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Depressive symptoms modify relationship between inflammation and physical symptoms in patients with heart failure

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Abstract

Background—Patients with heart failure (HF) often have physical symptoms that result in poor health-related quality of life and are antecedents of hospitalization. Inflammation, as part of the pathological response in HF, can produce physical symptoms. Depressive symptoms can affect this relationship.

Purpose—To examine the relationship between soluble tumor necrosis factor receptor 1 (sTNF-RI) and physical symptoms and the effects of depressive symptoms on this relationship in patients with HF, controlling for covariates (age, body mass index [BMI], social support, comorbidities, and medication).

Methods—Data on physical symptoms (Symptom Status Questionnaire-Heart Failure), depressive symptoms (Beck Depression Inventory [BDI]-II), and sTNF-RI (blood samples) were collected from 145 patients with HF (age 60±12 years; 51% New York Heart Association class III/IV). Data on sTNF-RI were square root transformed to achieve normality. Patients were divided into two groups based on their score on the BDI-II (non-depressed < 14 and depressed ≥ 14). Hierarchical multiple regression was used to analyze the data.

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Conflicts of Interest

For the remaining authors none were declared.

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Results—In the total sample, higher sTNF-RI was significantly related to more severe physical symptoms, controlling for covariates ($F = 7.915$, $p < .001$). In subgroup analyses, sTNF-RI was significantly related to physical symptoms only in the non-depressed subgroup, controlling for covariates ($F = 3.174$, $p = .005$).

Conclusion—Depressive symptoms as well as inflammation need to be considered physical symptoms in patients with HF. Further studies are needed to determine the effects of improvement in inflammation on improvement in physical symptoms, taking into consideration the effects of depressive symptoms.

Keywords

heart failure; physical symptoms; inflammation; depressive symptoms

Introduction

More than 90% of patients with heart failure (HF) suffer from physical symptoms, such as dyspnea, fatigue, edema, and sleeping difficulties.^{1, 2} Health-related quality of life (HRQOL) is poor in this population.³ Physical symptoms are strongly associated with poor HRQOL, explaining 36% of the variance in HRQOL.³ Heart failure symptoms are also closely associated with hospitalization and mortality. Indeed, approximately 90% or more than 90% of HF patients who visited emergency departments and were admitted to hospitals had HF symptoms.^{2, 4}

In patients with HF, levels of proinflammatory biomarkers, including tumor necrosis factor (TNF), interleukin-6 (IL-6), and soluble TNF receptors I and II (sTNF-RI and sTNF-RII) are higher than in healthy people.^{5–8} The mechanisms by which inflammation is connected to physical symptoms have not been determined, but several studies suggest a possible relationship between inflammation and physical symptoms. For instance, in animal and human studies, TNF-RI and TNF-RII have been shown to be involved in cardiac remodeling, hypertrophy, and apoptosis in mice with induced HF and patients with HF.^{6, 9, 10} Tumor necrosis factor receptor I exacerbates these processes, while TNF-R2 improves them.⁹ In patients with HF, IL-6 and sTNF-RI are associated with apoptosis signaling pathway.⁶ Further, in these patients, sTNF-RI and sTNF-RII are associated with levels of norepinephrine and brain natriuretic peptide.⁷ In addition, inflammation is associated with New York Heart Association (NYHA) functional class,⁷ which reflects functional impairment based on expression of dyspnea, fatigue, and palpitations in patients with HF.¹¹ Despite the suggested relationships between inflammation and physical symptoms, fatigue was not associated with TNF- α , IL-6, IL-10, and CRP in HF patients with non-preserved left ventricular function.¹² This study did not include TNF-R1 that has been suggested to be involved in cardiac remodeling, hypertrophy, and apoptosis.^{6, 9, 10} In addition, even though fatigue is one of the most common HF symptoms,² fatigue is not the only HF symptom that inflammation can affect. Thus, further studies are needed to examine the relationship between inflammation and common physical symptoms in patients with HF. To our knowledge, the relationships between inflammation and common HF physical symptoms, including dyspnea, fatigue, edema, sleeping difficulty, chest pain, and dizziness, have not been examined in patients with HF.

