the best long-term solution for advanced heart failure, many patients are not able to receive the treatment because of a shortage of donor hearts or because of their comorbidities [1,2]. Axial continuous flow left ventricular assist device (CF-LVAD) has been a viable option for patients with end-stage heart failure as a bridge to transplantation or the destination therapy, with a 1-year survival rate of 80% and a 2-year survival of 70% [3]. Despite the initial expectation of long-term support at 2 years for the LVAD, there are many patients remaining on the support for longer periods because of the extended wait time for donor hearts and improved post-implant survival of LVAD.

Studies in the existing literature have been done to investigate post-implant survival of LVAD therapy [3–5], but the

effects of risk factors on patients with CF-LVADs on waitlist survival and post-transplant survival has not been clearly defined. A recent study on heart transplant waiting list survival reported an increase for all patient groups (with or without ventricular assist devices) between 1996-2000 and 2011-2017 and indicated several significant risk factors associated with waiting list mortality between 1996 and 2017 [6]. Additionally, an earlier study investigated the effect of CF-LVAD as bridge to transplant (BTT) on the survival of heart transplant recipients

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listed between 2005 and 2012. Their study showed an improved waiting list survival for patients supported with an Heartmate II (HMII) LVAD as BTT compared with those who were not on LVAD support [7].

The aim of this study was to build a risk prediction model using data from the UNOS database on patients supported on CF-LVADs while waiting for a donor heart between 2010 and 2015. Patient demographics, status, and clinical data at listing and their associations to wait-list survival were assessed to generate a risk prediction model.

MATERIALS AND METHODS

Data on adult patients (aged ≥ 18 years) who were listed for heart transplantation between 2010 and 2015 and had an axial CF-LVAD (HMII) while on the waiting list were extracted from the UNOS registry of thoracic organ transplantation database. Patients listed for and who received multiorgan transplantation were excluded. Patients with $>50\%$ of the variables with missing values were excluded. The study cohort included 3344 patients, among which 3100 survived to heart transplantation.

Baseline patient characteristics, including age, race, height, weight, blood type, cigarette use, payment type, education, region of registration, and work for income, were assessed for their associations to the survival of wait-list patients on HMII. Additionally, measurements collected at listing were also assessed in the analysis, which included patient's medical records such as diabetes and malignancy, patient's functional status and initial status at listing, intravenous (IV) inotropes at listing, most recent hemodynamics diastolic and systolic pulmonary artery (BP) blood pressure at listing, and creatinine at listing. Days between listing and removal from the waiting list were determined as the time to event data. Patients removed from the waiting list because of reasons other than death were considered as censored data.

Statistical analysis

Cox-proportional hazards model was developed to study the correlations of different risk factors with the waiting list survival of patients on HMII support. Univariate analysis was performed, and variables with $P < .05$ were selected as inputs to the multivariate analysis. Variables were assessed by stepwise forward selection to be included in the multivariate model. The multivariate model was used to predict the survival probability 3, 6, and 12 months after being listed. Receiver operating characteristics (ROC) curves were generated, and area under the curve (AUC) were calculated to assess the accuracy of the prediction model. From the multivariate model, a score is determined for each variable according to the hazard ratio to develop a risk scoring system. Kaplan–Meier survival curves were generated to show the survival for patients in different risk groups and for patients who had and did not have LVAD support. All the analysis was performed using MATLAB software (MathWorks, Inc., Natick, MA, USA). This study was exempt from TTUHSC institutional review board (IRB) review.

RESULTS

Data Characteristics

After excluding patient records that did not match the selection criterion, 3344 patients were extracted during the study period. Within the study population, 244 recipients (7%) died while on the waiting list, while 3100 (93%) survived to transplant. The

patients in the deceased group were more likely to have blood type O, lower level of functionality at listing, and to have status 2. Patients who received IV inotropes at listing had higher mortality rate. Additionally, patients in the deceased group had higher levels of diastolic and systolic pulmonary artery (PA) blood pressure, body mass index, and creatinine at listing. Table 1 shows patient characteristics studied.

