Association between Kelch-like ECH-associated protein-1 and GRACE risk score in non-ST elevation myocardial infarction

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Abstract. – **OBJECTIVE:** In this study, we measured the levels of Kelch-like ECH-associated protein 1 (KEAP1), which has the potential antioxidant capacity, among non-ST elevation myocardial infarction (NSTEMI) patients compared with healthy controls. We also investigated the possible association between KEAP1 levels and the GRACE score, which is a universal risk score commonly used for patients with acute myocardial infarction.

PATIENTS AND METHODS: As the patient group, 78 patients admitted to our center with a diagnosis of NSTEMI were included in the study. As the control group, 77 individuals found to have normal coronary arteries after coronary arteriography were included (155 patients in total). GRACE risk scores and left ventricular ejection fractions (LVEFs) were calculated, KEAP1 levels were measured, and the usual blood tests were performed.

RESULTS: KEAP1 levels were significantly higher among the NSTEMI patients compared to the healthy control group (671.1 ± 120.7 *vs.* 262.7 ± 105.7, *p* < 0.001). We also found a moderate positive correlation between KEAP1 levels and GRACE risk scores among patients with NSTEMI (*r* = +0.521, *p* < 0.001). Additionally, a negative correlation between KEAP1 levels and LVEFs was detected (*r* = -0.264, *p* < 0.001).

CONCLUSIONS: Elevated KEAP1 levels have the potential to be used as a risk factor for NSTEMI in terms of clinical adverse events and poor prognosis at admission.

Key Words:
    Oxidative stress, Acute coronary syndrome, KEAP1, GRACE score.

Abbreviations

KEAP1: Kelch-like ECH-associated protein 1; NSTEMI: Non-ST elevation myocardial infarction; LVEF: Left ventricular ejection fractions; ECG: Electrocardiography; HR: Heart rate; ROS: Reactive oxygen species; SIRI: Systemic inflammatory response index; GRACE: Global Registry on Acute Coronary Events; eGFR: Estimated glomerular filtration rate; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase (ALT); hc-CRP: High-sensitivity C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Introduction

Acute coronary syndromes remain the leading cause of morbidity and mortality worldwide. The main pathophysiologic mechanism underlying such syndromes is the rupture of atherosclerotic plaque in epicardial coronary arteries with the resultant acute thrombosis and myocardial necrosis. This is called classical type 1 myocardial infarction. In terms of clinical management, acute myocardial infarction is classified on the basis of the presence or absence of ST-segment elevation on electrocardiography (ECG). There has been a steady increase in the proportion of non-ST segment elevation myocardial infarctions (NSTEMI) relative to ST-segment elevation myocardial infarctions (STEMI), and currently, more than half of patients with acute coronary syndromes present with NSTEMI[1].

Oxidative stress has long been identified as an important mediator of atherosclerotic plaque formation, progression to stable coronary artery disease, and plaque rupture in acute coronary syndromes[2,3]. Low-density lipoprotein cholesterol oxidation is also recognized as possibly the first step in the development of atherosclerotic plaque[4]. Reactive oxygen species (ROS) may contribute to the development of cardiovascular diseases, including atherosclerosis and myocardial hypertrophy. One ROS is the Kelch-like protein group.

Kelch-like proteins play important roles in the antioxidant functions of cells by mediating the ubiquitination of substrate proteins. There are nearly 40 proteins in this family, all of which perform various functions in physiological conditions[5]. Kelch-like ECH-associated protein-1 (KEAP1) is predominantly found in skeletal muscles and has important functions in cellular oxidative stress[6].

Since oxidative stress is a well-known factor in the pathogenesis of atherosclerosis and plaque rupture during acute coronary syndromes and Kelch-like protein, especially KEAP1, is a novel marker for the oxidative response, we hypothesized that in patients with NSTEMI, KEAP1 levels might indicate enhanced oxidative stress levels, which may be associated with adverse events and poor prognoses. Thus, in this study, we evaluated KEAP1 levels among NSTEMI patients and compared these levels with those of healthy controls. We also investigated a possible association between KEAP1 levels and the GRACE score, which is a universal risk score commonly used to determine poor prognoses[7] in patients with acute coronary syndromes.

