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Development and Validation of a Personalized Risk Score for Prediction of Patient-Specific Clinical Experiences with HeartMate 3 LVAD Implantation: An Analysis from the MOMENTUM 3 Trial Portfolio

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Purpose: There currently exist no validated biomarkers of donor primary graft dysfunction (PGD) risk. We hypothesized that proteomic profiling of cold-storage preservation solution may identify novel biomarkers of post-transplant allograft dysfunction.
Methods: 169 samples of HTK preservation solution were obtained between 2016 and 2018 at Duke University and analyzed using LC-MS. After QC, proteins quantified by two or more unique precursors were retained, and protein levels were log-transformed. Univariate logistic regression was performed to identify proteins associated with ISHLT-defined moderate-severe PGD ($p<0.05$). Significant proteins were included in an iterative Monte Carlo LASSO regression model; proteins retained in at least 50% of the 1000 total iterations were selected as a parsimonious model. We used AUC analysis to assess the predictive performance of the protein model compared to a clinical model including donor age, ischemic time and predicted heart mass.
Results: Out of 1340 proteins, 213 were nominally associated with PGD in univariate analysis. Sixteen of these proteins were retained in at least 50% of iterations of the LASSO model (Table 1). All of these proteins remained significant in multivariable analysis after adjustment for the aforementioned clinical covariates. AUC of the 16-protein model was 0.90 as compared to the clinical model at 0.68 ($p<0.001$). Two proteins (FMOD and CSN5) were modestly correlated with ischemic time ($R=0.28$ and $R=-0.15$, $p<0.05$) and four proteins (CMA1, CNDP1, CSN5, and HV323) were modestly correlated with donor predicted heart mass ($R=-0.24$ - 0.2, $p<0.05$).
Conclusion: Using non-targeted proteomic profiling of traditional cold storage preservation solution, we have identified a set of novel biomarkers that are associated with PGD. Key biologic candidates within this set include MYL4, FMOD, ELOC, and CMA1. Future studies are needed to validate these signals and elucidate their role in clinical care.

Table 1: Multivariable Logistic Regression of Proteins Retained in 50% of LASSO Iterations

ID	OR (95%CI)	p.value
COP-9 Signalosome Subunit 5 (CSN5)	0.149 (0.044,0.46)	0.00137
Integrin Beta 3 (ITB3)	0.147 (0.041,0.48)	0.00219
Myosin Light Chain 4 (MYL4)	1.93 (1.3,3)	0.00306
Major Vault Protein (MVP)	2.81 (1.4,5.9)	0.00445
Immunoglobulin Heavy Chain Variable 3-23 (HV23)	2.55 (1.3,5)	0.00516
C-Reactive Protein (CRP)	0.515 (0.31,0.82)	0.00732
Methylthioribulose-1-phosphate dehydratase (MTNB)	2.66 (1.3,5.6)	0.00784
Elongin C (ELOC)	5.03 (1.4,20)	0.0171
Chymase (CMA)	0.394 (0.18,0.85)	0.0188
Alpha-1,2-mannoside (MA1A1)	0.294 (0.1,0.8)	0.0201
Carnosine Dipeptidase (CNDP1)	0.522 (0.3,0.9)	0.0211
S100AC Calcium Binding Protein (S10AC)	1.91 (1.1,3.4)	0.0223
Fibromodulin (FMOD)	2.47 (1.1,5.7)	0.0273
S100P Calcium Binding Protein (S100P)	1.64 (1,2.7)	0.0378
Eukaryotic Translation Initiation Factor 3 Subunit A (EIF3A)	0.409 (0.17,0.96)	0.0426
Vitamin K Dependent Protein Z (PROZ)	1.83 (1,3.4)	0.0456

*Adjusted for donor age, ischemic time, donor predicted heart mass.

