

Serum Albumin Is a Marker of Myocardial Fibrosis, Adverse Pulsatile Aortic Hemodynamics, and Prognosis in Heart Failure With Preserved Ejection Fraction

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Background—Data regarding the phenotypic correlates and prognostic value of albumin in heart failure with preserved ejection fraction (HFpEF) are scarce. The goal of the current study is to determine phenotypic correlates (myocardial hypertrophy, myocardial fibrosis, detailed pulsatile hemodynamics, and skeletal muscle mass) and prognostic implications of serum albumin in HFpEF.

Methods and Results—We studied 118 adults with HFpEF. All-cause death or heart-failure–related hospitalization was ascertained over a median follow-up of 57.6 months. We measured left ventricular mass, myocardial extracellular volume, and axial muscle areas using magnetic resonance imaging. Pulsatile arterial hemodynamics were assessed with a combination of arterial tonometry and phase-contrast magnetic resonance imaging. Subjects with lower serum albumin exhibited a higher body mass index, and a greater proportion of black ethnicity and diabetes mellitus. A low serum albumin was associated with higher myocardial extracellular volume (52.3 versus 57.4 versus 39.3 mL in lowest to highest albumin tertile, respectively; $P=0.0023$) and greater N-terminal pro B-type natriuretic peptide levels, but not with a higher myocardial cellular volume (123 versus 114 versus 102 mL; $P=0.13$). Lower serum albumin was also associated with an increased forward wave amplitude and markedly increased pulsatile power in the aorta. Serum albumin was a strong predictor of death or heart failure hospitalization even after adjustment for N-terminal pro B-type natriuretic peptide levels and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (adjusted standardized hazard ratio=0.56; 95% CI=0.37–0.83; $P<0.0001$).

Conclusions—Serum albumin is associated with myocardial fibrosis, adverse pulsatile aortic hemodynamics, and prognosis in HFpEF. This readily available clinical biomarker can enhance risk stratification in HFpEF and identifies a subgroup with specific pathophysiological abnormalities. (*J Am Heart Assoc.* 2020;9:e014716. DOI: 10.1161/JAHA.119.014716.)

Key Words: heart failure • imaging • magnetic resonance imaging • myocardial fibrosis • prognosis

Heart failure (HF) with preserved ejection fraction (HFpEF) represents over half of all new HF diagnoses. With few evidence-based disease-modifying

therapies, patients with HFpEF remain at high risk for adverse events. Further defining the heterogenous HFpEF syndrome into different phenotypes will likely assist in both clinical trial development and risk stratification of HFpEF patients. Biomarkers represent one possible approach to HFpEF phenotyping. Serum albumin (ALB_{SER}) has been shown to be a strong prognostic factor in heart failure with reduced ejection fraction.¹ As a marker of several key pathophysiological pathways, including renal dysfunction, systemic inflammation, malnutrition, and liver fibrosis, ALB_{SER} may have particular utility in phenotyping and risk prediction in HFpEF.^{2–4} To date, data regarding the phenotypic correlates and prognostic value of albumin in HFpEF are scarce.

ALB_{SER} may be reduced in HF because of cachexia and/or sarcopenia. Patients with HFpEF have been shown to have acceleration of age-related decrease in muscle mass, and,

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Clinical Perspective

What Is New?

- Lower serum albumin is associated with more myocardial fibrosis and aortic pulsatility in HFpEF.
- Low serum albumin is associated with increased risk of adverse outcomes in HFpEF.

What Are the Clinical Implications?

- Serum albumin is an integrated marker of various pathophysiologic mechanisms in HFpEF.
- Measurement of serum albumin may enhance risk stratification among patients with HFpEF.

recently, pectoralis major muscle size was found to be an independent predictor of mortality in HFpEF.⁵ Therefore, the relationship between skeletal muscle mass and ALB_{SER} requires further research.

Excessive collagen deposition into the extracellular matrix in patients with HFpEF has been found on endomyocardial biopsies and correlates with diastolic dysfunction indices.⁶ Advances in cardiac magnetic resonance (CMR) imaging have allowed for quantification of extracellular volume (ECV) noninvasively through T₁ mapping, which has been linked to invasive measures of left ventricular (LV) diastolic dysfunction.⁷ These findings were extended to patients with HFpEF in whom diffuse myocardial fibrosis was associated with higher passive LV stiffness.⁸ Various recent studies have shown that ECV appears to be an independent predictor of death or HF hospitalization in patients with HFpEF.⁹ Expansion of the ECV may, in part, reflect downstream effects of systemic inflammation. As a negative acute-phase reactant, ALB_{SER} may help identify patients with more-advanced diffuse fibrosis on cardiac magnetic resonance imaging (MRI).¹⁰

Finally, a subset of patients with HFpEF exhibit derangements in aortic pulsatile hemodynamics, characterized by excessive aortic pulsatility.^{11–13} Increased aortic stiffness and excessive aortic pulsatility may contribute to target organ damage in high-flow, low-resistance vascular beds, such as the glomeruli and liver, which in turn may affect albuminemia. Data regarding the relationship between ALB_{SER} and detailed aortic hemodynamics measured by pressure-flow relations, the gold-standard method, are lacking.^{11–13}

In this study, we aimed to determine the association between ALB_{SER} and prognosis in HFpEF and assess its relationship with HFpEF phenotypes, specifically: (1) myocardial fibrosis assessed by CMR with T₁ mapping; (2) pulsatile central aortic hemodynamics as assessed by arterial tonometry, aortic flow measurements, and analyses of pressure-flow relations; and (3) axial muscle size.

Methods

This was an observational, prospective cohort study that included 118 subjects with HFpEF undergoing a cardiac MRI study. The protocol was approved by the Philadelphia VA Medical Center Institutional Review Board, and written informed consent was obtained from all participants. The data, analytical methods, and study materials are not publicly available for purposes of reproducing the results or replicating the procedures. Such data may be made available to other researchers for collaborative research, through the establishment of appropriate data-sharing agreements and regulatory approvals.

HFpEF was defined as symptomatic HF in the presence of left ventricular ejection fraction (LVEF) >50%. HFpEF was defined as: (1) New York Heart Association Class II to IV symptoms consistent with HF, in the absence of significant aortic stenosis; (2) LVEF >50%; and (3) a mitral E wave to annular e' ratio >14,¹⁴ or at least 2 of the following: (1) a mitral E wave to annular e' ratio >8; (2) treatment with a loop diuretic for control of HF symptoms; (3) left atrial volume index >34 mL/m² of body surface area; (4) NT-proBNP (N-terminal pro B-type natriuretic peptide) level >200 pg/mL; and (5) LV mass index >149 g/m² in men and 122 g/m² in women (measured by cardiac MRI).

