ORIGINAL ARTICLE

Perceived stress level is associated with coronary artery disease severity in patients with ST-segment elevation myocardial infarction

Algılanmış stres seviyesi ST-segment yükselmeli miyokart enfarktüsü hastalarında koroner arter hastalığı yaygınlığı ile ilişkilidir

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ABSTRACT

Objective: Stress is known to be a significant risk factor for coronary atherosclerosis and adverse cardiovascular events; however, the stress-related coronary atherosclerotic burden has not yet been investigated. The aim of this study was to investigate the relationship between the Perceived Stress Scale (PSS) and the SYNTAX scores in patients with ST-segment elevation myocardial infarction (STEMI).

Methods: A total of 440 patients with STEMI were prospectively enrolled and divided into 2 groups according to the PSS score with a ROC curve analysis cut-off value of 17.5. In all, 361 patients with a low PSS score were categorized as Group 1 and 79 patients with a high PSS score were categorized as Group 2.

Results: The SYNTAX score [Group 1, 16.0 (10.0–22.5); Group 2, 22.5 (15.0–25.5); p<0.001] and the SYNTAX score II were significantly higher in Group 2 [Group 1, 24.8 (19.0–32.6); Group 2, 30.9 (22.3–38.9); p<0.001]. Spearman analysis demonstrated that the PSS score was associated with the SYNTAX score (r=0.153; p=0.001) and the SYNTAX score II (r=0.216; p<0.001). Additionally, the PSS (odds ratio: 2.434, confidence interval: 1.446-4.096; p=0.001) was determined to be an independent predictor of a moderate-to-high SYNTAX score. The PSS score of patients with in-hospital mortality was also higher than those who survived [15 (10–20); 9 (4–16), respectively; p=0.007].

Conclusion: Stress appears to accelerate the coronary atherosclerotic process and the associated burden. An increased stress level was found to be an independent predictor of a high SYNTAX score.

ÖZET

Amaç: Stres koroner ateroskleroz ve kardiyovasküler sonlanımlar için önemli bir risk faktörüdür. Fakat, stres ile ilişkili koroner aterosklerotik yük daha önce araştırılmamıştır. Bu çalışmada, ST segment yükselmeli miyokart enfarktüsü (STYME) hastalarında algılanmış stres skalası (ASS) ile SYNTAX skorlarının ilişkisini araştırmayı amaçladık.

Yöntemler: Bu çalışmaya, STYME geçiren 440 hasta ileriye dönük olarak dahil edildi. ROC analizine göre belirlenen 17.5 eşik değerine göre ASS puanı düşük olan 361 hasta Grup 1'i, ASS puanı yüksek olan 79 hasta ise Grup 2'yi oluşturdu.

Bulgular: SYNTAX skoru [16.0 (10.0–22.5); 22.5 (15.0–25.5), p<0.001] ve SYNTAX skoru II [24.8 (19.0–32.6); 30.9 (22.3–38.9), p<0.001] grup 2 hastalarda anlamlı derecede yüksekti. Spearman analizinde ASS değeri SYNTAX skoru (r=0.153, p=0.001) ve SYNTAX skoru II (r=0.216, p<0.001) ile ilişkili saptandı. Ayrıca orta-yüksek SYNTAX skoru için ASS (Odds oranı: 2.434, Güven Aralığı: 1.446–4.096, p=0.001) bağımsız ön gördürücü olarak bulundu. Hastane içi mortalite gelişen grupta ise ASS skoru gelişmeyenlere göre daha yüksek saptandı [sırasıyla, 15 (10–20); 9 (4–16), p=0.007].

Sonuç: Stres, koroner aterosklerotik süreci ve yaygınlığı hızlandırıyor görünmektedir. Ayrıca, artmış stres seviyesi de yüksek SYNTAX skorunun bağımsız öngördürücüsü olarak bulunmuştur.

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Coronary artery disease (CAD) is still the leading cause of morbidity and mortality worldwide and ST-segment elevation myocardial infarction (STEMI) is known to be a life-threatening complication of CAD.[1] Although there has been an increasing trend in the survival rate in patients with STEMI, treatment of underlying mechanisms of coronary atherosclerosis remains essential. Several etiological factors have been described to explain adverse clinical outcomes in STEMI patients. The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, related to the atherosclerotic coronary plaque burden, is one of the most important prognostic factors for these patients. Thus, determining factors linked to the SYNTAX score is a credible means to add to treatment and the establishment of a prognosis in STEMI patients. The SYNTAX score II, which combines the basal anatomical SYNTAX score with the clinical baseline variables, has also improved the ability to predict cardiovascular mortality.[2]

Stress is known to be an important risk factor for coronary atherosclerosis. However, measurement of an individual's stress level is not easy as it is a complex structure made up of several different elements. The Perceived Stress Scale (PSS), a 10-item questionnaire, is the most widely used psychological instrument to measure the perception of stress.[3, 4] It has been demonstrated that a high PSS score was associated with an increased risk for CAD. In particular, a high PSS score was found to be associated with an increased number of cardiovascular atherosclerotic events.[5] In addition, stress negatively affects the cardiovascular function and the prognosis in patients with CAD. Increased sympathetic activation[6] and adrenal function,[7] induced-platelet activation,[8] smoking, and lack of physical exercise[3] are some of the un-derlying mechanisms of stress linked to coronary ath-erosclerosis and adverse cardiac events. However, to the best of our knowledge, the stress-related coronary atherosclerotic burden has not yet been studied. The aim of this study was to investigate the relationship between the PSS score and the coronary atheroscle-rotic burden in patients with STEMI.

