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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

Background—Tumor necrosis factor (TNF) levels are associated with risk for heart failure (HF). The soluble TNF type-1 (sTNF-R1) and type-2 (sTNF-R2) receptors are elevated in patients with manifest HF, but whether they are associated with risk for incident HF is unclear.

Methods and Results—Using Cox proportional hazard models, we examined the association between baseline levels of sTNF-R1 and sTNF-R2 with incident HF risk among 1285 participants of the Health, Aging, and Body Composition Study (age 74.0±2.9 years; 51.4% women; 41.1% black). At baseline, median (interquartile range) of 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. During a median follow-up of 11.4 (6.9, 11.7) years, 233 (18.1%) participants developed HF. In models controlling for other HF risk factors, 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). TNF-R1 was associated with a higher risk for HF with preserved versus reduced ejection fraction (HR, 1.81; 95%CI, 1.03, 3.18; P=0.038 for preserved vs. HR, 0.90; 95%CI, 0.56, 1.44; P=0.667 for reduced ejection fraction, interaction P=0.05).

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Disclosures None.

Conclusions—In older adults, elevated levels of sTNF-R1 are associated with an increased risk for incident HF. However, addition of TNF-R1 to the previously validated Health ABC HF risk model did not demonstrate material improvement in net discrimination or reclassification.

Keywords

heart failure; tumor necrosis factor; inflammation

While the incidence of cardiovascular diseases increase 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 inflammatory process. Stimuli that cause cytokine levels to rise may induce shedding of soluble receptors in an attempt to dampen the inflammatory response. Thus, elevated levels of soluble receptors may represent a more prolonged or severe underlying inflammation.[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 than cytokines themselves.[16-19] To date, the independent association of these receptors with risk for HF has not been rigorously evaluated.[20] In this study, we aimed to assess the association of baseline sTNF-R1 and R2 levels and incident HF risk in older adults.

Methods

Study Population

The study population included participants in the Health, Aging, and Body Composition (Health ABC) Study, a population-based cohort of 3,075 participants who were age 70 to 79 years at inception and 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.[21] The institutional review boards 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

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. 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

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, sTNFR1, and sTNF-R2 was lognormal these were log-transformed. Log_2 basis was used to facilitate interpretation; the hazard ratio per log_2 increase expresses the risk associated with doubling of 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 age, history of coronary heart disease, smoking, systolic blood pressure, creatinine, albumin, heart rate, fasting glucose, and left ventricular hypertrophy. We also controlled for ankle-arm index as a marker of subclinical vascular disease and time-varying incident coronary events.[20] 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, and effect of these markers on risk for HF with preserved vs. reduced ejection fraction was assessed. The proportional hazards assumption was evaluated by examining the Schoenfeld residuals. A two sided $p<0.05$ was accepted as statistically significant. Analyses were performed with STATA 12.1 (StataCorp LP, College Station, TX).

Results

Participant Characteristics

The mean age of the study participants was 74.0±2.9 years and 51.4% were women and 41.1% were black, Table 1. At baseline, median (interquartile range, IQR) 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. Patients who developed HF had higher baseline sTNFR1

(1.54 ng/ml, IQR 1.32, 1.93 vs. 1.45 ng/ml, IQR 1.32, 1.73; P=<0.001) and sTNF-R2 (3.55 ng/ml, IQR 3.00, 4.17 vs. 3.41 ng/ml, IQR 2.94, 3.97; P=0.02) levels. Age, adiposity, diabetes mellitus, hypertension, peripheral vascular disease, coronary heart disease, and albumin, creatinine and high-density lipoprotein levels modestly correlated with TNF and its soluble receptors, (supplemental data).

Incident HF

During median follow-up of 11.4 (6.9, 11.7) years, 233 (18.1%) participants developed HF and 431 died. Of the remaining 621 patients, information was not available after the 10-year follow up visit for 30 patients; therefore, loss to follow up accounted for 4.8% of censoring. Of those who developed HF, 171 (73.3%) had ejection fraction determined and documented at the time of HF diagnosis. The median ejection fraction was 41.5%. Overall 47.6% had preserved ejection fraction (≥45%) and 52.3 had reduced ejection fraction (<45%).

