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Diagnostic Comparison Of Troponin and Scube 1 Levels In Patients Diagnosed with Stemi and Nstemi In The Emergency Department

ABSTRACT
Objective: In the present study we aimed to compare the levels of troponin and SCUBE 1 markers to determine the diagnostic role of SCUBE 1 in patients with STEMI-NSTEMI.
Methods: This study was prospectively conducted with 119 patients diagnosed with acute myocardial infarction at the emergency department of DışkapıYıldırımBeyazıt Training and Research Hospital and 30 control subjects between 01.10.2016 and 01.02.2017. The relationship between age, sex, acute myocardial infarction (AMI) type, white blood cell (WBC), lymphocyte, neutrophil, neutrophil/lymphocyte ratio, red cell distribution width (RDW), thrombocyte count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), CK, CK-MB, troponin, and SCUBE 1 level was examined. Age, sex, and SCUBE 1 level were compared between the patient and control groups.
Results: The patients had a mean age of 61.5±14.5 years, and 68.9% of them were male. The patients had a SCUBE 1 level of 79.7 ng/mL and the control group 53.2 ng/ml. SCUBE 1 level was comparable between the patients with acute myocardial infarction and the control group (p>0.05). A correlation was found between SCUBE 1 level and age (p>0.05).Women in the patient group had a significantly higher SCUBE 1 level (p<0.05). There was a positive correlation between the WBC, CKMB, and troponin levels, and SCUBE 1 level in the patient group.cor No correlation was found between SCUBE 1 level and neutrophil, lymphocyte, neutrophil/lymphocyte ratio, RDW, platelet, AST, ALT, and CK levels (p>0.05). There was no significant correlation between infarction type and SCUBE 1 level (p>0.05).
Conclusions: SCUBE 1 level did not significantly rise in patients with acute myocardial infarction. As the test had lower sensitivity and specificity compared to the other markers, we believe that it is not suitable for practical use.
Keywords: SCUBE 1, Acute Myocardial Infarction, Troponin.

Acil Serviste Tanı Alan Stmı ve Nstmı Hastalarda Troponin Değerleri ve Scube 1 Değerlerinin Tanısal Karşılaştırılması

ÖZET
Amaç: Bu çalışmada ST elevasyonlu miyokard ifarktüsü (STEMI) ve ST elevasyonu olmayan miyokard ifarktüsü (NSTEMI) hastalarında troponin ve serum signal peptide-CUB-EGF domain-containing protein 1 (SCUBE 1) markerlarını karşılaştırıp erken tanıdaki SCUBE 1 değerinin tanısal önemini saptamayı amaçladık.
Gereç ve Yöntem: Çalışma 01.10.2016 ve 01.02.2017 tarihleri arasında Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi acil servisinde, akut miyokard infaktüsü tanısı konan 119 hasta ve 30 kontrol grubu ile prospektif olarak gerçekleştirildi. Hastaların yaş, cinsiyet, white blood cell (WBC), nötrofil, lenfosit, nötrofil/lenfosit, red cell distribution width (RDW), trombosit, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK) , CK-MB, troponin ve AMİ alt tipinin SCUBE 1 düzeyleri olan ilişkisi incelendi. Veriler SPSS Windows 22 versiyonunda analiz edildi.
Bulgular: Hastaların yaş ortalaması 61,5±14,5 yıl olup, %68,9'u erkekti. Hastaların SCUBE 1 düzeyi 79,7ng/mL, kontrol grubunun SCUBE 1 düzeyi 63,2 ng/ml olarak saptandı. AMI'li hastalar ve kontrol grubu arasında SCUBE 1 düzeyi benzerdi (p>0,05). SCUBE 1 düzeyi ve yaş arasında korelasyon saptanmadı (p>0,05). Hasta gruptaki kadınlarda SCUBE 1 düzeyi anlamlı olarak yüksekti (p<0,05).Hastalarda WBC, CK-MB ve troponin düzeyleri SCUBE 1 arasında pozitif yönlü korelasyon saptandı. Nötrofil, lenfosit, nötrofil/lenfosit oranı RDW, platelet, AST, ALT ve CK düzeylerinin SCUBE 1 ile arasında korelasyon saptanmadı (p>0,05). İnfaktüs tipi ve SCUBE 1 düzeyi arasında ilişki saptanmadı (p>0,05).
Sonuç: AMI'li hastalarda SCUBE 1 düzeyindeki artış anlamlı değildi. Testin spesifitesi ve sensitivitesinin diğer markerlara göre düşük olması sebebiyle, pratik kullanım için yetersiz olduğu kanısı doğmaktadır.
Anahtar Kelimeler: SCUBE 1, Akut Miyokard İnfaktüsü, Troponin

