

# The usefulness of tumor necrosis factor-like weak inducer of apoptosis in patients with acute ST-elevation myocardial infarction

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**Abstract. – OBJECTIVE:** We aimed to determine the utility of tumor necrosis factor-like weak inducer of apoptosis (TWEAK) for the early diagnosis and prognosis of acute ST-elevation myocardial infarction (STEMI).

**PATIENTS AND METHODS:** Patients presented with STEMI arrived at the hospital within 45 minutes after the onset of chest pain were included in this study. Blood samples for TWEAK, high-sensitivity C-reactive protein (hs-CRP), creatine kinase MB isoenzyme (CK-MB), and high-sensitivity cardiac troponin T (hs-TnT) levels were obtained at the time of arrival at the hospital. Subsequent samples were drawn at 4 h after primary percutaneous coronary intervention.

**RESULTS:** The study cohort comprised patients with confirmed STEMI between January 2022 and September 2022, for a total of 45 enrolled STEMI patients. Plasma TWEAK levels were markedly elevated at hospital arrival, followed by a decrease at 4 hours after successful primary percutaneous coronary revascularization (PPCI). High-sensitive troponin T (Hs-TropT), CK-MB, and CRP were found within normal limits at the hospital arrival. Conversely, increased levels of CRP, CKMB, and hs-TropT were observed at 4 hours after PPCI.

**CONCLUSIONS:** Plasma TWEAK levels were elevated earlier in the acute phase and decreased earlier after PPCI than other classic myocardial biomarkers.

*Key Words:*

Coronary artery disease, Myocardial infarction, Tumor necrosis factor-like weak inducer of apoptosis.

## Introduction

Acute myocardial infarction is a major cause of morbidity and mortality worldwide<sup>1</sup>. The rise of high-sensitivity cardiac troponin T (hs-TnT) or creatine kinase MB isoenzyme (CK-MB) could

be delayed, and the rapid diagnosis of ST-elevation myocardial infarction (STEMI) may be challenging<sup>2</sup>. Serum levels of the ideal biomarker are expected to rise rapidly after STEMI and decrease rapidly after successful primary percutaneous therapy (PPI). Inflammation plays an important role in acute myocardial infarction and the period of post-infarction recovery<sup>3</sup>. C-reactive protein (CRP) is a predictor of adverse outcomes in patients with acute coronary syndrome<sup>4</sup>. However, peak hs-CRP is reached 2-3 days after STEMI<sup>5</sup>. Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is expressed in several tissues, including the vasculature. TWEAK, a member of the tumor necrosis factor (TNF) superfamily, participates in the pathophysiology of cardiac remodeling. Proliferation, migration, differentiation, apoptosis, angiogenesis, and inflammation are a few of them<sup>6</sup>. TWEAK can be upregulated after injury<sup>7</sup>. The post-myocardial infarction (MI) phase is characterized by an increase in cardiomyocyte TWEAK levels, which has detrimental consequences on heart repair, according to experimental research<sup>8</sup>. Attenuation of metabolic adaptation and an increase in cardiac load caused by inhibition of peroxisome proliferator-activated receptor gamma co-activator 1alpha or by inducing macrophage infiltration that results in cardiac fibrosis are some of the mechanisms that account for the detrimental effects of TWEAK on cardiac repair<sup>9</sup>. Circulating TWEAK binds to the cell surface Fn14 receptor, TWEAK binds and causes Fn14 trimerization and signal transduction. Fn14 is expressed in the healthy vasculature and heart. It is rapidly and highly regulated in myocardial infarction, as demonstrated in experimental models<sup>10</sup>.