Univariate Analysis and Predictive Modeling

The univariate Cox regression analysis revealed significant correlations between the waiting list survival of patients on HMII support and diabetes, patient's initial status, IV inotropes at listing, patient's height, and creatinine at listing (Table 2). Type I diabetes elevated the risk for mortality among HMII patients by 2.37 times compared with those who did not have diabetes. Patients who had inotropes at listing showed 1.54 times higher risk than patients who did not. Additionally, patients who were classified as status 1A at listing had a higher risk than the patients in status 1B. The analysis also indicated that patients who were registered in regions 5 (Arizona, California, Nevada, New Mexico, Utah), 6 (Alaska, Hawaii, Idaho, Montana, Oregon, Washington), and 7 (Illinois, Minnesota, North Dakota, South Dakota, Wisconsin) had lower risk compared with those registered in the rest of the regions; taller patients had a lower mortality risk. Furthermore, creatinine at listing had significant effects on waiting list survival, and one-unit increase in creatine led to 18% increase in the mortality risk.

The multivariate model demonstrated 4 significant risk factors: diabetes, inotropes at listing, height, and creatinine at listing. Consistent observations were found in the multivariate analysis, ie, type I diabetes, presence of inotropes, and high creatinine increased the mortality risk among patients on HMII with a hazard ratio of 2.52, 1.57, and 1.18, respectively (Table 3). The model provided an AUC of 0.69, 0.65, and 0.63 respectively on the derivation data set and an AUC of 0.71, 0.65, and 0.60, respectively, on the validation data for 3-, 6-, and 12-month prediction of waiting list survival among HMII patients (Fig 1). At different operating points, the positive (ie, survival) predictive value varies between 0.98~1, 0.97~1, and 0.95~1, respectively on the derivation data set and 0.98~1, 0.95~1, and 0.83~1, respectively on the validation data set for 3-, 6-, and 12-month prediction. The highest negative predictive value is 0.17, 0.17, and 0.31, respectively on the derivation data set and 0.06, 0.09, and 0.12 on the validation data set respectively for 3-, 6-, and 12-month prediction. The multivariate model has a high precision for predicting survival among HMII patients, but the proportion of predicted death that are true death is low. The prediction model is more conservative in predicting death and tends to classify some survived patients into the deceased group. This is likely caused by the data imbalance between the survived group and the deceased group, and the ratio of patients who survived and did not survive by 3, 6, and 12 months is 41:1, 28:1, and 18:1, respectively. From the multivariate model, we developed a scoring system to predict the

