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Serum Albumin Concentration and Heart Failure Risk:

The Health, Aging, and Body Composition Study

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2009

Abstract

Serum Albumin Concentration and Heart Failure Risk:
The Health, Aging, and Body Composition Study

By Deepa Mangalat, M.D.

Aims: To evaluate the association between serum albumin concentration and risk for heart failure (HF).
Methods and Results: We evaluated 2907 participants without HF at baseline (age 73.6±2.9 years, 48.0% male, 58.7% white) from the community-based Health ABC Study. The association between baseline albumin and incident HF was assessed with nested multivariable Cox models controlling for HF predictors, inflammatory markers, and incident coronary events. During a median follow-up of 9.4 years, 342 (11.8%) participants developed HF (incidence, 14.9 per 1000 person-years). Serum albumin was a time-dependent predictor of HF, with significance retained for up to 4 years (baseline HR per -1g/L, 1.12; 95% CI, 1.05-1.19, P<0.001, annual rate of HR decline, 2.1%; 95% CI, 0.8-3.4%, P=0.002). This association persisted in models controlling for HF predictors, inflammatory markers, and incident coronary events (baseline HR per -1g/L, 1.11; 95% CI, 1.06-1.17, P<0.001 annual rate of HR decline, 0.5%, 95% CI, 0.1-1.0%, P=0.02), and was consistent in both sexes and in whites and blacks. Post-HF ejection fraction (EF) was available in 265/342 (77.5%) cases. In fully adjusted models, albumin was significantly associated with HF risk for the 136 cases with EF ≥40% (HR, 1.13; 95% CI, 1.03-1.25; P=0.009), but not for the 129 cases with EF <40% (HR, 1.10; 95% CI, 0.97-1.25; P=0.16).
Conclusion: Serum albumin concentration is associated with a time-dependent risk for HF; this association may be stronger for HF with preserved EF.

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INTRODUCTION

Heart failure is a growing epidemic facing the United States. Over 5 million Americans carry the diagnosis of heart failure and 550,000 new cases are diagnosed annually. Targeting known risk factors and identifying potential screening tools, such as albumin, might aid in facilitating early interventions to slow incident rates of heart failure and assist in targeting therapeutics in higher risk individuals. In this longitudinal analysis, we explore the association of baseline serum albumin on the development of incident heart failure and assess the independence from other clinical risk factors of heart failure while also evaluating the role of inflammation on this relationship.

BACKGROUND

Several prospective studies have demonstrated an association between low serum albumin and increased cardiovascular morbidity and mortality.[1-4] Serum albumin concentrations have also been associated with increased risk for incident coronary heart disease, especially in individuals with chronic kidney disease.[5-8] A reduction in serum albumin over time is associated with increased incidence of cardiovascular disease, even if the change is within normal albumin range.[9] Serum albumin has also been associated with sudden cardiac death.[10] In patients with established heart failure (HF), hypoalbuminemia is associated with 1- and 5-year all-cause mortality, HF mortality, and need for heart transplantation.[11] Patients on renal replacement therapy are shown to be at a higher risk for developing HF if they are hypoalbuminemic.[6] It has been recently shown that, among the elderly participants of the Health, Aging, and Body Composition Study (Health ABC Study), serum albumin concentrations were independently associated with risk for HF when baseline clinical variables were considered for 5-year HF risk prediction.[12] However, the form and time-course of this relationship has not been well delineated.

Theoretically, low serum albumin concentration may be associated with HF risk for several reasons. Hypoalbuminemia may be a marker of comorbidity burden.[13] Alternatively, low serum albumin may be a reflection of inflammatory burden [14-16], predisposing to HF either directly or through an increased incidence of interim cardiovascular events.[17] Irrespective of the underlying mechanism, however, and considering that measurement of serum albumin is relatively inexpensive and widely available, serum albumin could serve as a potential screening tool to identify individuals at risk for HF and facilitate early interventions. However, in order for serum albumin to be

used as a screening tool, the generalizability and robustness of association between serum albumin and HF risk needs to be demonstrated across race and sex-based subgroups. Finally, it is unclear whether the value of albumin for determination of HF risk is retained when information on inflammatory markers is available and/or whether the increased risk is exclusively mediated by interim coronary events.

In this study, we extend the earlier findings on the association between serum albumin concentrations and risk for incident HF among the elderly participants of the Health ABC Study. Using 10-year follow-up data, we report on the form and time course of this association, explore the impact of inflammation and interim coronary events, and provide stratified analyses for the major demographic subgroups.

METHODS

Null Hypothesis

There is no relationship between baseline albumin and incident heart failure.

Specific Aims

The specific aims of this study were to:

1) Examine the association between baseline albumin levels and the development of heart failure by describing the form of this relationship and exploring the time course of the association.
2) Examine the independence of albumin on incident heart failure development by
    a) controlling for known predictors of incident heart failure,
    b) controlling for inflammatory markers, and
    c) controlling for interim coronary heart disease.

Study Population

The Health Aging Body Composition Study is a population-based cohort of 3,075 well-functioning, community-dwelling men and women aged 70-79 years at inception. Participants were identified from black and white residents using Medicare beneficiary roles and residing in zip codes from the metropolitan areas of Pittsburgh, Pennsylvania and Memphis, Tennessee. The recruitment period was from March 1997 to July 1998. Eligibility criteria included: age 70-79 years at inception, no difficulties performing basic activities of daily living, self-report of no difficulty walking one-quarter of a mile or climbing 10 steps without resting, no reported use of a cane, walker, crutches, or other equipment for

movement, no history of active treatment for cancer in the previous three years, and no intention to move out of the area in the upcoming three years. The participant was excluded if participating in a trial involving a lifestyle intervention. The Institutional Review Boards at both sites approved the protocol.