Patients and Methods

This study had a cross-sectional design. Patients aged between 18-65 years and presenting with acute coronary syndrome without persistent ST-segment elevation (NSTEMI) were accepted as the patient group. This group comprised 78 patients admitted to our institution's coronary intensive care unit. Gender- and age-matched controls (the control group) were also enrolled. This group comprised 77 individuals, who were found to have normal coronary arteries after coronary arteriography due to stable chest pain or abnormal treadmill tests. In total, 155 patients were enrolled. Sixty-seven patients were excluded from the study according to the exclusion criteria listed below:
1. Additional comorbidities other than diabetes and hypertension.
2. Previous cardiac history (coronary stenting, coronary bypass operation, heart failure, or valve disease).
3. High-sensitivity troponin levels 99% above the standard upper limit (control group).
4. Patients who were already undergoing anti-remodeling therapy (ACE inhibitors, ARB blockers, or mineralocorticoid receptor antagonists).

5. Patients with decompensated heart failure.
6. Failure to fully meet the diagnosis of NSTEMI (high-sensitivity troponin levels not reaching the upper reference limit or absence of typical ECG findings).
7. Presence of atherosclerotic plaque in epicardial coronary arteries (control group).
8. Presence of any disease that required chronic drug treatment (rheumatological, chronic kidney or liver disease, etc.).
9. Pregnant or breastfeeding females.
10. Diagnosis of malignancy.

Venous blood samples were collected from individuals in both groups. Blood samples were taken using sterile techniques, and the collected blood samples were centrifuged at 4,000 revolutions per minute for 10 minutes. After the centrifugation process, the sera were collected and stored in a deep freezer at -80°C. KEAP1 levels were determined using the ELISA method in both the patient and control groups (Rel Assay DC, Gaziantep, Turkey).

Left ventricular ejection fractions (LVEF) were calculated using the 2D Simpson's method according to the apical 4-chamber view with echocardiography (GE Healthcare, Chicago, IL, USA).

GRACE risk scores of all NSTEMI patients were calculated using the MDCalc application (Md Aware, New York, NY, USA) according to parameters defined previously, such as creatinine levels, Killip class, age, heart rate, systolic blood pressure, elevated cardiac markers, ST segment deviation and presence of cardiac arrest at admission (Figure 1)[8].

A flow diagram of the study is presented in Figure 2.

Statistical Analysis

Continuous variables were determined using descriptive statistics (mean ± standard deviation or median-maximum and minimum). The conformity of the continuous variables to the normal distribution was assessed using the Shapiro-Wilks test. Comparisons of two variables that were independent and did not comply with the normal distribution were assessed using the Mann-Whitney U test. Comparisons between categorical variables were performed using the Chi-square test. Correlations between continuous variables that were not normally distributed were assessed using the Spearman rho correlation coefficient. The level of statistical significance was determined as $p < 0.05$. Analyses were performed using Med-Calc® Statistical Software version 19.7.2 (MedCalc Software Ltd., Ostend, Belgium).

When to Use ⌄	Pearls/Pitfalls ⌄	Why Use ⌄
Age	Norm: 0 - 0	years
Heart rate/pulse	Norm: 60 - 100	beats/min
Systolic BP	Norm: 100 - 120	mm Hg
Creatinine	Norm: 0,7 - 1,3	mg/dL ⇆
Cardiac arrest at admission	No	Yes
ST segment deviation on EKG?	No	Yes
Abnormal cardiac enzymes	No	Yes
Killip class (signs/symptoms)	No CHF	
	Rales and/or JVD	
	Pulmonary edema	
	Cardiogenic shock	

Figure 1. GRACE ACS Risk and Mortality Calculator.