Table 1. Patient characteristics

Covariates	Total (N = 3344)	Dead (n = 244)	Alive (n = 3100)	P value for death vs alive
Age	53.7(12)*	54.3(11.6)*	53.7(12.1)*	0.573
Diastolic PA blood pressure at listing	20.7(8.97)*	21.9(8.34)*	20.6(9.01)*	0.007
Systolic PA blood pressure at listing	42.9(14.4)*	45.6(13.8)*	42.7(14.5)*	0.001
BMI at listing	37.4(5.31)*	37.1(5.52)*	37.4(5.30)*	0.200
Height at listing	176(9.54)*	175(9.54)*	176(9.54)*	0.446
Weight at listing	87.8(17.7)*	89.9(17.9)*	87.7(17.7)*	0.072
Creatinine at listing	1.27(0.68)*	1.5(1.15)*	1.25(0.62)*	<0.001
Blood type				
A	37.1	28.7	37.8	0.005
AB	3.92	2.46	4.03	0.223
B	13.3	11.5	13.4	0.389
O	45.7	57.4	44.7	<0.001
Cigarette				
Yes	54.5	52.9	54.7	0.585
Diabetes				
No	66.7	64.3	66.9	0.420
Type I	1.85	2.87	1.77	0.222
Type II	31.5	32.8	31.4	0.643
Education				
Grade school (0-8)	2.96	2.87	2.97	0.930
High school (9-12) or GED	39.8	36.5	40.1	0.270
College/Technical school	26.2	25.0	26.3	0.659
Associate/Bachelor's degree	16.8	18.4	16.6	0.469
Post-college graduate degree	6.40	4.92	6.52	0.326
Other	7.86	12.3	7.52	0.008
Race				
White	65.5	64.8	65.5	0.802
Black	24.6	27	24.4	0.346
Hispanic	6.25	5.74	6.29	0.731
Other	3.71	2.46	3.81	0.284
Implantable defibrillator				
Yes	82	84	81.8	0.387
Functional status at listing, %				
20†	15.6	21.7	15.1	0.006
70†	17.3	20.1	17.1	0.235
90†	6.34	3.28	6.58	0.042
Other	2.23	1.90	2.25	0.421
Patient status at listing				
1A	29.1	23.8	29.5	0.056
1B	54.5	49.6	54.9	0.109
2	12.4	20.5	11.7	<0.001
Temporarily inactive	3.98	6.15	3.81	0.072
Intravenous inotropes at listing				
Yes	19.1	31.6	18.2	<0.001
Malignancy at listing				
Yes	7.06	5.33	7.19	0.273
Payment type				
Private insurance	47.4	49.6	47.2	0.470
Medicaid	12.8	12.3	12.9	0.796
Medicare Fee for Service	22.9	24.2	22.8	0.623
Medicare & Choice	12.5	10.2	12.6	0.275
Department of VA	2.33	2.05	2.35	0.761
Other	2.09	1.64	2.13	0.607
UNOS region				
1	3.74	5.74	3.58	0.087
2	10.3	9.43	10.4	0.646
3	9.93	13.1	9.68	0.084
4	12.4	14.3	12.2	0.326
5	10.1	6.15	10.4	0.033
6	4.22	2.05	4.39	0.080
7	12.0	11.5	12.0	0.808
8	6.73	4.92	6.87	0.241
9	8.10	10.2	7.94	0.203
10	9.99	7.38	10.2	0.158
11	12.6	15.2	12.4	0.208
Work for income at listing				
No	89.7	88.9	89.7	0.690
Yes	8.13	9.02	8.06	0.600
Unknown	2.18	2.05	2.19	0.882

BMI, body mass index; GED, General Educational Development; PA, pulmonary artery; VA, Veteran's Administration.

* Continuous variables expressed as mean \pm SD shown in parentheses; remainder of values are categorical variables expressed as percentages.

† 20%: Very sick, hospitalization necessary, active treatment necessary; 70%: Cares for self, unable to carry on normal activity or active work; 90%: Able to carry on normal activity, minor symptoms of disease.

