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Decision tree for adjuvant right ventricular support in patients receiving a left ventricular assist device

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BACKGROUND: Right ventricular (RV) failure is a significant complication after implantation of a left ventricular assist device (LVAD). It is therefore important to identify patients at risk a priori. However, prognostic models derived from multivariate analyses have had limited predictive power.

METHODS: This study retrospectively analyzed the records of 183 LVAD recipients between May 1996 and October 2009; of these, 27 later required a RVAD ($RVAD^+$) and 156 remained on LVAD only ($RVAD^-$) until transplant or death. A decision tree model was constructed to represent combinatorial non-linear relationships of the pre-operative data that are predictive of the need for RVAD support.

RESULTS: An optimal set of 8 pre-operative variables were identified: transpulmonary gradient, age, right atrial pressure, international normalized ratio, heart rate, white blood cell count, alanine aminotransferase, and the number of inotropic agents. The resultant decision tree, which consisted of 28 branches and 15 leaves, identified $RVAD^+$ patients with 85% sensitivity, $RVAD^-$ patients with 83% specificity, and exhibited an area under the receiver operating characteristic curve of 0.87.

CONCLUSIONS: The decision tree model developed in this study exhibited several advantages compared with existing risk scores. Quantitatively, it provided improved prognosis of RV support by encoding the non-linear, synergic interactions among pre-operative variables. Because of its intuitive structure, it more closely mimics clinical reasoning and therefore can be more readily interpreted. Further development with additional multicenter, longitudinal data may provide a valuable prognostic tool for triage of LVAD therapy and, potentially, improve outcomes.

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Mechanical circulatory support for end-stage heart failure has become an established therapeutic option with significant survival benefit. However, patients who receive a left ventricular assist device (LVAD) alone periodically develop post-operative right ventricular (RV) failure necessitating pharmacologic or mechanical support. This applies to ~10% to 30% of all LVAD patients[1–4] and is associated with increased morbidity and death.[5] Severe RV failure results in renal and hepatic dysfunction due to elevated central venous pressure as well as under-filling of the LVAD.[6] Post-operative RV failure also adversely affects outcomes of patients who are ultimately bridged to transplant.[3,7,8]

Conversely, implanting an RVAD bears its own risk of increased morbidity,[9] effectively doubling the likelihood of thrombosis, infection, and mechanical failure. Therefore, the prediction of RV failure before VAD implantation is critically important to an optimal course of treatment and clinical outcome. This prognosis is sometimes obscured by the complex interaction between pre-operative conditions, intra-operative factors, and immediate post-operative hemodynamic status.[9–11]

As a consequence, previous predictors of RV failure based on univariate and multivariate statistical analyses[1,3,5,11–16] have not provided adequate sensitivity and specificity for practical use. For example, a popular RV failure risk score, the University of Michigan Right Ventricular Failure Risk Score

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(RVFRS),[11] which has demonstrated an 80% positive predictive value of RV failure in LVAD candidates (based on a threshold value of 5.5), reports an overall sensitivity of only 35%. Furthermore, the performance of this index is prognostically inconsistent when evaluated in independent samples. Thus, there remains a need for a more accurate, sensitive, specific, and robust method to identify LVAD candidates at risk for RV failure.

This study aimed to develop an improved prognostic tool by capitalizing on recent advances in data mining and machine learning theory. These techniques are gaining popularity to predict future trends and discover unknown patterns in clinical outcomes, including breast cancer, pneumonitis,[17,18] and others.[19–21] The decision tree is one such algorithm that has been used extensively in medicine.[22–25] It has proved to be reliable and effective, providing high classification accuracy with a simple representation of gathered knowledge. Because of its tree structure, it can be readily interpreted and therefore more likely to be adopted than, say, an ambiguous numeric risk score.[26] This study used the decision tree algorithm combined with over-sampling and feature selection techniques to identify and represent the non-linear interactions among pre-operative variables.

Methods

Study design

This study retrospectively analyzed 183 de-identified patients enrolled in the Artificial Heart Program at the University of Pittsburgh Medical Center (UPMC) from May 1996 to October 2009. These patients initially received an LVAD, but 27 (15%) later required an RVAD ($RVAD^+$) and 156 (85%) remained on LVAD until the time of transplantation or death ($RVAD^-$). Multiple devices were used throughout this interval (Table 1 and Table 2), including BVS 5000 and AB 5000 (Abiomed, Danvers, MA), Bio-Medicus Perfusion System (Medtronic Inc, Minneapolis, MN), Novacor (Worldheart, Salt Lake City, UT); CentriMag, HeartMate XVE, Thoratec IVAD, Thoratec PVAD, and HeartMate II (Thoratec, Pleasanton, CA); Jarvik 2000 (Jarvik Heart Inc, New York, NY), and Ventrassist (Ventracor Ltd, Chatswood, NSW, Australia). Initial pulsatile-flow LVADs were implanted in 143 of the cohort (78.1%), comprised of 121 $RVAD^-$ and 22 $RVAD^+$ patients; and continuous-flow LVADs were implanted in 40 patients (21.9%), comprised of 35 $RVAD^-$ and 5 $RVAD^+$ patients.