Participants with HF, possible HF, or missing data on HF were excluded (n=140) from this analysis. Of the 2935 patients without prevalent HF, 2908 had albumin levels at baseline. One participant was excluded because of an extreme outlier albumin level. The remaining 2907 participants were included in this analysis (**Figure 1**).

Serum Albumin, Biochemistry, and Cytokine Measurements

Blood samples were obtained via venipuncture after an overnight fast, frozen at -70°C, and transported to the study's core laboratory at the University of Vermont. Standard chemistries were measured by a colorimetric technique on a Johnson & Johnson Vitros 950 analyzer. Cytokines (interleukin-6 [IL-6], tumor necrosis factor α [TNF-α], and C-reactive protein [CRP]) were measured in duplicate by an ELISA kit from R&D Systems. The detectable limit for IL-6 was 0.10 pg/mL and 0.18 pg/mL for TNF-α. Serum CRP was also measured in duplicate by ELISA on the basis of purified protein and polyclonal anti-CRP antibodies. The CRP assay was standardized according to World Health Organization First International Reference Standard with a sensitivity of 0.08 mg/L. The lower detection limit for CRP was 0.007 mg/L. Blind duplicate analyses (n=150) for IL-6, CRP, and TNF-α showed interassay coefficients of variation of 10.3%, 8.0%, and 15.8%, respectively.

Study Definitions

Race was self-defined by the participant. Diabetes mellitus was defined as a self-reported history of diabetes mellitus or use of antihyperglycemic medication. Smoking was defined as current, past (≥ 100 lifetime cigarettes), or never. Left ventricular hypertrophy was diagnosed from the electrocardiogram using the following voltage criteria: R amplitude > 26 mm in either V_5 or V_6, or R amplitude >20 mm in any of leads I, II, III, aVF, or R amplitude >12 mm in lead aVL or R amplitude in V_5 or V_6 plus S amplitude in V_1 >35 mm. Coronary heart disease was defined as: (1) history of surgical or percutaneous revascularization; or (2) electrocardiographic evidence of myocardial infarction; or (3) self-reported history of myocardial infarction or angina accompanied by use of anti-anginal medications. Hypertension was defined as self-reported history of physician diagnosis accompanied by use of antihypertensive medications. Incident coronary heart disease was defined as hospitalization for myocardial infarction or angina pectoris, or elective surgical or coronary revascularization.

Study Outcome

All participants were asked to report any hospitalizations, and every 6 months they were asked direct questions regarding interim cardiovascular events. Medical records for overnight hospitalizations were examined at each site. All first admissions with an overnight stay that was confirmed as related to HF, based on symptoms, signs, chest radiograph results, and echocardiographic findings, using criteria similar to those used in the Cardiovascular Health Study.[18] The criteria required at least HF diagnosis by a physician and treatment for HF.[19] All deaths were reviewed by the Health ABC Diagnosis and Disease Ascertainment

Committee and underlying causes of death were determined by central adjudication. Information on ejection fraction post-HF development was abstracted from the hospital medical records during the index hospitalization and was derived from echocardiography or left ventriculography reports.

Statistical Analysis

Descriptive statistics are presented as mean (standard deviation) for continuous and percentages for categorical variables. Differences in baseline characteristics between participants who did or did not develop incident HF were assessed with nonparametric rank sum test for continuous and Fisher's exact test for categorical variables. The correlations between co-morbidities, HF risk predictors, and inflammatory marker concentrations with baseline albumin level were evaluated by Spearman rank correlation. The relation between albumin and HF risk was examined with a Cox proportional hazards model; proportionality of hazards was examined by including an interaction term of albumin with time. We also evaluated albumin as a categorical variable using quartiles to construct Kaplan-Meier curves and demonstrate time-dependent effects.

In multivariable Cox models, we controlled for three sets of hierarchical, predefined models. First, we controlled for independent clinical predictors of incident HF as previously identified.[12] Secondly, as the relation of albumin and cardiovascular risk has been previously attributed to inflammation, the next set of variables included baseline markers of inflammation (IL-6, TNF-α, and CRP). Lastly, the impact of incident coronary events (incident myocardial infarction, angina, and either surgical or coronary revascularization) on the relationship of albumin and incident HF was included. The

proportional hazards assumption was evaluated by examining log-log survival plots and evaluation of interactions with time in extended-Cox models.

A two-sided $p<0.05$ was accepted as statistically significant. Analyses were performed with SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Participant Characteristics

The mean age of participants was 73.6 ± 2.9 years with 48.0% male and 58.7% white. Mean albumin was 39.8 g/L (range 28.0 to 50.0). Median follow-up was 9.4 years (interquartile range, 7.0-9.4 years). During this period, 342 (11.8%) participants developed HF corresponding to an incidence rate of 14.9 (95% CI, 13.4-16.5) new cases per 1000 person-years. **Table 1** presents the baseline characteristics of participants who developed HF versus those who did not. Baseline inflammatory markers (IL-6, TNF-α, and CRP) were higher in participants who developed HF. Data on post-HF ejection fraction were available for 265 of 342 (77.5%) new HF cases. Among these, 129/265 (48.7%) had impaired ejection fraction ≤40% whereas 136/265 (51.3%) had relatively preserved ejection fraction of >40%.

Serum Albumin and Heart Failure Risk

Correlation between albumin and heart failure risk factors and inflammatory markers were all less than 0.20, indicating no strong relationship of model variables and serum albumin level. The correlation between interim coronary heart disease (17.2% incidence in this cohort) and albumin proved also to be weak (rho -0.021, p-value 0.259). In univariate Cox models, there was a fairly linear, time-dependent association between baseline serum albumin concentrations and HF risk (**Table 3**, **Figure 5**). Lower serum albumin was associated with a significantly increased risk of incident HF for up to 4 years, in a diminishing rate; the risk was not statistically significant thereafter. This risk persisted in nested models adjusting for clinical predictors of HF, inflammatory markers, and incident coronary heart disease. **Figures 2 and 3** compare survival rates without incident HF among

participants with baseline serum albumin concentrations, classified by quartiles, in both unadjusted and adjusted models. The difference in baseline serum albumin concentration according to incident HF status over time is presented in **Table 4**.