Abbreviations:

ACEI	*Angiotensin-converting enzyme inhibitor*
ARB	*Angiotensin receptor blocker*
CAD	*Coronary artery disease*
CCB	*Calcium channel blocker*
CI	*Confidence interval*
COPD	*Chronic obstructive pulmonary disease*
CRP	*C-reactive protein*
DM	*Diabetes mellitus*
EF	*Ejection fraction*
HDL	*High density lipoprotein cholesterol*
HL	*Hyperlipidemia*
HT	*Hypertension*
LDL	*Low-density lipoprotein cholesterol*
LV	*Left ventricle*
LVEF	*Left ventricular ejection fraction*
OR	*Odds ratio*
PAD	*Peripheral artery disease*
PSS	*Perceived Stress Scale*
ROC	*Receiver operating characteristic*
STEMI	*ST-segment elevation myocardial infarction*
SYNTAX	*Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery*
TG	*Triglyceride*

METHODS

Study population

This research was approved by the local ethics committee at Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital on February 5, 2018 (no: 2018-02). Each participant in the study provided detailed, written, informed consent. This cross-sectional study was conducted at a single tertiary care center from March 2018 to May 2019. A total of 440 consecutive patients with STEMI were prospectively enrolled. The diagnostic criteria for STEMI were typical chest pain for more than 20 minutes and ST-segment elevation in at least 2 contiguous leads with the following cut-off points: ≥0.2mV in men ≥40 years old, ≥0.25mV in men <40 years old, and ≥0.15mV in women in leads V2–V3 and/or ≥0.1mV in the other leads. When indicated, posterior (V7–V9) and right (V3R–V4R) derivations were also obtained. There is also an established cut-off point of 0.05mV for V7-9 (≥0.1mV in men <40 years old) and ≥0.05mV for V3R and V4R (≥0.1mV in men <30 years old). Patients who underwent percutaneous coronary intervention or coronary artery bypass graft surgery as well as those with a psychiatric disorder or psychiatric medication usage were excluded.

Demographic and clinical parameters were recorded after performing a detailed cardiovascular and systemic examination. Biochemical analyses of a complete blood count and measures of the levels of serum creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), and serum electrolytes levels were assessed. The SYNTAX score, SYNTAX score II, and the PSS measurement were calculated for each patient. The study population was divided into 2 groups according to the PSS score.

Patients with a SYNTAX score >22 were categorized as the moderate-to-high SYNTAX score group.

Coronary angiographic evaluation

Coronary angiography of all of the patients was performed immediately after the examination through femoral or radial access. Two independent, experienced cardiologists evaluated the coronary angiographic images individually to calculate the SYNTAX score and SYNTAX score II.[2] First, the anatomical-based SYNTAX score was calculated. Briefly, the coronary arteries were evaluated as 16 separate segments and assessed for segments with 50% or more luminal stenosis and >1.5 mm diameter. Every segment has a pre-specified corresponding weighting factor as well as other determining factors, such as calcification and lesion length, which were used to calculate the SYNTAX score. Details of the clinical variables of age, gender, creatinine clearance level, left ventricular ejection fraction (LVEF), and the presence of peripheral artery disease (PAD) or chronic obstructive pulmonary disease (COPD) were collected to be included in the SYNTAX score II value. The SYNTAX score calculator (www.syntaxscore.com) was used to obtain the score for each patient.

Perceived Stress Scale

The PSS is a 10-item scale used to assess the perception of stress.[3,4] It is widely used to examine the appraisal of global stress in an individual's life using a focus on unpredictable or uncontrollable events and feeling overloaded in the prior month. A 5-point Likert scale from "never" (0 points) to "very often" (4 points) is used and a higher score indicates a greater perception of stress (Table 1).[3,4] While this scoring system does not reflect the present stress status, it demonstrates preexisting stress level in the study patients. The questionnaire was completed before discharge from the hospital.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 software (IBM Corp., Armonk, NY, USA). Pearson chi-square and Fisher exact tests were used for categorical variables. Normal distribution was analyzed with the Kolmogorov-Smirnov test. Data were expressed as mean±SD when normal distribution was present, median (25^{th}-75^{th} percentiles) in the event of abnormal distribution, and number (%) for categorical variables. An independent sample t-test was used to compare quantitative variables with normal distribution and the Mann-Whitney U test was used to compare means between groups without normal distribution. Spearman analysis was applied to evaluate

