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Machine Learning Algorithms Identify Distinct Phenotypes of Right Heart Failure After Left Ventricular Assist Device Implant

A. Nayak

Y. Hu

K. J. Patel

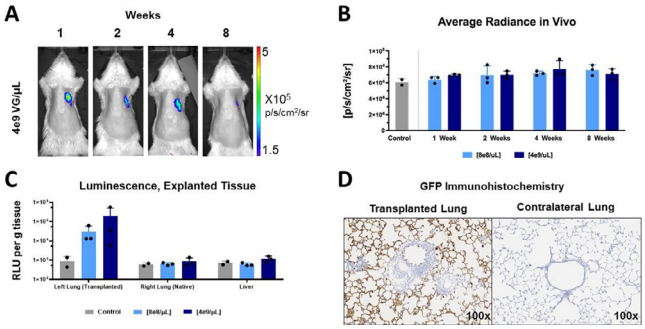
Y. Ko

A. K. Okoh

See next page for additional authors

Authors

A. Nayak, Y. Hu, K. J. Patel, Y. Ko, A. K. Okoh, J. Wang, A. Mehta, C. Liu, J. Pennington, R. Xie, J. K. Kirklin, R. L. Kormos, M. A. Simon, Jennifer A. Cowger, and A. A. Morris



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Genome-Wide DNA Methylation Analysis to Define Pulmonary Antibody-Mediated Rejection (AMR) Treatment Response

M. Jang,[1] K. Singh,[2] T. Andargie,[1] F. Seifuddin,[2] I. Tunc,[2] W. Park,[1] J. Lee,[1] H. Kong,[1] and S. Agbor-Enoh.[1] [1]Laboratory of Applied Precision Omics, Genomic Research Alliance for Transplantation (GRAfT), Division of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, MD; and the [2]Bioinformatics and Computation Core, Division of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, MD.

Purpose: Lung transplant patients with AMR often fail treatment. Defining the mechanisms involved may identify better drug targets, as well as biomarkers that can be used to tailor therapies and prevent downstream chronic lung allograft dysfunction (CLAD). Here, we perform whole-genome DNA methylome analysis to define the mechanisms associated to AMR non-responders.

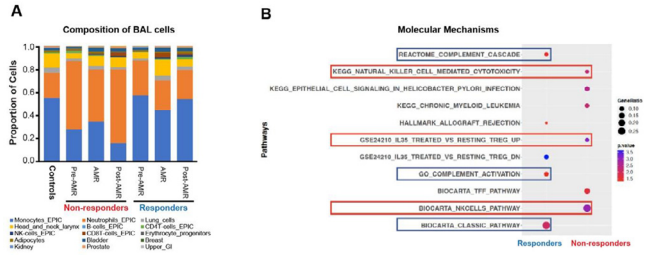
Methods: The case-control design included 26 patients with AMR and 21 controls, matched for race, sex and age.

Measurement: DNA was extracted from BAL cells for whole-genome bisulfite sequencing; controls samples were post-transplant time-matched to AMR samples.

Analysis: AMR patients were adjudicated as Non-responders if they developed CLAD within 2 years of diagnosis, otherwise, AMR patients were grouped as Responders. Bisulfite sequence reads were analyzed with an in-house computational workflow to map BAL cell-type composition, and molecular pathway differences between groups.

Results: AMR (14 Non-responders, 12 Responders) were diagnosed at a median 9.6 months post-transplant. We identified different BAL cell-type compositions; monocyte predominance for Responders vs. neutrophilic predominance for non-responders ($p<0.01$). The different cell composition was present before AMR diagnosis and persistent after treatment. Cell-composition was similar for Responders and Controls (**Fig A**). We also identified pathway differences; Responders showed classic complement activation pathways, while Non-responders showed NK-cells and other antibody-mediated cytotoxic pathways (**Fig B**).

Conclusion: We identified different BAL cell composition and mechanisms that correlate with response to AMR treatment. If validated, these features are poised to identify novel drug targets and may serve as biomarkers to tailor AMR treatment.



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Machine Learning Algorithms Identify Distinct Phenotypes of Right Heart Failure After Left Ventricular Assist Device Implant

A. Nayak,[1] Y. Hu,[1] K.J. Patel,[1] Y. Ko,[1] A.K. Okoh,[1] J. Wang,[1] A. Mehta,[1] C. Liu,[1] J. Pennington,[2] R. Xie,[2] J.K. Kirklin,[2] R.L. Kormos,[3] M.A. Simon,[4] J. Cowger,[5] and A.A. Morris.[1] [1]Emory University, Atlanta, GA; [2]University of Alabama, Birmingham, AL; [3]University of Pittsburgh Medical Center, Pittsburgh, PA; [4]University of California at San Francisco, San Francisco, CA; and the [5]Henry Ford Health System, Detroit, MI.