Key exclusion criteria were as follows: (1) claustrophobia; (2) presence of metallic objects or implanted medical devices in body; and (3) atrial fibrillation, flutter, or significant arrhythmia at the time of enrollment, which may compromise the study measurements. For this analysis, we also excluded subjects with a history of liver cirrhosis (n=8). At baseline, a phenotypic characterization was performed using a combination of CMR, arterial tonometry, and blood sampling.

CMR Imaging Protocol

Participants underwent a cardiac MRI using a 1.5 Tesla whole-body MRI scanner (Avanto or Espree; Siemens, Malvern, PA) equipped with a phase-array cardiac coil. LV and right ventricular volumes and ejection fraction were determined using balanced steady-state free-precession cine imaging. Typical parameters were as follows: repetition time=30.6 ms; echo time=1.3 ms; phases=30; slice thickness=8 mm; matrix size=192×192; parallel image (integrated parallel acquisition techniques) factor=2. Endocardial borders were manually traced in end-systole and end-diastole in a short-axis cine stack to quantify LV and right ventricular volumes and ejection fraction. LV mass was computed as the difference between epi- and endocardial volumes in end-diastole, multiplied by myocardial density. LV mass was normalized for body height in meters raised to the allometric power of 1.7.¹⁵

Assessment of Myocardial ECV Fraction

We assessed myocardial ECV using a modified Look–Locker inversion recovery sequence to assess T_1 times before and following the intravenous administration of gadolinium contrast (gadopentetate dimeglumine, 0.15 mmol/kg or equivalent) in a mid-ventricular short-axis slice.^{16,17} Scan parameters for modified Look–Locker inversion recovery were: field of view=340 mm²; matrix size=144×192; slice thickness=6 mm; repetition time=2.4 ms; echo time=1.18 ms; flip angle=30 degrees, bandwidth=1000 Hz/pixel, integrated parallel acquisition techniques=2. Myocardial T_1 measurements were performed before and at several time points (\approx 5, 10, 15, and 20–40 minutes) postgadolinium administration. Modified Look–Locker inversion recovery was performed with a 5-3-3 schema with (2 inversions, 5 echo times after inversion 1, 3 T_1 recovery heartbeats, and 3 echo times after inversion 2). All available blood and myocardial T_1 measurements were used to compute lambda (λ ; the myocardium-blood partition coefficient) as the slope of the myocardial $1/T_1$ over the blood $1/T_1$ change, by linear regression (Figure 1).¹⁷ The fraction of myocardial tissue comprised by the extracellular space (ECV fraction), equals $\lambda \times (1 - \text{hematocrit})$. Extracellular LV volume was computed as LV wall volume multiplied by ECV. Cellular LV volume was computed as LV wall volume multiplied

by $(1 - \text{ECV})$.¹⁸ ECV data were available for 64 study participants.

Assessment of Pulsatile Central Arterial Hemodynamics

We assessed arterial hemodynamics using carotid applanation tonometry and aortic flow measurements. Carotid tonometry was performed using a high-fidelity tonometer (Millar Instruments, Houston, TX). Radial tonometric waveforms were calibrated using brachial systolic and diastolic blood pressure, obtained using a validated oscillometric device (Omron HEM-705CP; Omron Corp, Kyoto, Japan or Accutorr Plus; Datascope Corp., Paramus, NJ). Mean arterial pressure was computed as the mean pressure from the radial pressure waveform (Figure 2).

The pressure-flow pair was used to perform pulsatile hemodynamic analyses (Figure 2). Custom-designed software programmed in Matlab (R2014b; The MathWorks, Inc, Natick, MA) was used to assess aortic pressure-flow relations, as described previously in detail.^{13,19} In brief, after alignment of signal-averaged central pressure and flow waveforms, we computed aortic input impedance as the ratio of central pressure/flow in the frequency domain. Aortic root characteristic impedance (Z_c) was