Fn14 is regulated by several growth factors, cytokines, and interleukins in endothelial cells and monocyte/macrophages present in the in-

jured vascular wall<sup>11</sup>. High circulating levels of TWEAK have been described in patients after myocardial infarction<sup>12,13</sup>. However, studies in patients presenting with STEMI are limited. TWEAK could be a biomarker for the diagnosis and prognosis of cardiovascular disease. Future studies will help to determine the relevance of TWEAK as a biomarker. Considering TWEAK and Fn14 fast regulation, we hypothesized that the plasma level of TWEAK might be elevated in the earlier stage and responded faster to primary percutaneous coronary revascularization (PPCI) than hs-TropT and CK-MB. We aimed to determine the utility of TWEAK for the early diagnosis and prognosis of STEMI. We also tried to evaluate their utility for predicting left ventricular (LV) systolic dysfunction and mortality, and compared prognostic value with CK-MB, and high-sensitive troponin T (hs-TropT).

## Patients and Methods

### Study Population

Patients who arrived with STEMI at the hospital within 45 minutes after the onset of chest pain were included in this study. The exclusion criteria were as follows: age < 18 years, any history of previous myocardial infarction, coronary intervention, or coronary artery bypass graft surgery, having experienced an acute infection with fever (temperature > 38°C), an estimated glomerular filtration rate < 30 mL/min per 1.73 m<sup>2</sup>, known active inflammatory diseases, suspected myocarditis or pericarditis, and known severe liver disease.

The project was approved by the local Ethics Committee with an approval number 2022.163.09.10.

### Sample Collection and Laboratory Measurements

Blood samples for TWEAK, hs-CRP, CK-MB, and hs-TnT levels were obtained at the time of arrival at the hospital. Subsequent samples were drawn 4 h after a successful PPCI. Serum samples were allocated and preserved at -80°C until TWEAK measurement. TWEAK was measured using an ELISA kit (ELK Biotechnology CO., Ltd. Wuhan, China).

### Echocardiography Imaging

All patients underwent transthoracic echocardiography (ClearVue 350, Philips Medical Sys-

tems, Andover, MA, USA) 1 month following PPCI. The movies were obtained in the apical four-chamber, two-chamber, and three-chamber views. The left ventricular ejection fraction (LVEF) was defined as follows: (left ventricular end-diastolic volume – left ventricular end-systolic volume)/left ventricular end-diastolic volume.

### Outcomes

TWEAK, hs-CRP, CK-MB, and hs-TropT levels were compared in blood tests obtained at the time of admission and the 4 h after successful PPCI. Patients were followed *via* outpatient clinic visits 1 month after discharge. Echocardiography was performed at 1 month. The primary objective was to investigate the utility of TWEAK as a biomarker for earlier diagnosis of STEMI and to evaluate TWEAK response time after PPCI. The secondary objective was to assess the association between TWEAK and LVEF at 1 month.

### Statistical Analysis

Continuous variables were analyzed for normality using the Kolmogorov-Smirnov test. Baseline and second samples were compared using the Paired Samples *t*-test (TWEAK, hs-TropT, and CK-MB) and Wilcoxon signed-ranks test (hs-CRP). Comparisons between LVEF ≤ 40% and LVEF > 40% groups were made using the Kolmogorov-Smirnov test. Data are presented as mean ± standard deviation or median according to data normality. The software SPSS, (version 18.0; IBM Corp., Armonk, NY, USA), was used for statistical analysis. All *p*-values < 0.05 were considered statistically significant.

## Results

### Study Population

Our prospective cross-sectional study consisted of patients with confirmed STEMI between January 2022 and September 2022, for a total of 45 enrolled STEMI patients. The main characteristics of the patients at baseline are described in Table I. The median age of the overall cohort was 55 (IQR 50-65) years. Pain-to-balloon time was 60 (IQR 45-75) min and did not differ between LVEF ≤ 40% and LVEF > 40% groups (*p* = 0.311).