Depressive symptoms may affect the relationship between inflammation and physical symptoms in patients with HF, because depressive symptoms are connected to both inflammation and physical symptoms. Approximately 30% to 60% of patients with HF suffer from depressive symptoms,^{13–15} and some studies suggest that levels of proinflammatory biomarkers (e.g., IL-6) are increased in depressed patients.^{16, 17} Depressive symptoms are also associated with physical symptoms in patients with HF.¹⁸ Thus, the relationship between inflammation and physical symptoms may be different in depressed and non-depressed patients with HF. In addition, factors affecting physical symptoms in both groups can be different. If factors affecting physical symptoms, including inflammation, in the two groups are different, this information can be used to develop interventions targeting improvement in physical symptoms for both groups. Therefore, the current study examined the relationships of inflammation (i.e., sTNF-RI) to physical symptoms in patients with HF. We also examined the relationships in depressed and non-depressed subgroups to taking into consideration the effects of depressive symptoms on this relationship. In our analyses, we controlled for covariates selected based on the literature (i.e., age, body mass index [BMI], social support, comorbidities, beta-blocker use, and left ventricular ejection fraction).^{12, 18–22}

Methods

Design, setting, and sample

Patients were recruited for this prospective, observational study between 2004 and 2009 from outpatient clinics at university-affiliated or community hospitals at three research sites (Southern and Midwestern) in the United States. Institutional Review Board approval was obtained from the appropriate institutions. Patients with a confirmed diagnosis of HF who were able to read and speak English, and who were taking stable doses of medications for two clinic visits or for 3 months were included. Patients with myocardial infarction or stroke within the previous 3 months were excluded because these conditions could affect study outcomes. Patients with severe cognitive or psychiatric problems were also excluded because these problems could make it difficult for patients to provide informed consent and answer questionnaires. Patients with valvular or postpartum HF etiology were also excluded. Eligible patients were identified by trained research associates using medical record review or clinicians who took care of the patients. Eligibility of all research subjects was confirmed through medical record review. Eligible patients were recruited by the clinicians or the research associates during clinic visits or by phone. Written informed consent was obtained from all participants.

Measures

Physical symptoms were defined as common HF-related physical symptoms and were assessed using the Symptom Status Questionnaire-Heart Failure this instrument assesses frequency, severity, and distress from the following HF symptoms: dyspnea during day time and when lying down, fatigue, chest pain, edema, sleeping difficulty, and dizziness. Frequency is rated using 4 response options, from 1 (*less than once per week*) to 4 (*nearly daily*). Severity is also rated using 4 response options, from 1 (*slight*) to 4 (*very much*). Distress is rated using 5 response options, from 0 (*not at all*) to 4 (*very much*). Possible

scores range from 0 to 84, with higher scores indicating more severe physical symptoms. Reliability was supported: Cronbach's alpha was .80.²³ Factor analysis and the significant relationships of physical symptoms to depressive symptoms, HRQOL, and event-free survival supported the validity of this instrument.²³ Cronbach's alpha in the current study was .93.

Depressive symptoms were assessed using the Beck Depression Inventory (BDI) II,^{24, 25} which consists of 21 items with 4 response options. Possible scores range from 0 to 63; scores ≥ 14 indicate at least mild depression.²⁵ In the current study, patients were divided into depressed and non-depressed subgroups based on the cut point of 14. Reliability has been supported by coefficient alphas $\geq .70$.^{25, 26} Construct validity has been supported by factor analysis and a significant relationship between depressive symptoms and anxiety.²⁴ Cronbach's α in the current study was .91.

Inflammation was defined as the level of sTNF-RI, which is a receptor to which TNF- α binds. The level of sTNF-RI in patients with HF is higher than in age- and gender-matched healthy controls.⁸ Blood was drawn from patients by nurses at the general clinical research center at each study site, and the plasma was divided into aliquots, frozen, and shipped on dry ice to the general clinical research center at the main site of the study. All samples were stored at -80°C until batch analyzed for sTNF-RI. The levels of serum sTNF-RI were determined using commercially available ELISA kits (R&D Systems, Minneapolis, MN). Because the level of sTNF-RI was skewed in this sample (as it is in most samples), it was normalized using a square root transformation. A coefficient of variation in the blood samples was below 10%.