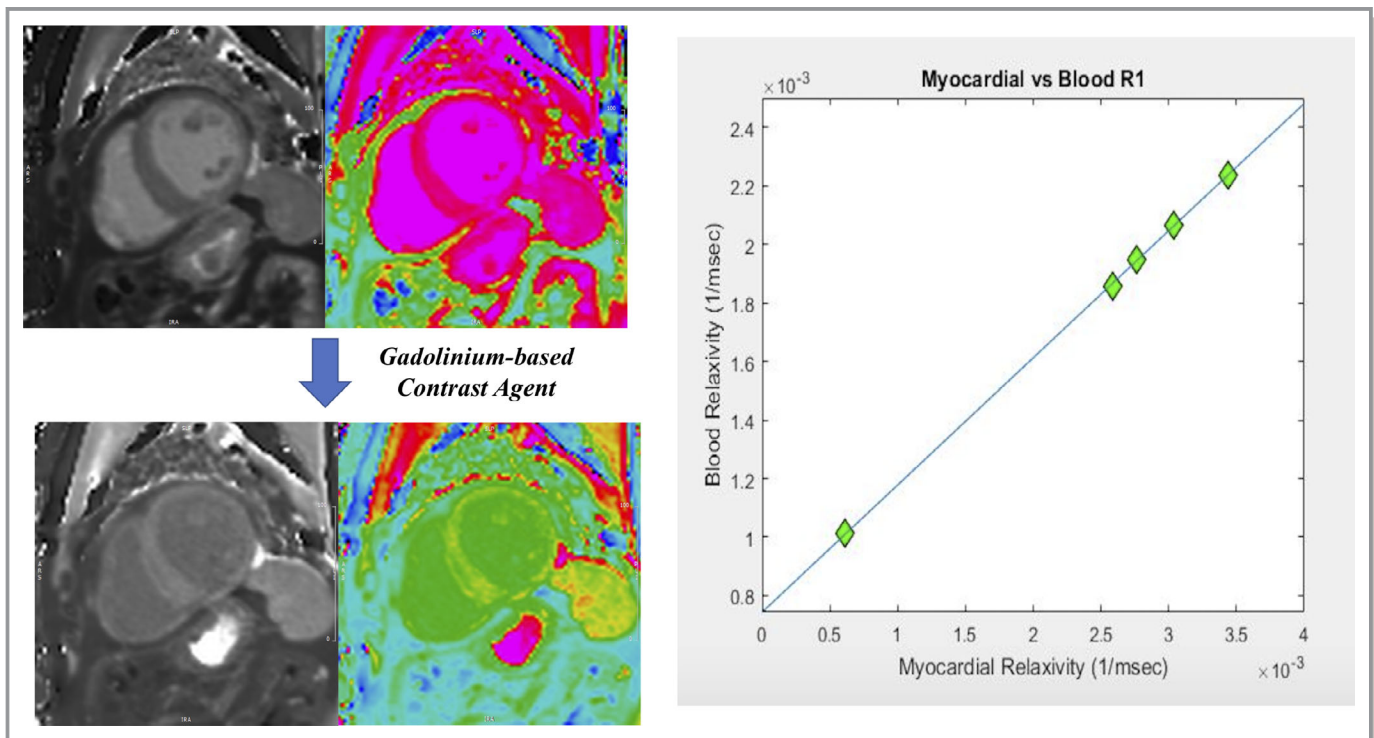


Figure 1. Myocardial T_1 measurements were performed before and several time points after gadolinium administration. The myocardium/blood partition coefficient (λ) was computed as the slope of the blood $1/T_1$ change to the myocardial $1/T_1$ change, determined with linear regression using all available measurements (right panel).

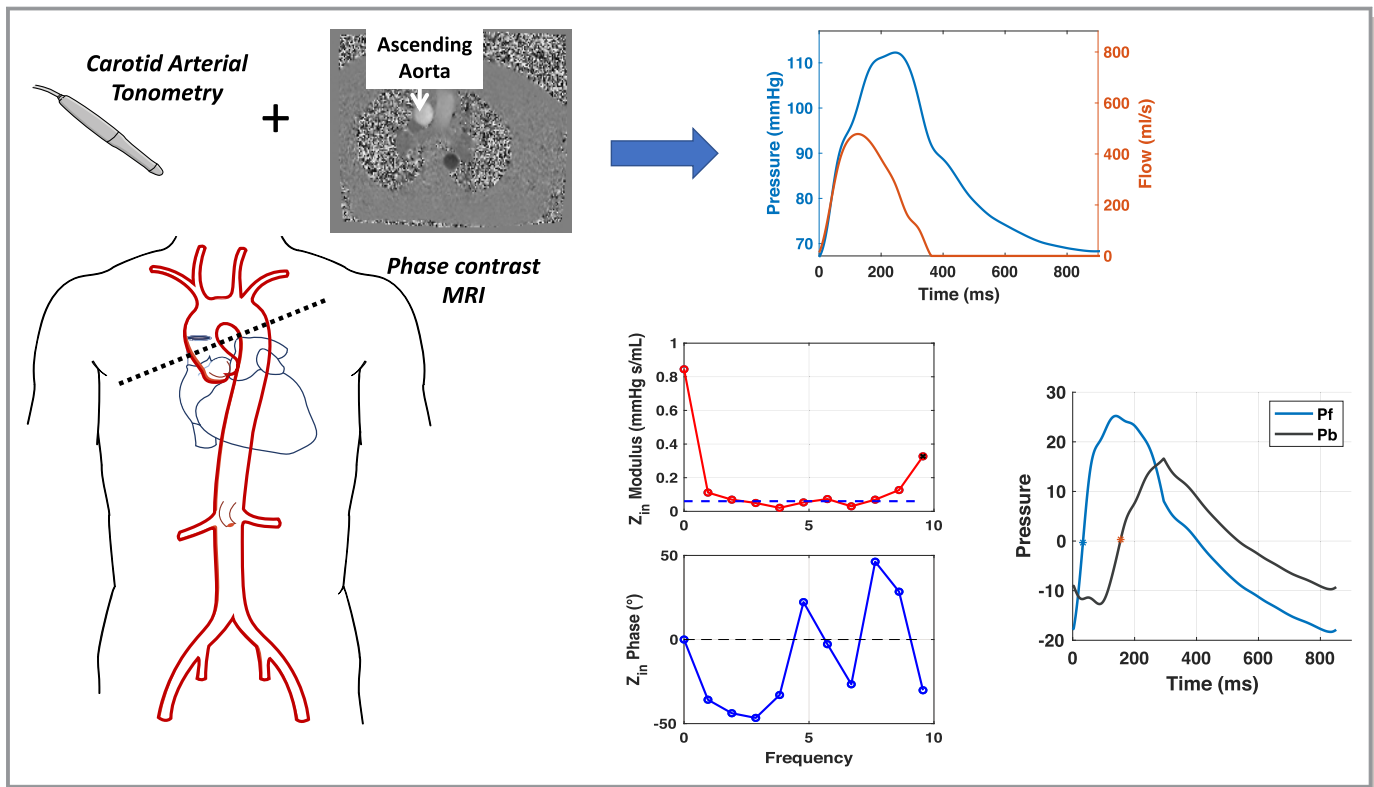


Figure 2. Assessment of pressure-flow relations and wave reflections. The central pressure waveform obtained by arterial tonometry and the flow waveform was obtained by through-plane phase-contrast MRI of the ascending aorta (left). Pressure and flow waveforms were time aligned (top right panel), and the modulus and phase of the aortic input impedance spectrum (Z_{in}) were computed. The dashed line in the panel the Z_{in} modulus plot represents the proximal aortic characteristic impedance (Z_C). The right bottom panel shows the results of wave separation analysis in which the pressure wave has been separated into forward (P_f) and backward (P_b) waves. MRI indicates magnetic resonance imaging; Z_C , characteristic impedance; Z_{in} , input impedance.

quantified as the average of impedance modulus at higher frequencies (Figure 2). Wave separation analysis was performed to obtain the amplitude of the forward (P_f) and backward (P_b) pressure waves. Reflection magnitude was defined as the ratio of P_b to P_f (P_b/P_f). Steady power (product of mean pressure and mean flow) and oscillatory power (product of oscillatory pressure and flow) were also computed. Oscillatory power is expressed both in absolute units (mWatts) and as fraction of total power. Aortic pulsatile hemodynamic data were available for 56 study participants.

