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Soluble Tumor Necrosis Factor Receptors and
Heart Failure Risk in Older Adults
The Health, Aging, and Body Composition Study

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ABSTRACT

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Background: Tumor necrosis factor (TNF) affects cardiac contractility and remodeling, and TNF levels are associated with risk for heart failure (HF). The soluble TNF type-1 (sTNFR1) and type-2 (sTNFR2) receptors are elevated in patients with manifest HF, but whether they are associated with risk for incident HF is unclear.

Methods: The Health Aging and Body Composition (ABC) Study is a prospective cohort study. Using Cox proportional hazard models, we examined the association between baseline levels of sTNF-R1 and sTNF-R2 and incident HF risk among 1285 participants of the Health ABC cohort (age 74 ± 2.9 years; 51.4% female; 41.1% black).

Results: At baseline, median (interquartile range) TNF, sTNF-R1, and sTNF-R2 levels were 3.14 (2.42-4.06)pg/ml, 1.46 (1.25-1.76)ng/ml, and 3.43 (2.95-4.02)ng/ml, respectively. Both sTNF-R1 and R2 levels modestly correlated with age, black race, and waist/thigh circumference ratio, serum creatinine, triglyceride, and low- and high-density lipoprotein levels. During a median follow-up of 11.4 (interquartile range 6.9, 11.7) years, 233 (18.1%) participants developed HF. In models controlling for the Health ABC HF Risk Model, TNF (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.02, 1.61 per \log_2 increase), and sTNF-R1 (HR, 1.68; 95%CI, 1.15, 2.46 per \log_2 increase), but not sTNF-R2 (HR, 1.15; 95%CI, 0.80, 1.63 per \log_2 increase), were associated with a higher risk for HF. These associations were consistent across whites and blacks (TNF, sTNF-R1, sTNF-R2, interaction $P=0.531, 0.091$ and 0.795 , respectively), and in both genders (TNF, sTNF-R1, sTNF-R2, interaction $p=0.491, 0.672$ and 0.999 , respectively).

Conclusions: In older adults, elevated levels of sTNF-R1 are associated with an increased risk for incident HF.

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INTRODUCTION

While the incidence of cardiovascular diseases increase dramatically with age, the predictive value of traditional risk factors diminishes in older individuals, suggesting the potential important role of alternate mechanisms and markers influencing risk in the elderly.(1-3) Inflammatory markers, including tumor necrosis factor (TNF) and its soluble receptors, TNF receptor type 1 (sTNF-R1) and TNF receptor type 2 (sTNF-R2), are elevated in patients with manifest heart failure (HF).(4-6) Cytokines, e.g. TNF are soluble polypeptides acting as immune regulators, and affect the inflammatory cascade, and myocardial function.(7, 8) Previous studies have suggested an association between circulating levels of inflammatory cytokines and risk of HF.(9-13) Circulating cytokine receptors may also play an important role in the deleterious effects of the inflammatory process. Stimuli that cause cytokine levels to rise may also induce shedding of soluble cytokine receptors in an attempt to dampen the inflammatory response. Thus, elevated levels of soluble receptors may represent a more prolonged or severe underlying inflammatory state.(14, 15) Soluble cytokine receptors may provide more reliable markers of chronic inflammation as they have a longer half-life and tend to have more consistent serum levels over time than the cytokines themselves.(16-19) Despite soluble TNF receptors association with severity of HF, to date the association of these receptors with risk for new onset HF has not been rigorously evaluated. Previous studies were small, precluding evaluation of incremental benefit of TNF receptors over traditional risk factors.(20) To better identify patients at high risk for incident HF, new predictive markers need to be established, especially in aged populations. In this study, we aimed to assess the association of baseline sTNF-R1 and R2 levels and incident HF risk in older adults.