Table 1 Left Ventricular Assist Devices Used in Patients Who Did Not Require a Right Ventricular Assist Device

Device	No. (%)
Pulsatile devices	121 (77.6)
Abiomed AB 5000	6 (3.8)
Novacor	43 (27.6)
HeartMate XVE	33 (21.2)
Thoratec IVAD	6 (3.8)
Thoratec PVAD	33 (21.2)
Continuous-flow devices	35 (22.4)
HeartMate II	15 (9.6)
JARVIK 2000	2 (1.3)
Ventrassist	18 (11.5)
Total	156 (100)

Table 2 Device Combination Used in the Patients Who Required a Right Ventricular Assist Device

RVAD device	LVAD device	No. (%)
Abiomed BVS 5000	Abiomed AB 5000	2 (7.4)
Abiomed BVS 5000	Novacor	1 (3.7)
Biomedicus	HeartMate XVE	1 (3.7)
CentriMag	HeartMate II[a]	3 (11.1)
CentriMag	Thoratec IVAD	1 (3.7)
CentriMag	Thoratec PVAD	3 (11.1)
CentriMag	Ventrassist[a]	1 (3.7)
Thoratec PVAD	HeartMate II[a]	1 (3.7)
Thoratec PVAD	HeartMate XVE	2 (7.4)
Thoratec PVAD	Novacor	3 (11.1)
Thoratec PVAD	Thoratec PVAD	9 (33.3)
Total		27 (100)

LVAD, left ventricular assist device; RVAD, right ventricular assist device.

[a]Patients with initial continuous-flow LVAD in $RVAD^+$ group (n = 5 in total).

A total of 39 pre-operative variables were selected based on a survey of the literature and their availability in the patient records, categorized as patient demographics (n = 6), hemodynamics (n = 14), blood chemistry and hematologic laboratory values (n = 13), and medications (n = 6), including digoxin, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, β-blockers, vasodilator, antiarrhythmics, and inotropic agents (Table 3).

Data were reviewed retrospectively from the UPMC Transplant Patient Management System (TPMS), a password-protected, Health Insurance Portability and Accountability Act-compliant, Institutional Review Board-approved, Web-based data repository for all patients who receive mechanical circulatory support. Data were extracted from pre-operative Day 14 to Day 1. For variables with multiple values, the value closest to the time of surgery was used. When data elements were missing, various interpolation techniques (mean, median, nearest neighbor) were implemented (Table 3). The primary end point was whether the LVAD patient received an RVAD after the index LVAD surgery, and the secondary end point was 1-year survival.

Analysis

The set of pre-operative variables was first ranked by chi-square analysis and then combined into incrementally sized sub-sets (n = 1, 2, . . ., 39). Further analyses were performed on each of the sub-sets to determine the optimal set that provided sufficient information without over-fitting. A well-known decision tree algorithm, C4.5, was used, implemented in an open-source software library[27] (WEKA, J48, University of Waikato, New Zealand). This analysis uses recursive partitioning methods to separate the 2 groups of patients into distinct sub-sets by identifying the significant non-linear interactions among the pre-operative variables and automatically constructing the decision branches. The corresponding breakpoints for each of the variables were selected with the criterion of maximization of the purity of the cohort after splitting. The algorithm also includes a "pruning" procedure to reflexively

Table 3 Pre-implant Characteristics for Two Groups of Patients

Variable [a]	Nearest neighbor[b]	RVAD$^-$ (n = 156)	RVAD$^+$ (n = 27)	p-value
Demographics				
Age, years		53.3 ± 12.7	49.9 ± 10.5	0.04[c]
Female, %		14	37	0.01[c]
Pulsatile-flow LVAD, %		78	81	0.80
Body mass index, mean kg/m^2		28.2 ± 6.1	27.8 ± 5.4	0.99
Weight, kg	15	89.3 ± 21.7	76.0 ± 17.3	0.06
Ischemic etiology, %		54	56	0.99
Hemodynamics				
Cardiac index, liter/min/m^2	20	2.3 ± 0.8	2.3 ± 0.8	0.80
Cardiac output, liter/min	10	4.3 ± 1.0	4.3 ± 1.4	0.22
Pulmonary capillary wedge pressure, mm Hg	10	26.6 ± 8.4	24.2 ± 8.9	0.42
Transpulmonary gradient, mm Hg	10	11.3 ± 6.0	13.4 ± 3.9	0.10
Pulmonary vascular resistance, mean WU		2.2 ± 2.6	3.6 ± 1.7	0.35
Mean pulmonary artery pressure, mm Hg	7	38.1 ± 9.4	37.8 ± 10.8	0.86
Pulmonary arterial systolic pressure, mm Hg	10	55.6 ± 14.6	56.8 ± 16.8	0.81
Pulmonary arterial diastolic pressure, mm Hg	10	27.4 ± 8.2	26.8 ± 9.8	0.75
Right atrial pressure, mm Hg	10	12.1 ± 6.2	9.9 ± 6.1	0.26
Right ventricular diastolic pressure, mm Hg	10	10 ± 6.3	11 ± 7.0	0.70
Pulmonary arterial oxygen saturation, %	15	51.8 ± 12.7	53.7 ± 13.8	0.53
Right ventricular systolic pressure, mm Hg	5	54.4 ± 15.8	56.4 ± 14.2	0.67
Heart rate, beats/min	15	93.0 ± 25.1	81.3 ± 28.5	0.18
Intra-aortic balloon pump, %		76	74	0.81
Laboratory tests				
Creatinine, mg/dl	15	1.5 ± 0.7	1.4 ± 0.7	0.23
Blood urea nitrogen, mg/dl	15	32.0 ± 20.5	28.6 ± 18.9	0.37
Aspartate aminotransferase, IU/liter	7	83.7 ± 162.8	60.7 ± 50.6	0.47
Alanine aminotransferase, IU/liter	15	92.8 ± 174.1	53.5 ± 36.3	0.76
Total bilirubin, mg/dl	15	1.2 ± 0.9	1.4 ± 1.6	0.75
Hematocrit, %	15	33 ± 7.0	35 ± 7.4	0.34
White blood cell count, 10^9/liter	10	9.4 ± 3.9	11.8 ± 7.3	0.16
Platelet count, 10^9/liter	20	207.7 ± 78.8	187.7 ± 94.0	0.23
International normalized ratio	15	1.3 ± 0.4	1.5 ± 0.7	0.48
Hemoglobin, g/dl	20	13.8 ± 10.4	14.6 ± 10.1	0.30
Albumin, g/dl	5	3.3 ± 0.6	3.4 ± 0.8	0.46
Prothrombin time, sec		56.6 ± 28.7	58.3 ± 29.6	0.92
Sodium, median mEq/liter		134.2 ± 5.8	133.5 ± 5.8	0.58