Assessment of Axial Skeletal Musculature

An axial stack of steady-state free precession images was obtained, as per our routine cardiac MRI protocol, spanning the entire thorax. Typical acquisition parameters were as follows: repetition time=30.6 ms; echo time=1.2 ms; flip angle=80; slice thickness=5 mm; space between slices=5 mm; matrix size=256×208; parallel image (integrated parallel acquisition techniques) factor=2.

Images were analyzed using Horos software version 1.2.1 as previously described.⁵ Level of the carina was established as a reference point for measurements of skeletal muscle cross-sectional area on all axial chest MRI images. Thoracic skeletal muscle was then manually traced bilaterally for pectoralis major, pectoralis minor, serratus anterior, latissimus dorsi, paraspinal, and trapezius muscles. We performed factor analysis to identify a latent factor that underlies the shared variability in the cross-sectional area of the studied muscles, which we used as an indicator of underlying skeletal muscle mass, as previously described.⁵

Statistical Analysis

Data for continuous variables are presented as mean±SD for normally distributed variables and median (interquartile range) for non-normally distributed variables. Categorical variables are presented as counts and percentages. Comparisons of general characteristics between subjects stratified according to tertiles of albumin levels were performed using ANOVA or

Table 1. General Characteristics of Study Participants Stratified by Tertiles of ALB_{SER}

	<3.7 g/dL (n=33)	3.7 to 3.9 g/dL (n=33)	>4 g/dL (n=46)	P Value
Age, y	66.2±10.7	65.5±8.5	64.8±9.4	0.8042
Sex (female)	27 (84.38%)	34 (91.89%)	42 (85.71%)	0.5883
Race/ethnicity				
White	10 (31.25%)	8 (21.62%)	29 (59.18%)	0.0046
Black	21 (65.62%)	27 (72.97%)	20 (40.82%)	
Other	1 (3.12%)	2 (5.41%)	0 (0.00%)	
Hypertension	29 (90.62%)	35 (94.59%)	43 (87.76%)	0.5580
Coronary artery disease	12 (37.50%)	12 (32.43%)	16 (32.65%)	0.8804
Diabetes mellitus	26 (81.25%)	24 (64.86%)	23 (47.92%)	0.0099
OSA	10 (31.25%)	17 (45.95%)	19 (38.78%)	0.4585
Medication use				
Beta blocker	25 (78.12%)	24 (64.86%)	31 (63.27%)	0.3379
Aspirin	22 (68.75%)	31 (83.78%)	31 (63.27%)	0.1078
Clopidogrel	2 (6.25%)	3 (8.11%)	8 (16.33%)	0.2908
ACE inhibitor or ARB	26 (81.25%)	23 (62.16%)	38 (77.55%)	0.1452
Furosemide	23 (71.88%)	19 (51.35%)	36 (73.47%)	0.0722
Spirolactone	2 (6.25%)	3 (8.11%)	2 (4.08%)	0.7333
Statin	24 (75.00%)	28 (75.68%)	32 (65.31%)	0.4925
CCB	13 (40.62%)	17 (45.95%)	18 (36.73%)	0.6903
BMI, kg/m ²	40.6 (34.7, 46.1)	34 (29.4, 39.9)	32.5 (28.2, 39.8)	0.0022
GFR, mL/min	68.5 (49.5, 94.5)	72 (59.5, 96.8)	75 (55.8, 102.3)	0.5282
Microalbuminuria	17 (56.67%)	19 (67.86%)	24 (42.86%)	0.0844
Total cholesterol, mg/dL	165 (139, 189)	149 (137, 177)	148 (133, 206)	0.5599
Triglycerides, mg/dL	101 (85, 155)	133 (92, 181)	139 (93, 198)	0.3588
HDL cholesterol, mg/dL	44 (36.3, 54.5)	39.5 (35.5, 47.5)	40.5 (36, 48.5)	0.3594
LDL, mg/dL	86 (71.5105)	88 (70.8103)	84 (68, 117)	0.9791
Mitral E/e' (septal)	12.8 (9.2, 15.6)	12.1 (10.3, 14.7)	11.1 (8.4, 13.7)	0.1821
Mitral E/e' (lateral)	9 (7.8, 12.7)	9.9 (6.5, 11.4)	8.4 (6.8, 11.1)	0.5477
PA systolic pressure, mm Hg	41 (26.5, 43)	34 (30.3, 37.3)	35 (29, 37.4)	0.6945
Left atrial volume Index, mL/m ²	38.3±13.1	39.9±14.3	33.8±13.3	0.1609

Values represent the mean±SD, median (interquartile range), or count (percentage), as appropriate. ACE indicates angiotensin-converting enzyme; ALB_{SER}, serum albumin; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium-channel blocker; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-pro BNP, N-terminal pro B-type natriuretic peptide; OSA, obstructive sleep apnea PA, pulmonary artery.

the Kruskal–Wallis test, as appropriate, for continuous variables and the chi-square or the Fisher's exact test, as appropriate, for categorical variables.

We identified compared key phenotypic traits between the strata, with post hoc pair-wise comparisons with Bonferroni correction. For these comparisons, normality was assessed with the Anderson–Darling test and log transformations were applied, as needed, to improve normality before constructing ANOVA models. In all cases, means and 95% CIs are expressed in the native (linear) scale.

We also assessed the relationship between ALB_{SER} and the risk of the composite end point of death and HF hospital admission using Cox regression, in unadjusted and models that adjusted for confounders, including: (1) body mass index (BMI), presence of diabetes mellitus, and black race (adjusted model 1) and (2) the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score (which incorporates multiple demographic, clinical, and laboratory variables) and NT-proBNP levels (adjusted model 2). We assessed Schoenfeld and Martingale residuals to test

the proportionality and linearity assumptions in Cox models. Incident death and HF admissions were adjudicated by electronic medical record review by a physician.

Statistical significance was defined as a 2-tailed $P < 0.05$. All probability values presented are 2-tailed. Analyses were performed using the Matlab statistics and machine learning toolbox (Matlab 2016b; The Mathworks, Inc) and R Statistical Software (v3.5.2; R Foundation for Statistical Computing, Vienna, Austria),

Results

We studied 118 adults with HFpEF. General characteristics of the study population stratified by tertile of ALB_{SER} are shown in Table 1. Lower ALB_{SER} was associated with higher BMI, greater proportion of black ethnicity, and greater proportion

of diabetes mellitus. Lower ALB_{SER} was associated with greater rates of aspirin use, but not increased prevalence of coronary artery disease. ALB_{SER} was not associated with lower glomerular filtration rate.

