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Validation of clinical scores for right ventricular failure prediction after implantation of continuous-flow left ventricular assist devices

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KEYWORDS:
left ventricular assist device;
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risk prediction model;
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BACKGROUND: Several clinical prediction schemes for right ventricular failure (RVF) risk after left ventricular assist device (LVAD) implantation have been developed in both the pulsatile- and continuous-flow LVAD eras. The performance of these models has not been evaluated systematically in a continuous-flow LVAD cohort.

METHODS: We evaluated 6 clinical RVF prediction models (Michigan, Penn, Utah, Kormos et al, CRITT, Pittsburgh Decision Tree) in 116 patients (age 51 ± 13 years; 41.4% white and 56.0% black; 66.4% men; 56.0% bridge to transplant, 37.1% destination therapy, 17.4% bridge to decision) who received a continuous-flow LVAD (HeartMate II: 79 patients, HeartWare: 37 patients) between 2008 and 2013.

RESULTS: Overall, 37 patients (31.9%) developed RVF, defined: as pulmonary vasodilator use for ≥48 hours or inotrope use for ≥14 days post-operatively; re-institution of inotropes; multi-organ failure due to RVF; or need for mechanical RV support. Median (Quartile 1 to Quartile 3) time to initial discontinuation of inotropes was 6 (range 4 to 8) days. Among scores, the Michigan score reached significance for RVF prediction but discrimination was modest (C = 0.62 [95% CI 0.52 to 0.72], p = 0.021; positive predictive value [PPV] 60.0%; negative predictive value [NPV] 75.8%), followed by CRITT (C = 0.60 [95% CI 0.50 to 0.71], p = 0.059; PPV 40.5%; NPV 72.2%). Other models did not significantly discriminate RVF. The newer, INTERMACS 3.0 definition for RVF, which includes inotropic support beyond 7 days, was reached by 57 patients (49.1%). The Kormos model performed best with this definition (C = 0.62 [95% CI 0.54 to 0.71], p = 0.005; PPV 64.3%; NPV 59.5%), followed by Penn (C = 0.61), Michigan (C = 0.60) and CRITT (C = 0.60), but overall score performance was modest.

CONCLUSION: Current schemes for post-LVAD RVF risk prediction perform only modestly when applied to external populations.

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The prevalence of Stage D heart failure (HF) continues to rise while availability of donor hearts remains extremely limited.[1] Left ventricular assist devices (LVADs) are

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increasingly used for the treatment of these patients, not only as a bridge to transplant (BTT) but also as destination therapy (DT). As LVAD technology and experience has progressed, 1-year post-implantation survival rates now approach 80%.[2] Despite this progress, LVAD implantation is still associated with risk for complications that challenge patient selection and adversely impact outcomes. Among the most puzzling complications has been right ventricular failure (RVF) after LVAD implantation.[3] The incidence of RVF in this population ranges from 10% to 40% and varies greatly by diagnostic criteria, institution and study population.[3] The definition of RVF has also been inconsistent and has included need for right ventricular assist device (RVAD), prolonged use or delayed reinstitution of inotropes, or prolonged use of inhaled pulmonary vasodilators.[3]

Recipients of LVADs who develop post-operative RVF have poor outcomes, including increased rates of multi-organ failure, post-operative hemorrhage, pulmonary complications and thromboembolic events.[4,5] These outcomes may be improved with appropriate patient selection for alternative strategies using RVF risk prediction models.[6,7] Thus, several clinical models have been developed for this purpose, including the Michigan,[8] Penn[9] and Utah[10] scores and, more recently, the Pittsburgh Decision Tree[11] and CRITT scoring.[12] Kormos et al also reported on multivariable predictors of RVF in a large cohort.[4] These clinical models take into account patients' demographics, medication profile, pre-implant hemodynamics and laboratory measures of organ damage. Older RVF risk scores[8–10] have been developed primarily on pulsatile-flow LVAD recipients. Limited validation studies have questioned the ability of these models to accurately predict RVF in the contemporary continuous-flow LVAD population. Newer models[4,11,12] have been developed from retrospective, single-center, primarily continuous-flow LVAD data in an attempt to improve RVF prediction. However, both older and newer risk score models have undergone limited external validation.[13]

Considering that RVF remains a major cause of morbidity and mortality after LVAD implantation, obtaining an RVF risk prediction score is essential for improving outcomes. In this study, we aimed to comprehensively assess the performance of both older and newer scores in their ability to discriminate RVF in a single-center continuous-flow LVAD cohort.