[a]Continuous data are presented as mean ± standard deviation or as indicated; categoric data as percentage.
[b]Values derived from nearest neighbor imputing method.
[c]Statistically significant ($p < 0.05$).

eliminate unnecessary branches, reduce the estimated errors, and generalize the model.

The objective function for this analysis was to minimize the error between the predicted and historical decision of RVAD implantation (RVAD$^+$/RVAD$^-$, defined above.) It was assumed here that the clinical cost of failing to initially implant an RVAD in a patient who developed RV failure would be comparable to the cost of implanting an RVAD unnecessarily. Synthetic Minority over Sampling Technique (SMOTE)[28–30] was applied to supplement the RVAD$^+$ data to compensate for the imbalanced RVAD$^+$-to-RVAD$^-$ ratio in the current cohort (1:6) and avoid unintended bias in the calculation of error rate.

Tenfold cross-validation was used to evaluate the predictive performance of the decision tree model, whereby the data were divided into 10 mutually exclusive sub-sets, 9 of which were used for training and 1 for evaluation. This was repeated 10 times, thereby using 10 different, but overlapping training sets, and 10 unique testing sets. The performance measures for evaluation of the decision tree analysis were:

1. true-positive rate, RVAD$^{+/+}$, in which the algorithm agrees with the historical clinical decision to implant an RVAD;
2. true-negative rate, RVAD$^{-/-}$, in which the algorithm and the historical clinical decision both agree to forgo an RVAD;
3. false-positive rate, RVAD$^{-/+}$, in which the model predicts RVAD implantation but the historical decision declined the RVAD; and
4. false-negative rate, RVAD$^{+/-}$, in which the model prediction disagreed with the historical decision of RVAD implantation.

Additional measures of performance were the area under the receiver operating characteristic (ROC) curve and κ statistics. The specificity and sensitivity of the model were defined as the RVAD$^{-/-}$ and RVAD$^{+/+}$ rates, respectively. To investigate the dependence of late RVAD implantation on the generation of

Table 4 Pre-operative Variables Significantly Correlated With Late Right Ventricular Assist Device Support

Pre-op variables	Late RVAD support Correlation (95% CI)	p-value
Sex	0.21 (0.07 to 0.35)	0.004
White blood cell count	0.18 (0.04 to 0.32)	0.012
Weight	−0.16 (−0.29 to −0.01)	0.004

CI, confidence interval; RVAD, right ventricular assist device.

the initial LVAD, this analysis was repeated in the sub-groups of patients with an initial pulsatile-flow LVAD ($n = 143$) and an initial continuous-flow LVAD ($n = 40$).

The performance in survival was provided by Kaplan-Meier analysis. Differences in actuarial survival were evaluated using the log-rank test. For comparison, the RVFRS[11] was also calculated for each patient, which stratified the cohort according to the published definition. Standard ROC curves were constructed to illustrate overall sensitivity and specificity.

Results

Baseline data and comparison between $RVAD^-$ ($n = 156$) and $RVAD^+$ ($n = 27$) groups are summarized in Table 3. The $RVAD^+$ group included CentriMag in 8 (30%), Abiomed BVS 5000 in 3 (11%), Biomedicus RVAD in 1 (4%), and Thoratec PVAD in 15 (55%). The demographic, hemodynamic, and laboratory data were typical of patients with advanced heart failure and were similar between $RVAD^-$ and $RVAD^+$ groups. The $RVAD^+$ group was younger (50 vs 53 years; $p = 0.04$) and had a higher proportion of women (37% vs 15% overall; $p = 0.01$). Pearson product-moment pairwise analysis identified 2 variables that were significantly positively correlated with the need of post-RVAD individually: female sex and elevated white blood cell (WBC) count ($RVAD^-$: $9.4 \pm 3.9 \times 10^9$/liter vs $RVAD^+$: $11.8 \pm 7.3 \times 10^9$/liter). Pre-operative weight was inversely correlated with late RVAD use ($RVAD^-$: 89.3 ± 21.7 kg vs $RVAD^+$: 76.0 ± 17.3 kg). The corresponding correlation coefficients and 95% confidence intervals (CI) are summarized in Table 4, which demonstrates significant differences between groups ($p < 0.05$) but generally weak correlations coefficients are close to zero.

Decision tree model

Feature selection resulted in 8 pre-operative variables comprising the decision tree model for the complete cohort: transpulmonary gradient (TPG), age, right atrial pressure (RAP), international normalized ratio (INR), heart rate (HR), WBC, alanine aminotransferase (ALT), and the number of inotropic agents. Pearson product-moment pairwise analysis identified 7 significant correlations ($p < 0.05$): number of inotropes was positively correlated with WBC, which indicated that an elevated WBC count was associated with a greater number of inotropic agents. Similar observations were found between WBC and RAP, ALT and RAP, INR and ALT, and INR and RAP. Yet, RAP and HR were inversely correlated with age, which reflects younger patients tending to have greater RAP and HR in this cohort. Figure 1 shows the corresponding correlation coefficients as well as 95% CI.