Differences in LV Structure

Phenotypic differences in study participants stratified by ALB_{SER} are shown in Table 2. Lower ALB_{SER} was associated with increased LV mass when indexed for height ($P=0.0112$), but not when indexed for body surface area ($P=0.0901$). Lower ALB_{SER} was associated with a higher ECV fraction ($P=0.0153$), ECV volume ($P=0.0023$), and indexed ECV volume ($P=0.0090$), but not in cellular volume ($P=0.1265$) or indexed cellular volume ($P=0.3142$), as shown in Figure 3. Lower ALB_{SER} was also associated with increased NT-proBNP levels ($P=0.0003$).

Table 2. Comparison of Key Phenotypic Traits Between Tertiles of Serum Albumin

	<3.7 g/dL Mean (95% CI)	3.7 to 3.9 g/dL Mean (95% CI)	>4 g/dL Mean (95% CI)	P Value
LV structure and NT-ProBNP levels				
LV mass index (g/BSA in m ²)	74.9 (67 to 82.7)	75.4 (68.3 to 82.6)	67.1 (62 to 72.3)	0.0901
LV mass index (g/height in m ^{1.7})	70.5 (62.9 to 78.1)	66.2 (59.8 to 72.7)	58.4 (53.8 to 63.1)	0.0112*
Cellular volume, mL	123 (104 to 143)	114 (96 to 132)	102 (90 to 114)	0.1265
Extracellular volume, mL	52.3 (44 to 60.7)	57.4 (49.1 to 65.7)	39.3 (33 to 45.5)	0.0023 [†]
Indexed cellular volume, mL/m ²	52.2 (44.8 to 59.5)	48.7 (41.8 to 55.5)	45.9 (41.1 to 50.7)	0.3142
Indexed extracellular volume, mL/m ²	21.1 (17.4 to 24.7)	22.6 (18.7 to 26.5)	16.8 (14.6 to 18.9)	0.0090 [†]
Extracellular volume fraction, %	29.2 (26.4 to 31.9)	32.2 (29.4 to 34.9)	27 (24.9 to 29)	0.0153 [†]
NT-proBNP, pg/mL	447 (164 to 730)	506 (179 to 833)	147 (67 to 226)	0.0003* [†]
Pulsatile arterial hemodynamics				
Forward wave amplitude, mm Hg	55.7 (44.5 to 66.9)	40.7 (33.9 to 47.5)	43.6 (37.9 to 49.3)	0.0366 [‡]
Backward wave amplitude, mm Hg	24.9 (19.9 to 29.9)	19.4 (15.2 to 23.6)	21.1 (17.8 to 24.4)	0.2519
Oscillatory power, mW	485 (338 to 632)	269 (202 to 337)	310 (250 to 370)	0.0050* [‡]
Steady power, mW	1633 (1309 to 1957)	1346 (1125 to 1567)	1297 (1130 to 1463)	0.1180
Oscillatory/total power	0.232 (0.204 to 0.261)	0.172 (0.148 to 0.196)	0.198 (0.179 to 0.217)	0.0093 [‡]
Axial muscle mass				
Muscle area latent factor	-0.16 (-0.48 to 0.159)	0.076 (-0.228 to 0.379)	-0.268 (-0.524 to -0.013)	0.2370
Pectoralis major area, cm ²	21.6 (18.5 to 24.8)	23 (19.6 to 26.5)	21.2 (18.5 to 24)	0.6781
RV structure and function				
RV end-diastolic volume, mL	161 (138 to 184)	165 (142 to 187)	161 (141 to 180)	0.9571
RV end-systolic volume, mL	70.1 (58.8 to 81.4)	77.7 (66 to 89.4)	74.6 (64.4 to 84.8)	0.6154
RV end-diastolic volume index, mL/m ²	71.8 (63.8 to 79.7)	73 (65.6 to 80.5)	76.4 (69.6 to 83.2)	0.6586
RV end-systolic volume index, mL/m ²	30.2 (25.8 to 34.6)	33.6 (29.1 to 38.2)	33.8 (29.6 to 38)	0.4058
RV ejection fraction, %	55.6 (51.8 to 59.3)	51.8 (48.3 to 55.4)	52.8 (49.5 to 56.0)	0.3462

LV indicates left ventricle; NT-proBNP, N-terminal pro B-type natriuretic peptide; RV, right ventricle.

*lowest vs highest tertile.

[†]highest vs mid tertile.

[‡]lowest vs mid tertile.