**Table I.** Baseline characteristics of the study population at arrival.

Variable	Total (n = 45)
Sex, male	32 (71)
Age, years	55 (50-65)
BMI, kg/m <sup>2</sup>	24.2 ± 1.8
Heart rate, bpm	77.3 ± 12.7
SBP, mmHg	143.5 ± 16.3
Smoking	32 (71)
Hypertension	26 (57)
Diabetes	15 (33)
S-A T, minutes	32 (20-45)
P-B T, minutes	60 (45-75)
TG, mg/dl	106 ± 22
HDL-C, mg/dl	52 ± 12
LDL-C, mg/dl	89 ± 25
Glucose, mg/l	98 ± 5
WBC, × 10 <sup>3</sup> U/l	7.9 ± 1.8
CRP, mg/l	13.2 ± 2.9
Hs-TnT, ng/l	10.1 ± 4
CK-MB, U/L	16.0 ± 7.1
TWEAK, ng/ml	523 ± 166
LVEDD, (mm)	59.3 ± 1.1
LVESD, (mm)	46.2 ± 7.4
Drugs, n (%)	
Beta-blocker	4 (8)
Renin-angiotensin system blockers	20 (44)
Calcium channel blockers	4 (8)
Aspirin	10 (22)
Oral anti-diabetics	15 (33)
Statin	10 (22)

Data presented are means ± SD or n (%). BMI, Body mass index; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; GLU, blood glucose; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; CK-MB, creatine kinase MB isoenzyme; SBP, systolic blood pressure; P-B T, Pain-to-balloon time; S-A T, Symptom onset to hospital arrival; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

### Measurement of Circulating Markers

The time trend of plasma biomarker levels is shown in Figure 1. Plasma TWEAK levels were markedly elevated at hospital arrival, followed by a decrease at 4 hours after successful PPCI. Hs-TropT, CK-MB, and CRP were found within normal limits at the hospital arrival. Figure 1 shows that, compared to baseline, levels of TWEAK decreased 4 hours after PPCI. Conversely, increased levels of CRP, CK-MB, and hs-TropT were observed at 4 hours after PPCI.

### Relationship Between TWEAK and Cardiac Echocardiography Imaging

Patients were stratified according to LVEF at 1 month (Table II). Diabetes and, elevated TWEAK at admission were more common in patients with

LVEF ≤ 40%. There was a negative correlation between TWEAK levels at admission and LVEF at 1 month ( $r = -0.55$ ,  $p = 0.002$ ); however, no significant correlations were observed between TWEAK levels at 4 h after PPCI and %LVEF at 1 month ( $p = 0.081$ ).

Patients were stratified according to the baseline of plasma TWEAK levels (Table II). 1-month rates of reinfarction and heart failure hospitalization were 2% (1/45), and 6% (3/45) in patients with higher plasma TWEAK.