BACKGROUND

Overall Population Impact of Heart Failure

Heart failure prevalence continues to rise and is expected to worsen as the proportion of elderly population increases.(1) Despite advances in therapy, absolute outcomes for these patients remain sub-optimal.(21) Heart failure is the leading cause of hospitalization, with an annual number of hospitalizations for HF now exceeding 1 million(22) and nearly half of all admitted patients being readmitted within six months of discharge.(23)

Incidence and Prevalence of Heart Failure

The American Heart Association (AHA) estimates that there are 670,000 new cases of HF diagnosed annually, most of which occurs among the elderly.(1) Annual incidence of HF approaches 10 per 1000 persons after age 65 and reaches as high as over 40 per 1000 persons in those over 85 years.(1, 24, 25) Furthermore, there are gender- and race-related differences in HF incidence.(25-27) In the Health, Aging, and Body Composition Study, men and blacks were more likely to develop HF.(28)

The Framingham investigators estimated that the lifetime risk of developing HF at age 40 is 21% for men and 20% for women. Despite the shorter risk exposure with increasing age, the higher absolute risk at older ages results in the lifetime risk to remain approximately one in five for both men and women.(29) This risk is higher among those with coronary heart disease.

Data on trends in incidence of HF have varied, with some reporting declining,(21, 30) some stable,(31) and others suggesting a rise in incidence over time.(32) However, although overall HF incidence appears to be relatively stable, the prevalence of HF has been

rising dramatically and has culminated in the current HF epidemic. It is estimated that there are 5.8 million people currently living with symptomatic HF in the United States(1) and this number is expected to increase with the aging population.(21, 25, 33)

Tumor Necrosis Factor and Heart Failure

Inflammation is a necessary response of the immune system to harmful stimuli such as infection or injury, producing cytokines and acute-phase proteins. However, when inflammation is chronic, it can have detrimental effects. Cytokines, such as TNF, are soluble polypeptides acting as important humoral regulators in immunoregulation, hematopoiesis, and the inflammatory cascade.(7) Inflammation has long been associated with chronic HF and may even play an important role in the pathogenesis of HF through direct effects on myocardial function.(8) Inflammatory markers, including TNF and its soluble receptors, TNF-R1 and TNF-R2, are known to be elevated in patients with HF.(4-6) In addition, recent evidence suggests these inflammatory cytokines are also elevated in individuals with asymptomatic left ventricular systolic and diastolic dysfunction.(34) Circulating cytokine receptors may also play an important role in the deleterious effects of the inflammatory process. Evidence suggests that stimuli causing cytokine levels to rise may also induce shedding of soluble cytokine receptors in an attempt to dampen the inflammatory response. Thus, elevated levels of soluble receptors may represent a more prolonged or severe underlying inflammatory state.(14, 15) In addition, soluble cytokine receptors may provide more reliable markers of chronic inflammation as they generally have a longer half-life and tend to have more consistent serum levels over time than the cytokines themselves.(16-19) In fact, previous studies conducted in smaller cohorts have suggested that soluble TNF receptors are more strongly associated with HF than TNF levels.(35)

Although HF is primarily a disease of the elderly(1) the predictive validity of traditional cardiovascular risk factors diminishes with increasing age.(2, 3) Therefore, to better identify patients at high risk for incident heart failure, new predictive markers need to be established, especially in aged populations. Previous studies have suggested a strong association between circulating levels of inflammatory cytokines and risk of HF.(9-13) However, the association between TNFR1 and TNFR2 and incident HF has not been fully evaluated in a large epidemiologic study. Furthermore, how TNFR1 and TNFR2 levels are associated with risk for HF in the elderly is unclear.

METHODS

Specific Aims:

1. To assess the association between levels of the circulating inflammatory cytokine receptors TNF-R1 and TNF-R2 with development of incident heart failure
2. To assess if TNF receptors provide additional predictive information after conditioning on the Health ABC Heart Failure Risk Score
3. To assess whether race and gender modify the association between TNF receptors and heart failure

Study Objective: In this study we sought to evaluate whether sTNF-R1 or sTNF-R2 (ng/ml) can be used to identify elderly individuals at increased risk for HF

Study design: Prospective cohort study

Study Population: The study population included participants in the Health, Aging, and Body Composition (Health ABC) Study, a population-based cohort of 3,075 community-dwelling men and women. Participants, age 70 to 79 years at inception, were recruited from April 1997 to June 1998 from areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. To be eligible, study participants had to, (1) report no difficulty in walking ¼ mile, climbing 10 stairs without resting, or performing basic activities of daily living; (2) be free of life-threatening illness; and (3) have no intention of moving within 3 years. Participants had telephone contacts every 6 months and clinical visits every year. Clinical diseases at baseline were ascertained using algorithms similar to the Cardiovascular Health

Study.(36) The institutional review boards at both study sites approved the protocol. These results represent the outcomes during 11.4 years of follow-up on the 1285 random participant samples that were evaluated for sTNF-R1 and R2 levels as part of an ancillary study.