Table 1. Perceived Stress Scale[3, 4]

1.	In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2.	In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3.	In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4.	In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5.	In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6.	In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7.	In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8.	In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9.	In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10.	In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

0 = Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often.

the correlation between the PSS and SYNTAX scores (SYNTAX score and SYNTAX score II). Receiver operating characteristic (ROC) curve analyses was conducted to determine the optimal PSS cut-off value to indicate a moderate-to-high SYNTAX score. PSS agreement was assessed using alpha (Cronbach) reliability analysis. Univariate and multivariate logistic regression analysis were used to evaluate independent predictors of a moderate-to-high SYNTAX score. A p-value <0.05 was considered statistically significant.

Table 2. Baseline demographic, clinical, and laboratory variables of the study group

	All patients	Group 1 Patients with a low PSS score (n=361)	Group 2 Patients with a high PSS score (n=79)	*p*
Gender (female), n (%)	85 (19.3)	63 (17.5)	22 (27.8)	0.034
Age (years)	55.4±11.5	55.1±11.2	56.9±12.8	0.209
Smoking, n (%)	239 (54.3)	196 (54.3)	43 (54.4)	0.982
Hypertension, n (%)	147 (33.4)	121 (33.5)	26 (32.9)	0.918
Diabetes mellitus, n (%)	93 (21.1)	75 (20.8)	18 (22.8)	0.692
Hyperlipidemia, n (%)	55 (12.5)	44 (12.2)	11 (13.9)	0.673
PAD, n (%)	21 (4.8)	14 (3.9)	7 (8.9)	0.063
COPD, n (%)	19 (4.3)	12 (3.3)	7 (8.9)	0.037
Hemoglobin (g/dL)	14.9 (13.6–15.9)	14.9 (13.9–15.9)	14.7 (12.7–15.7)	0.058
Leukocyte×10^3/mm^3	12.3 (9.91–15.02)	12.4 (9.98–14.92)	11.24 (9.4–15.33)	0.259
Thrombocyte×10^3/mm^3	261 (226–318)	261 (228–318)	256 (218–321)	0.286
BUN (mg/dL)	15.0 (12.0–18.0)	15.0 (12.0–18.0)	14.0 (12.0–19.0)	0.658
Creatinine (mg/dL)	0.85 (0.73–1.01)	0.84 (0.74–1.00)	0.88 (0.68–1.05)	0.797
Glucose (mg/dL)	135.5 (109.25–194.5)	134 (109–195)	137 (117–183)	0.364
AST (U/L)	25 (19–43)	25 (19–41)	26 (19–45)	0.963
ALT (U/L)	21 (16–30)	22 (16–30)	19 (15–30)	0.345
C-reactive protein (mg/L)	3.96 (1.81–9.11)	3.92 (1.77–8.33)	5.48 (2.3–14.15)	0.048
Total cholesterol (mg/dL)	201.2±42.7	202.1±41.7	197.6±47.2	0.402
LDL cholesterol (mg/dL)	122.1±37.7	121.9±36.5	123.1±42.9	0.802
HDL cholesterol (mg/dL)	41 (34–48)	41 (34–47)	40.5 (35–50)	0.278
Triglyceride (mg/dL)	174 (115.75–250.75)	182 (120.5–258)	141.5 (103–214)	0.007
Medication usage, n (%)				
Beta blocker	11 (2.5)	6 (1.7)	5 (6.3)	0.031
ACEI	61 (13.9)	48 (13.3)	13 (16.5)	0.462
ARB	29 (6.6)	23 (6.4)	6 (7.6)	0.691
CCB	32 (7.3)	23 (6.4)	9 (11.4)	0.120
Statin	69 (15.7)	52 (14.4)	17 (21.5)	0.115
Culprit vessel, n (%)				
LAD	232 (52.7)	188 (52.1)	44 (55.7)	0.739
CXA	55 (12.5)	47 (13.0)	8 (10.1)	
RCA	153 (34.8)	126 (34.9)	27 (34.2)	
Ejection fraction (%)	50 (40–55)	50 (40–55)	45 (38–50)	0.013

ACEI: Angiotensin-converting enzyme inhibitor; ALT: Alanine aminotransferase; ARB: Angiotensin receptor blocker; AST: Aspartate amino transaminase; BUN: Blood urea nitrogen; CCB: Calcium channel blocker; COPD: Chronic obstructive pulmonary disease; CXA: Circumflex artery; HDL: High-density lipoprotein; LAD: Left anterior descending; LDL: Low-density lipoprotein; PAD: Peripheral artery disease; PSS: Perceived Stress Scale; RCA: Right coronary artery.