Subgroup Analyses

Race and Gender

The association between serum albumin and incident HF was consistent across race and gender in both univariate and multivariate models (**Table 5**).

Ejection Fraction

When only cases with impaired ejection fraction were considered (n=129), albumin was neither a univariate (baseline HR per -1g/L, 1.11; 95% CI, 1.00-1.24; P=0.06; annual rate of HR decline, 2.4%; 95% CI, -0.2 to 4.9%; P=0.07) nor a multivariate predictor of incident HF (baseline HR per -1g/L in fully-adjusted model, 1.10; 95% CI, 0.97-1.25; P=0.16; annual rate of HR decline, 1.1%; 95% CI, -0.5 to 2.6%; P=0.16). When only cases with preserved ejection fraction were considered (n=136), albumin was both a univariate (baseline HR per -1g/L, 1.11; 95% CI, 1.02-1.21; P=0.02; annual rate of HR decline, 2.4%; 95% CI, 0.3 to 4.5%; P=0.03) and a multivariate predictor of incident HF (baseline HR per -1g/L in fully-adjusted model, 1.13 95% CI, 1.03-1.25; P=0.009; annual rate of HR decline, 0.8%; 95% CI, -0.2 to 2.0%; P=0.13). However, because ejection fraction was not systematically assessed in the Health ABC Study post HF development, these results need to be interpreted with caution.

DISCUSSION

In this elderly cohort, baseline serum albumin concentration was inversely associated with risk for incident HF in a time-dependent fashion. This relationship persisted after controlling for other known predictors of HF, several inflammatory biomarkers, and incident coronary heart disease.

Interestingly, as a result of this time-dependent association, the average baseline serum albumin in participants who developed HF during the entire 10-year follow-up period was not significantly lower compared to those who did not develop HF. This is related to the fact that most patients who develop HF earlier during follow-up had lower albumin concentration than later cases. The difference in baseline serum albumin concentrations between those who did and did not develop HF decreased over time, as did the hazard of developing HF with low serum albumin at baseline. Since we did not have serial albumin measurements in the Health ABC cohort, we do not know whether serum albumin is a risk predictor in the short and intermediate term but not in the long term, or whether individuals who presented with HF in the long term had developed lower albumin concentrations in the interim. Considering that changes in serum albumin over time have been previously associated with incident cardiovascular risk [6, 9], this is a plausible possibility. Another possible explanation is regression dilution (or attenuation) bias,[20] i.e. weakening of the association for those events that occur at remote follow-up periods, as baseline measurements may not be representative of the "true" underlying value of the variable of interest any more. Future studies evaluating serial changes in albumin and risk for incident HF are necessary to completely address these questions.

There are several reasons to believe that serum albumin most likely represents a risk marker for HF and not a true risk factor. Hypoalbuminemia has been attributed to a variety of factors, including exogenous albumin loss, albumin distribution, and volume overload states. Serum albumin concentrations are associated with increased inflammatory burden in the body. Inflammation has been associated with decreasing albumin synthesis rate and increasing albumin catabolism.[14] In turn, the inflammatory markers studied in this investigation (IL-6, TNF-α, and CRP) are elevated in patients with HF and asymptomatic left ventricular systolic and diastolic dysfunction,[21-25] and experimental studies have suggested that IL-6 and TNF-α are associated with left ventricular remodeling, fetal gene expression, myocyte hypertrophy, and myocyte apoptosis.[26] For these reasons, serum albumin may be considered as a surrogate marker of inflammatory status. However, controlling for inflammatory markers in our study had no effect on the association between serum albumin concentration and incident HF risk, suggesting that inflammatory status alone is not a compelling explanation for the albumin-HF link.

Another alternative explanation is that comorbidities associated with development of HF are also associated with worsening serum albumin profile and hence albumin may represent a surrogate marker of comorbidity burden. However, strong correlation between comorbidities and baseline albumin was not found in this analysis and in a previous study by our group, controlling for all such predictors did not change the association.[12] These observations suggest an interesting role for serum albumin as a strong surrogate marker for incident HF in the elderly, a marker that possibly integrates both known and unexplored pathways. Further insight into anti-thrombotic or anti-oxidant mechanisms, oxidative stress

due to the nitric oxide reservoir capabilities of serum albumin, or other unknown mechanisms may impact future therapeutic interventions.

Interestingly, in our study, low albumin levels had a stronger association with HF with preserved ejection fraction as opposed to HF with low ejection fraction (albeit a small difference despite statistical significance). This is possible, as low albumin is associated with inflammation that has in turn been linked with diastolic dysfunction in both animals and humans with hypertension and CHD [27, 28], and inhibition of inflammatory pathways improves LV function in experimental diabetic cardiomyopathy.[29, 30] As only three inflammatory markers were evaluated in this study, other inflammatory cytokines might be more persuasive in differentiating the two types of heart failure. Similarly, previous studies have shown a relation between albumin and several comorbidities; these comorbidities have been shown to be more common among patients with HF with preserved ejection fraction. This finding has important implications as HF is primarily a disease of the elderly and many of these individuals develop HF with preserved ejection fraction. However, cautious interpretation is needed because post-HF left ventricular function was not systematically assessed in Health ABC and theses findings are therefore subject to possible selection bias.

What are the implications of these findings? Considering that the association between serum albumin and incident HF (1) was continuous in nature, (2) was independent of other risk predictors, and (3) was consistent in both sexes and in whites and blacks, serum albumin may be used in assessing risk for future HF development in the elderly. Considering that measurement of serum albumin is relatively inexpensive and widely available, it may be feasible to use albumin in conjunction with other risk factors for this purpose.