Serum Biomarker Measurements (Predictor Variables): Blood samples were obtained in the morning, and after processing, the specimens were frozen at -70 degrees centigrade and shipped to the Health ABC Core Laboratory at the University of Vermont. Cytokines and cytokine soluble receptors were measured in duplicate by an enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, Minnesota). The detectable limit for TNF (HSTA50 kit), sTNF-R1 (DRT100 kit) and sTNF-R2 (DRT200 kit) was 0.18 pg/ml, 3 pg/ml and 1 pg/ml, respectively. Blind duplicate analyses (n=150) for TNF showed inter-assay coefficients of variation of 15.8%.

Study outcomes: All first overnight hospitalization adjudicated to be related to HF were classified as incident HF (outcome variable). All participants were asked to report any hospitalizations and every 6 months were asked for information about interim events. When an event was reported, hospital records were collected and verified by the Health ABC disease adjudication committee at each site. Adjudication criteria required, in addition to a physician diagnosis of HF: 1) medical record documentation of HF symptoms and signs; 2) supporting clinical findings e.g. chest radiography or echocardiography; and 3) medical therapy for HF, including at least a diuretic and a vasodilator and/or digitalis. Incident coronary heart disease was defined as hospitalization for myocardial infarction, angina

pectoris, or elective coronary revascularization, either surgical or percutaneous. Date and causes of death were taken from the death certificate.

Statistical Analysis: Descriptive analyses were performed and data are presented as mean (standard deviation) for continuous and percentage for categorical variables. Differences between groups were assessed using the nonparametric rank sum test (Mann-Whitney) for continuous and Fisher's exact test for categorical variables. Univariate relationship between TNF, sTNF-R1 and sTNF-R2 with HF risk was examined with Cox proportional hazards models. Because the distribution of TNF, sTNF-R1, and sTNF-R2 was lognormal in our sample, we log-transformed these variables prior to including in Cox models. We used a \log_2 basis to facilitate interpretation; the hazard ratio per \log_2 increase expresses the risk associated with doubling of biomarker levels. Incident HF rates were calculated with the Kaplan-Meier method. The multivariable Cox models were controlled for the Health ABC HF Risk Model which includes the following variables: age, history of coronary heart disease, smoking, systolic blood pressure, creatinine, albumin, heart rate, fasting glucose, and left ventricular hypertrophy. The association between TNF, sTNF-R1 and sTNF-R2 with incident HF was evaluated for effect modification with sex and race using appropriate interaction terms. For these analyses, we divided the cohort by the corresponding median biomarker level. The proportional hazards assumption was evaluated visually and by examining the Schoenfeld residuals. A two sided $p < 0.05$ was accepted as statistically significant. Analyses were performed with SAS (version 9.2, SAS Institute Inc, Cary, NC).

RESULTS

Participant Characteristics: The mean age was 74.0 ± 2.9 years with 51.4% women and 41.1% black participants, **Table 1**. At baseline, median (interquartile range) TNF, sTNF-R1, and sTNF-R2 levels were 3.14 (2.42-4.06) pg/ml, 1.46 (1.25-1.76) ng/ml, and 3.43 (2.95-4.02) ng/ml, respectively, **Table 2**. Age had a modest positive correlation with TNF as well as sTNF-R1 and sTNF-R2 levels. Measures of adiposity (body mass index and waist to thigh ratio), baseline diabetes mellitus, hypertension, peripheral vascular disease, coronary heart disease, and albumin, creatinine and high density lipoprotein levels, also had modest correlations with TNF and its soluble receptors, **Table 3**. Women had lower TNF-R1 levels (by -0.09) and TNF-R2 (by -0.07) compared to men.

sTNF-R1, sTNF-R2 and Incident HF: During median follow-up of 11.4 (6.9, 11.7) years, 233 (18.1%) participants developed HF. Baseline TNF was associated with a significantly higher risk of HF (hazard ratio [HR], 1.52; 95%CI 1.23, 1.89 per \log_2 increase; $P=0.0001$), as was sTNF-R1 (HR, 2.36; 95%CI, 1.71, 3.25 per \log_2 increase; $P<0.0001$) and sTNF-R2 (HR, 1.52; 95%CI, 1.16, 2.00 per \log_2 increase; $P=0.003$). After controlling for the Health ABC HF Risk Score, TNF and sTNF-R1 remained associated with a higher risk for HF (HR, 1.28; 95%CI, 1.02, 1.61; $P=0.037$ for TNF, and HR, 1.68; 95%CI, 1.15, 2.46; $P=0.008$ for sTNF-R1); whereas the association of sTNF-R2 with HF risk was not significant (HR, 1.15; 95%CI, 0.80, 1.63; $P=0.45$). **Table 4**.