Table 3. Angiographic evaluation of patients according to the PSS score

	All patients	Group 1 Patients with a low PSS score (n=361)	Group 2 Patients with a high PSS score (n=79)	*p*
SYNTAX score, n (%)				
0–22	305 (69.3)	266 (73.7)	39 (49.4)	<0.001
>22	135 (30.7)	95 (26.3)	40 (50.6)	
SYNTAX score	16.5 (11.0–23.3)	16.0 (10.0–22.5)	22.5 (15.0–25.5)	<0.001
SYNTAX score II	25.9 (19.5–34.0)	24.8 (19.0–32.6)	30.9 (22.3–38.9)	<0.001

PSS: Perceived Stress Scale; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

RESULTS

A total of 440 consecutive patients with STEMI were enrolled in this prospective study. The entire group was divided into 2 groups according to the PSS measurement: a sum of the responses to positively and negatively stated questions. The PSS demonstrated high reliability (Cronbach's alpha: 0.928). ROC analysis was conducted to determine the optimal PSS cut-off value to indicate moderate-to-high SYNTAX score. The highest combined sensitivity and specificity values crossed the curve at 17.5 (sensitivity: 29.6%; specificity: 87.2%). The area under the curve was 0.593 [95% confidence interval (CI): 0.534–0.653; p=0.002]. In all, 361 patients with a low PSS score were categorized as Group 1 and 79 patients with a high PSS score were placed in Group 2. The baseline demographic, clinical, and laboratory variables of the groups are demonstrated in Table 2. There were no statistically significant differences in age, smoking status, hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), PAD, hemoglobin, leukocyte, thrombocyte, aspartate amino transaminase, alanine aminotransferase, glucose, blood urea nitrogen, creatinine, total cholesterol, LDL cholesterol, HDL cholesterol, culprit vessels, or use of angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), calcium channel blocker (CCB) or statin medications between the 2 groups. While the number of female patients (Group 1: n=63, 17.5%; Group 2: n=22, 27.8%; p=0.034) and C-reactive protein (CRP) level [Group 1 median: 3.92 mg/L (1.77–8.33 mg/L); Group 2 median: 5.48 mg/L (2.3–14.15 mg/L); p=0.048] were significantly higher in Group 2, the TG level was lower in this group [Group 1 median: 182 mg/dL (120.5–258 mg/dL); Group 2 median: 141.5 mg/dL (103–214 mg/

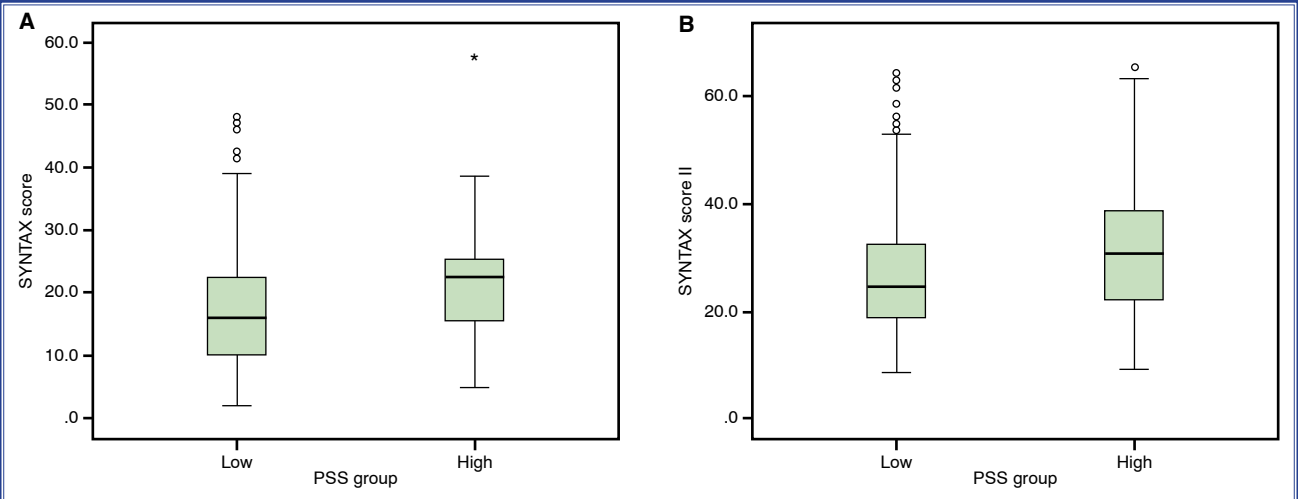

Figure 1. (A) SYNTAX score in PSS Group 1 and Group 2; **(B)** SYNTAX score II in PSS Group 1 and Group 2. The SYNTAX score and SYNTAX score II were significantly higher in patients with a high PSS score. PSS: Perceived Stress Scale; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