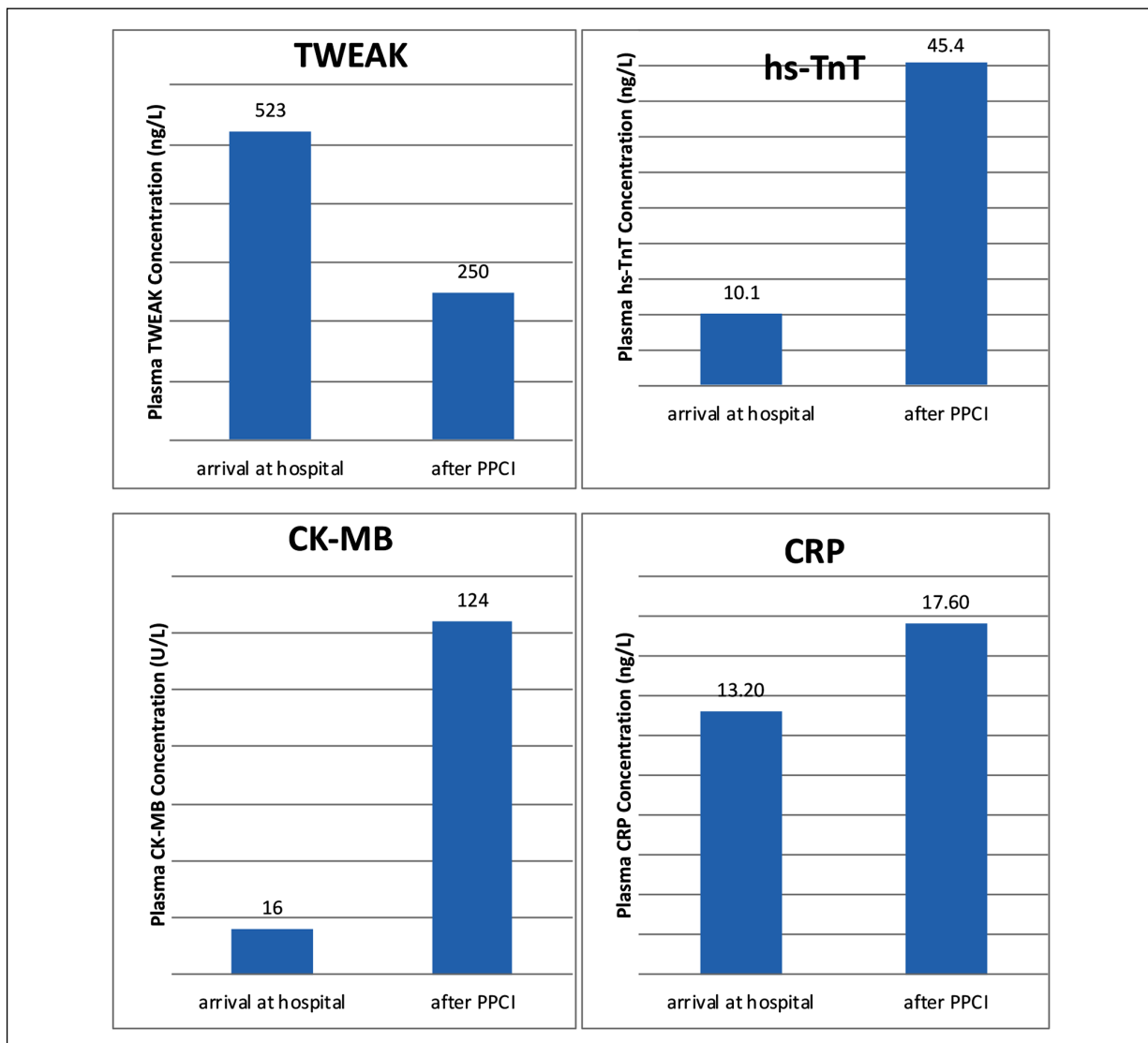
### Relationship Between TWEAK and Culprit Coronary Artery

The right coronary artery (RCA) was the more common culprit coronary artery than the left anterior descending coronary artery (LAD) [RCA = 52/90, LAD = 48/90, circumflex (CX) = 0]. TWEAK levels examined at the arrival to the hospital ( $p = 0.075$ ) and after 4 h of PPCI ( $p = 0.233$ ) did not differ between RCA and LAD.

## Discussion

Here we demonstrate, for the first time, that TWEAK is upregulated prior to hs-TnT, and downregulated response to successful PPCI prior to hscTnT in patients with ST-elevation myocardial infarction. The study's findings are as follows: high plasma level of TWEAK was identified in STEMI, plasma TWEAK levels were elevated earlier in the acute phase and decreased earlier after PPCI than other classic myocardial biomarkers. Fast regulation may be used in the diagnosis and in monitoring treatment efficacy in patients presented with ST-elevation. In addition, plasma TWEAK level at admission was an independent predictor of low LVEF at 1 month.