Results

In this study, 78 patients with NSTEMI and 77 healthy controls were evaluated. There were 46 male and 32 female patients in the NSTEMI group and 41 males and 36 females in the control group. There was no significant difference between the groups in terms of gender or age. In addition, the presence and ratio of comorbidities, such as diabetes and hypertension, were similar between the two groups. Demographic data, gender, systolic and diastolic blood pressure values, and heart rates (HR) at baseline were retrieved from the archive of the medical data system at our institution. The results of routine biochemistry blood parameters tested at admission were recorded, including hemogram, fasting blood glucose, kidney function tests (estimated glomerular filtration rate) (eGFR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), LDL cholesterol, high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic pep-
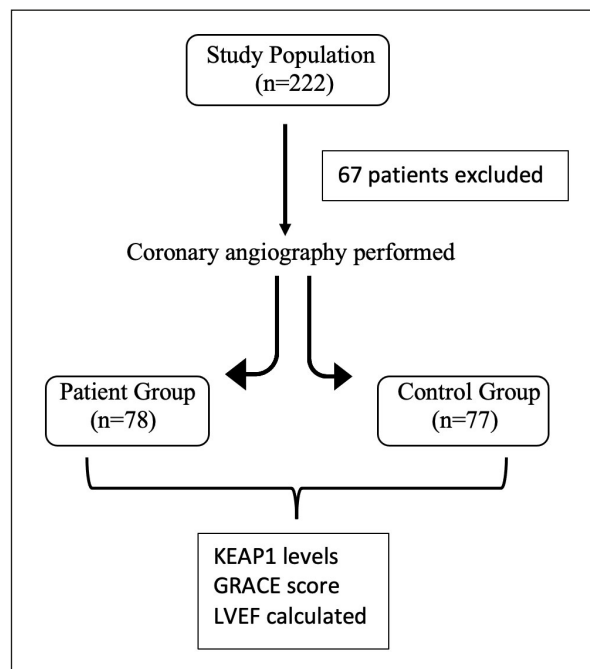

Figure 2. Flow chart describing the design of the study.

tide (NT-proBNP) and high-sensitivity cardiac troponin I. The baseline demographic data of the patients and controls are summarized in Table I.

As expected, systolic left ventricular function in the patient group was decreased due to acute myocardial infarction (the LVEF value was 54.7 ± 4.9 in the control group and 52.9 ± 5.5 in the NSTEMI patients, $p = 0.002$). Renal function, as assessed by eGFR, was also similar between the groups ($p = 0.056$). hs-CRP levels, as expected, were significantly higher among the patients with NSTEMI compared to the healthy controls due to inflammatory processes during acute myocardial infarction (9.6 ± 3.6 *vs.* 3.5 ± 2.8, $p = 0.001$). KEAP1 levels were also significantly higher among the NSTEMI patients compared to the healthy controls (671.1 ± 120.7 *vs.* 262.7 ± 105.7, $p < 0.001$). In the subgroup analysis, there were no significant correlations between KEAP1 levels and the presence or absence of comorbidities, such as diabetes, hypertension, smoking, or lung disease, among the patients with NSTEMI (Table II).

We also found a moderate positive correlation between KEAP1 levels and GRACE risk scores among the patients with NSTEMI ($r = +0.521$, $p < 0.001$) (Table III, Figure 3). Additionally, there was a slight negative correlation between KEAP1 levels and LVEF ($r = -0.264$, $p < 0.001$) (Table IV, Figure 4). However, no statistically significant correlation was observed between KEAP1 levels and hs-CRP ($p = 0.45$).

Table I. Baseline demographic and clinical data of patient and control groups.

	Patient Group (n = 78)	Control Group (n = 77)	p-value
Age (years)	59.1 ± 13.3	59.4 ± 12.2	0.45
Gender			
Male n (%)	46 (59%)	41 (53.2%)	0.47
Female n (%)	32 (41%)	36 (46.8%)	
BMI (kg/m²)	26.8 ± 2.4	25.4 ± 2.9	0.006
Diabetes n (%)	50 (64.1%)	44 (57.1%)	0.37
Hypertension n (%)	49 (62.8%)	46 (59.7)	0.69
Smoker n (%)	50 (64.1%)	44 (57.1%)	0.37
LVEF (%)	52.9 ± 5.5	54.7 ± 4.9	0.002
hsCRP (mg/L)	9.6 ± 3.6	3.5 ± 2.8	0.001
Troponin	473.2 ± 23.4	10.7 ± 8.1	< 0.001
eGFR (mL/min/1.73 m²)	95.4 ± 27.3	90.2 ± 38.6	0.056
GRACE risk score	105.8 ± 22.8	0 ± 0	< 0.001
KEAP1 levels	671.1 ± 120.7	262.7 ± 105.7	< 0.001

BMI: body mass index, LVEF: left ventricular ejection fraction, eGFR: estimated glomerular filtration rate, GRACE; Global registry on Acute Coronary Events, KEAP1: Kelch-like ECH associated protein 1.