The resulting decision tree built upon the above data set with 5X synthetic $RVAD^+$ samples is provided in Figure 2. In this model, TPG is the initial splitting feature, with a breakpoint of 7 mm Hg. The branch of TPG ≤ 7 mm Hg predicts no need of RVAD support. The branch of TPG > 7 mm Hg leads to age as the secondary splitting feature, with a breakpoint of 59. On the third level, different thresh-

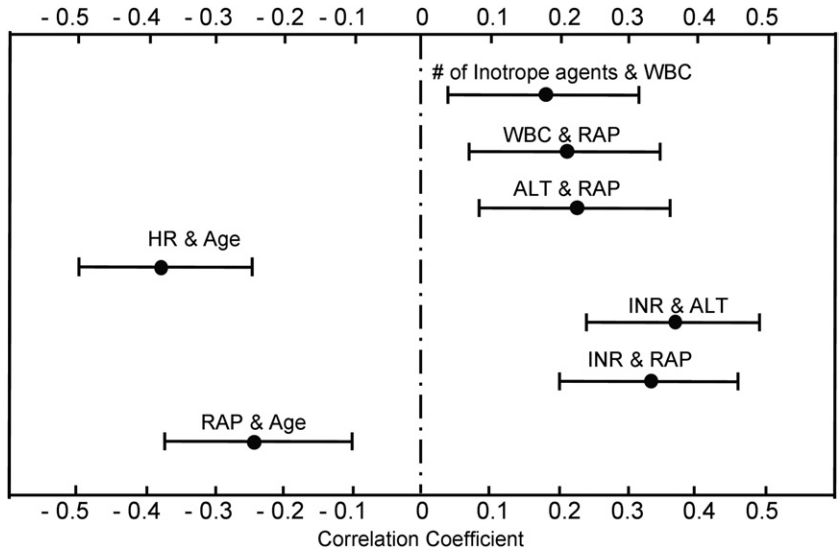

Figure 1 Significant correlations among the pre-operative variables involved in the decision tree. Range bars show the 95% confidence intervals of correlation coefficients. ALT, alanine aminotransferase; HR, heart rate; INR, international normalized ratio; RAP, right atrial pressure; WBC, white blood cell count.

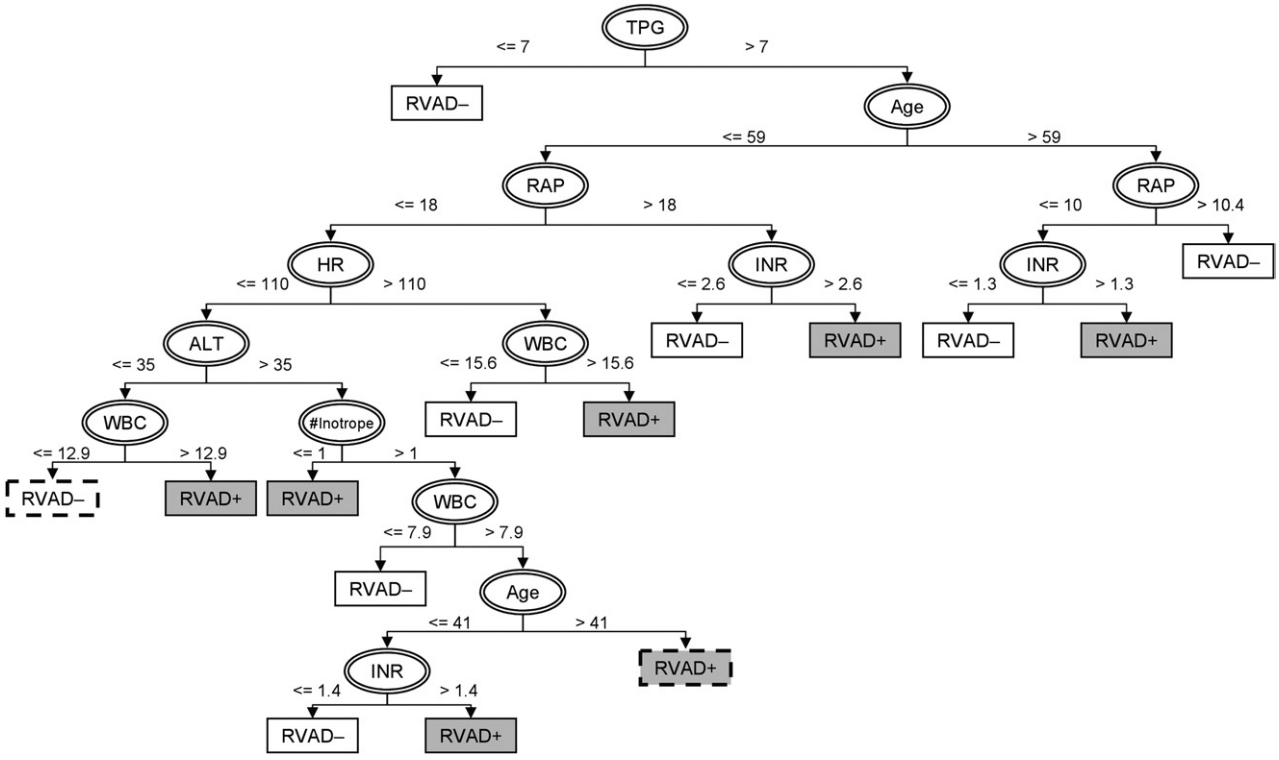

Figure 2 Decision tree for optimal identification of right ventricular assist device (RVAD) support in left ventricular assist device (LVAD) patients. Features used for splitting the cohort are indicated by ellipses. Rectangles indicate the predicted outcomes following corresponding branches: white, freedom of RVAD support; gray, necessity of RVAD; dashed borderline, simplified leaves. ALT, alanine aminotransferase; HR, heart rate; INR, international normalized ratio; RAP, right atrial pressure; TPG, transpulmonary gradient; WBC, white blood cell count.

olds of RAP exist, depending on age: 18 mm Hg ($\leq$ 59 years) and 10 mm Hg ($>$ 59 years). This demonstrates the apparent non-linear relationship among these pre-operative features. Thereafter, additional splits unveil the complicated patterns embedded in the $RVAD^+$ and $RVAD^-$ data sets. The tree eventually terminates in 15 leaves representing 1 of 2 outcomes: $RVAD^-$ or $RVAD^+$. This model indicates that elevated INR and/or WBC are common to the branches with increased risk of the need of RVAD support. This model achieved 85% sensitivity and 83% specificity (Table 5A.)