Incident Heart Failure Subgroup Analyses: Levels of TNF, sTNF-R1 and sTNF-R2 and incident HF risk were consistent across whites vs. blacks (interaction $p=0.531$, 0.091 and

0.795 for TNF, sTNF-R1, sTNF-R2 respectively) and across both genders (interaction $p=0.491$, 0.672 and 0.999 for TNF, sTNF-R1, sTNF-R2, respectively), **Table 5**.

DISCUSSION

To better identify patients at risk for and to effectively intervene to prevent HF in the elderly, novel markers and pathways are needed, considering that traditional markers are of limited value in the elderly. In this large cohort of well-phenotyped older adults, we observed that elevated serum levels of sTNF-R1 are associated with increased risk for incident HF. sTNF-R1 had a stronger association with incident HF than TNF. This association persisted in models adjusting for established HF risk factors in older adults. Importantly, consistent with the cytokine analysis of the vesnarinone trial,⁽³⁷⁾ these findings were consistent across sex and race.

Inflammation has long been associated with chronic HF and even plays an important role in the pathogenesis of HF through direct effects on myocardial function.⁽⁸⁾ Previous studies have suggested a strong association between circulating levels of inflammatory cytokines and risk of HF.⁽⁹⁻¹³⁾ In the Framingham Heart Study⁽⁹⁾, there was a 68% increase in risk of incident HF per tertile increment in TNF (mg/dL) among participants with no prior history of myocardial infarction or HF in models controlling for established risk factors.⁽⁹⁾ Although most studies relating inflammatory markers and HF incidence have been conducted primarily in younger individuals, a recent paper from the Health ABC study demonstrated a significant association between the inflammatory markers interleukin-6, C-reactive protein, and TNF, and heightened risk of incident HF among older persons, which also persisted despite controlling for known HF risk factors.⁽¹³⁾ In addition, there is evidence to suggest that these inflammatory cytokines are elevated in individuals with asymptomatic left ventricular systolic and diastolic dysfunction.⁽³⁴⁾ These recent studies, in

addition to results from the current study, support a more direct role for inflammation in HF development than was previously thought.(9, 10, 12, 13)

We found that sTNF-R1 was associated with incident HF, while increased levels of sTNF-R2 were not.(38) Aside from erythrocytes, sTNF-R1 is expressed in nearly all cell types, including vascular and myocardial cells.(39) sTNF-R2 is found primarily in cells of the immune system but also in the heart, and plays a major role in the lymphoid system. While the consequences of sTNF-R2 signaling are less well characterized, it is known that sTNF-R2 mediates signals that promote tissue repair and angiogenesis.(40) On the other hand, pro-inflammatory and apoptotic pathways are mediated largely through sTNF-R1.(38) One study found that higher levels of sTNF-R1 were not only associated with a poor HF prognosis, but sTNF-R1 emerged as the strongest independent predictor and the most accurate prognosticator, regardless of follow-up duration and independent of established markers of HF severity.(41)

TNF contributes to the progression of HF through a variety of mechanisms.(42) TNF is known to exert direct effects on cardiomyocyte contractility(43, 44) and can influence left ventricular remodeling and hypertrophy.(45-47) In the failing heart, TNF induces β -adrenergic receptor uncoupling,(48) increases reactive oxygen species formation,(49) and increases inducible nitric oxide synthase synthesis resulting in high output nitric oxide formation,(49) all of which contribute to contractile dysfunction. Apart from its functional effects, sustained expression of TNF at high concentrations contributes to structural alterations in the failing heart, such as cardiomyocyte hypertrophy, increased cardiomyocyte apoptosis and cardiac fibrosis. In addition to direct myocardial effects, inflammatory cytokines have been implicated in the pathogenesis of other aspects of the HF syndrome such as pulmonary edema, skeletal muscle atrophy and cachexia.(50, 51)

Circulating cytokine receptors play an important role in these deleterious effects of the inflammatory process. In fact, previous studies conducted in smaller cohorts suggest that circulating levels of sTNF-R1 and sTNF-R2 are more strongly correlated with severity of HF than TNF.(35, 41, 52) Our study further supports these findings, demonstrating the incremental value of sTNF-R1 levels in prediction of incident HF among the elderly, while elevated levels of TNF did not add any incremental predictive value over traditional HF risk factors.