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Transcriptional Changes of Left Ventricle Biopsy During Reperfusion Predict the Outcome of Heart Transplants

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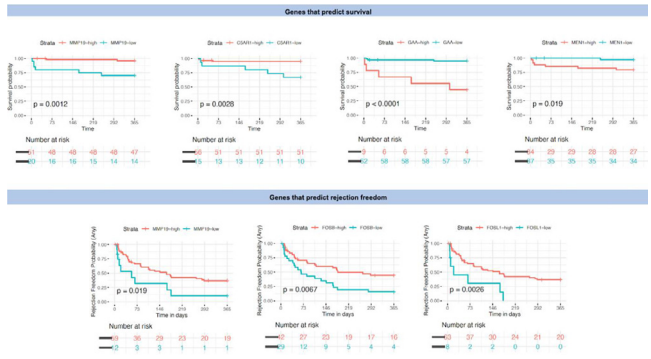
Purpose: Ischemia-reperfusion injury may predispose heart transplant to acute rejection and early mortality. Contemporary treatment possibilities are limited. We hypothesize that investigating transcriptomic changes and the underlying biological processes of ischemia-reperfusion injury could yield information on the outcome of the recipient as well as on possible therapeutic targets.
Methods: RNA was extracted and sequenced from 144 left ventricle biopsies that were procured immediately before and 1 hour after reperfusion of the heart transplant. Primary endpoints of the study were acute rejection and graft-related mortality within 1 year after transplantation.
Results: Next-generation sequencing confirmed that a total of 802 genes had significantly changed their expression 1 hour after reperfusion, of which 590 were upregulated and 212 were downregulated. Alteration of certain differentially expressed gene profiles, such as downregulation of C5AR1, GAA, and MEN1 led to a higher probability of graft-related mortality within 1 year, whereas downregulation of FOSB and FOSL1 were associated with a higher risk of acute rejection. Downregulation of MMP19 were shown to predict both mortality as well as acute rejection (Figure 1). Gene ontology pathway analysis showed that these genes are involved in several biological processes, including neutrophil mediated immunity, regulation of protein serine/threonine kinase activity, and response to corticosteroids.
Conclusion: Our study describes the changes in gene expression of the left ventricle biopsies and their related biological processes associated with ischemia-reperfusion injury after heart transplantation. We have confirmed that alterations in certain gene profiles may predict acute rejection and graft-related mortality within 1 year after transplantation. Understanding the biological pathways associated with these gene profiles could be beneficial for identification of possible therapeutic targets.



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Development and Validation of a Personalized Risk Score for Prediction of Patient-Specific Clinical Experiences with HeartMate 3 LVAD Implantation: An Analysis from the MOMENTUM 3 Trial Portfolio

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Purpose: Although clinical trials inform on efficacy of left ventricular assist device (LVAD) therapy, individualized risk assessments for outcome prediction are important in guiding implementation of such treatment. In this analysis based on the MOMENTUM 3 trial portfolio (studies sponsored by Abbott), we seek to develop and validate patient-specific risk scores to facilitate the evaluation of candidates for HeartMate 3 (HM3) LVAD implantation.

Methods: The MOMENTUM 3 trial portfolio includes 2200 patients that underwent HM3 LVAD implantation in the pivotal trial and Continued Access Protocol (CAP) study, between 2014-2018. Patients were followed for 2 years, and the primary results were presented at ISHLT 2021 and published in *Eur J Heart Fail*. 2021;23:1392-1400. In this analysis, we shall randomly assign all enrolled patients implanted with the HM3 LVAD to a Derivation Cohort or an internal Validation Cohort. The Derivation Cohort will be used to develop multivariate regression models incorporating common, pre-implant patient parameters that are typically assessed when an informed decision is established. Calculation of the risk scores will be based on the parameter estimates of the final derived models. Receiver operating characteristic curve analysis will be used to evaluate the discriminatory ability of each risk score. The ability of the risk scores to predict outcomes after HM3 LVAD implantation will be tested independently in the Validation Cohort (results expected by February 2022). To avoid bias in the development of the scores, the Validation Cohort will only be analyzed after the risk models are derived. The risk scores will include estimates (and range of individual outcomes) for endpoints including short and long-term survival, hospitalization burden, quality of life, hemocompatibility and non-hemocompatibility related adverse events.