ROC curves were generated for the decision tree model, and the RVFRS was calculated for this cohort (Figure 3). Comparison of AUC showed that decision tree exhibited better performance than RVFRS in this cohort (AUC, 0.87 vs 0.54.) The figure also depicts the RVFRS ROC curve reported in Matthews et al,[11] in which the reported AUC is 0.73.[11] When this weighted score was applied in the present cohort, 18.5% $RVAD^+$ patients were identified as high risk and 64.1% $RVAD^-$ as low risk, leaving 22.2% $RVAD^+$ patients and 19.2% $RVAD^-$ patients as medium risk.

Survival outcome

Kaplan-Meier 1-year survival curves of the 2 groups with respect to historical decisions of $RVAD^-$ and $RVAD^+$ are provided in Figure 4 (log-rank $p = 0.0008$). Survival for the $RVAD^-$ and $RVAD^+$ groups was 89% and 78%, respectively, at 30 days post-LVAD, 78% and 60% at 90 days, 73% and 37% at 180 days, and 51% and 19% at 1 year. Figure 5 provides the survival curves for the sub-set of patients in the $RVAD^{-/-}$ and $RVAD^{+/+}$ groups. Compared with Figure 4, short-term post-LVAD survivals between the groups were similar: 89% and 84% at 30 days and 77% and 65% at 90 days, respectively. However, the 1-year survivals are much more distinct: 51% for $RVAD^{-/-}$ and 0% $RVAD^{+/+}$. The overall curves were statistically different (log-rank $p = 0.0108$).

Comparison of first- and second-generation LVADs

In the sub-group of patients who received a continuous-flow (second-generation) LVAD, the incidence of late-RVAD implantation was 12.5%, which was relatively lower than the 15.4% in those who received a pulsatile-flow (first-generation) LVAD. The performance of the aggregate model (Figure 2) with this sub-group was 80% sensitivity and 86% specificity, which was similar to the full cohort (Table 5B).

The decision tree model developed exclusively on the continuous-flow cohort re-prioritized the predictive variables, promoting the importance of body mass index, cardiac output, and diastolic pulmonary artery pressure. It also demoted the prognostic values of INR and WBC. It exhibited 100% sensitivity and 97% specificity based

Table 5 The Expected Performance of the Aggregate Model

(A) Performance evaluated on the complete cohort (n = 183)

	Clinical decision	
Prediction	$RVAD^{+}$	$RVAD^{-}$
$RVAD^{+}$	$RVAD^{+/+}$ (true positive) Sensitivity: 85%	$RVAD^{-/+}$ (false positive) False positive rate: 17%
$RVAD^{-}$	$RVAD^{+/-}$ (false negative) False-negative rate: 15%	$RVAD^{-/-}$ (true negative) Specificity: 83%

RVAD, right ventricular assist device.

(B) Performance evaluated on the sub-group with initial continuous-flow LVAD ($n = 40$)

	Clinical decision	
Prediction	$RVAD^{+}$	$RVAD^{-}$
RVAD+	$RVAD^{+/+}$ (true positive) Sensitivity: 80%	$RVAD^{-/+}$ (false positive) False-positive rate: 20%
$RVAD^{-}$	$RVAD^{+/-}$ (False Negative) False negative rate: 14%	$RVAD^{-/-}$ (true negative) Specificity: 86%

RVAD, right ventricular assist device.
Predictive outcomes are suggested by the model; clinical decisions are made by the experts in hospital.

on 10-fold cross validation. However, when tested on the pulsatile-flow LVAD group, it exhibited only 18% sensitivity ($RVAD^{+/+}$) and 84% specificity ($RVAD^{-/-}$). Similarly, the model developed exclusively with the subset of patients with the initial pulsatile-flow LVAD performed poorly when tested on the continuous-flow LVAD group, exhibiting 20% sensitivity ($RVAD^{+/+}$) and 89% specificity ($RVAD^{-/-}$).