Table 2. Univariate cox regression analysis

Covariates	HR			P value
	Mean	95% CI		
Age	1.01	0.999	1.02	0.083
Diastolic PA blood pressure at listing	1.00	0.988	1.02	0.680
Systolic PA blood pressure at listing	1.00	0.995	1.01	0.309
BMI at listing	1.02	0.991	1.05	0.185
Height at listing	0.99	0.970	1.00	0.033
Weight at listing	1.00	0.993	1.01	0.846
Creatinine at listing	1.18	1.07	1.27	<0.001
Blood type				
O	1	/	/	
A	0.942	0.689	1.29	0.707
AB	1.17	0.476	2.88	0.731
B	0.824	0.499	1.36	0.449
Cigarette				
Yes	1	/	/	
No	1.14	0.862	1.51	0.353
Diabetes				
No	1	/	/	
Type I	2.37	1.11	5.08	0.026
Type II	0.956	0.701	1.30	0.773
Education				
High school (9-12) or GED	1	/	/	
Grade school (0-8)	0.918	0.335	2.51	0.867
College/Technical school	1.16	0.810	1.66	0.419
Associate/Bachelor's degree	1.25	0.832	1.89	0.280
Post-college graduate degree	0.957	0.507	1.81	0.892
Other	1.73	1.09	2.76	0.020
Race				
White	1	/	/	
Black	1.05	0.462	2.38	0.911
Hispanic	0.875	0.628	1.22	0.432
Other	0.897	0.496	1.62	0.720
Implantable defibrillator				
Yes	1	/	/	
No	0.783	0.527	1.16	0.224
Functional status at listing				
Other	1	/	/	
20%*	1.22	0.846	1.75	0.289
70%*	0.933	0.641	1.36	0.717
90%*	0.569	0.250	1.29	0.178
Patient status at listing				
1B	1	/	/	
1A	1.46	1.02	2.10	0.038
2	1.26	0.868	1.84	0.223
Temporarily inactive	1.69	0.966	2.96	0.066
Intravenous inotropes at listing				
No	1	/	/	
Yes	1.54	1.13	2.09	0.006
Malignancy at listing				
No	1	/	/	
Yes	0.819	0.433	1.55	0.538
Payment type				
Private insurance	1	/	/	
Medicaid	1.07	0.685	1.66	0.777
Medicare Fee for Service	1.20	0.854	1.70	0.290
Medicare & Choice	1.070	0.671	1.70	0.779
Department of VA	0.553	0.175	1.75	0.312
Other	0.470	0.116	1.91	0.292
UNOS region				
4	1	/	/	
1	0.973	0.502	1.88	0.935
2	0.728	0.414	1.28	0.270
3	0.714	0.416	1.23	0.222
5	0.469	0.237	0.929	0.030
6	0.319	0.113	0.902	0.031
7	0.538	0.308	0.939	0.029
8	0.485	0.224	1.05	0.067
9	0.702	0.406	1.22	0.207
10	0.583	0.321	1.06	0.077
11	0.764	0.463	1.26	0.291
Work for income at listing				
No	1	/	/	
Yes	1.10	0.684	1.77	0.696
Unknown	1.27	0.521	3.09	0.598

BMI, body mass index; CI, confidence interval; GED, General Educational Development; HR, hazard ratio; PA, pulmonary artery; VA, Veteran's Administration.

* 20%: Very sick, hospitalization necessary, active treatment necessary; 70%: Cares for self, unable to carry on normal activity or active work; 90%: Able to carry on normal activity, minor symptoms of disease.

Table 3. Multivariate Cox Regression Analysis

Covariates	HR			P value
	Mean	95% CI		
Creatinine at listing	1.18	1.08	1.28	<0.001
Height at listing	0.983	0.969	0.998	0.022
Diabetes				
No	1	/	/	
Type I	2.517	1.17	5.40	0.018
Type II	0.926	0.678	1.26	0.626
Intravenous inotropes at listing				
No	1	/	/	
Yes	1.57	1.15	2.13	0.005

CI, confidence interval; HR, hazard ratio.

mortality risk for waiting list patients supported with HMII. The score is shown in Table 4, where all patients were divided into low-, intermediate-, and high-risk groups. The low-, intermediate-, and high-risk groups have a mortality rate of 0.06, 0.11, 0.15, respectively (Fig 2). The Kaplan-Meier survival curves of the 3 groups over a period of 12 months are shown in Fig 3.

Waiting List Survival of Patients on CF-LVAD Support

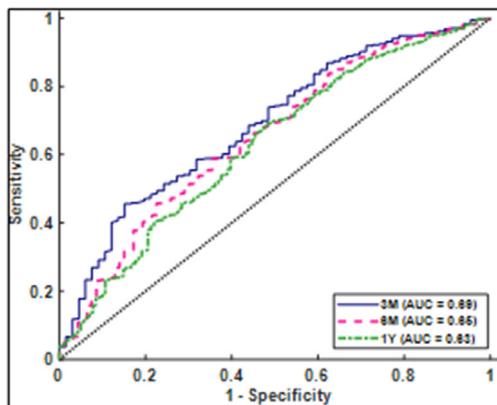
The waiting list survival of patients on CF-LVAD (HMII) is shown in Fig 4. Patients were divided into 2 groups; one group included those who were implanted with HMII before listing and the second group included those who were implanted with the device while waiting on the list. Total patients at risk were 2045 and 1299, respectively in the groups of implantations before and after listing. The analysis indicated a slightly improved survival for patients who were supported with HMII before being added to the waiting listing (HR, 1.29; $P = .048$).