Covariates were selected based on the literature.^{12, 18–22} Data on these covariates, including sociodemographic characteristics (i.e., age and BMI) and clinical characteristics (beta-blocker use, comorbidities, and left ventricular ejection fraction) were collected using a standard sociodemographic questionnaire and a standard clinical questionnaire. Comorbidities were assessed using the Charlson Comorbidity Index, which was included in the clinical questionnaire. Data on left ventricular ejection fraction were collected using medical records. Data on social support (one covariate) were collected using the Multidimensional Scale of Perceived Social Support,^{27, 28} on which higher scores indicate more social support. Reliability and construct validity for the instrument are acceptable.^{27, 28} Data on physical and depressive symptoms, social support, and sociodemographic characteristics were collected by self-administered questionnaires. Data on clinical characteristics were collected by face-to-face interviews and medical record review using the standard clinical questionnaire.

Data on other sociodemographic and clinical characteristics, including education level, gender, marital status, ethnicity, etiology of HF, and NYHA functional class, were collected using the same sociodemographic and clinical questionnaires. New York Heart Association functional class was determined by trained research team members through in-depth patient interviews using the clinical questionnaire.

Data Analysis

Independent t-tests and chi-square tests were used to compare the sociodemographic and clinical characteristics, inflammation status, and physical symptoms between depressed and non-depressed patients with HF. Hierarchical multiple regression modeling was used to examine the relationships of sTNF-RI to physical symptoms in the total sample and depressed and non-depressed groups, controlling for covariates. The data were met the assumptions for these data analyses methods. All statistical tests were two-tailed with $p < .05$ considered statistically significant.

Results

One hundred forty-five patients with HF participated in the study. Forty-five (31.0%) patients had depressive symptoms (BDI-II score ≥ 14). Patients with depressive symptoms were younger, had lower levels of education, less social support, more comorbidities, and more severe physical symptoms than patients without depressive symptoms (Table 1). In addition, patients with depressive symptoms were more often classified in NYHA class III/IV than patients without depressive symptoms. There was no difference between patients with and without depressive symptoms in the levels of sTNF-RI ($p = .788$). In addition, there were no differences between patients with and without depressive symptoms with regard to BMI, left ventricular ejection fraction, gender, marital status, ethnicity, etiology of HF, and beta-blocker use.

Relationships of Inflammation (sTNF-RI) to Physical Symptoms In the total sample, sTNF-RI was associated independently with physical symptoms, controlling for covariates (Table 2). Among the covariates, BMI, social support, and comorbidities also were associated with physical symptoms. Patients who had lower levels of sTNF-RI, lower BMI, more social support, and fewer comorbidities reported less severe physical symptoms. Age, beta-blocker use, and left ventricular ejection fraction were not related to physical symptoms in the sample.

Among patients with depressive symptoms, sTNF-RI was not associated with physical symptoms, controlling for covariates (Table 3). Upon examining the covariates, lower BMI, more social support, fewer comorbidities, and higher left ventricular ejection fraction, but not age and beta-blocker use, were associated with less severe physical symptoms in patients with depressed symptoms.

Among patients without depressive symptoms, sTNF-RI was significantly associated with physical symptoms, after controlling for covariates (Table 4). Patients with lower level of sTNF-RI, lower BMI, and more social support had less severe physical symptoms. Age, comorbidities, beta-blocker use, and left ventricular ejection fraction were not associated with physical symptoms.

Discussion

In the current study, we found a relationship between inflammation and physical symptoms and demonstrated that a role of depressive symptoms on the relationship. The significant