Our study has several limitations. Diagnosis of HF was based on hospitalization. Because some participants may have developed HF without requiring hospitalization, HF rates are likely underestimated. Echocardiography was not performed at baseline in the Health ABC Study and thus participants with asymptomatic structural heart abnormalities may have been included in the analysis. Also, left ventricular function during hospitalization for HF was not prospectively assessed in the Health ABC Study and information on left ventricular ejection fraction was based on chart review in a subset (77.4%) of participants with incident HF; therefore, the differential association of albumin with risk for HF with preserved vs. reduced ejection fraction should be interpreted with caution. Because our cohort included persons of age 70 or older, these findings might not apply in younger populations. Finally, only baseline albumin measurements were available in this study; serial measurements likely would have provided additional information on the mechanisms underlying serum albumin as a predictor for incident HF.

In conclusion, in this study we demonstrate that baseline serum albumin concentrations independently predict risk for incident HF among older adults in a time-dependent fashion. This association appears to be consistent across demographic subgroups, and may be stronger for individuals with HF with preserved ejection fraction than those with depressed ejection fraction. Further studies are needed to delineate the screening potential of serum albumin for high-risk individuals, clinical utility, and other applications based on the findings in this study.

1. Gillum, R.F. and D.M. Makuc, *Serum albumin, coronary heart disease, and death.* Am Heart J, 1992. **123**(2): p. 507-13.

2. Klonoff-Cohen, H., E.L. Barrett-Connor, and S.L. Edelstein, *Albumin levels as a predictor of mortality in the healthy elderly.* J Clin Epidemiol, 1992. **45**(3): p. 207-12.

3. Kuller, L.H., et al., *The relation between serum albumin levels and risk of coronary heart disease in the Multiple Risk Factor Intervention Trial.* Am J Epidemiol, 1991. **134**(11): p. 1266-77.

4. Phillips, A., A.G. Shaper, and P.H. Whincup, *Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes.* Lancet, 1989. **2**(8677): p. 1434-6.

5. Beddhu, S., et al., *Association of serum albumin and atherosclerosis in chronic hemodialysis patients.* Am J Kidney Dis, 2002. **40**(4): p. 721-7.

6. Foley, R.N., et al., *Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease.* J Am Soc Nephrol, 1996. **7**(5): p. 728-36.

7. Savage, T., et al., *Calcified plaque is common in the carotid and femoral arteries of dialysis patients without clinical vascular disease.* Nephrol Dial Transplant, 1998. **13**(8): p. 2004-12.

8. Stenvinkel, P., et al., *Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure.* Kidney Int, 1999. **55**(5): p. 1899-911.

9. Schalk, B.W., et al., *Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal Aging Study Amsterdam.* Am J Epidemiol, 2006. **164**(10): p. 969-77.

10. Parekh, R.S., et al., *The association of sudden cardiac death with inflammation and other traditional risk factors.* Kidney Int, 2008. **74**(10): p. 1335-42.

11. Horwich, T.B., et al., *Albumin levels predict survival in patients with systolic heart failure.* Am Heart J, 2008. **155**(5): p. 883-9.

12. Butler, J., A Kalogeropoulos, Vasiliki Georgiopoulou, R Belue, N Rodondi, M Garcia, DC Bauer, S Satterfield, AL Smith, V Vaccarino, AB Newman, TB Harris, PWF Wilson, SB Kritchevsky and for the Health ABC Study, *Incident Heart Failure Prediction in the Elderly: The Health ABC Heart Failure Score.* Circ Heart Failure, 2008. **1**: p. 125-133.

13. Baumgartner, R.N., et al., *Serum albumin is associated with skeletal muscle in elderly men and women.* Am J Clin Nutr, 1996. **64**(4): p. 552-8.

14. Don, B.R. and G. Kaysen, *Serum albumin: relationship to inflammation and nutrition.* Semin Dial, 2004. **17**(6): p. 432-7.

15. Rao, M., et al., *Plasma interleukin-6 predicts cardiovascular mortality in hemodialysis patients.* Am J Kidney Dis, 2005. **45**(2): p. 324-33.

16. Yeun, J.Y., et al., *C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients.* Am J Kidney Dis, 2000. **35**(3): p. 469-76.

17. Cesari, M., et al., *Inflammatory markers and onset of cardiovascular events: results from the Health ABC study.* Circulation, 2003. **108**(19): p. 2317-22.

18. Fried, L.P., et al., *The Cardiovascular Health Study: design and rationale.* Ann Epidemiol, 1991. **1**(3): p. 263-76.

19. Rodondi, N., et al., *Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death.* Arch Intern Med, 2005. **165**(21): p. 2460-6.

20. Clarke, R., et al., *Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies.* Am J Epidemiol, 1999. **150**(4): p. 341-53.

21. Torre-Amione, G., et al., *Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD).* J Am Coll Cardiol, 1996. **27**(5): p. 1201-6.

22. Tsutamoto, T., et al., *Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure.* J Am Coll Cardiol, 1998. **31**(2): p. 391-8.

23. Levine, B., et al., *Elevated circulating levels of tumor necrosis factor in severe chronic heart failure.* N Engl J Med, 1990. **323**(4): p. 236-41.

24. Raymond, R.J., et al., *Elevated interleukin-6 levels in patients with asymptomatic left ventricular systolic dysfunction.* Am Heart J, 2001. **141**(3): p. 435-8.

25. Williams, E.S., et al., *C-reactive protein, diastolic dysfunction, and risk of heart failure in patients with coronary disease: Heart and Soul Study.* Eur J Heart Fail, 2008. **10**(1): p. 63-9.