Additionally, patients were grouped by creatinine and survival of each group is shown in Fig 4. Patients with a creatinine at listing between 1.2 and 2 mg/dL had a significantly higher risk (1.45 times higher) than those whose creatinine level were <1.2 mg/dL; patients with a creatinine at listing >2 mg/dL had an even higher risk (2.71 times higher) than those whose creatinine at listings were <1.2 mg/dL. Lower creatinine at listing led to an increased 12-month survival probability from 0.07 to 0.20 among waiting list patients on HMII support ($P < .001$; Fig 5).

Post-transplant Survival of CF-LVAD Patients

The post-heart transplant survival of patients who had HMII support before transplantation is shown in Fig 5. Patients were divided into 2 groups: those who were implanted with HMII before listing and those who were implanted with HMII after

Training



Validation

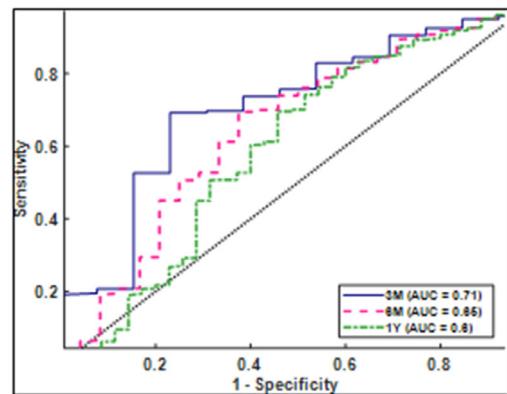


Fig 1. ROC curves for training and validation cohorts. AUC, area under the curve; ROC, receiver operating characteristic.

Table 4. Risk score for the 12-month waiting list survival

	Category	Score
Creatinine	≤ 1.2	0
	1.2~2	1
	> 2	2
Height at listing	≤ 180 cm	1
	> 180 cm	0
Diabetes	Other	0
	Type I	2
Intravenous inotropes at listing	No	0
	Yes	2

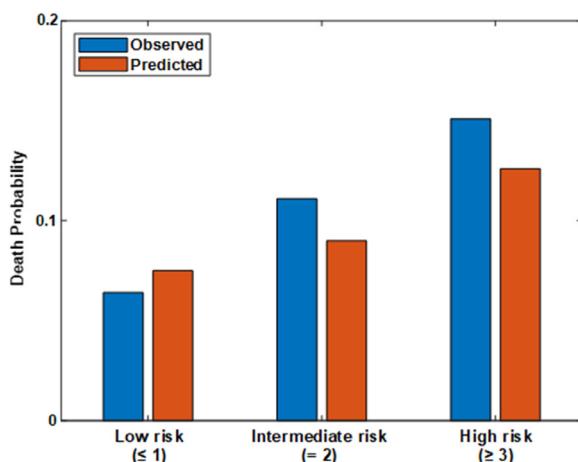


Fig 2. Mortality rate for wait-list patients on Heartmate II in different risk groups.

listing. Both groups have a 4-year post-transplant survival of about 0.22. No significant difference was observed between the 2 groups, which indicates that implantation of HMII before or after listing did not have a great effect on post-transplant survival, as shown in Fig 6. Furthermore, comparison of survival of patients who had HMII support before transplantation to patients who did not have LVAD support had significantly lower 5-year survival probability than those who did not need a LVAD support, as shown in Fig 7.