An implication from this study concerns the potential benefit of TWEAK for the early detection of STEMI. Elevation of classical myocardial biomarkers such as hs-TnT and CK-MB does not occur within two hours of the onset of STEMI<sup>14,15</sup>. This situation may hinder the rapid diagnosis of STEMI, particularly in patients presenting to the emergency department with atypical symptoms and/or electrocardiograms (ECGs). In STEMI patients, TWEAK elevation due to coronary artery plaque rupture and thrombus formation occurs before the increase in hs-TnT and CK-MB levels due to myonecrosis<sup>16</sup>. In our study, plasma TWEAK levels rose 30 minutes after the onset of STEMI, significantly better than hs-TnT and



**Figure 1.** Time trends of plasma TWEAK, hs-TnT, CK-MB, and CRP levels in patients with STEMI.

CK-MB. TWEAK can help us diagnose STEMI earlier and potentially improve clinical outcomes by enabling faster triage and reperfusion therapy initiation. In addition to its value in the early detection of STEMI, high TWEAK levels were an important biomarker in predicting low LVEF, an indicator of prognosis one month after STEMI. Despite the unknown mechanisms, several possible causes may explain the relationship between TWEAK and clinical outcomes. As is known, inflammation plays an important role in the development and progression of atherosclerosis. Previous studies<sup>17,18</sup> have shown that CRP, a classic biomarker of systemic inflammation, is useful in predicting adverse clinical outcomes in

various cardiovascular disease states. Like CRP, TWEAK is a sensitive, concentration-dependent biomarker associated with the extent and consequences of inflammation, as demonstrated herein and in the literature. Particularly in this study, TWEAK levels were a stronger predictor of prognosis than CRP.

Our study demonstrates the behavior of TWEAK concentrations in STEMI patients. Our results showed a significant decrease in TWEAK titers, despite continued increases in hs-TropT and CRP titers within 4 hours after successful PPCI. LVEF showed a correlation with TWEAK concentrations at baseline, and 4 hours after successful PPCI. Together, when these data are eval-

**Table II.** Patients were stratified according to LVEF at 1 month and baseline characteristics at admission.

Variable	LVEF $\leq$ 40 % (n = 23)	LVEF > 40 % (n = 22)	p-value
Sex, male	17 (73)	15 (68)	0.121
Age, years	58 (52-65)	52 (50-59)	0.245
BMI, kg/m <sup>2</sup>	26.1 $\pm$ 1.5	22.7 $\pm$ 2.1	0.089
Heart rate, bpm	78.1 $\pm$ 8.7	75.1 $\pm$ 9.1	0.432
SBP, mmHg	145.2 $\pm$ 11.1	141.5 $\pm$ 6.2	0.211
Smoking	18 (78)	14 (63)	0.098
Hypertension	14 (60)	12 (54)	0.321
Diabetes	11 (47)	4 (18)	0.002
S-A T, minutes	36 (31-45)	29 (20-35)	0.266
P-B T, minutes	64 (59-75)	55 (45-61)	0.311
TG, mg/dl	100 $\pm$ 28	112 $\pm$ 12	0.411
HDL-C, mg/dl	48 $\pm$ 7	58 $\pm$ 11	0.352
LDL-C, mg/dl	84 $\pm$ 21	92 $\pm$ 17	0.224
Glucose, mg/l	119 $\pm$ 9	88 $\pm$ 6	0.425
WBC, $\times 10^3$ U/l	7.6 $\pm$ 2.1	8.1 $\pm$ 2.2	0.318
CRP, mg/l	14.1 $\pm$ 3.1	12.9 $\pm$ 1.1	0.177
Hs-TnT, ng/l	12.1 $\pm$ 2.2	8.9 $\pm$ 4	0.098
CK-MB, U/L	19.1 $\pm$ 4.1	15.2 $\pm$ 6.2	0.149
TWEAK, ng/ml	632 $\pm$ 143	411 $\pm$ 216	0.001
LVEDD (mm)	61.3 $\pm$ 2.1	58.4 $\pm$ 0.8	0.08
LVESD (mm)	49.1 $\pm$ 8.2	45.3 $\pm$ 7.4	0.04
Drugs, n (%)			
Beta-blocker	2 (8)	2 (9)	0.941
RAAS	12 (52)	8 (34)	0.214
CCA	2 (8)	2 (9)	0.913
Aspirin	6 (26)	4 (18)	0.214
Oral anti-diabetics	13 (56)	2 (9)	0.003
Statin	6 (26)	4 (18)	0.213