Table II. Subgroup analysis of patients with NSTEMI showing the association between KEAP1 levels and clinical comorbidities.

	KEAP1 Levels		
	Positive	**Negative**	**p-value**
Diabetes mellitus	442.9 (119-2,566) (n = 28)	401.2 (154-2,645) (n = 50)	0.723
Hypertension	446.8 (119-2,252) (n = 29)	377.5 (154-2,645) (n = 49)	0.605
Smoking	619.2 (119-2,645) (n = 28)	319.5 (154-2,566) (n = 50)	0.161
Lung disease	413.6 (119-2,645) (n = 56)	482 (179-2,252) (n = 22)	0.267
CAD	379 (119-2,645) (n = 56)	611.7 (180-2,566) (n = 0)	0.414
KEAP1 levels	671.1 ± 120.7	262.7 ± 105.7	< 0.001

KEAP1: Kelch-like ECH associated protein-1, CAD: coronary artery disease.

Table III. Correlation between Kelch level and GRACE risk score in patients with NSTEMI.

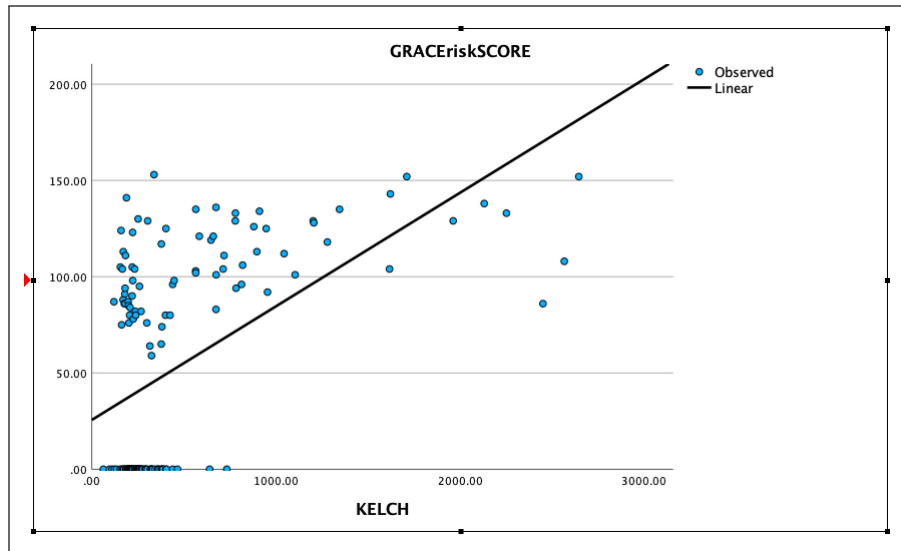|	Grace Risk Score	Kelch
Grace Risk Score	–	r = +0.521 p < 0.001
Kelch	r = +0.521 p < 0.001	–

r: Spearman Rho correlation coefficient.

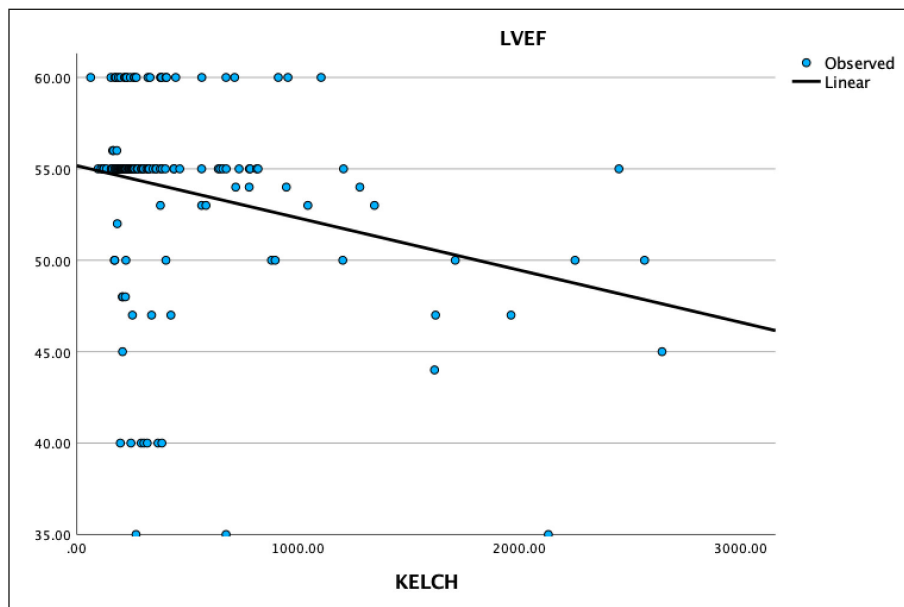**Figure 3.** Correlation-regression analysis of GRACE risk score and KELCH.