DISCUSSION

This study investigated the survival of wait-list patients on HMII support and generated a risk prediction model using the UNOS database population. The multivariate analysis identified type I diabetes, presence of inotropes at listing, and high creatinine at listing as significant risk factors of patients on the wait list. Some variables such as patients in status 1B being taller than patients in status 1A, and the UNOS region 5, 6, and 7 having a higher proportion of type I diabetes patients were shown to be significant in univariate analysis, but did not meet criteria for multivariate analysis.

Patients who were implanted with HMII before listing had a slightly better survival than patients who had the implantation while waiting on the list (HR, 0.78; $P = 0.048$), which suggested that an early LVAD implantation strategy could benefit the BTT patients by extending their wait-list survival.

As for post-transplant survival, patients supported with HMII while on the wait list demonstrated lower survival rate than patients without LVAD support, which is possibly because of LVAD BTT patients being sicker than those without LVADs before transplant. Existing literature shows that differences in post-transplant survival exist with different types of assist devices [8].

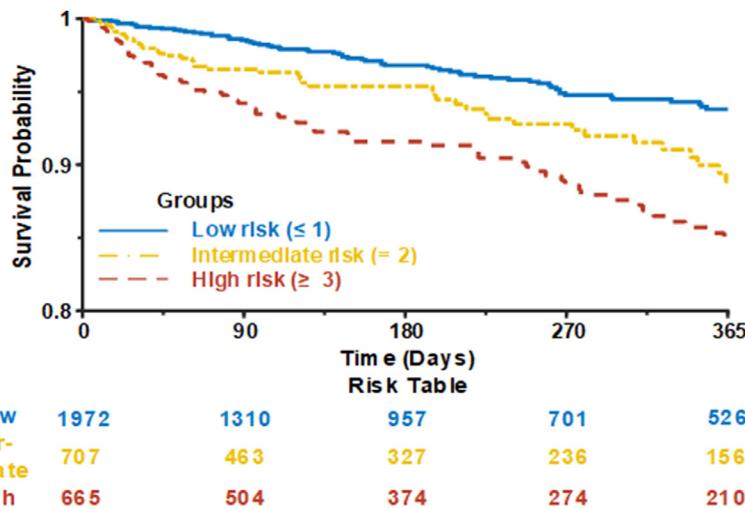


Fig 3. Survival probability of wait-list patients on Heartmate II in different risk groups.

Merits and Limitations

This investigation arrived at a risk prediction model for the first time for survival of patients on the wait list. However, the study had its limitations in that it was retrospective and further studies would be required to validate the usage of this risk prediction model for wait-list survival analysis in other databases possibly involving multiple centers. The UNOS database has limited wait-list clinical data, hence additional studies with other databases would be valuable to explore more clinical variables and their effects on wait-list survival. Use of machine learning techniques and artificial intelligence (AI)-driven algorithms using large databases would be the future direction to refine risk factor modeling.

CONCLUSIONS

The present study investigated the wait-list survival of patients listed for heart transplantation with an axial CF-LVAD between 2010 and 2015. A risk stratification model was developed for the first time to predict the 12-month survival based on a group of regularly available characteristics collected at listing. The model provides a simple tool to guide the management of wait-list patients on CF-LVAD. Additionally, analysis of the timing of LVAD implantation (ie, implantation before or after listing) had implications on the wait-list survival and post heart transplantation survival. It was found that the patients with HMII implanted before listing showed better survival than those who had implantation after listing. Patients without an LVAD on the wait list showed a better survival than those who had an LVAD