26. El-Menyar, A.A., *Cytokines and myocardial dysfunction: state of the art.* J Card Fail, 2008. **14**(1): p. 61-74.

27. Kuwahara, F., et al., *Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation?* Hypertension, 2004. **43**(4): p. 739-45.

28. Bahrami, H., et al., *Novel metabolic risk factors for incident heart failure and their relationship with obesity: the MESA (Multi-Ethnic Study of Atherosclerosis) study.* J Am Coll Cardiol, 2008. **51**(18): p. 1775-83.

29. Westermann, D., et al., *Tumor necrosis factor-alpha antagonism protects from myocardial inflammation and fibrosis in experimental diabetic cardiomyopathy.* Basic Res Cardiol, 2007. **102**(6): p. 500-7.

30. Van Linthout, S., et al., *Anti-inflammatory effects of atorvastatin improve left ventricular function in experimental diabetic cardiomyopathy.* Diabetologia, 2007. **50**(9): p. 1977-86.

Table 1. Baseline Participant Characteristics

Characteristic	Overall (N=2907)	Heart failure (N = 342)	No heart failure (N = 2565)	*P* Value
Age, years	73.6 (2.9)	74.2 (2.9)	73.5 (2.9)	<0.001
Female, N (%)	1513 (52.0)	156 (45.6)	1357 (52.9)	0.010
Black race, N (%)	1201 (41.3)	163 (47.4)	1038 (40.5)	0.015
Smoking status, N (%)				
Current	305 (10.5)	51 (15.0)	254 (9.9)	<0.001
Past	1311 (45.2)	167 (49.0)	1144 (44.7)	
Body mass index, kg/m^2, N (%)				
< 25	947 (32.6)	107 (31.3)	840 (32.8)	0.001
25-30	1222 (42.0)	121 (35.4)	1101 (42.9)	
>30	738 (25.4)	114 (33.3)	624 (24.3)	
Systolic blood pressure, mm Hg	136.0 (21.0)	142.8 (23.3)	135.1 (20.5)	<0.001
Diastolic blood pressure, mm Hg	71.4 (11.7)	72.9 (12.9)	71.2 (11.5)	0.061
Heart rate, beats per min	65.3 (11.0)	67.4 (12.3)	65.0 (10.8)	0.002
Hypertension, N (%)	1257 (43.5)	188 (55.1)	1069 (42.0)	<0.001
Diabetes, N (%)	424 (14.7)	72 (21.1)	352 (13.8)	<0.001
Depression, N (%)	60 (2.1)	7 (2.1)	53 (2.1)	0.576
Cerebrovascular disease, N (%)	197 (6.8)	33 (9.9)	164 (6.5)	<0.001
Coronary heart disease, N (%)	472 (16.5)	111 (33.0)	361 (14.3)	<0.001
Left ventricular hypertrophy, N (%)	346 (11.9)	56 (16.4)	290 (11.3)	0.006
Fasting glucose, mg/dL	104.0 (34.2)	112.3 (45.0)	102.9 (32.3)	<0.001
Albumin, g/L	39.8 (3.1)	39.6 (3.1)	39.8 (3.1)	0.216
Creatinine, mg/dL	1.05 (0.4)	1.15 (0.5)	1.0 (0.4)	<0.001

Table 1. Baseline Participant Characteristics (continued)

Characteristic	Overall (N=2907)	Heart failure (N = 342)	No heart failure (N = 2565)	*P* Value
Total cholesterol, mg/dL	203.2 (38.3)	199.4 (39.3)	203.7 (38.1)	0.052
High density lipoprotein, mg/dL	54.3 (17.0)	52.0 (17.1)	54.6 (17.0)	0.001
Low density lipoprotein, mg/dL	121.9 (34.6)	120.0 (34.8)	122.2 (34.5)	0.190
Triglycerides, mg/dL	136.9 (77.0)	137.3 (71.9)	136.8 (77.7)	0.575
Interleukin-6, pg/mL	2.4 (1.9)	2.9 (2.1)	2.3 (1.8)	<0.001
C-reactive protein, µg/mL	3.0 (4.7)	3.8 (6.5)	2.9 (4.7)	<0.001
Tumor necrosis factor α, pg/mL	3.4 (1.7)	3.9 (1.9)	3.4 (1.7)	<0.001

Values for continuous variables are shown as mean (SD); categorical variables are represented by mean (%).

Table 2. Correlation between Heart Failure Risk Factors and Inflammatory Biomarkers and Serum Albumin

Variable	Value[¥]	Rho*	P-value
HF Risk Factors			
Smoking, present %[†]	19.2	0.0008	0.976
Coronary heart disease, definite, %[†]	16.2	0.035	0.064
Systolic blood pressure, mm Hg	134 (122, 148)	0.104	<0.001
Heart rate, beats per minute	64 (57, 72)	0.057	0.002
Creatinine, mg/dL	1.0 (0.9, 1.2)	0.037	0.047
Serum fasting glucose, mg/dL	94 (87, 105)	0.053	0.005
Left ventricular hypertrophy, %	11.3	0.005	0.782
Age, year	73 (71, 76)	-0.051	0.006
Inflammatory Biomarkers			
IL-6 (pg/mL)	1.8 (1.2, 2.7)	- 0.138	<0.001
CRP	1.7 (1.0, 3.1)	- 0.105	<0.001
TNF-α	3.1 (2.4, 4.1)	- 0.043	0.026

[¥]Value for continuous variables represents median (interquartile range).
*Spearman's rank correlation for rho for continuous variables; for binary variables (1=present, 0=absent), the z score of the rank sum test is transformed into the corresponding rho value for comparison purposes; rho=1 denotes perfect correlation, rho=-1 denotes perfect negative correlation and rho=0 denotes no correlation.
[†]Past smoking history and possible coronary heart disease categories were taken out for this analysis

