PHENOTYPING OF HEART FAILURE WITH PRESERVED EJECTION FRACTION VIA TENSOR FACTORIZATION

1. SPECIFIC AIMS

In contrast to heart failure with reduced ejection fraction, no disease-modifying therapy exists to date for heart failure with preserved ejection fraction (HFpEF), a condition that accounts for approximately 50% of all heart failure cases and affects an estimated 3 million patients in the United States.[1-3] This stalemate in development of new therapies for HFpEF has been largely attributed to the multifactorial pathophysiology of HFpEF and the resultant heterogeneity of patients.[4] In turn, this heterogeneity has prevented targeting the appropriate patient populations in clinical trials and has led to neutral results to date.[5] However, pathophysiological mechanisms tend to cluster within patient groups and multiple mechanisms are in action for each patient.[6] To move forward with new therapies for HFpEF, we need to identify a distinct number of pathophysiologically different but also clinically relevant HFpEF patient groups ("phenotypes") characterized by reasonable differentiation. **Therefore, besides reaching statistically significant differentiation between groups, we need these phenotypes to be clinically interpretable to target pathophysiological pathways with appropriate treatment strategies.**

Previous efforts to classify HFpEF patients into phenotypes have adopted variations of clustering analysis that lead to phenotypes with limited clinical interpretation.[7] In this application, we propose to classify a well characterized cohort of 450 patients with HFpEF who have received care in Emory Healthcare into a number of clinically relevant phenotypes using nonnegative tensor factorization, a novel computational phenotyping approach developed by Dr. Jimeng Sun's lab at the Georgia Institute of Technology.[8] This approach has been previously implemented by Dr. Sun and colleagues to derive candidate clinical phenotypes in a large heart failure population using electronic health records data.[8] We hypothesize that there are multiple distinct clinical phenotypes in our HFpEF population that can be characterized using the tensor factorization approach. We will then examine 2-year outcomes (death and hospitalizations) to identify differential responses to medications (neurohormonal antagonist classes, i.e. angiotensin-modulating agents, beta blockers, mineralocorticoid receptor antagonists) across these clinical phenotypes. Response to medications will be defined by the composite rates of death plus hospitalization by 2 years in models taking into account time-varying exposure to certain medication classes and clinical factors known to be associated with outcomes in HFpEF. We hypothesize that the various neurohormonal antagonist classes could have differential treatment effects according to phenotype. Our specific aims are:+

Aim 1: To identify significantly distinct phenotypes among HFpEF patients from a well-characterized, Emory-based cohort, using a novel nonnegative tensor factorization algorithm. For this purpose, we will first construct a multi-way tensor based on clinical information of HFpEF patients. We will then factorize that tensor to extract significant phenotypes characterized by various clinical features such as demographics, concomitant diagnoses, medications, symptoms, and lab results.

Aim 2: To identify differential responses to major classes of medications used in the treatment of heart failure patients across phenotypes. For this purpose, we will use appropriate regression models to examine 2-year outcomes (death and hospitalization) in association to medication exposure across HFpEF phenotypes after taking into account established risk factors in this patient population.

Our plan is to apply for external funding building on data and results developed through this innovation project, with the goal to refine and validate a tensor factorization algorithm for HFpEF phenotyping using large-scale electronic health records data with limited expert supervision. We also plan to explore a long-term multi-site collaboration for validation of the phenotyping method and potential differential responses to treatment.

Patients with HFpEF are a growing population at high-risk for adverse events who may benefit from an individualized, phenotype-based approach to therapeutic discoveries. Our long-term goal is to introduce an approach that will target the pathophysiological mechanisms that best characterize each HFpEF phenotype.

2. SIGNIFICANCE

The Conundrum of HFpEF: In recent studies, heart failure with preserved ejection fraction (HFpEF) is estimated to account for 40% to 60% of HF cases,[1,2] corresponding to an estimated 3 million patients in the Unites States.[3] Patients with HFpEF have unfavorable outcomes, comparable to those of patients with heart failure and reduced ejection fraction.[1,9,10] In contrast to heart failure with reduced ejection fraction, however, there is no disease-modifying therapy for HFpEF to date. Proven therapies for heart failure with reduced ejection fraction have failed to replicate similar treatment effects in HFpEF and most clinical trials with novel targets in HFpEF have not yielded encouraging signals despite plausible pathophysiological mechanisms.[5,11,12]