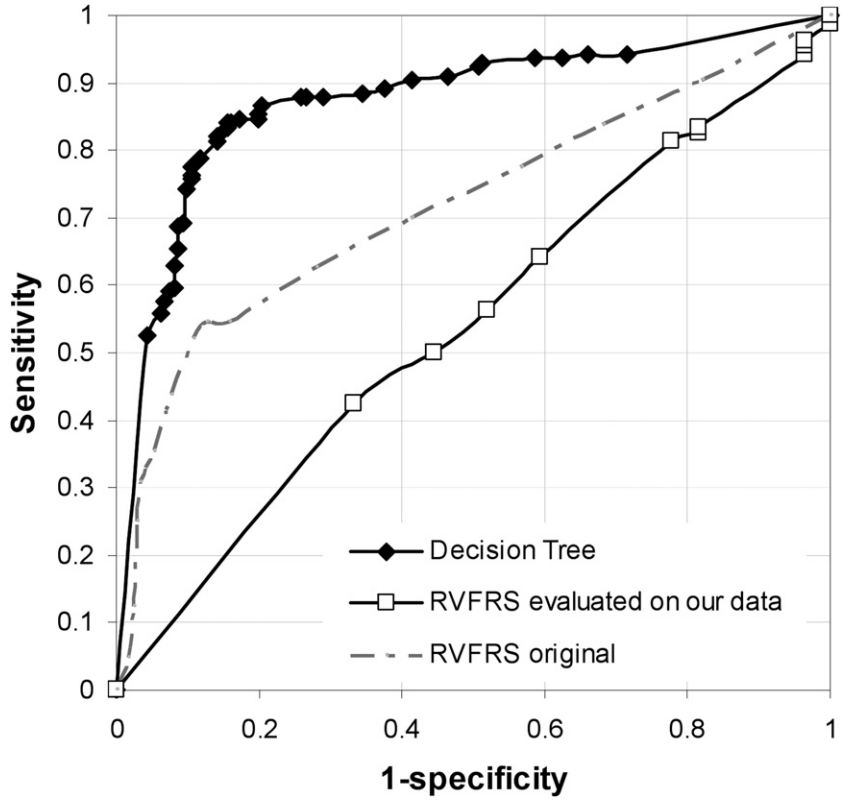

Figure 3 Receiver operating characteristic curve of our decision tree model, Right Ventricular Failure Risk Score (RVFRS) evaluated on our cohort and RVFRS published in the Matthews et al[11] study.

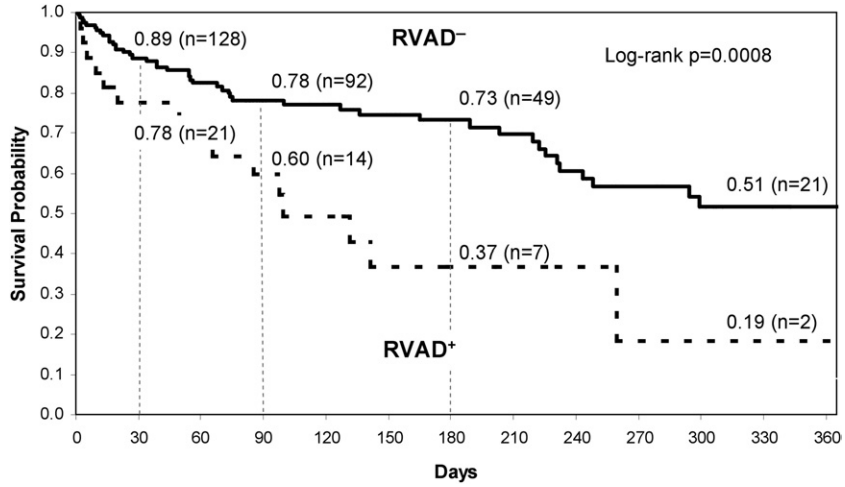

Figure 4 Kaplan-Meier survival curve for retrospective *clinical decision* in patients supported with a left ventricular assist device who did ($RVAD^{+}$) and did not ($RVAD^{-}$) require right ventricular assist device support.

Discussion

The complex pathophysiology of post-operative RV failure[11] and care[31] makes the pre-operative prediction of RV failure difficult and hinders the optimal course of treatment for an individual candidate.[8,10,31,32] In lieu of sole univariate analysis or traditional linear multivariate analysis, the current study sought to develop a decision tree to facilitate the identification of patients who may require RV support. As contrasted to a weighted combination of independent variables, the decision tree is better able to represent the complicated, non-linear relationships and synergy between variables that underlie the development of RV failure after LVAD implantation. An added benefit of the decision tree model is its ability to graphically illustrate the prediction logic, compared with a purely mathematically derived index that requires "blind faith" of the decision maker.

The decision tree presented here includes predictive pre-operative variables that are supported by previous RV failure studies and further reveals potentially counterintuitive dependencies on variables not previously emphasized. For example, the first splitting variable found by the model, elevated TPG, has been previously identified as a significant predictor of RV dysfunction after LVAD implantation.[33] However, the decision tree model further qualifies this splitting criterion for instances in which TPG exceeds 7 mm Hg, in which case additional factors should be considered. Although this cut point would not appear to be clinically relevant, particularly with respect to historical linear analyses, the current study suggests that even a modest elevation of TPG may impart risk when considered with other variables. Likewise, age, also identified by Fukamachi et al[15] as an important predictor, appears twice in the decision tree, in each case further qualified by subordinate variables.

INR, also previously correlated with RV failure,[2,11,16] is incorporated into the decision tree in a somewhat complex fashion. For example, for a patient with TPG $>$ 7 mmHg, age $<$ 59, RAP $>$ 18 mm Hg, and elevated INR $>$ 2.6, the

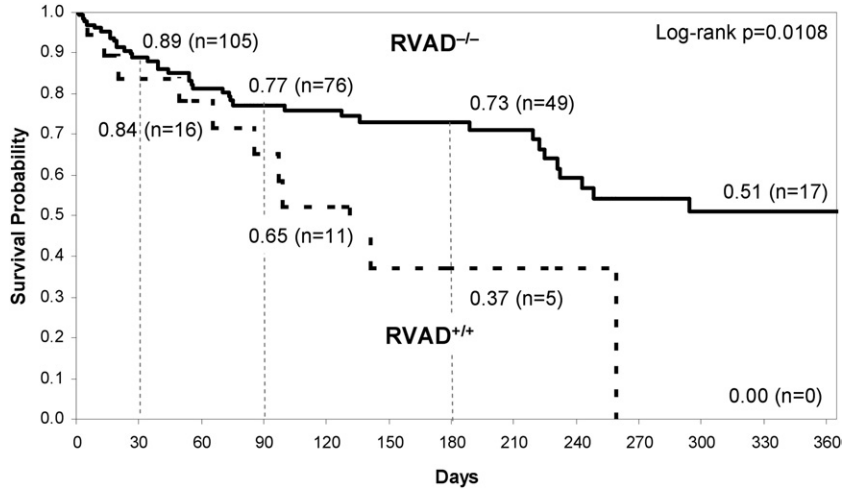

Figure 5 Kaplan-Meier survival curve for right ventricular assist device $(RVAD)^{+/+}$ patients, in which the algorithm agrees with historical clinical decision to implant an RVAD, and $RVAD^{-/-}$ patients, in which the algorithm and clinical decision both agree to forego RVAD.