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 (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 sTNF-R2 was not significant anymore (HR, 1.15; 95%CI, 0.80, 1.63; P=0.45). Additional adjustment for baseline ankle-arm index and time varying incident coronary events attenuated the association for TNF but not sTNF-R1, Table 2. Addition of TNF-R1 to the Health ABC HF model did not demonstrate material improvement in net discrimination or reclassification, Table 3.

Subgroups

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). After adjusting for Health ABC HF Risk Model and stratified by baseline coronary heart disease, no significant differences were found between levels of sTNFR1 and sTNF-R2 above and below the median and incident HF among several subgroups including, age, gender, race, smoking status, presence of left ventricular hypertrophy, type 2 diabetes and coronary heart disease, Figure. TNF-R1 was associated with a higher risk of incident HF in patients who developed HF with preserved ejection fraction (≥45%) (HR, 1.81; 95%CI, 1.03, 3.18; P=0.038) and not those with reduced ejection fraction (<45%) (HR, 0.90; 95%CI, 0.56, 1.44; P=0.667, interaction P=0.05). Table 4.

Discussion

The traditional risk markers for cardiovascular disease have limited predictive value in the elderly. Moreover, risk prediction for incident HF is less studied than coronary diseases, especially in the elderly, and currently there are no targeted HF risk assessment and prevention recommendations, barring control of individual comorbidities like hypertension. However, considering the growing elderly population and the projected worsening of HF

epidemiology,[22] concentrated efforts are needed for assessment of traditional and novel risk factors for HF risk prediction, but more importantly to elucidate pathways that mediate the high risk in order to develop effective prevention interventions. In this cohort of 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, baseline markers of subclinical atherosclerosis, and interim coronary events. Importantly, consistent with the cytokine analysis of the vesnarinone trial,[23] these findings were consistent across sex and race.

Inflammation has long been associated with chronic HF and 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.[9] A study 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.[13] In addition, there is evidence to suggest that these inflammatory cytokines are elevated in individuals with asymptomatic left ventricular systolic and diastolic dysfunction.[24] 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.[25] Aside from erythrocytes, sTNF-R1 is expressed in nearly all cell types, including vascular and myocardial cells.[26] sTNF-R2 is found primarily in cells of the immune system but also in the heart. 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.[27] On the other hand, pro-inflammatory and apoptotic pathways are mediated largely through sTNF-R1.[25] Previous research suggests that while the relationship of sTNF-R1 and sTNF-R2 signaling is complex, it appears that sTNF-R1 aggravates, while sTNF-R2 ameliorates, chamber remodeling and hypertrophy, largely due to disparate, opposing effects on nuclear factor-kB, inflammatory activation and apoptosis.[28] These differential receptor functional properties might explain why the risk associated with these receptors might vary. One study found that sTNF-R1 emerged as the strongest independent predictor, regardless of follow-up duration and independent of established markers, of HF severity.[29]

TNF contributes to the progression of HF through a variety of mechanisms.[30] TNF is known to exert direct affects on cardiomyocyte contractility[31, 32] and can influence left ventricular remodeling and hypertrophy.[33-35] In the failing heart, TNF induces ß-adrenergic receptor uncoupling,[36] increases reactive oxygen species formation,[37] and increases inducible nitric oxide synthase synthesis resulting in high output nitric oxide formation,[37] 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.[38, 39] 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.[29, 40, 41] 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.

It is interesting to note that sTNF-R1 levels were associated with a higher risk for HF with preserved ejection fraction than reduced ejection fraction. These data should be interpreted with caution since the ejection fraction data at the time of the diagnosis of HF were not uniformly available and therefore these results are prone to selection bias and other confounding. Nevertheless, it is interesting to note that inflammation is more important predictor of incident HF with preserved ejection fraction in older adults and these data complements the recent interest in the role of systemic inflammation as a common denominator explaining the relationship between comorbidity burden and risk for HF with preserved ejection fraction. These data need further validation.[42]

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. Furthermore, echocardiography was not performed at baseline in the Health ABC Study; therefore, participants with asymptomatic structural heart abnormalities may have been included in the analysis. However, because HF is unlikely to remain undiagnosed for several years, the observed associations cannot be ascribed merely to undetected HF at baseline.

