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Psychosocial Syndemics and Multimorbidity in Hospitalized Patients with Heart Failure

STATISTICAL ANALYSIS PLAN

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Kenneth E. Freedland, PhD, Principal Investigator
Brian C. Steinmeyer, MS, Senior Statistical Analyst

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Note: This statistical analysis plan was updated after the grant was funded but before the start of enrollment, due to post-funding changes in the study protocol that were necessary because of the COVID-19 pandemic. Aims that were changed after funding are marked “revised.”

Planned Sample Size

The plan is to enroll **n=535** patients with heart failure (HF) within one month after hospital discharge, including 268 (50%) women, 135 (25%) African American patients, and 25 (5%) Asian American patients. Very few patients at the recruitment site identify as Hispanic or Latino.

Data Loss and Imputation

Participants with Dementia: The only data to be collected from patients with dementia will be from electronic medical records. Consequently, little if any data loss is expected in this subgroup.

Participants without Dementia: Participants without dementia will be asked to complete an interview and questionnaires on one occasion, as soon as possible after enrollment. Based on our previous studies of patients with HF, we anticipate that up to 5% of these participants will fail to complete some or all of the baseline assessments due to illness, fatigue, logistical barriers, or other problems. Based on these considerations, we expect to obtain complete data on approximately n=508 patients. We will use multiple imputation for data that are likely missing at random (MAR).

Planned Statistical Analyses

Aim 1. Coprevalence Analyses: We will use one-way Chi-square goodness-of-fit tests to identify comorbidities for which the coprevalence is significantly higher than would be expected by chance alone. These analyses will be limited to conditions that occur in >5% of the sample.

Aim 2. Synergistic Effects of Coprevalent Conditions: The coprevalences of comorbid conditions (even the most common ones) are likely to be too low to support adequately powered interaction tests. As an alternative, we will create ordinal **syndemic exposure factors (SEFs)** representing the number of conditions present in each comorbidity pair (0, 1, or 2). The relationship between the SEF and the outcome of interest can be linear or curvilinear; the latter is more consistent with a synergistic effect. The primary analyses will focus on psychiatric-medical comorbidities and pairs of psychiatric comorbidities; additional analyses will test syndemic relationships between pairs of medical comorbidities.

Aim 2a (Revised). Multiple All-Cause Readmissions: We will fit separate marginal proportional rates models[1] to each pair of coprevalent conditions, to test the hypothesis that higher SEF scores predict more all-cause hospital readmissions, after adjusting for covariates that predicted multiple all-cause readmissions in a previous study (Freedland et al., under review), including age, New York Heart Association (NYHA) class, diabetes, chronic obstructive pulmonary disease (COPD), hypertension, and estimated glomerular filtration rate (eGFR). For any given model, the factors that comprise the SEF will be excluded from the covariate list. For example, COPD will be removed from the list of covariates in a model in which the SEF refers to the combination of depression and COPD. Additional covariables that are needed for Aim 3 (below) will be added.

Aim 2b. (Revised). Self-Care of Heart Failure: We will regress the Maintenance, Management, and Confidence scores from the Self-Care of Heart Failure Index (SCHFI v7.2) on each SEF in one-way analysis of covariance (ANCOVA) models, adjusting for known correlates of HF self-care including age, race, education, number of medications, and smoking status. Additional covariables that are needed for Aim 3 (below) will be included. Statistical inference will be based on the planned model contrasts: $C1 = \mu 0 - \mu 1$, $C2 = \mu 0 - \mu 2$, and $C3 = \mu 1 - \mu 2$, where μi represents the mean response within level i of the SEF.

Aim 2c. Perceived Global Health: We will regress the 12-item PROMIS Global Health short form V1.2 on each SEF in one-way analysis of covariance (ANCOVA) models, adjusting for known correlates of perceived health in patients with HF including NYHA class, race, and perceived sufficiency of income.[2] Additional covariables that are needed for Aim 3 (below) will be included.

Aim 3. Vulnerable Subgroups

For the purposes of this study, vulnerable subgroups will be defined by race, sex, and social determinants of health (SDOH). Examples of SDOHs include financial difficulties, limited access to health care services, and exposure to violence.

Aim 3a. Effects of Race, Sex, and SDOH on Outcomes: Vulnerable subgroups of patients with HF will be examined in the same models that will be tested for Aim 2.

Aim 3b. Clustering of Syndemic Conditions within Vulnerable Subgroups: We will fit proportional odds models to test the relationship of each vulnerability factor (e.g., race) to each SEF. The odds ratio associated with the vulnerability factor (OR_{vf}) is the effect of interest.

Aim 4. Effects of Syndemic Clusters on Outcome Disparities in Vulnerable Subgroups: We will add SEFs to the Aim 3a models. If adding the SEF attenuates the effect of the vulnerability factor on the outcome, this supports the hypothesis that the syndemic pair partially accounts for the effect of the vulnerability factor on the outcome.

Aim 5. Effects of Multimorbidity on Outcomes

This aim focuses on the effects of the overall burden of multimorbidity on hospital readmissions, HF self-care, and perceived global health. The Centers for Medicare & Medicaid Services (CMS) has found that costs and readmissions are dramatically higher in patients with ≥6 chronic conditions than patients who have <6 conditions.[3] Since all participants in this study will have heart failure, we will reduce the multimorbidity cut point by one to ≥5 (vs. <5) comorbidities. This categorical variable will be used in the primary analyses because of the CMS findings and because of the skewness of multimorbidity counts. The raw counts will be used in secondary analyses, along with the Charlson and Deyo weighted indices.

Aim 5a. Overall Effects of Multimorbidity: We will use a marginal proportional rates model to test the hypothesis that multimorbidity is an independent predictor of hospital readmissions, after controlling for known predictors including age and NYHA class and excluding comorbidities. We will use one-way ANCOVAS to examine the effects of multimorbidity on the HF self-care and global health outcomes.

Aim 5b. Differences in Multimorbidity Between Vulnerable Subgroups: We will use logistic regression models to examine the effect of multimorbidity on the dichotomous vulnerabilities discussed in Aim 3a.

Aim 5c. Differences in Multimorbidity as Explanations for Outcome Disparities: We will use the same analytic approach described in Aim 4 except that the SEF will be replaced by multimorbidity category.

Exploratory Aims:

1. Logistic regression will be used to investigate associations between prevalence SDOHs and prevalent psychiatric comorbidities.

2. The Liu et al. model will be used to model the relationship between HF self-care and readmissions.

References

1. Liu D, Schaubel DE, Kalbfleisch JD. Computationally efficient marginal models for clustered recurrent event data. *Biometrics*. 2012;68(2):637-47. doi:10.1111/j.1541-0420.2011.01676.x

2. Carlson B, Pozehl B, Hertzog M, Zimmerman L, Riegel B. Predictors of overall perceived health in patients with heart failure. *J Cardiovasc Nurs*. May-Jun 2013;28(3):206-15. doi:10.1097/JCN.0b013e31824987a8

3. Chronic Condition Charts (CMS.gov) (2017).