Part of this stalemate has been attributed to the multifactorial pathophysiology of HFpEF and the resulting heterogeneity of patients.[13] Next to the conventional concept of diastolic dysfunction, several other contributory mechanisms have been implicated in HFpEF, including reduced left ventricular systolic reserve, systemic and pulmonary vascular dysfunction, reduced nitric oxide bioavailability, reduced chronotropic reserve, right ventricular dysfunction, impaired autonomic tone, and left atrial dysfunction.[6] However, not only is impractical to investigate isolated pathophysiological and contributory mechanisms in humans, but it is also biologically implausible that these mechanisms act in isolation. Mechanisms tend to cluster in groups ("phenotypes") of HFpEF patients and multiple mechanisms are active in each patient.[6] In addition, it is biologically implausible to expect that patients will be categorized into mutually exclusive phenotypes.[7] A clinically relevant approach should allow patients to belong to more than one phenotype if clinically meaningful. Therefore, we need to identify a reasonable number of distinct but clinically meaningful HFpEF patient phenotypes in order to move forward with new HFpEF therapies. These phenotypes will allow us to overcome the limitations of the current "one-size-fits-all" approach and identify appropriate pathophysiological targets according to the most active pathways and key abnormalities in each phenotype. **No study to date has attempted to classify HFpEF patients into phenotypes based on a comprehensive approach using multiple clinical characteristics. Also, no study to date has evaluated for differential treatment effects of medication classes according to HFpEF phenotypes.**

3. INNOVATION

Comprehensive Approach to HFpEF Phenotypes: Most previous studies have examined a single characteristic that was thought to identify HFpEF patients with a distinct pathophysiology. Examples include various forms of left ventricular remodelling, comorbidities (e.g. diabetes), and biomarkers (e.g. inflammatory). Focusing on a single characteristic has definite merit from a pathophysiological perspective. However, a single characteristic can identify a therapeutic target only in select cases (e.g. left ventricular dyssynchrony in patients with heart failure and reduced ejection fraction or left ventricular hypertrophy in HFpEF). For most patients with HFpEF, however, individual clinical characteristics are unlikely to identify patients who mighty benefit from established or novel therapeutic interventions. **We therefore suggest a paradigm shift in our approach to HFpEF. Instead of focusing on individual characteristics, we propose to group these characteristics into a reasonable number of phenotypes that each has a high prevalence ("loading") of certain pathophysiological perturbations and therefore are clinically interpretable**. For example, a dominant metabolic phenotype might be characterized by diabetes, hypertension, and lipid abnormalities, whereas a dominant vascular disease phenotype might be characterized by combinations of coronary artery, peripheral artery, and cerebrovascular disease. Similarly, a phenotype might be related to heart senescence accelerated by comorbidities like renal disease and musculoskeletal abnormalities. It is reasonable to assume that these patient groups will respond differently to medications and other treatment modalities (e.g. exercise programs).

Nonnegative Tensor Factorization: Dr. Sun and colleagues have developed a suite of phenotyping algorithms based on nonnegative tensor factorization, which can generate phenotype candidates without expert supervision. We view our nonnegative tensor factorization model as a building block for computational phenotyping from clinical research data or electronic health records data. In particular, nonnegative tensor factorization methods have the following highly desirable properties:

1. Derive multiple phenotypes simultaneously from the data without user supervision or domain expertise.
2. Captures data source interaction, such as the diagnosis and medication interaction.
3. Generates concise phenotype definitions that are easy for clinicians to understand each phenotype.
4. Provide soft phenotype assignments so that a patient can have multiple phenotypes with different degrees of association.

Ability to Expand to Unsupervised Approach for Electronic Health Records Application: The tensor factorization methods have been applied successfully on electronic health records data.[8] In this study, we plan to extract and define phenotypes based on more fine-grained and high-quality research data that have already been collected by Dr. Kalogeropoulos' team. Therefore, we will be able to develop the algorithm on highly adjudicated data. As a long-term goal, we plan to validate the extracted phenotypes using large-scale electronic health records data from Emory and possibly from other institutions through a multi-site study.

4. APPROACH

4.1. Overview of Study Design

This is an observational, retrospective study. We are planning to apply a novel nonnegative tensor factorization algorithm in 450 patients with HFpEF to cluster these patients into a reasonable number of clinically relevant

phenotypes. Briefly, we will construct an input tensor that captures different aspects of patient characteristics (e.g., symptom and concomitant diagnosis as shown in **Figure 1** below). Each element in the tensor corresponds to the co-occurrence of a specific symptom and concomitant diagnosis on a given patient. We then factorize the input tensor into *R* rank-one tensors (phenotypes). Here *R* is the number of phenotypes we discover from the data. Each phenotype has several factors, one for each aspect (e.g., patient, symptom, and diagnosis factors). More specifically, patient factor specifies which patients have this phenotype, while symptom and diagnosis factors describe the relevant symptoms and diagnoses for this phenotype. Note that the nonnegative tensor factorization can be viewed as a powerful generalization of principal component analysis, where we only have nonnegative elements in the data and in the model, and can deal with multi-way data instead of a 2-way matrix as in principal component analysis. Such tensor methods have shown great promises in phenotyping electronic health records data.

