ARIC Manuscript Proposal #3917 (revised)

PC Reviewed: 10/12/21	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. **a. Full Title:**

Proteomic Markers Linking Frailty and Heart Failure: The ARIC study.

b. Abbreviated Title (Length: 26 characters): Frailty Biomarkers

2. Writing Group:

Writing group members: Diego Ramonfaur, Brian Claggett, Hicham Skali, Dalane Kitzman, Beverly Gwen Windham, Priya Palta, Jennifer Schrack, Fangyu Liu, Suma Konety, Chiadi Nduleme, Keenan Walker, Josef Coresh, Bing Yu, Amil Shah others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. DRG

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:

We will begin analysis once the proposal is approved and anticipate manuscript completion in approximately 6 months following proposal approval.

4. Rationale and Motivation:

Frailty is a clinical syndrome predominantly found in older adults. It is characterized by slow gait speed, poor grip strength, low energy expenditure, exhaustion, and weight loss.(1) The incidence and prevalence of both frailty and heart failure (HF) are greatest in late life.(2) Frailty is common in patients with prevalent HF, among whom frailty predicts higher risk of mortality and hospitalization.(3–5) In the Cardiovascular Health Study, frailty has also been associated with larger left atrial volumes, lower stroke volume indexes, and higher estimates of pulmonary artery systolic pressure (6) among older adult participants, as well as with increased LV mass index (7) among individuals free of heart disease. Frailty is also a risk factor for the development of HF, including both HF with preserved (HFpEF) and reduced (HFrEF) ejection fraction. Inflammation has been implicated as a potential pathophysiologic mechanism for both frailty and HF, especially HFpEF. In particular, inflammatory biomarkers such as interleukin-6 (Il-6), C-reactive protein, and tumor necrosis factor alpha (TNF-a) are associated with frailty but also with risk of incident HF. Cardiac troponin T, a circulating marker of myocardial injury robustly associated with HF risk, is also associated with frailty.(8) These data support potential shared mechanistic pathways underlying frailty and HF in late-life, and illustrate the potential for serum proteins to reveal shared markers of HF risk and the frailty syndrome. Despite these associations, the molecular mechanisms linking frailty to HF are unclear. High throughput aptamer-based proteomics, measuring ~5,000 circulating proteins, offer an unprecedented opportunity to discover novel markers of shared risk for HF and frailty to inform potential shared molecular mechanisms. This knowledge may be relevant to early detection of disease, as well as to inform potential therapeutic targets to mitigate disease progresson. Our study aims to utilize the rigorous phenotyping and proteomic data available in ARIC to explore potential molecular pathways underlying the association of frailty with HF risk.

5. Main Hypothesis/Study Questions:

We hypothesize that a subset of HF-associated proteins will also be associated with frailty in late life, that these proteins will associate with adverse cardiac remodeling in late life, and that they will help identify molecular pathways shared between frailty and HF. We will address the following Aims:

Aim 1: To estimate the association of HF-associated proteins with frailty at visit 5, and the development of frailty between visits 5 and 6.

Aim 2: To estimate the association of HF- and frailty-associated proteins from Aim 1 with cardiac structure and function at visit 5, and with changes in cardiac structure and function between Visit 5 and Visit 7.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present):**

Study design:

This is a longitudinal analysis using data from ARIC visits 3, 5, 6 and 7. We will use clinical covariates, frailty parameters, and echocardiographic data, as well as adjudicated HF events (including preserved and reduced ejection fraction). First, we will identify proteins associated with incident HF at Visit 3 and at Visit 5. Among that subset of proteins, we will identify the subset that also relate to prevalent frailty at Visit 5 and to the development of frailty from Visit 5 to Visit 6 and 7. Additional exploratory analyses will explore whether associations with frailty are stronger among the sub-set of proteins associated with incident HFpEF or HFrEF post-Visit 5.

Inclusion/Exclusion criteria:

We will include ARIC participants who have SomaLogic data and frailty status assessment at visit 3 and/or visit 5.