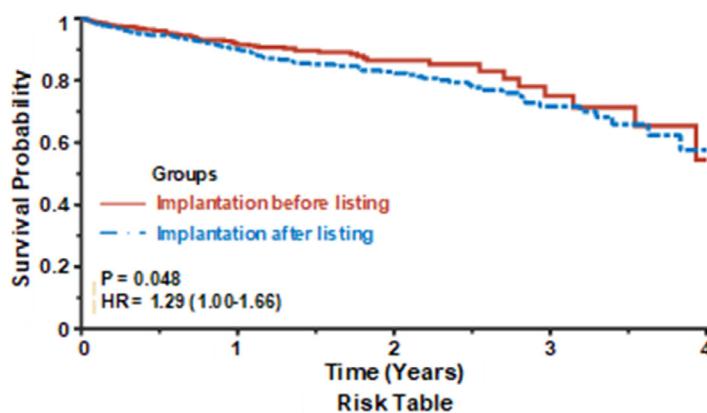


Fig 4. Wait-list survival of patients on continuous flow left ventricular assist device support.

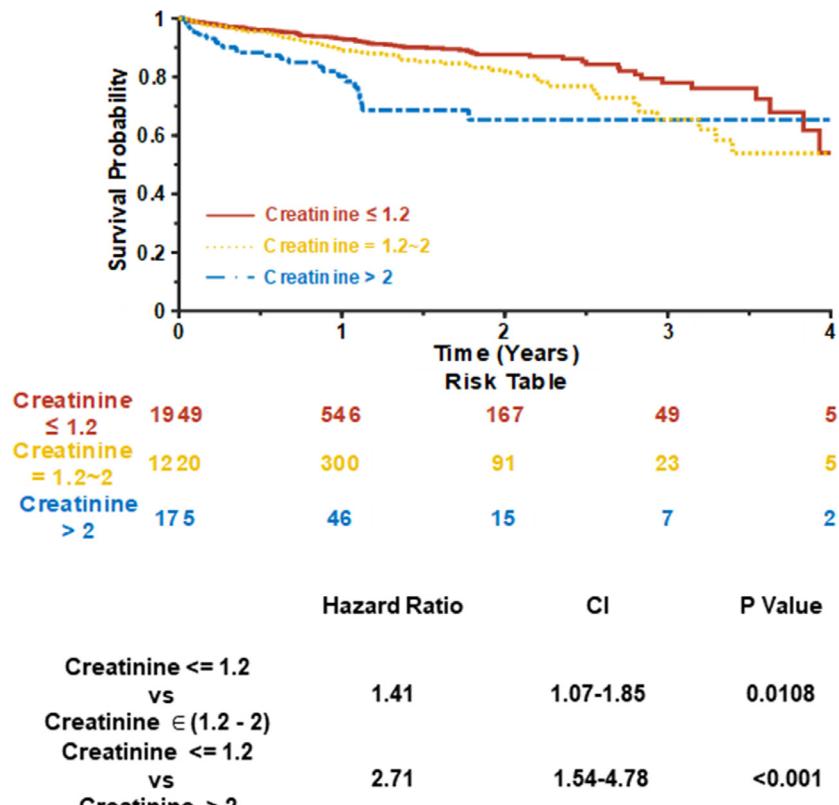
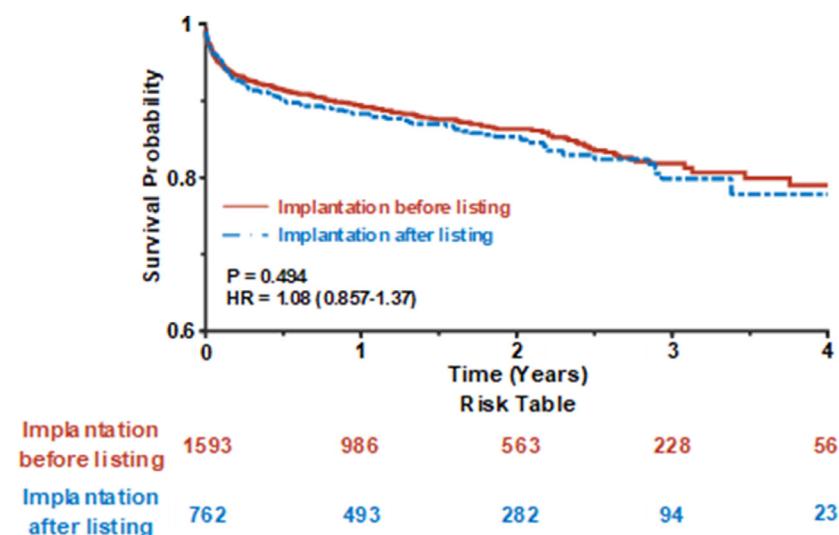


Fig 5. Wait-list survival of patients on continuous flow left ventricular assist device support at different creatinine levels.