Purpose: The challenges of predicting right heart failure (RHF) post-Left Ventricular Assist Device (LVAD) may reflect heterogenous underlying pathophysiology. We hypothesized that 1) machine learning (ML) algorithms applied to multidimensional phenotypic data from patients with confirmed post-LVAD RHF will allow identification of distinct RHF phenotypes, 2) identified phenotypes will have unique clinical trajectories.

Methods: Patients with acute post-LVAD RHF (RVAD and/or ≥ 14 days inotropes post-implant, n=2,550) were identified from the ISHLT Mechanically Assisted Circulatory Support database (n=15,428); and divided into a derivation (DC, n=1,531) and validation cohort (VC, n=1,019). First, unsupervised ML (blinded to clinical outcomes) was applied to 41 pre-implant variables to identify distinct phenotypes. Then, resultant phenotypes were clinically validated by comparing outcomes of 1) RVAD/ death during index hospitalization 2) ICU Length of Stay. Results were validated in the VC. Risk discrimination of existing RHF risk scores was compared between phenotypes.

Results: Four distinct RHF phenotypes were identified. (Figure 1) Phenotype I had the worst, and Phenotype III had the best outcomes. Results were validated in the VC. RHF risk scores were modestly accurate at predicting RHF in those with severe shock (Phenotype I) pre-implant; but performed poorly for phenotypes without prominent shock. (Table 1)

Conclusion: ML identifies novel pathophysiological phenotypes of RHF, among which current risk scores were useful to predict RHF only in patients in severe shock prior to implant.

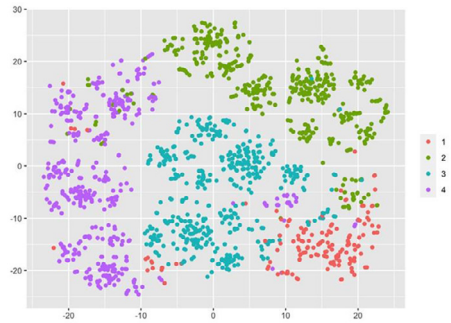

Figure 1: T- Distributed Stochastic Neighbor Embedding (t-SNE) representation of distinct RHF phenotypes: Unsupervised machine learning applied to 41 pre-implant variables in patients who met criteria for acute post-LVAD RHF identified 4 mutually exclusive RHF phenotypes.

	Phenotype I (n = 170)	Phenotype II (n = 458)	Phenotype III (n = 478)	Phenotype IV (n = 425)
	Severe shock phenotype (SCAI stage C-D)	ICM with low grade shock (SCAI stage B-C)	ICM without shock	NICM without shock
	Selected characteristics of identified phenotypes			
Age (years)	≈55	≈55	≈55	≈65
HF Etiology	≈35% ICM	≈95% ICM	100% ICM	100% NICM
BMI	⇌ or ↑	⇌	↑	⇌ or ↑
INTERMACS profile1-2	≈85%	≈20%	≈15%	≈10%
Index hospitalization characteristics	≈85% mechanically ventilated (MV), ≈15% on dialysis	<10% MV or on dialysis	<10% MV or on dialysis	<10% MV or on dialysis
Liver function tests	↑↑	↑	⇌	⇌
C Reactive Protein	↑↑	↑	⇌ or ↑	⇌ or ↑
Pulmonary Artery Pulsatility Index (PAPi)	⇌ or ↓	⇌ or ↓	⇌	↑
Tricuspid regurgitation (TR) by TTE	≈20% with moderate-severe TR	100% with moderate-severe TR	None with moderate-severe TR	≈35% with moderate-severe TR
	Clinical outcomes			
RVAD/death during index hospitalization (OR[95% CI])	2.58 [1.75 – 3.79]	0.98 [0.70 – 1.35]	0.62 [0.43 – 0.87]	REF
ICU LOS (median days [IQR])	21 [14, 35]	15 [8, 28]	13 [8, 25]	15 [8, 27]
	Area Under the Receiver Operating Characteristics Curve (AUROC) for RHF risk scores			
Michigan Score AUROC	0.75 [0.72 -0.79]	0.58 [0.56 -0.60]	0.53 [0.51 -0.55]	0.49 [0.47 -0.51]
Utah Score AUROC	0.61 [0.56-0.66]	0.52 [0.50-0.55]	0.56 [0.53-0.58]	0.48 [0.45 -0.51]

Table 1: Selected clinical characteristics, clinical outcomes, and AUROC of commonly used RHF risk scores for identified phenotypes: Phenotype I had the worst outcomes, followed by II and IV; and Phenotype III had the best outcomes. Traditional RHF risk scores were modestly accurate at predicting RHF in those with severe shock (Phenotype I) pre-implant, mostly due to variables representative of shock. Models failed to predict RHF in those phenotypes without prominent shock (Phenotypes II-IV). *SCAI: Society of Cardiovascular Angiography and Intervention*