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. However, addition of TNF-R1 to the previously validated Health ABC HF risk model did not demonstrate material improvement in net discrimination or reclassification. The diagnostic and therapeutic meaning of these results need further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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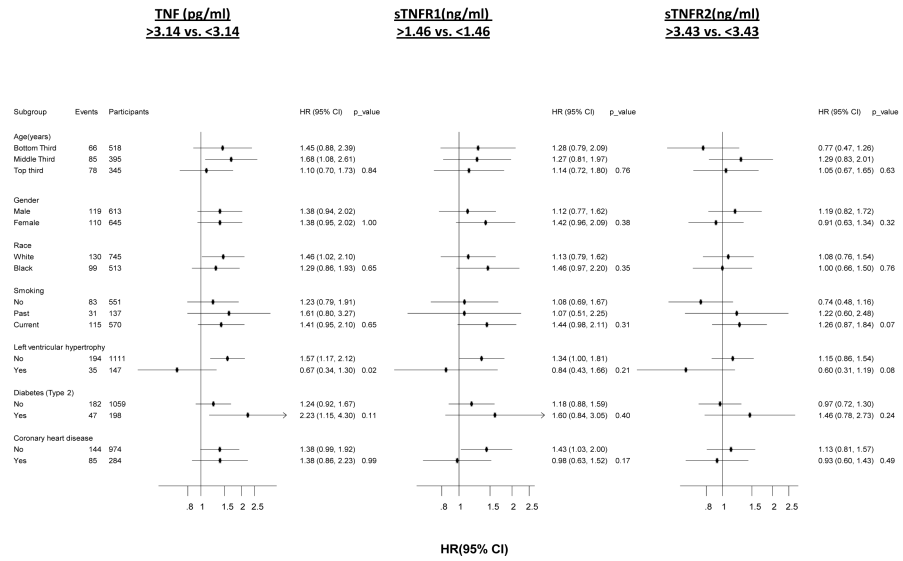

Figure.

Comparison of association of markers of inflammation with risk of incident heart failure in the Health ABC study.

** HR [95% CI] is reported for a comparison of biomarker values below versus above the median of the biomarker distribution. TNF=Tumor Necrosis Factor; sTNF-R1=Tumor Necrosis Factor Receptor Type I; sTNF-R2=Tumor Necrosis Factor Receptor Type II Analysis is adjusted for Health ABC HF risk score variables

Table 1

Baseline Participant Characteristics

Characteristic	Overall	Heart failure	No heart	
Age, years	73.6 (2.9)	74.2 (2.9)	73.4 (2.9)	<0.001
Men, n (%)	624 (48.6)	120 (52)	504 (48)	0.321
Blacks, n (%)	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
Waist to thigh ratio	1.9 (0.2)	2.0 (0.2)	1.9 (0.2)	0.063
Smoking, n (%)				
Current	577 (44.9)	115(49)	462(44)	
Past	140 (10.9)	31(13)	109(10)	
Never	568 (44.2)	87(37)	481(46)	0.055
Alcohol consumption, n (%)				
Never	654(51)	124(53)	530(50)	0.524
<1 drink/week	257(20)	44(19)	213(20)	
1–7 drinks/week	279(21.7)	44(19)	235(22)	
>7 drinks/week	93(7.2)	20(9)	73(7)	
Diabetes, n (%)	205(16)	48(21)	157(15)	0.033
Hypertension, n (%)	629(48.9)	137(59)	492(47)	0.001
Coronary Heart Disease, n (%)	284(22.1)	85(36)	199(19)	<0.001
Cerebrovascular disease, n (%)	97(7.5)	29(12)	68(6)	0.001
Peripheral arterial disease, n (%)	72(5.6)	20(9)	52(5)	0.024
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
Heart rate, beats/min	65.4(11.0)	66.7(12.2)	65.2(10.6)	0.061
Fasting glucose, mg/dl*	94.0(87.0,105.0)	96(89.0,115.0)	94(87.0,104.0)	0.001
Albumin, g/dl	4.0(0.3)	3.9(0.3)	4.0(0.3)	0.02
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
Triglycerides, mg/dl*	119.0(89.0,166.0)	126(89.0,169.0)	118(89.0,165.0)	0.741
Beta-blockers, n (%)	162(12.6)	44(19)	118(11)	0.002
Angiotensin-converting enzyme inhibitors, n (%)	174(13.5)	47(20)	127(12)	0.001
Calcium channel blockers, n (%)	301(23.4)	80(34)	221(21)	<0.001
Statins, n (%)	163(12.7)	34(15)	129(12)	0.342
Steroids, n (%)	29(2.3)	5(2)	24(2)	0.895
Nonsteroidal anti-inflammatory agents, n (%)	712(55.4)	150(64)	562(53)	0.002