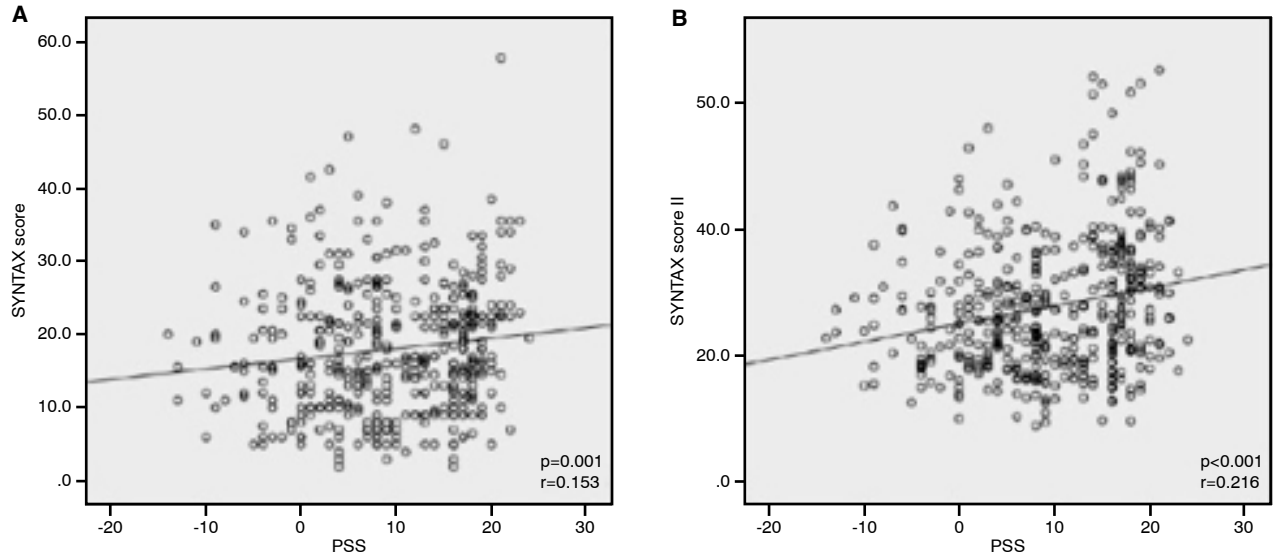

Figure 2. **(A)** Correlation between the SYNTAX score and the PSS score; **(B)** Correlation between the SYNTAX score II and the PSS score. The SYNTAX score and the SYNTAX score II were positively correlated with PSS measurement. PSS: Perceived Stress Scale; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

dL); p=0.007]. The ejection fraction (EF) of Group 2 was significantly lower than that of Group 1 [Group 1 median: 50% (40–55%); Group 2 median: 45% (38-50%); p=0.013]. Additionally, the incidence of COPD (Group 1: n=12, 3.3%; Group 2: n=7, 8.9%; p=0.037), and beta blocker usage (Group 1: n=6, 1.7%; Group 2: n=5, 6.3%; p=0.031) was significantly higher in Group 2.

The angiographic severity of entire study group is presented in Table 3. The SYNTAX score [Group 1 median: 16.0 (10.0–22.5); Group 2 median: 22.5 (15.0–25.5); p<0.001] and the SYNTAX score II [Group 1 median: 24.8 (19.0–32.6); Group 2 median: 30.9 (22.3-38.9); p<0.001] of the high PSS group were statistically significantly higher (Fig. 1). A greater percentage of patients in Group 2 had a moderate-to-high SYNTAX score [Group 1: n=95, 26.3%; Group 2: n=40, 50.6%; p<0.001).

Spearman correlation analyses demonstrated that the PSS score was associated with the SYNTAX score (r=0.153; p=0.001) and the SYNTAX score II (r=0.216; p<0.001) (Fig. 2).

Univariate and multivariate logistic regression analyses were used to evaluate independent predictors of moderate-to-high SYNTAX score. Variables with statistical significance in univariate and multivariate

Table 4. Univariate and multivariate logistic regression analyses of independent predictors of a moderate-to-high SYNTAX score

	Univariate			Multivariate		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age	1.027	1.009–1.046	0.003			
Ejection fraction	0.961	0.941–0.981	<0.001	0.969	0.948–0.990	0.005
Peripheral artery disease	0.310	0.127–0.754	0.010			
Chronic obstructive pulmonary disease	0.378	0.150–0.953	0.039			
C-reactive protein	1.008	1.001–1.015	0.016			
Hemoglobin	0.884	0.790–0.989	0.031			
Perceived Stress Scale	2.872	1.743–4.732	<0.001	2.434	1.446–4.096	0.001

CI: Confidence interval; SYNTAX: Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

Table 5. PSS score of patients with and without in-hospital mortality

	Patients with in-hospital mortality (n=15)	Patients without in-hospital mortality (n=425)	p
PSS measurement	15 (10–20)	9 (4–16)	0.007
High PSS group, n (%)	6 (40)	73 (17.2)	0.036

PSS: Perceived Stress Scale.

logistic regression analyses are provided in Table 4. The PSS measurement [odds ratio (OR): 2.434, CI: 1.446–4.096; p=0.001] and a lower EF (OR: 0.969, CI: 0.948–0.990; p=0.005) were found to be predictors of moderate-to-high SYNTAX score.