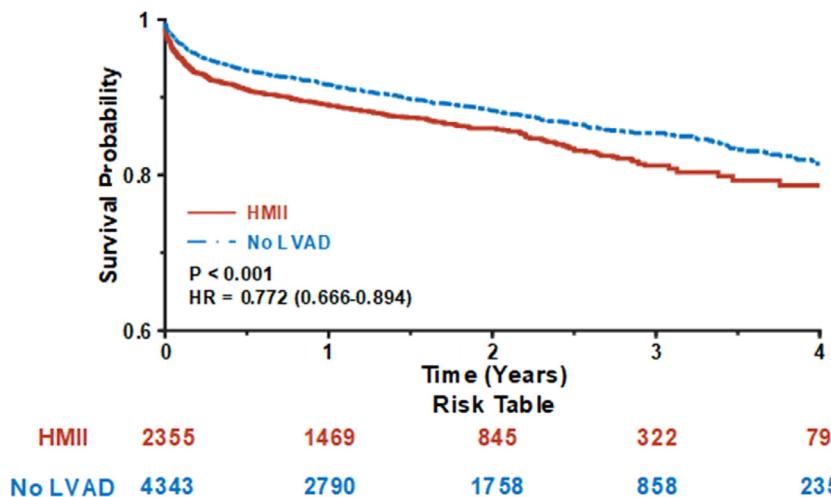


Fig 7. Post heart transplant survival of patients on HMII support without LVAD. HMII, Heartmate II; LVAD, left ventricular assist device.

in terms of post-transplant survival. Further studies will be required to analyze clinical characteristics in the perioperative period to refine risk factor identification and modeling. Use of AI-driven algorithms may help predict outcomes better on the waitlist and post-transplant survival [9,10].

DATA AVAILABILITY

Data will be made available on request.

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REFERENCES

[1] Alraies MC, Eckman P. Adult heart transplant: indications and outcomes. *J Thorac Dis* 2014;6:1120-8.

[2] Feldmann C, Chatterjee A, Haverich A, Schmitto JD. Left ventricular assist devices - a state of the art review. *Adv Exp Med Biol* 2018;1067:287-94.

[3] Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015;34:1495-504.

[4] Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. *Circulation* 2007;116:497-505.

[5] Zimpfer D, Fiane AE, Larbalestier R, Tsui S, Jansz P, Simon A, et al. Long-term survival of patients with advanced heart failure receiving an left ventricular assist device intended as a bridge to transplantation: the registry to evaluate the heartware left ventricular assist system. *Circ Heart Fail* 2020;13:e006252.

[6] Bakhtiyar SS, Godfrey EL, Ahmed S, Lamba H, Morgan J, Loor G, et al. Survival on the heart transplant waiting list. *JAMA Cardiol* 2020;5:1227-35.

[7] Trivedi JR, Cheng A, Singh R, Williams ML, Slaughter MS. Survival on the heart transplant waiting list: impact of continuous flow left ventricular assist device as bridge to transplant. *Ann Thorac Surg* 2014;98:830-4.

[8] Seese L, Hickey G, Keebler ME, Mathier MA, Sultan I, Gleason TG, et al. Temporary left ventricular assist devices as a bridge to heart transplantation. *J Card Surg* 2020;35:810-7.

[9] Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart* 2018;104:1156-64.

[10] Miller DD. Machine intelligence in cardiovascular medicine. *Cardiol Rev* 2020;28:53-64.