Methods

Study population

We collected pre-operative and outcomes data for 116 consecutive patients who underwent elective LVAD implantation in the Emory University hospital system between January 2008 and December 2013. All patients received continuous-flow LVADs, either the HeartMate II (Thoratec, Inc.) or the HeartWare HVAD (HeartWare, Inc.). Patients with pre-operative plans for biventricular support were excluded from the study. We used the Emory electronic medical record system (EeMR) to collect pre-operative demographic and clinical data, including medical and surgical history, right heart catheterization reports, laboratory data and detailed data on pre-operative status, as this approach yielded several key predictors of RVF in previous work.[4,8–12] The EeMR was also used to track post-operative clinical outcomes and RVF adjudication elements, including duration and recurrence of pulmonary vasodilator and inotropic support, hemodynamic evidence of RVF, renal and hepatic dysfunction, and death.

Risk models and application of scores

Table 1 summarizes the predictive models evaluated and their scoring systems. For the Michigan, Penn, Utah, and CRITT models, we calculated and applied the score as originally described. Kormos et al did not suggest a specific score[4]; therefore, we simply refitted the 3 model variables in our cohort. The Pittsburgh Decision Tree assigns a probability of 0 or 1 for RVAD need according to an algorithm.[11] We calculated the assigned probability based on the algorithm and used it as binary predictor to evaluate model performance.

Outcome definition

Although not all models were developed using the same definition of RVF, and some were developed specifically to predict need for RVAD,[11,12] we evaluated performance using a unified definition of RVF to: (1) maintain comparability across predictive models; and (2) evaluate their wider clinical applicability. The primary definition against which we evaluated all models was RVF within 90 days of LVAD implantation, defined as: (1) $\geq$48-hour nitric oxide (or other pulmonary vasodilator, such as iloprost) use; (2) multi-organ failure due to persistent hypotension without evidence of sepsis (to capture patients with RVF but short duration of inotropic support because of death); (3) inotropes for $\geq$14 days post-LVAD or late re-institution of inotropes ($>$14 days post-LVAD); or (4) need for RVAD. This definition incorporates the events evaluated in the Michigan, Penn, Utah and Kormos et al models. However, this definition differs notably from the INTERMACS Protocol 3.0 definition (current at the time of initiation of this study), which requires symptoms and signs of persistent RV dysfunction (central venous pressure $>$18 mm Hg with a cardiac index $<$2.0 liters/min/m^2 in the absence of pulmonary capillary wedge pressure $>$18 mm Hg, tamponade, ventricular arrhythmias or pneumothorax) requiring RVAD or inhaled nitric oxide or inotropic therapy for $>$1 week at any time after LVAD implantation.[14] We therefore performed additional analyses with the INTERMACS definition as a secondary definition. We did not validate models against the need for RVAD alone because of the small number of events ($n = 3$).

Statistical analysis

The demographic and clinical characteristics and outcomes are described using mean and standard deviation for normal continuous variables, median and interquartile range for skewed continuous variables and number (%) for discrete variables. The characteristics are compared between patients with versus without RVF using Student's *t*-test, Mann–Whitney *U*-test and Fisher's exact test, respectively. We assessed the performance of the scores by entering each score in a logistic regression model with RVF as the outcome. For Kormos et al, we refitted the model variables in our cohort because no fixed-parameter estimates (score) were originally suggested. The Pittsburgh Decision Tree was entered as a single binary predictor. For each score, we fitted a logistic