Key variables of interest:

1. Clinical covariates (Visits 3, 5, 6, and 7): Age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, atrial fibrillation, prior stroke, heart failure, eGFR, serum creatinine, hemoglobin, hematocrit, HbA1c, fasting glucose, frailty measures (grip strength, self-reported exhaustion, weight, walking speed, physical activity), and heart failure (HFpEF or HFrEF).
2. Echocardiographic variables (Visits 5 and 7): (1) LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass); (2) LV diastolic function (E wave, A wave, E', E/e' ratio, LAVi, and LA diameter); (3) LV systolic function (LVEF, global longitudinal strain, global circumferential strain)
3. Cardiac biomarkers (Visit 5 and 7): NT-proBNP, hs-cTnT, CRP.
4. Proteomic data from Visit 3 and Visit 5.

Data Analysis:

Aim 1: To estimate the association of HF-associated circulating proteins with prevalent frailty at Visit 5 and incident frailty between Visit 5 and Visit 6 or 7.

Exposures: Proteins significantly associated with HF. Proteins associated with HF will be identified using data from both Visit 3 and Visit 5. For data from each visit, multivariable Cox proportional hazards regression models will be used to estimate the association of proteomics with incident HF events (ICD-based events post-Visit 3; adjudicated events post-Visit 5). For incident HF post-Visit 3, we will include all participants with proteomic data at Visit 3 and free of prevalent HF at Visit 3. For incident HF post-Visit 5, we will include all participants with proteomic data at Visit 5, free of prevalent HF at Visit 5, and free of prevalent frailty at Visit 5. Multivariable models will adjust for

demographics, hypertension, diabetes, coronary artery disease, atrial fibrillation and smoking status. Proteins associated with incident HF post-Visit 3 at Bonferroni significance accounting for 4,877 proteins will then be assessed for association with incident HF, HFpEF, and HFrEF post-Visit 5. Proteins demonstrating significant associations at Bonferroni corrected $p < 0.05$ will consistute the candidate 'HF-associated proteins', and will be the primary exposures for Aim 1.

Outcomes:

- Prevalent frailty at Visit 5
- Incident frailty from Visit 5 to Visit 6 or 7.

Analyses

- Among participants free of prevalent HF at Visit 5, we will use multivariable logistic regression models to estimate the association of HF-related proteins (derived as above) with prevalent frailty at Visit 5. We will adjust regression models for Visit 5 demographic characteristics (age, sex, and race-center), lifestyle characteristics (smoking and alcohol consumption), and clinical characteristics (coronary artery disease, diabetes mellitus, hypertension, eGFR, BMI).
- Amog the subset of HF-associated proteins that associate cross-sectionally with frailty at Visit 5, we will assess their association with incident frailty at visit 6 or 7.
- Among participants free of HF and frailty at Visit 5 and with frailty assessment at Visit 6, we will use multivariable logistic regression models to estimate the association of candidate proteins with incident frailty. Model covariates will be the same as those specified above. We will test key assumptions of the Cox proportional hazards regression models. We will assess non-linearity using restricted cubic splines.
- We will conduct separate analyses according to sex given the established differences in HF epidemiology by sex.
- We will also conduct analyses stratified by race given established race-based differences in HF epidemiology, risk factor burden, and burden of social drivers of health that may exert downstream physiological effects.

Aim 2: To estimate the association of HF- and frailty-associated circulating proteins with cardiac structure and function.

Population: All participants who were free from HF and frailty at Visit 5, underwent echocardiography at Visit 5, and had available proteomics measurements at Visit 5.

Exposures: Proteins significantly associated with HF and frailty identified as described for Aim 1 above.

Outcomes:

- LV Structural Measures: LVEDD, LVEDV, LVEDVi, LVMI, MWT, RWT
- LV Systolic function: LVEF, GCS, GLS, LVESD, LVESV, LVESVi
- LV Diastolic function: E wave, e', E/e', E/A ratio, LAVi, LA with, peak TR velocity.