Table 3. Baseline Serum Albumin Concentration and Risk for Incident Heart Failure

Extended Cox Model	HR[Ψ]	95% CI	P-value
Baseline HR	**1.12**	**(1.05, 1.19)**	**<0.001**
Time-dependent interaction	0.979	(0.966, 0.992)	0.002
Model 1: Other clinical predictors of incident heart failure[†]			
Baseline HR	**1.16**	**(1.09, 1.23)**	**<0.001**
Time-dependent interaction	0.978	(0.965, 0.991)	0.001
Model 2: Model 1 plus inflammatory markers[¥]			
Baseline HR	**1.16**	**(1.09, 1.23)**	**<0.001**
Time-dependent interaction	0.978	(0.965, 0.991)	0.001
Model 3: Model 2 plus incident coronary heart disease[€]			
Baseline HR	**1.11**	**(1.06, 1.17)**	**<0.001**
Time-dependent interaction	0.995	(0.990, 0.999)	0.02

*Albumin (continuous variable) expressed as -1g/L per unit increase in HR
[†]Age, history of coronary heart disease, systolic blood pressure, history of smoking, creatinine, heart rate, fasting glucose, and left ventricular hypertrophy
[¥]Inflammatory markers include IL-6, CRP, and TNF-α
[€]Incident coronary heart disease defined as incident myocardial infarction, angina, or coronary revascularization (percutaneous or surgical)
[Ψ]HR: Hazard ratio

Table 4. Baseline Serum Albumin Concentrations by Incident HF Status Over Time

Year	Heart Failure		No Heart Failure		Mean Δ (95% CI)	
	N	Albumin (g/L)	N	Albumin (g/L)	Albumin (g/L)	P-value
1	39	38.3 ± 3.4	2868	39.8 ± 3.1	1.5 (0.4, 2.6)	0.009
2	32	38.7 ± 3.3	2836	39.8 ± 3.1	1.1 (0.3, 1.9)	0.007
3	38	38.7 ± 3.4	2798	39.8 ± 3.1	1.1 (0.5, 1.8)	0.001
4	45	38.8 ± 3.3	2770	39.9 ± 3.1	1.0 (0.5, 1.6)	<0.001
5	36	39.1 ± 3.3	2725	39.8 ± 3.1	0.7 (0.2, 1.2)	0.006
6	39	39.3 ± 3.3	2689	39.8 ± 3.1	0.6 (0.1, 1.0)	0.017
7	41	39.4 ± 3.2	2650	39.8 ±3.1	0.4 (0.01, 0.8)	0.042
8	29	39.5 ± 3.1	2609	39.8 ± 3.1	0.3 (-0.03, 0.7)	0.071
9	13	39.6 ± 3.1	2580	39.8 ± 3.1	0.3 (-0.09, 0.6)	0.137
10	28	39.6 ± 3.1	2567	39.8 ± 3.1	0.2 (-0.1, 0.6)	0.167

Table 5. Association of Serum Albumin with Incident Heart Failure: Subgroup Analyses

	Albumin (g/L)	Univariate HR* (95% CI)	P-value	Multivariate HR¥ (95%CI)	P-value
Race					
White (n=1707)	39.9 ± 3.1	1.11 (1.03, 1.19)	0.004	1.10 (1.03, 1.16)	0.003
Black (n=1200)	39.6 ± 3.1	1.12 (1.05, 1.20)	0.001	1.11 (1.04, 1.18)	0.001
Gender					
Male (n=1394)	40.0 ± 3.2	1.13 (1.05, 1.20)	0.001	1.11 (1.05, 1.18)	<0.001
Female (n=1513)	39.6 ± 3.0	1.11 (1.04, 1.20)	0.003	1.12 (1.05, 1.19)	<0.001

*HR = Hazard ratio per -1g/L baseline albumin concentration

¥ Multivariate analysis: Model included clinical predictors of HF, inflammatory markers, and incident coronary events (described in Table 3, Model 3)