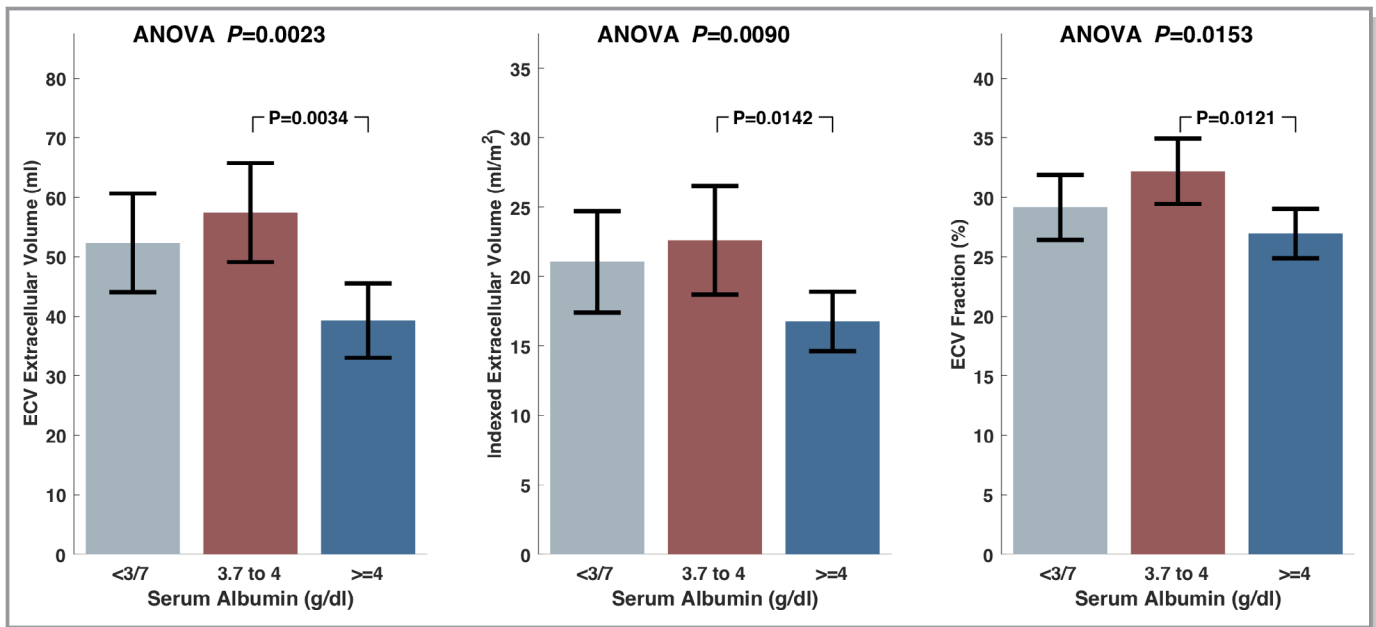


Figure 3. Comparison of extracellular volume (ECV), indexed ECV, and ECV fraction by tertiles of serum albumin.

Relationship With Axial Muscle Mass

There was no relationship found between ALB_{SER} and axial muscle mass. Similarly, after adjustment for sex, race, and

BMI, no significant differences were found in muscle areas between the groups in the muscle area latent factor ($P=0.2370$) or in pectoralis major area ($P=0.6781$).

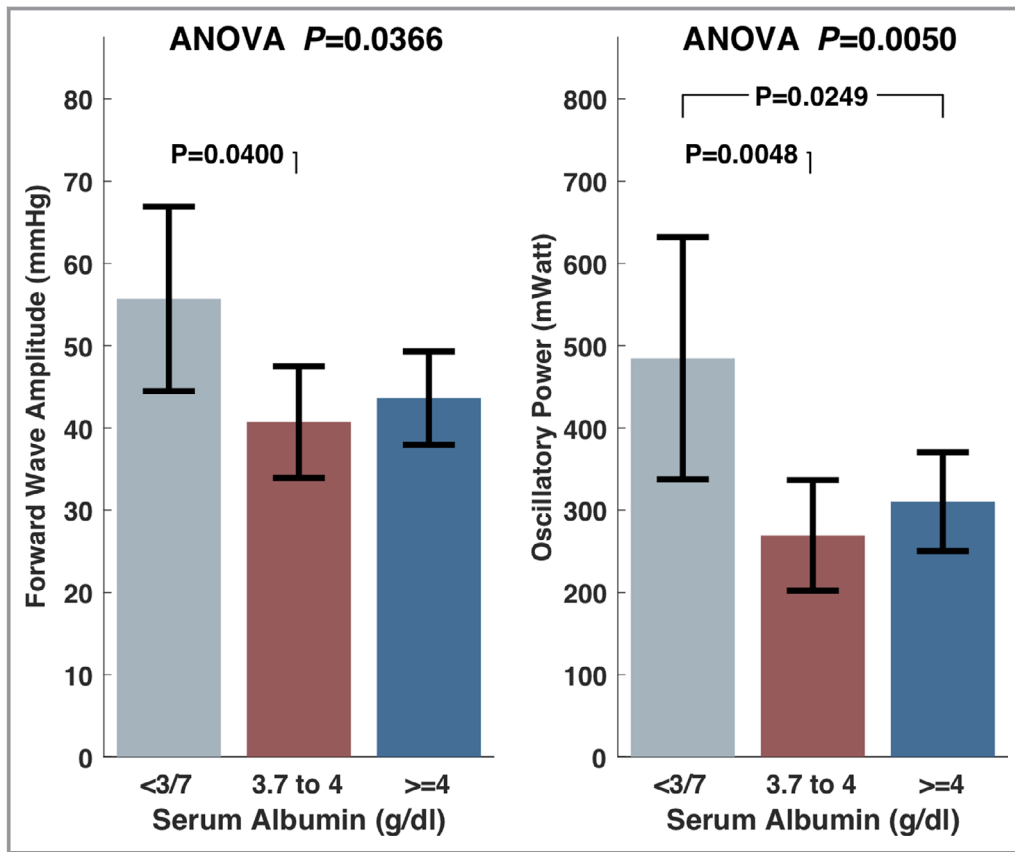


Figure 4. Comparison of forward wave amplitude and oscillatory power by tertiles of serum albumin.