Analyses

- We will use linear regression models to estimate the association of HF- and frailty-related proteins (derived as above) with continuous echo measurements. We will adjust regression models for Visit 5 demographic characteristics (age, sex, and race-center), lifestyle characteristics (smoking and alcohol consumption), and clinical characteristics (coronary artery disease, diabetes mellitus, hypertension, eGFR, BMI).
- We will conduct separate analyses according to sex and race.
- Additional analyses will assess the association of HF- and frailty-related proteins with change in echo measurements from Visit 5 to Visit 7. The analytic approach will be similar to that described above, except models will additionally adjust for heart rate and systolic blood pressure at each visit given their potential impact on echocardiographic measures.
- We will perform a sensitivity analysis using proteomic measures associated with HF and pre-frailty or frailty at Visit 5 (instead of frailty alone).

Analyses will be performed with Stata IC-16.

Anticipated methodologic limitations

- Cohort attrition may bias our findings. We will attempt to mitigate the impact of selective survival by performing sensitivity analyses incorporating inverse probability of attrition weighting. Probability weights will be based on clinical, characteristics at visit 5.
- The weight loss criterion on the frailty score does not discriminate between intentional or unintentional weight loss at visit 5. This will be addressed by doing a sensitivity analysis assuming all weight loss was unintentional and then assuming all was intentional. This approach will be done using the weight loss variable “wtlosscomp10” in the dataset. We are taking a conservative approach by defininining weight loss as a loss of 10% body weight between visit 4 and 5, as 5% weight loss is tipically considered clinically significant.
- An additional sensitivity analysis defining frailty with a 4-item score (9), as opposed to a 5-item score will be performed to assess for validity using this proposed frailty measurement scale.
- Our analyses will not be able to fully disentangle proteins reflecting shared pathways between frailty and HF from those mediating a causal effect of frailty on HF, or those mediating a causal effect of HF on frailty. We have attempted to optimize our ability to identify shared pathways between frailty and HF through our selection of the study population and temporal sequence of exposures and outcomes for each analysis.

7. a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _x__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No

8. **a. Will the DNA data be used in this manuscript? __X__ Yes ____ No**

   b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? __X__ Yes ____ No

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

   ___x___ Yes _____ No

10. **What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

    ARIC Manuscript Proposal # 1158 Prevalence and correlates of mitral, tricuspid, and aortic regurgitation in middle-aged and elderly African-Americans: the ARIC study

    ARIC Manuscript Proposal #0633 Pulmonary function and left ventricular mass in African Americans: the Atherosclerosis Risk in Communities (ARIC) study

    ARIC Manuscript Proposal #XXXX Physical Activity Trajectories from Midlife to Older Adulthood and their Associations with Older Adulthood to Later Life Physical Function and Frailty: The Atherosclerosis Risk in Communities (ARIC) Study.

    ARIC Manuscript Proposal #XXXX Systemic inflammation in midlife as a predictor of frailty in late-life: The ARIC Study

    ARIC Manuscript Proposal #XXXX Comparison of cardiac and clinical characteristics between frailty and heart failure in the elderly: The ARIC Study

    ARIC Manuscript Proposal #XXXX Proteomic analysis, hypertension risk and progression in the community

ARIC Manuscript Proposal #XXXX Proteomics and risk prediction for incident cardiovascular disease, recurrent cardiovascular disease, and chronic kidney disease progression: A validation analysis

ARIC Manuscript Proposal #XXXX Association of Plasma Proteomic Markers With Left Atrial Function in the Elderly: The Atherosclerosis Risk in Communities (ARIC) study

ARIC Manuscript Proposal #XXXX A proteomic analysis of incident dementia: The ARIC Study

ARIC Manuscript Proposal #XXXX Proteomic Profiling and Heart Failure Risk in the Atherosclerosis Risk in Communities (ARIC) Study

11. **a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes __ __ No**

    b. If yes, is the proposal _X__ A. primarily the result of an ancillary study (list number* _2015.34; 2017.27, 2018.19_) ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)
    *ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. **a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

    b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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