relationship between inflammation and physical symptoms observed in the current study is consistent with findings in cancer patients.^{29, 30} In several cancer studies,^{29–31} TNF- α and IL-6 were associated with levels of fatigue and pain,^{30, 31} and sTNF-RI was associated with fatigue and a composite score of several physical and emotional symptoms.²⁹ In contrast, in HF patients with non-preserved left ventricular function,¹² fatigue was not related to the levels of TNF- α , IL-6, IL-10, and CRP. These contradict relationships between this prior study and the current study may be related to the type of inflammatory biomarkers (TNF- α , IL-6, IL-10, and CRP vs. sTNF-R1), types of HF physical symptoms (fatigue vs. seven common HF symptoms), and the characteristics of the samples (patients with non-preserved left ventricular function vs. patients with preserved and non-preserved left ventricular function). TNF-R1 has been suggested to be involved in cardiac remodeling, hypertrophy, and apoptosis,^{6, 9, 10} and it is more sensitive than TNF- α and IL-6 in its relationship to apoptosis signaling pathway.⁶ Thus, sTNF-R1 can be more closely related to common HF symptoms than some other inflammatory biomarkers. Fatigue is one of the most stressful HF symptoms,² but considering the relationships of sTNF-R1 to cardiac function, inflammation may also affect some other symptoms, including dyspnea, edema, chest pain, and sleep difficulty. Thus, a composite symptom score may be more closely associated with inflammation than one symptom. In a HF study,⁷ levels of sTNF-RI and sTNF-RII have been associated with NYHA functional class, which reflects level of functional impairment based on symptoms, such as dyspnea, fatigue, and palpitations.¹¹ In addition, infusion of a TNF antagonist (Enbrel) improved functional status in patients with HF.³² Thus, the findings of the current and prior studies suggest that levels of inflammatory biomarkers are associated with physical symptoms in patients with HF, but further studies are needed to examine the relationships of inflammation and physical symptoms in subgroups of patients with HF.

The effects of sTNF-RI and sTNFRII on cardiac remodeling and hypertrophy and on the apoptosis signaling pathway may, in part, explain the relationship of inflammation to physical symptoms.^{6, 9, 10} For instance, in univariate analyses, levels of sTNF-RI, sTNF-RII, TNF- α , and IL-6 were associated with levels of soluble Fas ligand, which is a major apoptosis signaling pathway.⁶ However, in multivariate analysis, only level of sTNF-RI and IL-6 were significantly related to levels of soluble Fas ligand. In HF mice,⁹ TNF-RI exacerbates cardiac remodeling, cardiac hypertrophy, and apoptosis processes. These findings suggest the importance of TNF receptors for cardiac function, and in turn, possibly physical symptoms.

The findings of the current study also suggest that depressive symptoms may affect the relationships between inflammation and physical symptoms. Inflammation was associated with physical symptoms in patients without depressive symptoms, but not in patients with depressive symptoms, even though there was no difference between the subgroups in the level of inflammation. The finding of no relationship between level of inflammation and depressive symptoms in the current study was inconsistent with the findings in prior depressed patients and patients with HF.^{16, 17, 33–37} In these studies, levels of IL-1, IL-6, TNF- α , sTNF-R1, and sTNF-R2 were higher in depressed patients and HF patients with depressive symptoms than healthy controls or HF patients without depressive symptoms. Even though it is difficult to compare levels of inflammation across studies, the level of

sTNF-RI in the current study was higher in both patients with and without depressive symptoms than in those in another HF study (2.0 and 2.1 ng/ml vs. 1.6 and 1.1 ng/ml.).³⁷

There were several differences between patients with and without depressive symptoms in the current study, including age, education level, comorbidities, and NYHA functional class. However, only comorbidities were significantly associated with physical symptoms in depressed patients. Thus, comorbidities might affect the relationships between inflammation and physical symptoms in the two groups. More importantly, the levels of physical symptoms in the two groups significantly differed. Depressed patients might have more severe physical symptoms, or they perceived and reported physical symptoms differently from non-depressed patients. The difference could affect the relationships between inflammation and physical symptoms in the two groups. This suggests that depressive symptoms may contribute to more of the variation in physical symptoms than inflammation. In a prior HF study,¹⁸ depressive symptoms were associated with physical symptoms, and depressive symptoms were the strongest factor associated with physical symptoms, suggesting that depressive symptoms as well as inflammation should be managed to improve physical symptoms in these patients.

Some interventions have improved depressive symptoms in patients with HF. For instance, a clinic-based comprehensive management program was effective in improving depressive symptoms and reducing hospitalization rates.³⁸ The program led by a multidisciplinary team that consisted of a cardiologist, a nurse manager, and a dietitian, and the team provided information about HF, its signs and symptoms, and its treatment (e.g., diet and medication). A home-based disease management program also improved depressive symptoms.³⁹ In that study, patients watched an educational video to learn about HF and its management and received materials on mediations, diet, exercise, self-maintenance, and symptom management. In addition to traditional disease management programs, alternative therapy strategies have been used to improve depressive symptoms in patients with HF. For instance, a combination of mindfulness meditation, training in coping skills, and provision of social support improved depressive symptoms, even though the overall effects were not great.⁴⁰ Training in coping skills consisted of traditional education components, stress management, and spiritual and health. Thus, clinicians can use these types of interventions to improve depressive symptoms in patients with HF.