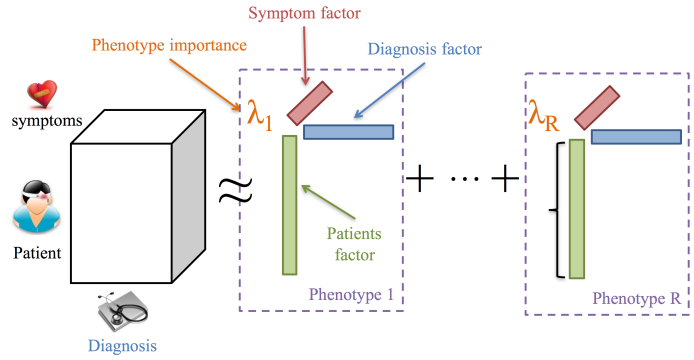

Figure 1. *Generating candidate phenotypes using tensor factorization.*

In this study we seek to apply, extend, and validate the tensor methods for targeting a specific disease condition, namely HFpEF. We will then examine the association of the identified phenotypes with outcomes using regression models. In addition, we will examine whether the main medication classes used in heart failure have a differential effect on outcomes (death and hospitalization) according to identified HFpEF phenotypes.

4.2. Study Population

To identify and characterize this HFpEF population in detail, we have already individually reviewed the records of adults (age ≥18) who received outpatient care associated with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 402.X1, 404.X1, 404.X3, and 428.XX between January 1, 2012 and April 30, 2012 in Emory Healthcare by cardiologists. These (ICD-9-CM) codes are aligned with the definitions used by the Centers for Medicare & Medicaid Services to capture heart failure.[14] Medical records were reviewed for symptoms, signs, and treatment of heart failure, last reported left ventricular ejection fraction, previous left ventricular ejection fraction documentation, and special causes of heart failure. Patients were considered to have HFpEF if heart failure diagnosis was verified, current left ventricular ejection fraction was >40%, and all previous left ventricular ejection fraction were >40%. These cutoff points have been used in recent clinical trials.[15] We excluded patients with (1) specific cardiomyopathies, e.g. hypertrophic, stress-induced, infiltrative, restrictive, chemotherapy-induced; (2) complex congenital heart disease as the etiology of heart failure; (3) previous heart transplant or mechanical circulatory support; (4) primary right-sided disease, e.g. right ventricular cardiomyopathy, Class I pulmonary arterial hypertension; (5) primary valvular disease; and (6) loss to follow up (no further encounters) or lack of data on left ventricular ejection fraction.

4.3. Baseline Characteristics and Comorbid Conditions

Baseline demographic, anthropometric, vital signs, laboratory, and medications data and comorbid conditions were collected through the Emory Electronic Medical Record system from the index clinic visit. We defined the presence of coronary artery disease as documented history of acute myocardial infarction, acute coronary syndrome, or stable angina; cerebrovascular disease as history of ischemic stroke, transient ischemic attack, or carotid endarterectomy or stenting; and peripheral arterial disease as history of claudication or vascular surgery or intervention. We classified percutaneous procedures unrelated to coronary artery disease (valve procedures, defect closures, electrophysiology procedures except pacemaker or implantable defibrillator implantation) as non-coronary percutaneous interventions. Other comorbid conditions, including chronic lung disease, sleep apnea, depression, and dementia, were defined on the basis of medical record documentation, including physician diagnosis and relevant therapy. History of cancer was considered positive if non-localized cancer with systemic spread potential was reported. Smoking status was classified as current, former, or never based on self-report status. For renal function, we considered estimated glomerular filtration rate (Modification of Diet in Renal Disease formula), serum creatinine, and blood urea nitrogen. Diabetes was considered present if the patient reported history of diabetes accompanied by use of antidiabetic medications or fasting glucose was >125 mg/dL. Both paroxysmal and chronic atrial fibrillation conferred excess risk for adverse outcomes; we therefore treated atrial fibrillation as a single condition. We used the New York Heart Association classes to

quantify HF status. For ease of interpretation, we have merged New York Heart Association Class I with II and New York Heart Association Class III with IV.