*Value expressed as median (interquartile range) because of highly skewed distributions. All other values expressed as mean (standard deviation) unless otherwise stated.

Table 2

Inflammatory Biomarkers and Incident Heart Failure

Inflammatory	Unadjusted		*Model 1		†Model 2	
Marker	HR (95% CI)	P Value	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	1.14 (0.89-1.46)	0.274
sTNF-R1, per log_2	2.36 (1.71-3.25)	<0.0001	1.68 (1.15-2.46)	0.008	1.51 (1.01-2.24)	0.042
sTNF-R2, per log_2	1.52 (1.16-2.00)	0.003	1.15 (0.80-1.63)	0.45	1.12 (0.76-1.68)	0.583

HR expressed per log_2 (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

†Model 2: model 1 variables plus ankle-arm index and time-varying incident coronary events.

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

Table 3

Risk discrimination and reclassification with sTNF-R1

Discrimination	
C-index (95% CI): Health ABC risk predictors*	0.732(0.673,0.791)
Change in C index (95% CI) on adding sTNFR1	0.003(0.015-0.009)
Reclassification	
Participants who did not develop heart failure at 5 years	
Appropriately reclassified	35(3.38%)
Inappropriately reclassified	30(2.90%)
Participants who developed heart failure at 5 years	
Appropriately reclassified	2(2.53%)
Inappropriately reclassified	1(1.27%)
† **Net reclassification index (95% CI) Events**	0.0152(0.0331, 0.0635)
† **Net reclassification index (95% CI) Non Events**	0.0011(−0.014,0.016)
† **Net reclassification index (95% CI) Overall**	0.0163(−0.032,0.065)
† **Integrated discrimination index (95% CI)**	0.0034(−0.001,0.008)

** Health ABC heart failure* risk model included age, smoking status, heart rate, history of coronary heart disease, systolic blood pressure, fasting glucose, serum albumin and creatinine

†The reference risk prediction model included the Health ABC heart failure risk model, which was then extended to additionally include sTNFR1 as the alternative model sTNF-R1=soluble tumor necrosis factor receptor Type I

Table 4

Associations with heart failure and preserved vs. reduced ejection fraction

	TNF			TNFR1			TNFR2		
Ejection Fraction	**HR (95% CI)**	***P***	**P-value interaction**	**HR (95% CI)**	***P***	**P-value interaction**	**HR (95% CI)**	***P***	**P-value interaction**
Reduced (<45%)	1.08(0.72-1.64)	0.702	0.90	0.90(0.56-1.44)	0.667	0.05	0.96(0.50-1.83)	0.891	0.25
Preserved (>45%)	1.11(0.75-1.65)	0.592		1.81(1.03-3.18)	0.038		1.72(0.87-3.42)	0.121	

TNF=Tumor Necrosis Factor; TNFR1=Tumor Necrosis Factor Receptor Type I; TNFR2=Tumor Necrosis Factor Receptor Type II