Interaction for race: Univariate = 0.72
Multivariate = 0.67

Interaction for gender: Univariate = 0.76
Multivariate = 0.09

Figure 1. Flowchart for Study Participants Evaluated in Analysis

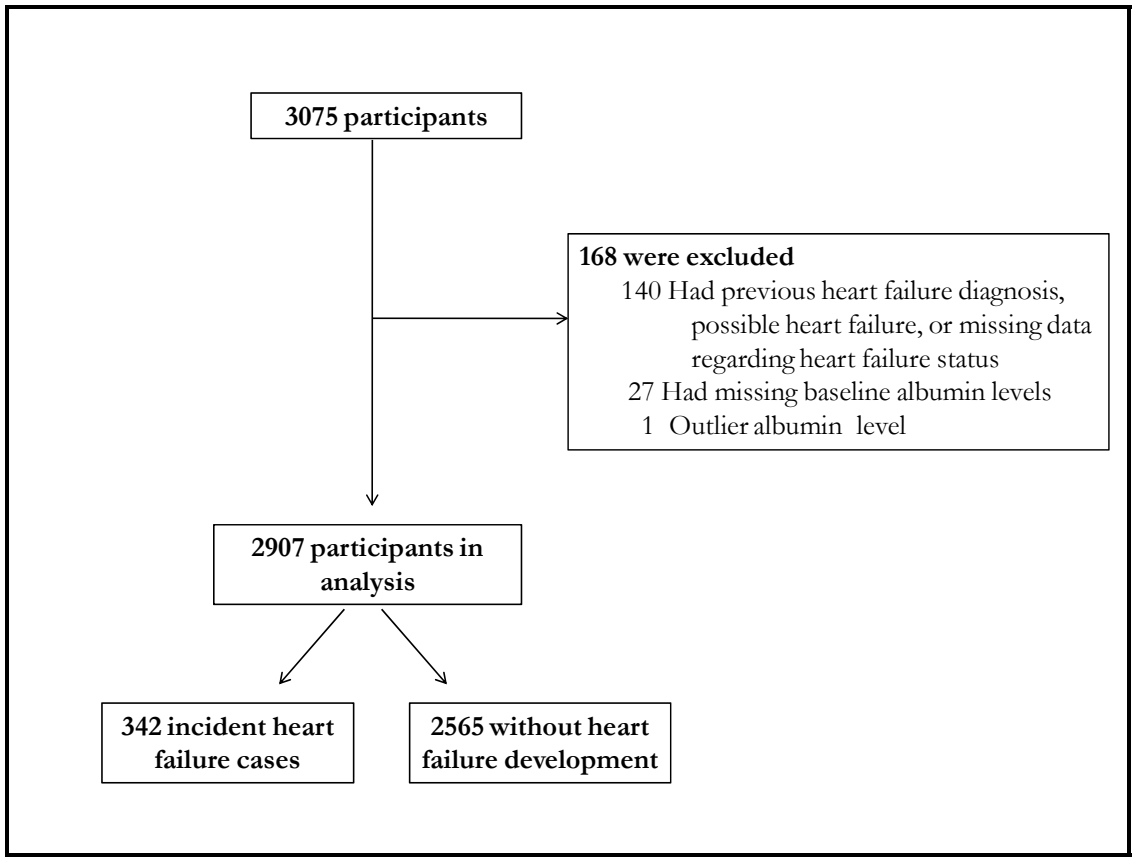
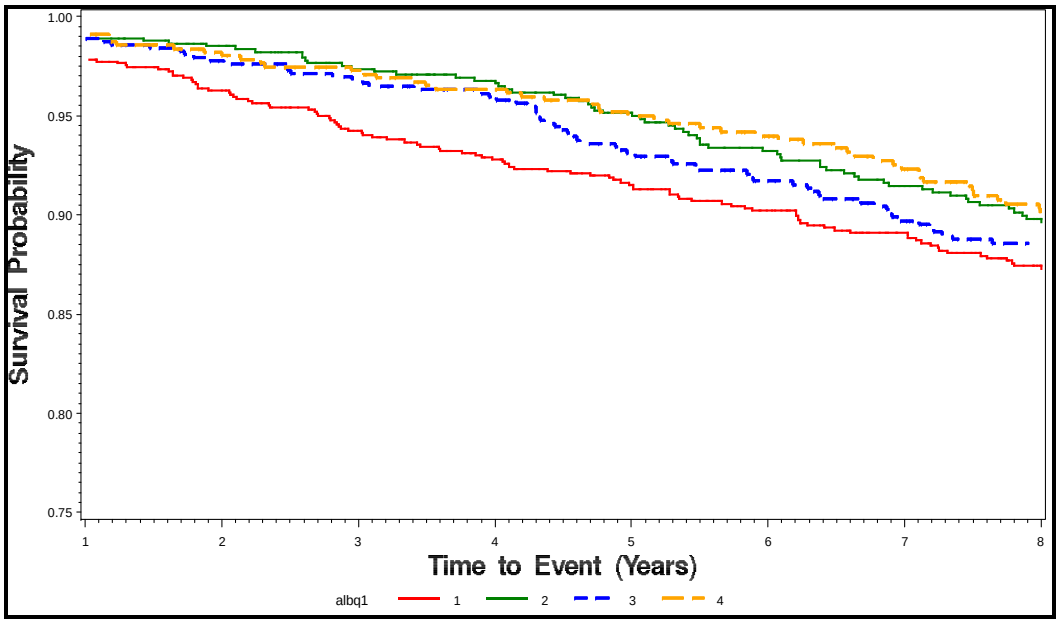
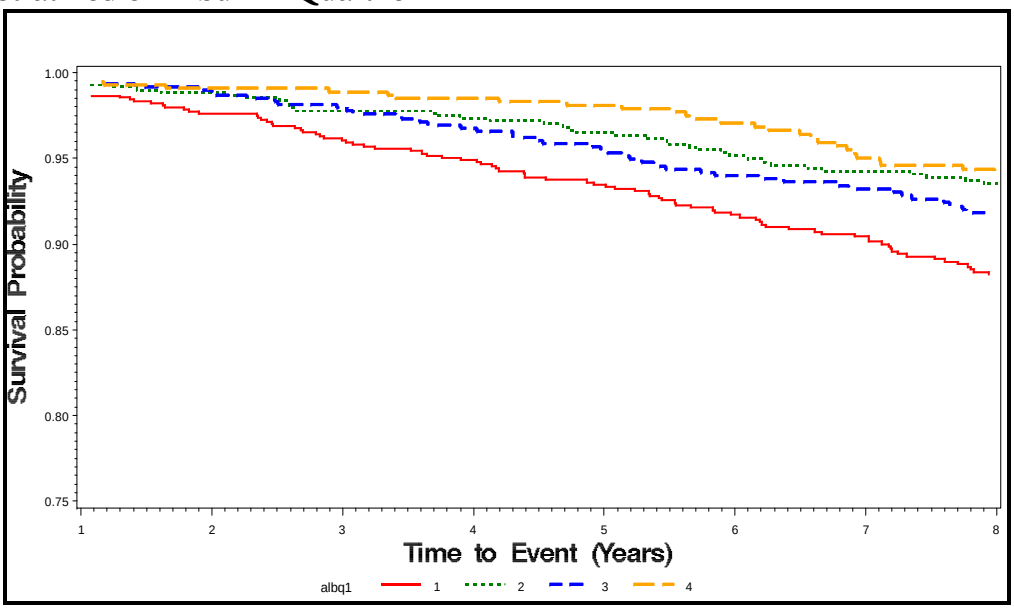