The baseline characteristics of the study population are presented in **Table 1**. Median left ventricular ejection fraction is 55% (25^{th} – 75^{th} percentile, 50 to 60). Patients have median age of 73 years, representative of this population, with elevated body mass index, are predominately female, and 45% are black. Most patients have hypertension, while other comorbidities are present in over 20% of the population including diabetes, coronary artery disease, atrial fibrillation, chronic lung disease, and sleep apnea. The medications mix reflect the fact that there is no specific evidence-based recommendation for the treatment in patients with HFpEF.

Table 1. Baseline Patient Characteristics (N=445)

Characteristic	Value	Characteristic	Value
Age, years	73 (63, 83)	Atrial fibrillation/flutter, N (%)	190 (42.7)
Women, N (%)	257 (57.8)	Cerebrovascular disease, N (%)	61 (13.7)
Race, N (%)		Peripheral vascular disease, N (%)	40 (9.0)
White	227 (51.0)	Chronic lung disease, N (%)	111 (24.9)
Black	199 (44.7)	Sleep apnea, N (%)	105 (23.6)
Other	19 (4.3)	Depression, N (%)	66 (14.8)
Hispanic ethnicity, N (%)	7 (1.6)	Dementia, N (%)	18 (4.0)
Marital status, N (%)		History of systemic cancer, N (%)	49 (11.0)
Married	218 (49.0)	Renal replacement therapy, N (%)	15 (3.4)
Single	56 (12.6)	Estimated GFR, * ml/min/1.73m^2	57.0 (41.8, 75.5)
Divorced/Separated	61 (13.7)	Hemoglobin, g/dL	12.1 (10.8, 13.2)
Widowed	110 (24.7)	Sodium, mEq/dL	139 (137, 140)
Body mass index, kg/m^2	30.9 (26.1, 37.8)	Potassium, mEq/dL	4.1 (3.8, 4.5)
Systolic blood pressure, mmHg	313 (119, 147)	Fasting glucose, mg/dl	104 (91, 132)
Diastolic blood pressure, mmHg	70 (60, 80)	Blood urea nitrogen, mg/dl	22 (15, 31)
Smoking status, N (%)	151 (33.9)	Creatinine, mg/dl	1.16 (0.90, 1.49)
Current smoker	36 (8.1)	Total protein, g/dL	7.0 (6.6, 7.4)
Former smoker	115 (25.8)	Serum albumin, g/dl	3.6 (3.3, 3.9)
NYHA class, N (%)		Total cholesterol, mg/dL	150 (123, 178)
I–II	335 (76.0)	LDL cholesterol, mg/dL	77 (58, 104)
III-IV	107 (24.0)	HDL cholesterol, mg/dL	43 (35, 53)
Hypertension, N (%)	404 (90.8)	Triglycerides, mg/dL	102 (70, 156)
Diabetes, N (%)	194 (43.6)		
Coronary artery disease, N (%)	194 (43.6)		
Coronary revascularization, N (%)	163 (36.6)		
Non-coronary cardiac surgery, N (%)	42 (9.4)		

* Calculated with the Modification of Diet in Renal Disease study equation. ACE: angiotensin converting enzyme; NYHA: New York Heart Association. Continuous variables are expressed as median (25^{th}–75^{th} percentile)

4.4. Outcomes Ascertainment and Endpoints

Outcomes data (death, hospitalizations, and emergency department visits) were collected through the Emory Electronic Medical Record system up to 2 years of follow up after the date of index visit. For patients who were alive during the last encounter but did not continue to receive care in our system throughout the 2-year follow-up period, the last encounter was considered the last date of follow up. **All hospitalizations were individually adjudicated for primary admission reason.** We classified hospitalizations into cardiovascular and non-cardiovascular on the basis of the primary admission diagnosis. Cardiovascular hospitalizations were further classified into heart failure related and non-heart failure. For analysis of outcomes, we will consider (1) rates of all-cause, cardiovascular, and heart failure related hospitalizations over the entire follow-up period; and (2) composite time-to-event endpoints, including death or first any-cause hospitalization, death or first cardio-vascular hospitalization, and death or first heart failure related hospitalization.

Median follow up in our population is 2.0 years, for a total of 787 patient-years. There have been 44 deaths (9.9%). Kaplan-Meier mortality at 1 and 2 years is 5.8% and 10.6%, respectively. There is total of 609 all-cause hospitalizations (rate: 77.4 per 100 patient-years; 95% confidence interval [CI]: 67.4--87.3). Of these, 260 (42.7%) were for cardiovascular causes inclusive of heart failure (rate: 33.0 per 100 patient-years; 95%CI: 26.9--39.2) and 173 (28.4%) had specifically heart failure as the primary admission diagnosis (rate: 22.0 per 100 patient-years; 95%CI: 16.9--27.1). The 2-year rate of death or all-cause hospitalization (whichever comes first) was 58.6% (95%CI: 53.9%--63.3%), death or cardiovascular hospitalization 36.6% (95%CI: 32.2%--41.4%), and death or heart failure related hospitalization 28.0% (95%CI: 24.0%--32.6%).