model indicates the need of an RVAD; yet for a patient with the same profile—except RAP < 18 mm Hg—the prediction is much more complicated and depends on HR, WBC, ALT, and number of inotropes. This interdependence of variables may possibly reflect their causality; for example, it is less likely that elevated INR contributes directly to RV failure than it is indicative of other underlying pathologies that adversely affect outcomes. Accordingly, the model does *not* imply that altering a patient's INR would affect the risk of RV failure. Rather, it is more likely that a prevailing condition leading to a high INR is further associated with many other physiologic abnormalities that eventually culminate in RV failure. Being a retrospective study, it is impossible to eliminate the bias potentially introduced by the "human in the loop."

The present study also revealed that multiple decision tree structures might provide equivalent results. (See, for example the decision tree of Figure 6, which is a variant of the present model with comparative performance to the model shown in Figure 2.) This non-uniqueness can be considered an asset because it accommodates multiple sets of data elements. Therefore, the user may select from an assortment of decision trees most consistent with the (limited) data available.

Although not reported here, it is intuitive that the performance of the decision tree would deteriorate as data elements are excluded. Conversely, the addition of more sensitive indices of RV function, such as echo-derived ejection-phase metrics[34] would *improve* the decision tree. But again, the data are often incomplete in practical situations; and therefore, the decision tree can make the best use of the limited data available—in contradistinction to existing functional scores that cannot be computed without each of the component data elements.

It is important to note that the objective function for this study was the "error" between the prediction and the eventual decision, as contrasted with a definitive measure of RV failure. Therefore, the model as it stands serves essentially to replicate expert judgment before LVAD insertion. Its clinical utility *in its present form* is twofold:

1. to codify best practices within a single institution and perhaps alert the clinician or practice when an initial evaluation before LVAD insertion is at variance with the model, and
2. to transfer expertise from experienced, successful medical centers to those less experienced.

The single-center experience might negatively affect the generality of this model, and the reader is cautioned from blindly extrapolating these results to their clinical service. Until the model has been calibrated and validated on a multicenter data set, readers are advised to repeat the analysis with data from their own VAD programs to assure consistency before it is used in clinical practice.

A related limitation is the very definition of what constitutes RV failure, which is a continuum of disease with varying severity and has changed over the extended time course of this study, and is also somewhat subjective, hence influenced by institutional bias. This study assumed that the expert decisions represented ground truth; that is, "more correct" than the model. This would imply that the model may have overlooked additional, perhaps subconscious, factors.[35] This applies to the set of independent variables as well as to the definition of optimal outcome.

In this regard, it is intriguing to consider the cases in which the model disagreed with the historical clinical decision (Figure 7). Those that the model predicted the need for RVAD but in which the patient did not receive one ($RVAD^{-/+}$) appear to have very similar survival characteristics to $RVAD^{-/-}$. In these cases, it may be concluded that the expert decision was correct and the model incorrect. Those patients who did receive an RVAD contrary to the model prediction ($RVAD^{+/-}$) faired much more poorly than those RVAD recipients for whom the model and expert

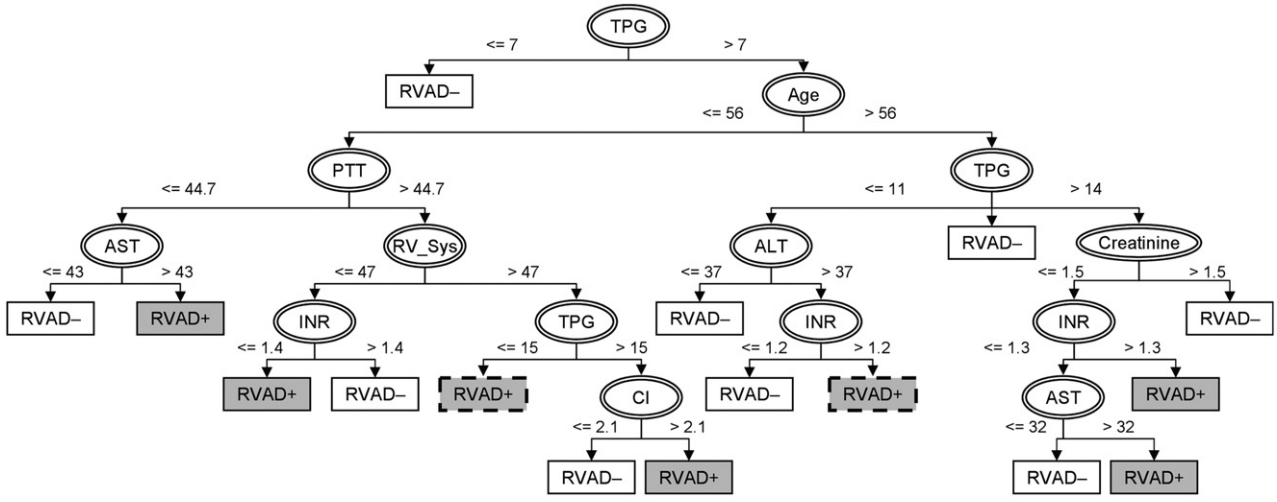

Figure 6 A variant of the aggregate decision tree model with comparative performance to the model shown in Figure 2. White, freedom of RVAD support; gray, necessity of RVAD; dashed borderline, simplified leaves. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, cardiac index; INR, international normalized ratio; PTT, prothrombin time; RV_sys, right ventricular systolic pressure; TPG, transpulmonary gradient.