Several possible factors may improve inflammation in these patients. Beta-blockers^{41, 42} and angiotensin converting enzyme inhibitors and furosemide⁴³ have reduced levels of TNF- α and IL-6. In addition, an observational study of 145 hemodialysis patients found that a higher ratio of n-6 to n-3 polyunsaturated fatty acid intake was associated with a higher level of C-reactive protein.⁴⁴ In an intervention study of 43 severe non-ischemic HF patients,⁴⁵ high dose intake of n-3 polyunsaturated fatty acid (4 g per day) decreased IL-6, and low dose intake (1 g per day) showed a trend toward reduction. Yoga and meditations also reduced levels of proinflammatory cytokines and their transcripts in cancer patients and family dementia caregivers.^{46, 47} Thus, clinicians and researchers may consider some alternative approaches in addition to traditional HF treatment, including n-3 polyunsaturated fatty acid, yoga, and meditation, to improve inflammation status in patients with HF. A HF study showed that self-care management was related to reduction of inflammation status.⁴⁸

Adherence to self-care management is commonly inadequate in patients with HF.⁴⁹ Thus, improvement in self-care management may be related to improvement in inflammation status in patients with HF.

The findings of the current study show some additional possible targets of interventions to reduce physical symptoms. Lower BMI and more social support were associated with less severe physical symptoms in the total sample and also in both patients with and without depressive symptoms. The European Society of Cardiology recommends reducing body weight in obese (BMI > 30 kg/m²) patients with HF to decrease physical symptoms,²⁰ and the Heart Failure Society of America also recommends keeping a normal body weight.⁵⁰ Body mass index at the extreme ends of spectrum are related to high rates of hospitalization in patients with HF.⁵¹ Thus, clinicians may consider BMI related to managing physical symptoms. Clinicians can also talk with the caregivers of patients with HF about the importance of support in maintaining less severe physical symptoms.

There are some limitations of the current study. Depressed symptoms in the current study were measured using the BDI-II.²⁵ This instrument has been commonly used for patients with HF to assess depressive symptoms.^{52, 53} However, some items of the BDI-II may assess some physical symptoms, such as lack of energy or fatigue, and this may affect relationship between depressive and physical symptoms. One study, however, showed that removal of the question asking fatigue from the BDI-II did not change the relationship between fatigue and depressive symptoms in patients with coronary artery disease.⁵⁴ The mean age of the sample in the current study is relatively young. In one study,¹⁸ older age was related to more severe physical symptoms. Thus, physical symptoms in older people with HF can be different from those reported in the current study. Nonetheless, the findings of the current study provide valuable information about the relationship between inflammation and physical symptoms in patients with HF and the effects of depressive symptoms on this relationships.

Conclusions

Depressive symptoms as well as inflammation need to be considered to manage physical symptoms in patients with HF. Further studies are needed to determine the effects of improvement in inflammation on improvement in physical symptoms, taking into consideration the effects of depressive symptoms.

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Table 1

Characteristics of Sample

Characteristics	Depressed (n = 45)	Non-depressed (n = 100)	Total Sample (N =145)	p value
	Mean (± SD)	Mean (± SD)	Mean (± SD)	
Mean age (years)	56.1 (± 9.2)	62.1 (± 12.3)	60.3 (± 11.7)	.004
Education level (years)	12.5 (± 2.6)	13.9 (± 3.3)	13.5 (± 3.2)	.014
Body mass index (kg/m ²)	31.3 (± 6.7)	30.5 (± 7.3)	30.8 (± 7.1)	.533
Social Support	56.1 (± 21.9)	70.3 (± 15.6)	65.9 (± 18.9)	< .001
Comorbidities	3.8 (± 2.0)	3.0 (± 1.8)	3.2 (± 1.9)	.008
LVEF (%)	33.3 (± 12.5)	34.6 (± 14.1)	34.2 (± 13.6)	.595
sTNF-RI (ng/ml)	2.0 (± 1.0)	2.1 (± 1.3)	2.1 (± 1.2)	.788
Physical symptoms	36.9 (± 15.1)	20.4 (± 15.3)	25.5 (± 17.0)	< .001
	<u>n</u> (%)	<u>n</u> (%)	<u>n</u> (%)	
Gender (male)	32 (71.1)	66 (66.0)	98 (67.6)	.543
Marital status (married)	22 (48.9)	52 (52.0)	74 (51.0)	.729
Ethnicity (Caucasian)	34 (75.6)	72 (72.0)	106 (73.1)	.655
Etiology (ischemic)	22 (48.9)	45 (45.0)	67 (46.2)	.664
NYHA III/IV	31 (68.9)	43 (43.0)	74 (51.0)	.004
Beta-blocker use	39 (86.7)	88 (88.0)	127 (87.6)	.822