4.5. Analytic Plan

Aim 1 - Data Preparation: We will carefully check for outliers (as these can distort analysis) and transform variables as needed to achieve reasonably normal distributions for analysis purposes. In addition, we plan to

group the low-level medical codes such as ICD-9-CM codes into meaningful categories using appropriate medical ontology such as the Systematized Nomenclature of Medicine[16] and Clinical Classifications Software [17] developed by the Agency for Healthcare Research and Quality.

Aim 1 - Stability Considerations: We plan to conduct stability analysis of the tensor factorization to ensure the statistical significance of the results. We automatically derive multiple candidate phenotypes from the data and analyze the factors for stability, conciseness, predictive power, and clinical relevance. Specifically, we will assess how many alternating minimization iterations are necessary to converge to a stable solution. Also we will evaluate whether the generated phenotypes are stable towards perturbation and different initializations.

Aim 2 - Association of Phenotypes with Outcomes: For analysis of association of phenotypes with 2 –year outcomes, we will use (1) negative binomial regression models for hospitalization rates (to account for over-dispersion, which is commonly encountered in these data) and (2) proportional hazards models for composite time-to-event endpoints (death or first any-cause hospitalization, death or first cardiovascular hospitalization, and death or first heart failure related hospitalization). We will account for clinical risk factors known to be associated with outcomes in patients with HFpEF based on existing literature.[18] We will also assess response to medications by examining time-varying exposure to major medication classes prescribed for heart failure.

4.6. Study Team

Andreas Kalogeropoulos, MD MPH PhD (PI), Assistant Professor of Medicine (Cardiology) at Emory, has an established record in HF research and over 130 peer-reviewed publications. He will be responsible for study conduct, data acquisition, data completeness and quality, and regulatory aspects. Dr. Kalogeropoulos will be responsible for statistical analysis and deliverables (abstracts and manuscripts).

Jimeng Sun, PhD (Co-PI), Associate Professor in the School of Computational Science and Engineering, at College of Computing in Georgia Institute of Technology, focuses on health analytics using electronic health records and data mining, especially in designing novel tensor analysis and similarity learning methods and developing large-scale predictive modeling systems. He has published over 70 papers, filed over 20 patents (5 granted). He has received the International Conference on Data Mining best research paper award in 2008, SDM best research paper award in 2007, and Knowledge Discovery and Data Mining Dissertation runner-up award in 2008. Dr. Sun will be responsible for developing the modeling methodology and algorithm validation.

Andy Smith, MD (Co-I), Professor of Medicine in the Emory University School of Medicine, is the Director of the Heart Failure program at Emory since 1992 and has substantial experience with clinical studies, ensuring the feasibility and successful implementation of the current proposal. He will provide clinical expertise and input and facilitate availability of data and any clinical resources needed for the study.

4.7. Potential Challenges and Mitigation Strategies

Inadequate Sample Size: If phenotyping algorithms encounter limitations because of sample size, we will expand the cohort with additional patients continuing data extraction throughout calendar year 2012. Based on our available preliminary data (450 patients from 1/2012 to 4/2012), we expect to be able to double the number of eligible unique patients with this approach.

Unclear Clinical Phenotypes: Because we aim to develop clinically actionable phenotypes, if we encounter clinically unclear phenotypes (i.e. phenotypes that do not clearly correspond to one or more pathophysiological pathways), we will supplement phenotyping by extracting and incorporating echocardiographic data.

4.8. Timeline

Considering that our data are already available in REDCap, which has data cleaning, validation, and export capabilities, we expect minimal delays for start-up and final data preparation. We already have Emory IRB approval for use of these data (IRB00004584) and we therefore expect expedited IRB approval for this project. Also, Dr. Sun and his team have already developed the fundamentals of the algorithm. Therefore, we expect to present our results by the end of the funding period and apply for external funding afterwards (**Table 2**).

Table 2. Timeline of Proposed Activities

Activity	7/2016	8/2016	9-12/2016	1-3/2017	4-6/2017
Study start up and IRB approval	X				
Data cleaning and database lock		X			
Identification of phenotypes (Aim 1)			X		
Effect of phenotypes on outcomes (Aim 2)				X	
Prepare manuscripts			X	X	X
Prepare external funding application					X

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