During hospitalization, 15 patients (3.4%) died, with a mean follow-up time of 5.53±1.40 days. The PSS score of patients with in-hospital mortality was higher than that of those without mortality [Group 1 median: 15 (10–20); Group 2 median: 9 (4–16); p=0.007]. Additionally, there were more patients with a high PSS score among those with in-hospital mortality (Group 1: n=6, 40%; Group 2: n=73, 17.2%; p=0.036) (Table 5).

DISCUSSION

In the present study, we found an association between an increased level of perceived stress measured with the PSS and CAD severity calculated using the SYNTAX score and SYNTAX score II. To the best of our knowledge, this was the first prospective study investigating the relationship between the PSS and SYNTAX scores. The PSS measurement was correlated with both SYNTAX scores and was a predictor of a moderate-to-high SYNTAX score. It was also demonstrated that patients with in-hospital mortality had a higher PSS score.

Stress is a known predictor of the atherosclerotic process with a negative effect on the cardiovascular prognosis. Stress is also related to progressive coronary atherosclerosis. Although stress has been linked to CAD, the underlying mechanisms of perceived stress, related coronary atherosclerosis, and adverse cardiovascular outcomes are still unclear and multifactorial. Some behavioral factors, such as smoking, drinking alcohol, lack of physical exercise, increased sleep and medication usage, occur against stressors.[3] They accelerate inflammation and the immune process, resulting in an increased risk of the atherosclerotic process. Another pathway is stress-related endocrine responses. Psychologically stressful life events activate 2 endocrine systems: the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenal-medullary system.[9,10] Cortisol hypersecretion is the main actor in an activated hypothalamic-pituitary-adrenocortical axis, and has been associated with the inflammatory process and a variety of diseases. The increased presence of HT, dyslipidemia, type 2 DM, and metabolic syndrome are risk factors and predisposing factors for coronary atherosclerotic disease and cardiovascular morbidity and mortality.[11–14] Activation of the sympathetic-adrenal-medullary system leads to secretion of catecholamines, which affect the cardiovascular, pulmonary, hepatic, skeletal-muscle, and immune systems.[6] Prolonged and repeated activation of these systems results in an increased inflammatory process and risk of atherosclerotic disease. These activated systems and the hormones released also affect the immune system through direct innervation of lymphatic tissue, as well as behavioral responses, such as smoking. Thus, stress can alter immune function and be a predictor of atherosclerotic disease. Stress also has an effect on cardiovascular disease due to induced platelet activation, increased blood clotting, and decreased fibrinolysis,[8,15,16] and furthermore, stress also impairs the vagal tone, which increases the risk of cardiovascular disease.[17] All of these pathophysiological mechanisms are important factors in the atherosclerotic process and cardiovascular disease. However, the stress-related coronary atherosclerotic burden has not yet been evaluated. These mechanisms may also affect coronary atherosclerotic disease severity. This could be an important contributor to adverse cardiovascular events in patients with increased level of perceived stress. Our study is the first to demonstrate a relationship between an increased level of perceived stress and the atherosclerotic coronary plaque burden, reflected by the SYNTAX score and SYNTAX score II. Though

the PSS records a stress level from the previous month, acute coronary syndrome can also result in a higher stress level . Although increased stress linked to acute cardiac events could affect our study population, it could also be a predictor of patients with a higher stress status. Our results demonstrated an increased coronary atherosclerotic burden due to existing stress not originating only with STEMI. A previous study demonstrated that patients with acute coronary syndrome had a high PSS score with a mean value of 29.6±8.2 while the PSS score of the control subjects was 19.8±7.8.[18] Similarly, in the same population, a higher inflammation status can cause an increased atherosclerotic coronary plaque burden. This was revealed in the relationship between stress level and SYNTAX scores. However, this relationship and the presence of CAD are multifactorial, which may explain the weak correlation of PSS and SYNTAX scores in our study.

In the light of these data, it appears that stress is a significant risk factor for the progression and prognosis of CAD. Studies have demonstrated a positive association between perceived stress and subclinical atherosclerosis[19] and cardiovascular risk factors.[20] An increased risk of manifest CAD and myocardial infarction has also been found to be correlated with psychological stress. In a meta-analyses from 6 large, prospective, observational, cohort studies that included 118,696 participants, a higher level of perceived stress was found to be related to a CAD risk ratio of 1.27.[5] In this study, it was determined that an increased level of perceived stress was associated with a 27% increase in CAD risk, the equivalent of a 50 mg/dL increase in LDL cholesterol, a 2.7/1.4 mmHg increase in blood pressure, or 5 more cigarettes a day. It is also known that stress is related to increased mortality rates in patients with coronary atherosclerosis, especially in STEMI patients. Von Känel et al.[21] found that stress was associated with rehospitalization and increased reintervention rates in patients with STEMI. Stress-targeted treatment modalities have been reported to reduce mortality rates in patients with coronary atherosclerosis.[22] Thus, stress linked to the atherosclerotic coronary plaque burden may be a prominent underlying mechanism of adverse cardiovascular events. The SYNTAX score was developed to detect CAD severity and burden, and a higher PSS score was found to be an independent risk factor of a higher SYNTAX score in our study.