LVEF = left ventricular ejection fraction. NYHA = New York Heart Association functional class. SD = standard deviation. sTNF-RI = soluble tumor necrosis factor receptor I

Table 2

Relationships of Inflammation to Physical Symptoms in the Total Sample

	Variable	Standardized β	t statistics	p value	R ²	F statistics	p value
Model 1	Age	.132	1.661	.099	.209	12.444	< .001
	Body mass index	.298	3.778	< .001			
	Social support	-.372	-4.918	< .001			
Model 2	Age	.056	.689	.492	.266	8.346	< .001
	Body mass index	.267	3.296	.001			
	Social support	-.355	-4.784	< .001			
	Comorbidities	.233	3.001	.003			
	Beta-blocker use	.049	.666	.506			
	LVEF	-.058	-.744	.458			
Model 3	Age	.028	.338	.736	.288	7.915	< .001
	Body mass index	.247	3.056	.003			
	Social support	-.372	-5.030	< .001			
	Comorbidities	.200	2.546	.012			
	Beta-blocker use	.032	.433	.666			
	LVEF	-.047	-.605	.546			
	sTNF-RI	.158	2.043	.043			

LVEF = left ventricular ejection fraction. sTNF-RI = soluble tumor necrosis factor receptor 1

Table 3

Relationships of Inflammation to Physical Symptoms in the Depressed Subgroup

	Variable	Standardized β	t statistics	p value	R ²	F statistics	p value
Model 1	Age	.027	.218	.828	.355	7.526	< .001
	Body mass index	.485	3.835	< .001			
	Social support	-.312	-2.477	.017			
Model 2	Age	-.100	-.809	.424	.487	6.020	< .001
	Body mass index	.503	3.793	.001			
	Social support	-.371	-3.123	.003			
	Comorbidities	.255	1.995	.053			
	Beta-blocker use	.117	.996	.325			
	LVEF	-.271	-2.084	.044			
Model 3	Age	-.087	-.702	.487	.510	5.495	.001
	Body mass index	.565	4.041	< .001			
	Social support	-.350	-2.944	.006			
	Comorbidities	.287	2.225	.032			
	Beta-blocker use	.165	1.348	.186			
	LVEF	-.297	-2.279	.029			
	sTNF-RI	-.175	-1.299	.202			

LVEF = left ventricular ejection fraction. sTNF-RI = soluble tumor necrosis factor receptor 1

Table 4

Relationships of Inflammation to Physical Symptoms in the Non-Depressed Subgroup

	Variable	Standardized β	t statistics	p value	R ²	F statistics	p value
Model 1	Age	.280	2.695	.008	.130	4.794	.004
	Body mass index	.290	2.805	.006			
	Social support	-.255	-2.334	.022			
Model 2	Age	.247	2.197	.031	.138	2.472	.029
	Body mass index	.277	2.541	.013			
	Social support	-.221	-2.250	.027			
	Comorbidities	.091	.862	.391			
	Beta-blocker use	.015	.155	.877			
	LVEF	-.002	-.017	.987			
Model 3	Age	.198	1.792	.076	.195	3.174	.005
	Body mass index	.259	2.443	.016			
	Social support	-.249	-2.595	.011			
	Comorbidities	.045	.429	.669			
	Beta-blocker use	.001	.015	.988			
	LVEF	.016	.156	.876			
	sTNF-R1	.254	2.551	.012			

LVEF = left ventricular ejection fraction. sTNF-R1 = soluble tumor necrosis factor receptor 1