Data presented are means  $\pm$  SD or n (%). BMI, Body mass index; TG, triglyceride; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; GLU, blood glucose; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; CK-MB, creatine kinase MB isoenzyme; SBP, systolic blood pressure; P-B T, Pain-to-balloon time; S-A T, Symptom onset to hospital arrival; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RAAS, Renin-angiotensin system blockers; CCA, calcium channel blockers.

uated, it becomes clear how important TWEAK is on the first day after acute MI. Better awareness of inflammatory risk during early follow-up of myocardial infarction may contribute to the creation of new therapeutic approaches. In order to achieve reliable outcomes analysis in our study, we require a larger sample size. Additionally, comparing the predictive value of TWEAK, CK-MB, and hs-TnT is unlikely to yield significant results.

TWEAK could help in the characterization of inflammatory mechanisms in acute STEMI. The rapid response of the serum TWEAK level to successful PPCI could be used to monitor the success of the treatment. Patients with decreased TWEAK levels after PPCI had significantly higher LVEF at 1 month. Taken together, these data indicate that TWEAK may represent a risk stratification tool, that is available in the very early phase after STEMI. Today, new biomarkers that

can be used in the diagnosis and prognosis of acute coronary syndrome continue to be investigated. According to the literature, no biomarker has been reported to peak and decrease within 4 hours after STEMI. Zhang et al<sup>19</sup> determined that S100A12 was identified as STEMI more accurate than hs-TropT within the first 2 h after symptom onset. Plasma S100A12 levels were markedly elevated 30 min after hospital arrival, peaked at 1-2 h, and remained elevated for 12 h. Considering the S100A12 and TWEAK 4<sup>th</sup>-hour data, it can be interpreted that the response of serum TWEAK levels to successful post-penetrating keratoplasty glaucoma (PPKG) may be faster.

### Study Limitations

Our population included in the study was under lipid-lowering and antiplatelet therapies as part of the standard of care, whose anti-inflammatory effects may have affected the study results.

In addition, all inflammatory biomarkers and chemoattractants could not be evaluated in the study. TWEAK is not specific to cardiac disease. Other diseases, such as stroke and inflammatory diseases, are also related to plasma TWEAK levels. TWEAK levels may have low specificity, and the diagnosis of STEMI will depend on the clinical characteristics. Additional confirmatory studies with a larger population are needed. However, commercial clinical laboratory analyzers for plasma TWEAK concentrations are unavailable. The sample size needs to be bigger for reliable outcomes analysis.

### Conclusions

In the current study, plasma levels of TWEAK were increased earlier than CK-MB or hs-TnT in patients with STEMI. Compared with classical biomarkers of myocardial necrosis, TWEAK provides several advantages for early assessment. We observed a significant improvement in TWEAK balance with successful PPCI. These findings suggest that residual inflammatory risk is reduced after a successful PPCI. TWEAK is independently related to LV dysfunction. TWEAK may be useful in earlier identifying patients who are at an increased risk for LV dysfunction after STEMI.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Informed Consent

Patients and/or their families signed informed consent forms.

### Authors' Contribution

CA, AD designed this study. AÇ, AD, CA provided funding. CA and AD revised the manuscript. AD, CA, and AÇ finished the manuscript and analyzed the data. AD, CA, and AÇ collected the clinical data. AÇ contributed to the literature search.

### Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

### Ethics Approval

The present study was approved by the Medical Ethics Committee of the Tekirdağ Namık Kemal University (2022.163.09.10).

### Funding

None.

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