Endpoints: The scientific discovery and validation of personalized risk scores will inform clinicians on expectations of individualized outcomes through the clinical journey following HM3 LVAD implantation. Such risk scores and individualized estimates for outcomes will facilitate enhanced decision-making and guide communication among clinicians and patients when considering LVAD therapy in advanced heart failure.

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Concomitant Valvular Procedures During LVAD Implantation and Outcomes: An Analysis of the MOMENTUM 3 Trial Portfolio

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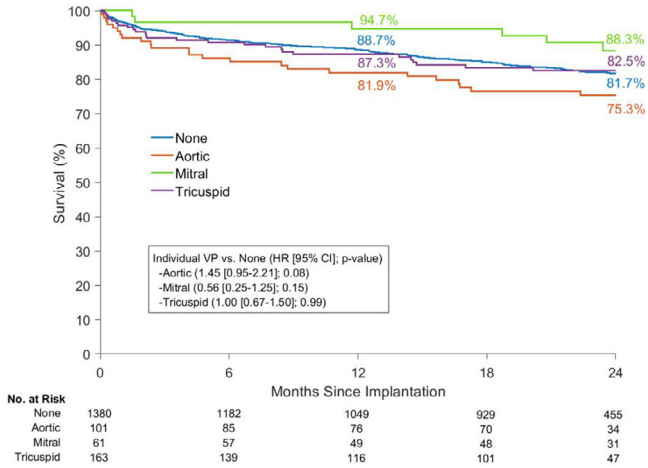
Purpose: Correction of valvular pathology is often undertaken in patients undergoing LVAD implantation but impact on outcomes is uncertain. We compared clinical outcomes with HeartMate 3 (HM3) LVAD implantation in those with concurrent valve procedures (VP) to those with an isolated LVAD implant within the MOMENTUM3 trial portfolio, including the Pivotal Trial (n=515, NCT02224755) and Continued Access Protocol/CAP (n=1685, NCT02892955).

Methods: The study included 2200 HM3 implanted patients. Among 820 concurrent procedures (including VP, CABG, RVAD, LAA closure), 466 (21.8%) were VPs (HM3+VP), including 81 aortic, 61 mitral, 163 tricuspid, and 85 patients with multiple VPs. Short and Long-term outcomes including peri-operative complications and healthcare resource use, major adverse events and survival were analyzed.

Results: Patients undergoing HM3+VP were older (63[54-70] vs. 62[52-68] yrs), with a sicker INTERMACS profile (1-2:41% vs.31%) and higher central venous pressure (11[8-16] vs. 9[6-14] mmHg) compared to HM3 alone (all $p<0.05$). The cardiopulmonary bypass time (124 [97-158] vs.76[59-96] mins); ICU (8.5 [5-16] vs. 7 [5-13]) and hospital length of stay (20 [15-30] vs. 18 [14-24] days) were longer in HM3+VP (all $p<0.0001$). A significantly higher incidence of stroke (4.9% vs. 2.4%), bleeding (33.9% vs. 23.8%) and right heart failure (41.5% vs. 29.6%) was noted in HM3+VP for 0-30 days post-implant (all $p<0.01$), but 30-day survival was similar between groups (96.7% vs. 96.1%). There was no difference in 2-year survival in HM3+VP vs HM3 alone patients (HR[95%CI]:0.93 [0.71-1.21];p=0.60). Analysis of individual VPs showed no significant differences in survival compared to HM3 alone (Figure).

Conclusion: Concurrent VPs are commonly performed during LVAD implantation, are associated with increased morbidity during the index hospitalization, but short and long-term survival are not impacted adversely when compared with those that undergo an isolated LVAD procedure.



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A Multi-Center Evaluation of Outflow Graft Obstruction with a Fully Magnetically Levitated Left Ventricular Assist Device

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