With the increasing number of older adults in the population, the prevalence of HF is projected to increase substantially.(21, 25, 33) Hospitalization rate and cost of care are enormous and these will only increase with the aging population.(1, 53, 54) Research efforts should therefore not only focus on new HF therapies but also ways to prevent HF development by targeting at risk individuals. Future studies are needed to further explore the potential role of sTNF-R1 in predicting increased risk of HF among the elderly and to also elucidate the pathophysiologic link between TNF and its receptors with HF development. This could lead to future research investigating these receptors as therapeutic targets.

Our study has several limitations. Diagnosis of HF was based on HF hospitalization. Therefore, the rate of incident HF in our study was likely underestimated as some participants may have developed HF while not requiring hospitalization. In addition, censoring due to death from other causes may not be independent of death from HF, therefore violating the independent censoring assumption in the cox model.

In conclusion, we demonstrate a significant association between elevated levels of the TNF receptor, sTNF-R1, and risk of HF in older adults. These findings were consistent across sex and race based groups and persisted after controlling for HF risk factors.

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Table 1. Baseline Participant Characteristics (N=1,285)

Characteristic	Overall	Heart failure cases	No heart failure	P-value
	Mean(SD) or %	Mean(SD) or %	Mean(SD) or %	
Age(years)	73.6(2.9)	74.2(2.9)	73.4(2.9)	<0.001
Men	624(48.6)	120(52)	504(48)	0.321
Black Race	528(41.1)	102(44)	426(40)	0.357
Body Mass Index, kg/m ²	27.6(4.9)	28.4(5.2)	27.4(4.8)	0.004
Diabetes	205(16)	48(21)	157(15)	0.033
Hypertension	629(48.9)	137(59)	492(47)	0.001
Coronary Heart Disease	284(22.1)	85(36)	199(19)	<0.001
Left ventricular hypertrophy, n (%)	151(11.8)	36(15)	115(11)	0.053
Systolic blood pressure (mm Hg)	135.4(20.7)	139.1(22.7)	134.6(20.1)	0.002
Creatinine, mg/dl*	1.0(0.9,1.2)	1(0.9,1.2)	1(0.9,1.1)	0.11
Total cholesterol, mg/dl	202.0(37.0)	201.2(38.1)	202.2(36.7)	0.695
Low-density lipoprotein, mg/dl	121.7(33.8)	122.1(34.1)	121.6(33.7)	0.832
High-density lipoprotein, mg/dl	53.1(16.5)	50.8(15.8)	53.6(16.6)	0.02

*Value expressed as median (interquartile range) because of highly skewed distributions. α value=0.05

**Table 2. Median (Interquartile Range) Inflammatory Marker Values
According to Incident Heart Failure Development**

Marker	Total Cohort (n=1,258)	Participants Without Incident HF (n=1,052)	Participants With Incident HF (n=233)	P-value
TNF, pg/ml	3.14 (2.42-4.06)	3.07 (2.40, 3.97)	3.49 (2.61, 4.40)	<0.001
sTNF-R1, ng/ml	1.46 (1.25, 1.76)	1.45 (1.23, 1.73)	1.54 (1.32, 1.93)	<0.001
sTNF-R2, ng/ml	3.43 (2.95, 4.02)	3.41 (2.94, 3.97)	3.55 (3.00, 4.17)	0.02