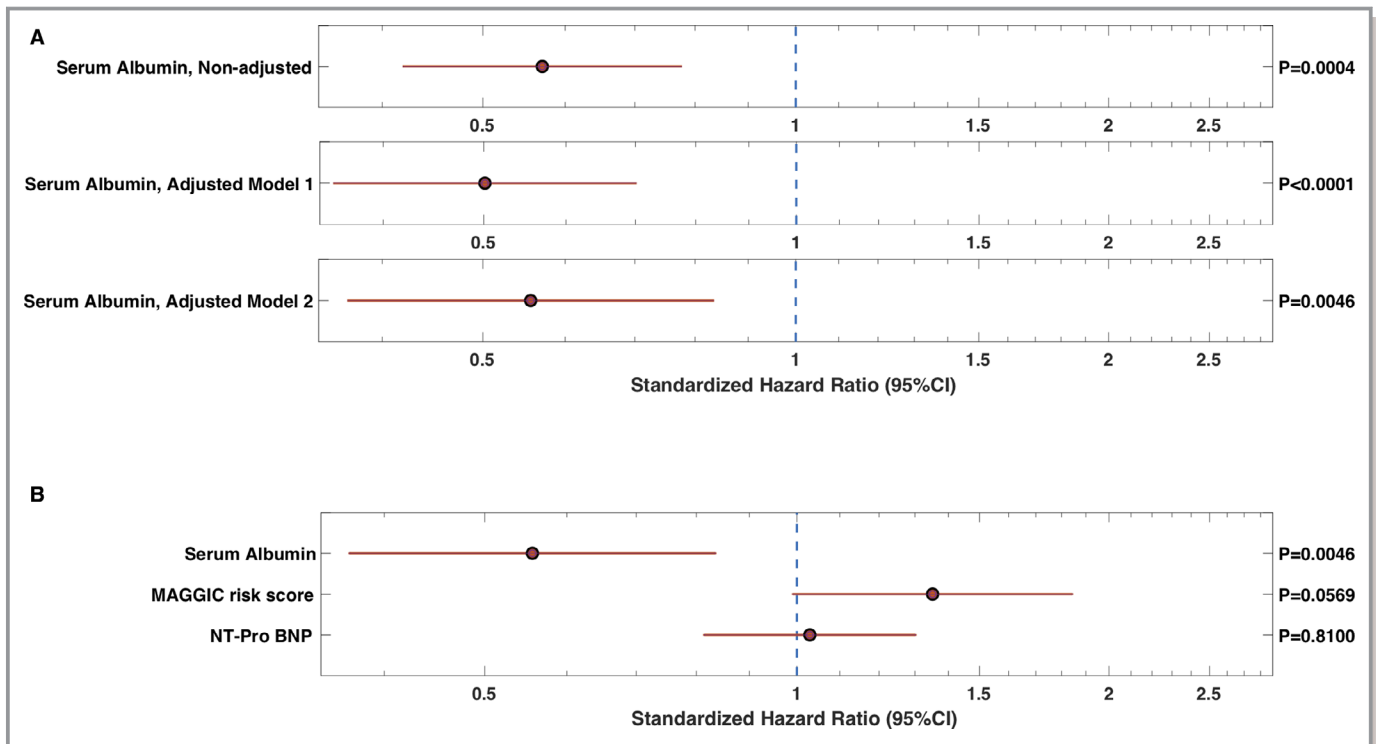


Figure 5. **A**, Standardized hazard ratios of serum albumin as a predictor of death of HF admission in unadjusted modeling, after adjustment for BMI, diabetes mellitus, and black ethnicity (adjusted model 1), and after adjustment for the MAGGIC risk score and NT-proBNP (adjusted model 2). **B**, Standardized hazard ratios for serum albumin, NT-proBNP, and MAGGIC as independent predictors of death or HF-related hospitalization. BMI indicates body mass index; HF, heart failure; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Differences in Pulsatile Arterial Hemodynamics

Lower ALB_{SER} was associated with higher forward wave amplitude ($P=0.0366$) and a marked increase in oscillatory power ($P=0.0050$; Figure 4). However, there were no significant differences in steady power ($P=0.1180$). Accordingly, there was an increased ratio between oscillatory power and total power in patients with lower ALB_{SER} ($P=0.0093$).

Prognostic Value of ALB_{SER}

Median duration of follow-up among subjects who did not develop the composite end point was 57.6 months (interquartile range, 44.3–69.8). During follow-up, 20 subjects developed an HF-related hospitalization, 26 died, and 38 reached the composite outcome.

In unadjusted analyses, ALB_{SER} predicted risk of death or HF admission (standardized hazard ratio=0.54; 95% CI=0.38–0.77; $P=0.0004$; Figure 5A). After adjustment for diabetes mellitus, BMI, and black ethnicity, albumin remained strongly predictive of death/HF admission (standardized hazard ratio=0.50; 95% CI=0.36–0.70; $P<0.0001$; adjusted model 1 in Figure 5A).

Similarly, after adjustment for the MAGGIC risk score and NT-proBNP, albumin remained strongly predictive of outcomes (standardized hazard ratio=0.56; 95% CI=0.37–0.83; $P=0.0046$;

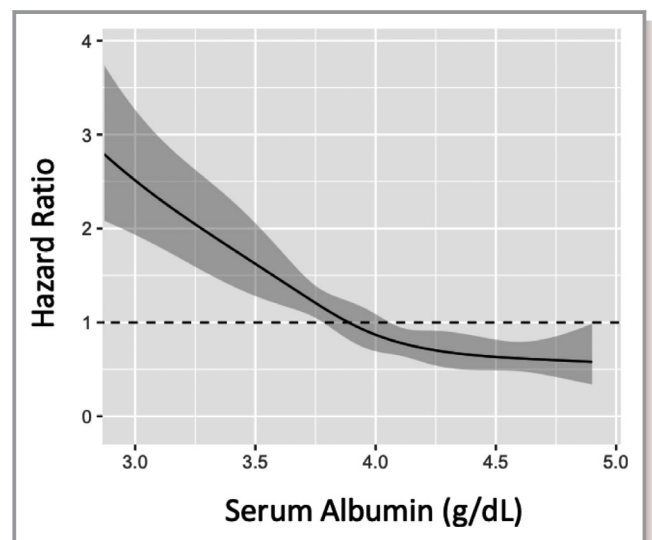


Figure 6. Spline modeling of ALB_{SER} level against the hazard ratio for death or heart-failure-related hospitalization. ALB_{SER} indicates serum albumin.

adjusted model 2 in Figure 5A). In the latter multivariable model, albumin, but not NT-proBNP or the MAGGIC risk score, was independently predictive of death/HF admission (Figure 5B). Finally, we analyzed risk of incident death/HF admission across a continuum of ALB_{SER} values (Figure 6). Risk started to increase even at ranges of ALB_{SER} that are still considered clinically normal, with an inflection at ≈ 4 g/dL.

Discussion

In this study, we examined the correlation between ALB_{SER} with several relevant deep phenotypic traits, as well as incident adverse outcomes in HFpEF. We demonstrate that lower ALB_{SER} was associated with higher BMI, black ethnicity, and diabetes mellitus. A low ALB_{SER} was associated with increased myocardial interstitial expansion, as evidenced by higher myocardial ECV, without being increased in cellular myocardial volume. Lower ALB_{SER} was also associated with adverse aortic pulsatile hemodynamics, including increased forward wave amplitude and a markedly increased pulsatile power. In contrast to our hypothesis, there was no association between ALB_{SER} and axial skeletal muscle size. Finally, ALB_{SER} was a strong predictor of death or HF hospitalization even after adjustment for NT-proBNP levels and the MAGGIC risk score. This study adds to our current understanding of the significance of ALB_{SER} in HFpEF.