Figure 4. Correlation-regression analysis of KELCH and left ventricular ejection fraction.

Table IV. Correlation between Kelch level and left ventricular ejection fraction in patients with NSTEMI.

	LVEF	Kelch
LVEF	–	$r = -0.264$ $p < 0.001$
Kelch	$r = -0.264$ $p < 0.001$	–

r: Spearman Rho correlation coefficient, LVEF: left ventricular ejection fraction.

Discussion

Oxidative stress is a well-known factor in the pathogenesis of atherosclerosis and atherosclerotic plaque rupture associated with acute coronary syndromes. Kelch-like protein, especially KEAP1, is a novel marker for oxidative response. In this study, we hypothesized that in patients with NSTEMI, KEAP1 levels may indicate enhanced oxidative stress levels, which may be associated with adverse events and poor prognoses. Hence, we evaluated KEAP1 levels among NSTEMI patients and compared these levels with those of healthy controls. We also investigated the possible association between KEAP1 level and GRACE risk score, which is a universal risk score commonly used to determine poor prognosis in patients with acute coronary syndrome. The main finding of our study was that among patients with NSTEMI, KEAP1 levels were significantly elevated compared to those of healthy controls. Moreover, KEAP1 levels showed a significant positive correlation with GRACE risk score and a moderate negative correlation with left ventricular systolic function in NSTEMI patients.

Reactive oxygen species (ROS) may contribute to the development of cardiovascular diseases, including myocardial hypertrophy or peripheral or coronary atherosclerosis. Several studies[9] have reported increased ROS generation during arterial restenosis after angioplasty. In addition, NADPH oxidase activation, which is the main source of ROS in the vessel wall, has been observed in arteriosclerotic lesions. Therefore, cellular defenses against oxidative stress are crucial in maintaining vascular homeostasis.

To prevent irreversible tissue damage from ROS, the redox state is strictly counterbalanced by various antioxidant systems. The NRF2-KEAP1 system plays a critical role in cellular resistance to oxidative stress. Normally, NRF2 is rapidly taken up by KEAP1 in the cytoplasm, triggering ubiquitin-dependent proteolysis. However, in the presence of ROS, KEAP1 is inactivated through the modification of cysteine residues. Thus, the NRF2/KEAP1 pathway is unified as a cytoprotective system that rapidly responds to oxidative stress[10]. Since atherosclerosis is currently accepted as a chronic inflammatory disease, the role of oxidative stress in coronary artery disease is gaining more interest. The key factor in the development and progression of atherosclerotic plaque is believed to be an imbalance between oxidative stress and the antioxidant capacity of endothelial cells[11].

There is a wealth of data and evidence regarding the pathophysiologic role of the KEAP1-NRF2 pathway in various diseases, including autoimmune, respiratory, gastrointestinal, metabolic, cardiovascular, neurodegenerative, and neoplastic conditions[12].

To our knowledge, our study is the first to evaluate KEAP1 levels among patients with NSTEMI. We found a significant difference in KEAP1 levels between the NSTEMI patients and healthy controls (671.1 ± 120.7 *vs.* 262.7 ± 105.7, respectively, $p < 0.001$). Since inflammation and oxidative stress are known to play significant roles in the pathogenesis of acute coronary syndromes, this result is not surprising. As it is an important antioxidant enzyme, Leocadio et al[13] evaluated serum paraoxonase 1 (PON1) activity as a prognostic marker among patients with NSTEMI and unstable angina. In the long-term follow-up of up to five years, low PON1 paraoxonase activity was associated with a higher risk of mortality in patients with NSTEMI. In addition, in the course of the transition from stable coronary artery disease to acute coronary syndrome, the levels of oxidative stress-related biomarkers also showed active alteration.