Several clinical variables were added to the basal SYNTAX score to provide a more sensitive clinical risk score in the SYNTAX score II. Several studies have demonstrated that the SYNTAX score II was associated with adverse cardiovascular events and mortality in patients with CAD. In a study with 1912 participants, the SYNTAX score II was found to be strongly related to in-hospital and long term mortality in patients with STEMI.[23] Therefore, SYNTAX score II-related parameters are valuable in the detection and treatment of STEMI patients. Our results indicated that a high PSS score was associated with a high SYNTAX score II. This could be explained by the underlying mechanisms of stress-related atherosclerosis and it could be a very important reason stress is linked to an increased mortality rate in patients with STEMI.

As a result of the mechanisms described above, an increased stress level would appear to be related to a higher atherosclerotic coronary plaque burden, whether or not it is linked to an acute coronary event.

Although our study did not demonstrate a sufficient clinical correlation, the results are meaningful. The impact of the relationship between stress status and CAD severity should be further examined in large-scale studies with long-term, clinical follow-up.

In previous studies, women have been found to be more sensitive to certain psychosocial risk factors and it has been reported that women have greater levels of perceived stress than men.[24] In a study by Xu et al.,[25] 2358 women and 1151 men with acute myocardial infarction were evaluated and it was demonstrated that the women had a higher PSS score than the men. While the mean PSS score of the women was 19.7±8.2, it was 16.4±7.6 in men ($p<0.001$). In addition, among 665 patients with CAD, a higher level of psychosocial distress was found to be associated with myocardial perfusion abnormalities in women.[26] In another study, a higher level of psychological stress was shown to be related to increased cardiovascular adverse events in women with stable CAD.[27] Consistent with these results, in our study, the number of female patients was higher in the high PSS score group.

Stress can have a depressor effect on the left ventricle (LV) myocardium. The underlying mechanism of this effect is multifactorial. One of the most common pathophysiological pathways in the development of the impairment of LV myocardium func-

tion is catecholamine-induced cardiotoxicity. It has been demonstrated that myocardial contraction band necrosis, neutrophil infiltration, and fibrosis can occur in the presence of catecholamine overexpression and result in a depressive effect on the LV myocardium.[28] Another mechanism is that catecholamine linked to increased cyclic adenosine monophosphate production triggers the formation of free radicals, initiating the expression of stress response genes and inducing apoptosis.[29] A stress-related increase in coronary atherosclerosis and cardiovascular risk factors also amplifies the effect of stress on the LV myocardium. Thus, impairment of the myocardium can occur due to a higher stress status. This would appear to be corroborated by the lower EF observed in our patients with a higher PSS score and support a relationship between a lower EF and a moderate-to-high SYNTAX score.

Conclusion

This study demonstrated that the PSS score was associated with coronary atherosclerotic plaque burden. A greater stress level was also a predictor of a moderate-to-high SYNTAX score. Patients with in-hospital mortality also had a higher stress level.

Study limitations

A relatively small sample size is the main limitation of our study, as well as the lack of control group. In addition, stress management and modification of stress behavior on coronary atherosclerotic severity and burden were not investigated in our study. Finally, the effect of increased perceived stress on short- and long-term cardiovascular events was not evaluated.

Ethical statement: This study was approved by the local ethics committee at Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital. (date: February 5, 2018, no: 2018-02).