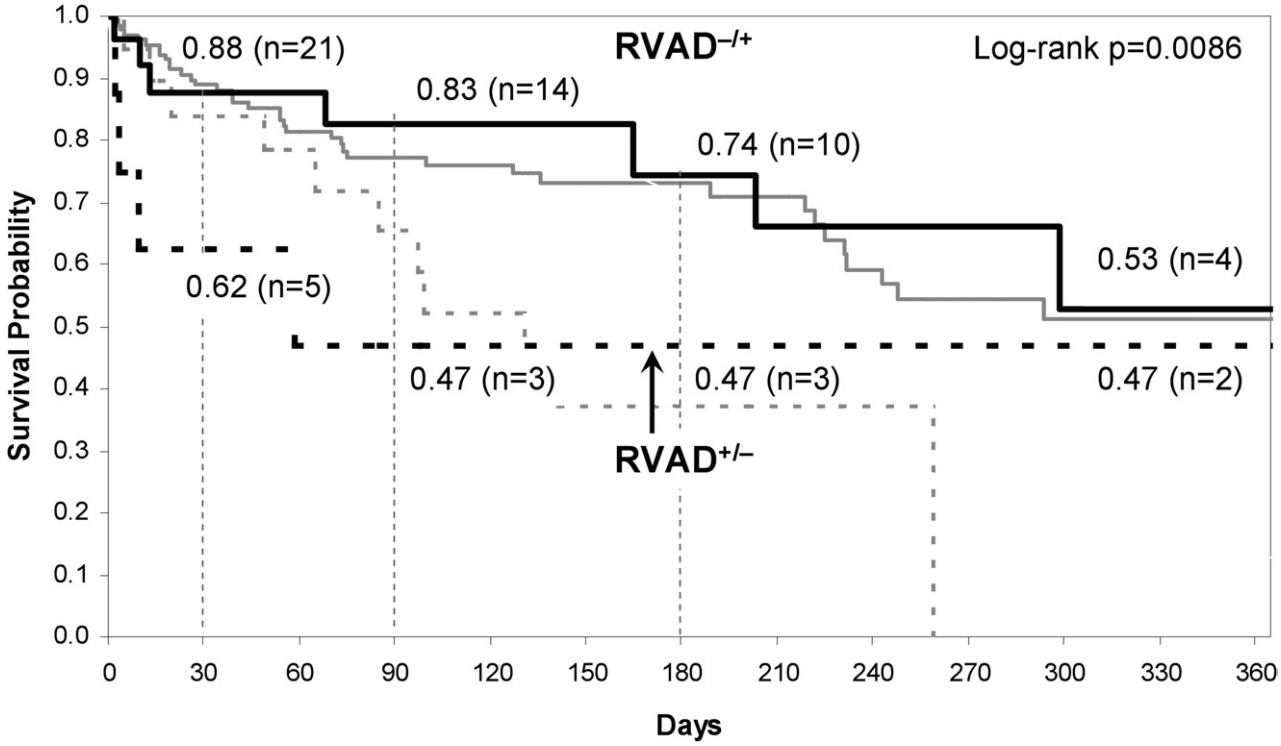

Figure 7 Kaplan-Meier survival curve for right ventricular assist device $(RVAD)^{-/+}$ patients and $RVAD^{+/-}$ patients, superimposed the survival curves of $RVAD^{-/-}$ and $RVAD^{+/+}$ (gray line). $RVAD^{+/+}$, algorithm agrees with historical clinical decision to implant an RVAD; $RVAD^{-/-}$, algorithm and clinical decision both agree to forgo an RVAD; $RVAD^{-/+}$, model predicts RVAD implantation while historical decision declined the RVAD; $RVAD^{+/-}$, model prediction disagreed with the historical decision of RVAD implant.

agreed ($RVAD^{+/+}$). Early death was far more common in this, albeit small, sub-set of 8 patients. However, 2 patients who survived past the critical 90-day period exhibited similar 1-year survival as the $RVAD^{-}$ cohort. This disparity is difficult to explain without knowledge of the patient history and re-examination of the raw data.

This illustrates that clinical judgment cannot be defined in terms of pure mathematics.[35] There are many circumstances in which the need for an RVAD is plainly obvious, such as the presentation of ventricular tachycardia, cardiogenic shock with multiorgan failure, or confounding issues such as a ventricular septal defect. Likewise, there are circumstances in which an RVAD is clearly unnecessary and a computer is not required to make a decision. The greatest clinical impact of a decision support model therefore may be in discriminating the marginal cases: to determine who will recover with a temporary RVAD and who will require long-term support.

Future improvements to this model will inevitably require additional complexity and sophistication. It would also clearly benefit from enlarging the data set and inclusion of more patients from multiple centers being implanted with the current generation of LVAD technology, which would alleviate many of the deficits caused by the limited patient cohort and single-center experience. A prospective study would allow differentiation between various degrees of RV failure, the need for short-term vs long-term support, eliminate subjectivity and related institutional bias, and allow focus on more modern LVAD devices rather than the wide assortment devices of the present study spanning from 1996 to 2009.

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