As an acute-phase reactant, ALB_{SER} levels are decreased in both acute and chronic illness.^{2,20–22} Low ALB_{SER} has been shown to predict incident HF among asymptomatic adults without cardiovascular disease.^{23,24} Once HF is manifest, studies have generally shown ALB_{SER} levels to predict worse outcomes.^{1,25–27} These studies were generally limited to patients with HF with reduced ejection fraction, and conflicting data exist about the predictive role of albumin in HFpEF.^{25,28}

In HFpEF, diastolic dysfunction and elevated filling pressures that are manifest either at rest or exercise may be related to passive stiffness and underlying myocardial fibrosis. This is supported at the cellular level through endomyocardial biopsy in HFpEF patients, which revealed expansion of the extracellular matrix.²⁹ Biomarkers in patients with HFpEF reveal a shift toward procollagen biomarkers.^{10,30} Furthermore, the amount of collagen deposition and cross-linking at the microscopic level was linked to indices of diastolic dysfunction by echocardiography.⁶ With improvement in cardiac imaging techniques, the ability to quantitate the degree of myocardial interstitial expansion by CMR has enhanced our phenotyping of cardiac structure in HFpEF. Myocardial ECV fraction has been shown to correlate with histological collagen volume fraction both in vivo and in vitro.^{31,32}

Early work in recipients of cardiac transplant linked myocardial fibrosis by MRI to invasively determined LV stiffness parameters, both load independent and load

dependent.⁷ These findings were more recently extended to an HFpEF population, in which higher ECV measured by CMR was independently associated with elevated load-independent passive LV stiffness constant. In contrast, patients with lower ECV exhibited predominant abnormalities in active relaxation.⁸ Importantly, these 2 groups of HFpEF patients had similar echocardiographic findings, demonstrating that CMR provides important incremental information regarding the nature of diastolic dysfunction in HFpEF. Several studies have also confirmed that ECV is predictive of adverse outcomes.^{33–36} Therefore, it is noteworthy in our study that lower ALB_{SER} was significantly associated with an increased ECV and ECV fraction, but not myocardial cellular volume or overall LV mass. Given these findings, it appears that 1 or more pathophysiological processes in HFpEF causes both ECV expansion and low ALB_{SER}. Candidate mechanisms underlying this association include liver dysfunction, nutritional factors, and inflammation, which should be examined in future studies. Although it is unlikely that ALB_{SER} is causally implicated in myocardial fibrosis, it represents a readily accessible marker for specific HFpEF phenotypes.

Our study also demonstrates that low ALB_{SER} is strongly associated with adverse arterial pulsatile hemodynamics as determined by arterial pressure-flow analyses. Specifically, we found that increased forward wave amplitude was associated with ALB_{SER} levels. In contrast, reflected wave amplitude and reflection magnitude did not differ between the groups. This suggests a prominent role of proximal aortic stiffening and/or mismatch of aortic root stiffness and flow requirements, as a correlate of ALB_{SER}. Adverse arterial pulsatile hemodynamic profiles are important in HFpEF, given that they can contribute to exercise intolerance, target organ damage, and important comorbidities in this population. Metrics of arterial stiffness and pulsatile hemodynamics have been found to differentiate patients with and without HFpEF who presented with undifferentiated dyspnea on exertion.³⁷ Earlier work by our group showed that although both steady and oscillatory power are increased in HFpEF, in diabetic HFpEF in particular there is a relative increase in oscillatory power rather than steady power, such that the ratio of oscillatory to steady power also increased.³⁸ We demonstrate that low ALB_{SER} is a marker of increased aortic forward wave amplitude (which depends on cardiac ejection against the aortic root³⁹ and is amplified by wave reflections that are rectified at the heart).^{11,40} Importantly, these abnormalities are associated with pulsatile power in the large arteries, which can contribute to microvascular damage and dysfunction in target organs.^{41–45} We found that a low ALB_{SER} was associated with markedly increased pulsatile power in the aorta.

Our study also evaluated the relationship between ALB_{SER} and skeletal muscle size, which is an important prognostic factor in HF.^{5,46} Loss of muscle mass occurs with normal

aging, but is accelerated with chronic illnesses, including HF.⁴⁷ Lean muscle mass has been shown to be predictive of prognosis in HF patients independent of BMI.⁴⁶ Recently, our group showed that axial thoracic skeletal muscle areas measured by MRI was an independent predictor of all-cause mortality in individuals both with and without HF. In particular, the pectoralis major group was the best representing group.⁵ This finding is noteworthy in that loss of lean muscle often precedes the onset of cardiac cachexia, which, once manifest, carries a poor prognosis.⁴⁸ Contrary to our hypothesized relationship between ALB_{SER} and muscle mass, lower ALB_{SER} was associated with obesity, but not associated with axial muscle mass, indicating that a low ALB_{SER} is not simply a marker of sarcopenia/cachexia in HFpEF, but rather represents a composite marker of multiple underlying processes and phenotypes, as discussed above.

Finally, we showed that ALB_{SER} is a strong independent predictor of adverse outcomes in this well-phenotyped HFpEF population. ALB_{SER} was strongly predictive of outcomes, comparing favorably to other established predictors, and was independent of the MAGGIC risk score (which is, in itself, a powerful predictor of outcomes) and NT-proBNP levels. Interestingly, in a multivariable model that included these 3 predictors, ALB_{SER} (but not the MAGGIC risk score or NT-proBNP) was independently predictive of outcomes, supporting its role as a robust independent prognostic factor. The robust and strong association between ALB_{SER} and adverse outcomes likely reflects the association between ALB_{SER} with multiple pathophysiological pathways that portend poor prognosis in HFpEF patients. It is noteworthy that ALB_{SER} is associated with increased risk, even at levels that are considered clinically normal, with an inflection at ≈ 4 g/dL. Our study indicates that ALB_{SER} is strongly prognostic in HFpEF and further expands our understanding of the phenotypic underpinnings of the variation of this readily available biomarker in this patient population.

Strengths of our study include its prospective nature and the use of advanced noninvasive methods for the characterization of myocardial interstitial expansion and aortic pulsatile hemodynamics. Our population also had adequate representation of blacks, which is lacking in some HFpEF studies. Our study has several limitations. All patients were recruited at a Veterans Administration medical center, and the results of this study may not be generalizable to other HFpEF populations. Additionally, there were few women in this study, given that it was carried out at a Veterans Administration medical center. Finally, the number of subjects and clinical events are small in this cohort study, which may lead to lack of power in the statistical analysis and insignificance of some findings.

In conclusion, we demonstrate that low ALB_{SER} is associated with increased myocardial fibrosis and adverse pulsatile hemodynamics, but not sarcopenia, in HFpEF. We add to the

increasing body of literature supporting the role of ALB_{SER}, a readily available biomarker in clinical practice, as a strong and robust prognostic marker in HFpEF.

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