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worldwide (1). The term acute coronary syndrome (ACS) is applied to patients in whom there is a suspicion or confirmation of acute myocardial ischemia or infarction (AMI) (2). AMI is diagnosed on the basis of patient history, physical examination, electrocardiogram (ECG), and biochemical markers (3). As cardiac troponins are more sensitive and specific for myocardial injury, they are preferred over conventional markers including creatine kinase (CK), its isoenzyme CK-MB, and myoglobin. A rise in cardiac troponins indicates an irreversible myocardial injury, with elevated troponins in the presence of myocardial ischemia (chest pain, ST-segment changes) being indicative of myocardial infarction (MI) (4).

Fexex SCUBE 1 is a cell surface molecule deposited in the alpha granules of inactive thrombocytes, which is activated by thrombin and translocated to the thrombocyte surface. These molecules, which are released in the form of small and soluble particles, are incorporated into thrombus structure. SCUBE 1 deposition has been immunohistochemically detected in the subendothelial matrix of advanced atherosclerotic lesions in humans (5). Prior studies have reported that, albeit insensitive, SCUBE 1 protein is detectable within 6 hours of the onset of ischemic symptoms and may be a good marker for acute thrombotic diseases (5, 6).

Herein, we aimed to compare troponin and SCUBE 1 to determine the diagnostic role of the latter in patients with STEMI-NSTEMI.

MATERIAL AND METHODS

Our study was performed as a prospective, single-center study after its approval by Dışkapı Yıldırım Beyazıt Training and Research Hospital local ethics committee (No:34/22; Date:16.01.2017). It was conducted in compliance with the Helsinki Declaration and the guidelines for good clinical practice. It enrolled 119 patients who were diagnosed with AMI at the Emergency Department Clinic between 01.10.2016 and 01.02.2017, and 30 healthy controls. In order to reduce the effects of age and sex on the SCUBE 1 level, the control subjects were selected in an age- and sex-matched fashion. Aimed at determining the diagnostic role of SCUBE 1 protein in patients with chest pain, the present study enrolled volunteering patients with AMI aged 18 years or older, who were free of any other disease potentially elevating SCUBE 1 levels. Patients with history of end-stage renal failure, liver failure, decompensated heart failure, known or suspected inflammatory or neoplastic diseases, major surgical intervention or major trauma within last 3 months, cerebral ischemia, acute mesenteric ischemia, peripheral vascular disease, hypertension, pregnancy predisposing to thrombosis, pulmonary embolism history were excluded.

The relationships between SCUBE 1 levels and age, sex, acute myocardial infarction (AMI) type, white blood cell (WBC), lymphocyte, neutrophil, neutrophil/lymphocyte ratio, red cell distribution width (RDW), thrombocyte count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), CK, CK-MB, and troponin were examined. Age, sex, and SCUBE 1 level were compared between the patient and control groups.

SCUBE-1 was studied at 0 h in STMI patients and at 6 h in NSTEMI patients. Patients with STEMI on ECG and 6th hour troponin elevation in STEMI were included in this study. SCUBE1 patients were compared with the patients with definite diagnosis. In order to measure SCUBE 1 level, a 2-cc blood sample was taken from each subject and put into tubes containing standard gel but no anticoagulant. The samples were then centrifuged at 4000 rpm at +4 degrees for 15 minutes. A 1-cc sample was drawn from each subject's serum, put into an Eppendorf tube, and stored at -80 degrees Celsius until the day of biochemical analysis. Twenty-four hours before SCUBE 1 analysis, the Eppendorf tubes were transferred to +4 degrees Celsius, and then slowly thawed to room temperature in a period of 24 hours for the analysis of SCUBE 1 level.

Statistical Analysis: Study data were analyzed with Statistical Package for the Social Sciences (SPSS) 22.0 software package. The normality of data distribution was tested with the Kolmogorov-Smirnov test. Sensitivity and specificity assessed by ROC analysis. Parametric quantitative data were expressed as mean, standard deviation (SD); nonparametric data as the median and interquartile range (IQR); and qualitative data as the number(n) and percentage (%) of the cases. Parametric data were analyzed by Student t-test; non-parametric data by Mann Whitney U test; qualitative data by Pearson Chi-square test; correlation of qualitative data by Spearman's correlation test. A P value of less 0.05 was considered statistically significant.

RESULTS

It enrolled 119 patients who were diagnosed with AMI at the Emergency Department and 30 healthy controls. The mean age of the AMI patients and the control group were 61.5±14.5 years and 62.0±14.1 years, respectively. No significant difference was found between the two groups with respect to mean age (p>0.05).