Lubrano et al[14] evaluated changing levels of oxidative stress markers during acute coronary events. They revealed that reactive oxygen metabolites showed a progressive increase, and that antioxidant capacity showed a progressive decrease during acute coronary syndromes. This finding suggests that, in addition to being a risk and prognostic factor in acute coronary syndromes, systemic oxidative stress also progressively increases in the course of acute myocardial infarction.

Another important finding of our study was a significant correlation between GRACE scores and KEAP1 levels among patients with NSTEMI. There was also a significant difference in KEAP1 levels between the NSTEMI patients and healthy controls.

Since their first introduction into clinical practice, Global Registry on Acute Coronary Events (GRACE) scores have gained wide acceptance and are still recommended for use in patients with acute coronary syndromes in current European guidelines[15,16]. In this study, KEAP1 levels were found to be significantly higher among patients with higher GRACE scores ($p < 0.001$). This strong positive correlation suggests that KEAP1 levels may be a surrogate marker for harder clinical endpoints and increased mortality among NSTEMI patients. Thus, they could make it easier to determine which NSTEMI patients will have poor prognoses and outcomes in the short- and mid-term periods.

There are numerous studies[17-20] devoted to finding an ideal prognostic factor or a biological marker for patients with acute coronary syndromes. Han et al[17] evaluated systemic inflammatory response index (SIRI) as a prognostic factor in patients with ACS. They revealed that SIRI was a strong and independent risk factor for adverse outcomes in acute coronary syndrome patients. Similarly, their findings indicated that SIRI was able to improve the prognostic value of GRACE scores.

As for the subgroup analysis, among patients with NSTEMI, KEAP1 levels did not show any significant association when considering the presence or absence of diabetes, hypertension, lung disease, and smoking status. However, there was a negative correlation between LVEF and KEAP1 levels ($r = -0.264$, $p < 0.001$). As left ventricular systolic function deteriorated, KEAP1 levels increased significantly.

Oxidative stress is also currently accepted to have a significant role in the pathophysiology of heart failure[18,19]. Along with its pathophysiologic role, markers of oxidative stress also show a promising role in predicting the prognosis of heart failure. Gtif et al[20] developed an oxidative stress marker-driven prognostic model for heart failure patients. They revealed that the addition of total antioxidant capacity increased the prognostic accuracy of standard variables, such as LVEF and NT-proBNP. Based on these cytoprotective effects on cell metabolism, the high KEAP1 levels observed in NSTEMI patients and the correlation of this level with GRACE risk scores make our study valuable.

Limitations

The main limitation of our study was the relatively small study population. Additionally, important results could be gained by obtaining short- and mid-term clinical follow-up data showing the impact of KEAP1 on prognosis. However, since KEAP1 is a novel prognostic marker, we believe that the data we gathered still comprise a valuable contribution to the mechanism understanding, role, and prognostic significance of this marker for patients with acute coronary syndromes.

Conclusions

Among patients with NSTEMI, KEAP1 levels were significantly elevated compared to those of healthy controls. In addition, KEAP1 levels showed a significant positive correlation with GRACE risk score and a moderate negative correlation with left ventricular systolic function in NSTEMI patients. Elevated KEAP1 levels have the potential to be used as a risk factor for patients with NSTEMI in terms of clinical adverse events and poor prognosis. Future comprehensive studies with short- and mid-term clinical follow-up could reveal the potential clinical utility of KEAP1 and other oxidative stress markers for identifying patients who will have worse prognoses in terms of morbidity and mortality for acute coronary syndromes.

Informed Consent
Informed consent was acquired from all patients.

Availability of Data and Materials
The dataset analyzed to generate the findings for this study is available from the corresponding author upon reasonable request.

Ethics Approval
The database used in our study was approved by the Institutional Review Board of Gaziantep University and does contain protected health information (approval number: 2021-172).

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