TNF=Tumor Necrosis Factor; sTNF-R1=Tumor Necrosis Factor Receptor Type I;

sTNF-R2=Tumor Necrosis Factor Receptor Type II; HF=Heart Failure

α value=0.05

Table 3. Correlates of TNF, sTNF-R1 and sTNF-R2 in Health ABC Participants

Correlate	TNF			sTNF-R1		sTNF-R2	
	N	rho	P-value	rho	P-value	rho	P-value
Age	1285	0.08	0.01	0.16	<0.001	0.15	<0.001
Sex (men=0, women=1)	1285	-0.04	0.14	-0.09	<0.001	-0.07	0.02
Race (white=0, black=1)	1285	-0.11	<0.001	-0.17	<0.001	-0.1	<0.001
Body mass index	1285	0.08	0.004	0.14	<0.001	0.09	0.001
Diabetes mellitus (no=0, yes= 1)	1284	0.07	0.01	0.11	<0.001	0.08	0.01
Hypertension (no=0, yes= 1)	1277	0.09	<0.001	0.11	<0.001	0.11	<0.001
Coronary heart disease (no=0, probable=1, definite=2)	1259	0.16	<0.001	0.1	<0.001	0.08	<0.001
Systolic blood pressure	1285	0.03	0.28	0.02	0.41	0.03	0.24
Creatinine	1284	0.25	<0.001	0.4	<0.001	0.36	<0.001
Low-density lipoprotein	1266	-0.01	0.63	-0.08	<0.001	-0.09	<0.001
High-density lipoprotein	1284	-0.31	<0.001	-0.21	<0.001	-0.19	<0.001

All correlation (rho) values refer to Spearman nonparametric rank correlation coefficients. α value=0.05

TNF=Tumor Necrosis Factor; sTNF-R1=Tumor Necrosis Factor Receptor Type I; sTNF-R2=Tumor Necrosis Factor Type II

Table 4. Inflammatory Biomarkers and Incident Heart Failure

Inflammatory Marker	Univariate		Multivariate*	
	HR (95% CI)	P-value	HR (95% CI)	P-value
TNF, per log ₂	1.52 (1.23-1.89)	0.0001	1.28 (1.02-1.61)	0.037
sTNF-R1, per log ₂	2.36 (1.71-3.25)	<0.0001	1.68 (1.15-2.46)	0.008
sTNF-R2, per log ₂	1.52 (1.16-2.00)	0.003	1.15 (0.80-1.63)	0.45

HR expressed per log₂ (logarithm with basis 2), equivalent to the HR per doubling of the original value of the parameter

*Model 1: Adjusted for Health ABC heart failure model variables: age, history of coronary heart disease, smoking, systolic blood pressure, creatinine, albumin, heart rate, fasting glucose, and left ventricular hypertrophy

HR=Hazard ratio; CI=confidence interval; TNF=Tumor Necrosis Factor;

sTNF-R1= Tumor Necrosis Factor Receptor Type I; sTNF-R2= Tumor Necrosis Factor

α value=0.05

Table 5. TNF, sTNF-R1 and sTNF-R2 and Incident Heart Failure: Subgroup Analyses

	sTNF-R1 *	Univariate HR	Multivariate HR
	(median serum level)	(95% CI)	(95% CI)†
Race			
White	1.49 (1.29,1.79)	1.93 (1.22,3.04)	1.21 (0.77,1.90)
Black	1.45 (1.21,1.73)	3.34 (2.14,5.20)	1.79 (1.13,2.83)
Gender			
Men	1.51 (1.31,1.82)	2.66 (1.70,4.15)	1.59 (1.03,2.47)
Women	1.39 (1.17,1.68)	2.05 (1.29,3.23)	1.29 (0.82,2.03)
	sTNF-R2*	Univariate HR	Multivariate HR
	(median serum level)	(95% CI)	(95% CI)†
Race			
White	3.50 (3.03,4.05)	1.43 (1.00,2.03)	1.08 (0.71,1.64)
Black	3.32 (2.83,3.98)	2.09 (1.20,3.64)	1.12 (0.64,1.96)
Gender			
Men	3.46 (3.02,4.06)	1.45 (1.05,2.01)	1.15 (0.78,1.71)
Women	3.39 (2.86,3.98)	1.65 (0.94,2.89)	1.00 (0.58,1.74)

HR expressed per \log_2 (logarithm with basis 2), equivalent to the HR per doubling of the original value of the parameter

sTNF-R1=Tumor Necrosis Factor Receptor Type I; sTNF-R2=Tumor Necrosis Factor Receptor Type II

*Value expressed as median (interquartile range) because of highly skewed distributions.

†Adjusted for Health ABC heart failure model variables: age, history of coronary heart disease, systolic blood pressure, creatinine, albumin, heart rate, fasting glucose, and left ventricular hypertrophy. α value=0.05