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REFERENCES

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation 2019;139:e56–e528.
2. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639–50. [CrossRef]
3. Cohen S, Williamson G. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, editors. The Claremont Symposium on Applied Social Psychology. The social psychology of health. Newbury Park, CA: Sage Publications, Inc.; 1988. p. 31–67.
4. Erci B. Reliability and validity of the Turkish version of Perceived Stress Scale. Journal of Ataturk University School of Nursing 2006;9:58–63.
5. Richardson S, Shaffer JA, Falzon L, Krupka D, Davidson KW, Edmondson D. Meta-analysis of perceived stress and its association with incident coronary heart disease. Am J Cardiol 2012;110:1711–6. [CrossRef]
6. Fechir M, Schlereth T, Purat T, Kritzmann S, Geber C, Eberle T, et al. Patterns of sympathetic responses induced by different stress tasks. Open Neurol J 2008;2:25–31. [CrossRef]
7. Strike PC, Steptoe A. Psychosocial factors in the development of coronary artery disease. Prog Cardiovasc Dis 2004;46:337–47. [CrossRef]
8. Reid GJ, Seidelin PH, Kop WJ, Irvine MJ, Strauss BH, Nolan RP, et al. Mental-stress-induced platelet activation among patients with coronary artery disease. Psychosom Med 2009;71:438–45. [CrossRef]
9. Cohen S, Kessler RC, Gordon UL, editors. Strategies for measuring stress in studies of psychiatric and physical disorder. Measuring Stress: A Guide for Health and Social Scientists. Oxford University Press, New York; 1995. p. 3–26.
10. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9. [CrossRef]
11. Rosmond R, Dallman MF, Björntorp P. Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. J Clin Endocrinol Metab 1998;83:1853–9. [CrossRef]
12. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403–14.
13. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009;5:374–81. [CrossRef]
14. Novak M, Björck L, Giang KW, Heden-Ståhl C, Wilhelmsen L, Rosengren A. Perceived stress and incidence of Type 2 diabetes: a 35-year follow-up study of middle-aged Swedish men. Diabet Med 2013;30:e8–e16. [CrossRef]
15. Brunner E, Davey Smith G, Marmot M, Canner R, Beksinska M, O'Brien J. Childhood social circumstances and psychoso-

cial and behavioural factors as determinants of plasma fibrinogen. Lancet 1996;347:1008–13. [CrossRef]
16. von Känel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease?. Psychosom Med 2001;63:531–44. [CrossRef]
17. Porges SW. Cardiac vagal tone: a physiological index of stress. Neurosci Biobehav Rev 1995;19:225–33. [CrossRef]
18. Katsarou A, Triposkiadis F, Skoularigis J, Griva E, Neroutsos G, Karayannis G, et al. Evaluating the role of perceived stress on the likelihood of having a non - fatal acute coronary syndrome: a case-control study. Open Cardiovasc Med J 2014;8:68–75. [CrossRef]
19. Troxel WM, Matthews KA, Bromberger JT, Sutton-Tyrrell K. Chronic stress burden, discrimination, and subclinical carotid artery disease in African American and Caucasian women. Health Psychol 2003;22:300–9. [CrossRef]
20. Labbate LA, Fava M, Oleshansky M, Zoltec J, Littman A, Harig P. Physical fitness and perceived stress. Relationships with coronary artery disease risk factors. Psychosomatics 1995;36:555–60. [CrossRef]
21. von Känel R, Hari R, Schmid JP, Saner H, Begré S. Distress related to myocardial infarction and cardiovascular outcome: a retrospective observational study. BMC Psychiatry 2011;11:98. [CrossRef]
22. Linden W, Phillips MJ, Leclerc J. Psychological treatment of cardiac patients: a meta-analysis. Eur Heart J 2007;28:2972–84. [CrossRef]
23. Karabağ Y, Çağdaş M, Rencuzogullari I, Karakoyun S, Ar-taç İ, İliş D, et al. Comparison of SYNTAX score II efficacy with SYNTAX score and TIMI risk score for predicting in-hospital and long-term mortality in patients with ST segment elevation myocardial infarction. Int J Cardiovasc Imaging 2018;34:1165–75. [CrossRef]
24. Xu X, Bao H, Strait K, Spertus JA, Lichtman JH, D'Onofrio G, et al. Sex differences in perceived stress and early recovery in young and middle-aged patients with acute myocardial infarction. Circulation 2015;131:614–23. [CrossRef]
25. Xu X, Bao H, Strait KM, Edmondson DE, Davidson KW, Beltrame JF, et al. Perceived Stress After Acute Myocardial Infarction: A Comparison Between Young and Middle-Aged Women Versus Men. Psychosom Med 2017;79:50–8. [CrossRef]
26. Pimple P, Hammadah M, Wilmot K, Ramadan R, Al Mheid I, Levantsevych O, et al. The Relation of Psychosocial Distress With Myocardial Perfusion and Stress-Induced Myocardial Ischemia. Psychosom Med 2019;81:363–71. [CrossRef]
27. Pimple P, Lima BB, Hammadah M, Wilmot K, Ramadan R, Levantsevych O, et al. Psychological Distress and Subsequent Cardiovascular Events in Individuals With Coronary Artery Disease. J Am Heart Assoc 2019;8:e011866. [CrossRef]
28. Williams R, Arri S, Prasad A. Current Concepts in the Pathogenesis of Takotsubo Syndrome. Heart Fail Clin 2016;12:473–84. [CrossRef]
29. Litvinov IV, Kotowycz MA, Wassmann S. Iatrogenic epinephrine-induced reverse Takotsubo cardiomyopathy: direct evidence supporting the role of catecholamines in the pathophysiology of the "broken heart syndrome". Clin Res Cardiol 2009;98:457–62. [CrossRef]

Keywords: Coronary artery disease; perceived stress scale; ST-segment elevation myocardial infarction; SYNTAX score.

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