Figure 2. Unadjusted Kaplan Meier Curves: Survival without Incident Heart Failure Stratified on Albumin Quartile



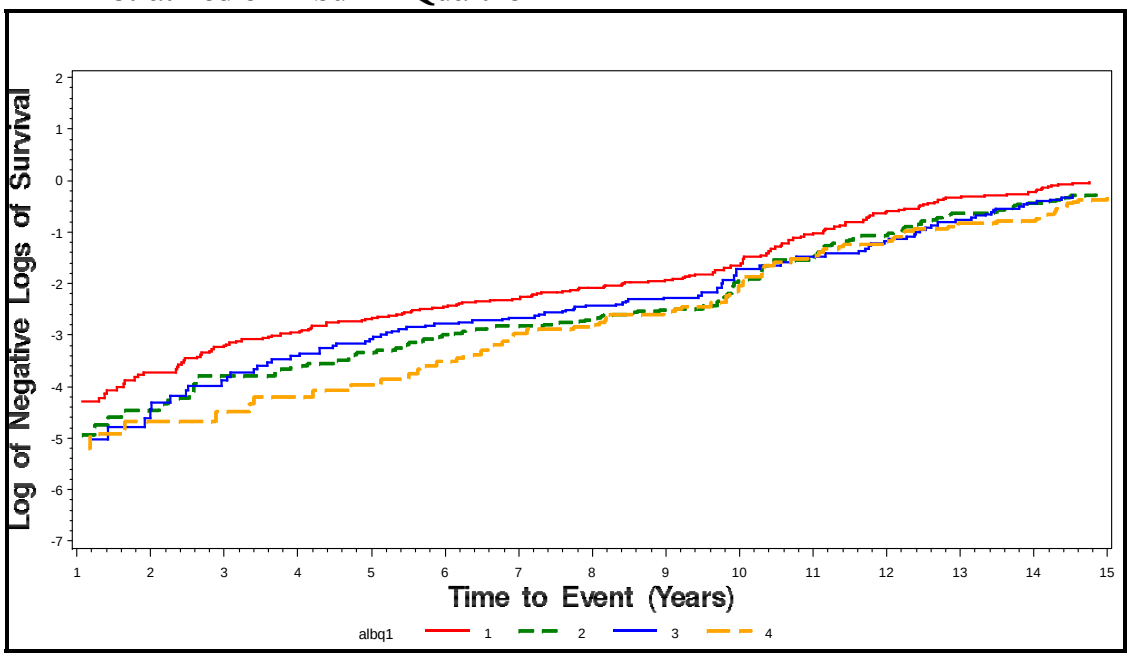
*Albumin quartile: 1 (lowest quartile) to 4 (highest quartile)

Figure 3. Fitted Kaplan-Meier Curves: Survival without Incident Heart Failure Stratified on Albumin Quartile



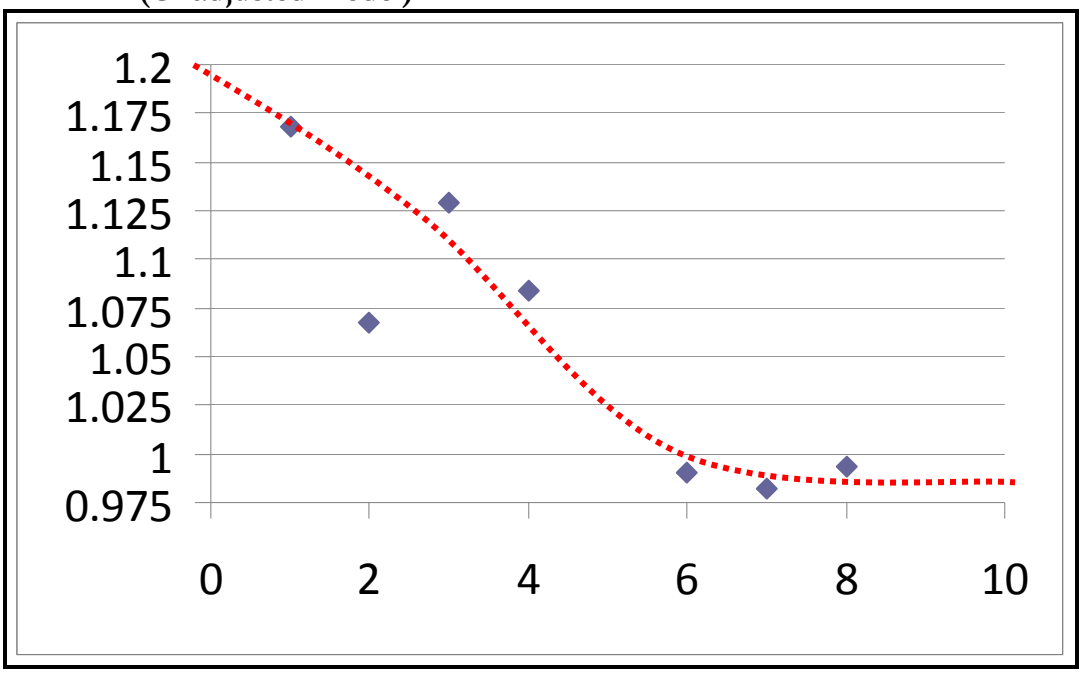
*Using a model included clinical predictors of HF, inflammatory markers, and incident coronary events (described in Table 3, Model 3)
*Albumin quartile: 1 (lowest quartile) to 4 (highest quartile)

Figure 4. Log-Log Survival Curves of Albumin Association to Incident Heart Failure, Stratified on Albumin Quartile



*Log-log survival curves show intersection of the albumin quartiles, suggesting time-dependency of albumin variable

Figure 5. Hazard Ratio of Albumin Over Time, Evaluated at 1 Year Intervals (Unadjusted Model)



*Albumin lost predictive significance after four years in both unadjusted and adjusted models