Eighty-two (68.9%) AMI patients were men and 37 (31.1%) were women; 18 (60.0%) control subjects were men and 12 (40.0%) were women. The two groups did not differ significantly with respect to sex distribution (p>0.05).

The mean complete blood count, cardiac enzymes and other laboratory parameters of the patients are given in the table (Table 1).

The median SCUBE 1 level of the patient and control groups were 79.7ng/mL (IQR:40.8) and 63.2 ng/mL (IQR:75.4), respectively. The SCUBE 1 levels of both groups were comparable (p>0.05) (Figure 1).

Table 1. Complete blood count results of the patients

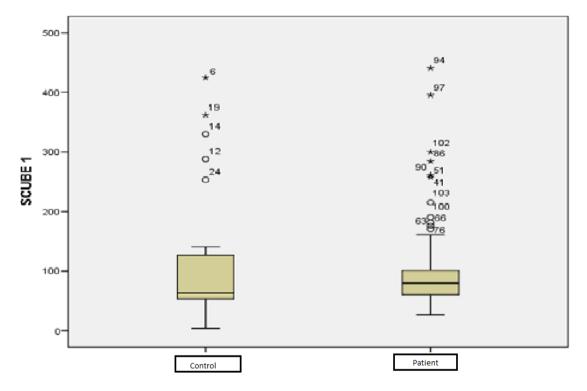| Parameters	Median (IQR)	Minimum maximum
WBC (103/mm3)	10.5 (4.6)	5.1-27.7
Neutrophil (%)	7.1 (4.6)	2.8-87.5
Lymphocyte (%)	2.4 (2.0)	0.3-28.4
Neutrophil /lymphocyte	2.5 (4.1)	0.3-52.9
RDW (%)	13.8 (2.1)	1.9- 22.0
Thrombocyte (103/mm3)	253 (84)	111-617
AST (U/L)	26 (17)	11-349
ALT (U/L)	24 (20)	4-128
CK (ng/mL)	137 (157)	17-3284
CKMB (ng/ml)	19 (20)	5-533
TROPONIn (ng/ml)	0.15 (0.82)	0-99.4

Figure 1. Graphical representation of the comparison between the SCUBE 1 levels of the study groups

In the patients included in the study, the area under the curve was 0.552, the appropriate cut-off value was 64.4 ng / ml, and the sensitivity was 69.7% and the specificity was 46.7% at this cut-off value.

There was a positive correlation between the SCUBE 1 level and WBC in AMI patients (p<0.05). There was not any significant correlation between SCUBE 1 level and lymphocyte, neutrophil, and thrombocyte counts, and neutrophil/lymphocyte ratio, and RDW level in AMI patients (p>0.05)(Table 2).

No significant correlation was found between SCUBE 1 level and AST, ALT, and CK levels in AMI patients (p>0.05). A positive correlation was present between CK-MB, troponin levels, and SCUBE-1 level in AMI patients (Table 2).

Table 2. Correlation between complete blood count parameters and scube 1 level

Parameters	r	p
WBC (103/mm3)	0.233	**0.011**
Neutrophil (%)	-0056	0.549
Lymphocyte (%)	-0.153	0.099
Neutrophil /lymphocyte	0.103	0.268
RDW (%)	0.150	0.109
Thrombocyte (103/mm3)	-0.007	0.939
AST (U/L)	-0.069	0.454
ALT (U/L)	-0.133	0.148
CK (ng/mL)	0.119	0.199
CKMB (ng/ml)	0.218	**0.017**
TROPONIn (ng/ml)	0.306	**0.001**

Spearman's correlation analysis

There was no correlation between age and SCUBE 1 level in AMI patients (p>0.05). The median SCUBE 1 level in men and women was 72.3ng/mL (IQR:40.5) and 92.0 ng/mL (IQR:40.3), respectively. Women had a significantly higher median SCUBE 1 level than men (p<0.05) (Table 3).

Table 3. Comparison of SCUBE 1 level by sex

	Men (n:82) Median (IQR)	Women (n:37) Median (IQR)	p
SCUBE 1	72.3 (40.5)	92(40.3)	0.028

Mann Whitney-U test

The median SCUBE 1 levels of the NSTEMU and STEMI patients were 89.2 ng/ml (IQR:39.4) and 72.2 ng/ml (IQR:46.4), respectively. There was not a statistically significant difference between the two groups' SCUBE 1 levels (p>0.05)(Table 4).

Table 4. Comparison of the SCUBE 1 levels of the AMI subtypes

	NSTEMI (n:69) Median (IQR)	STEMI (n:50) Median (IQR)	p
SCUBE 1	89.2 (39.4)	72.2 (46.4)	0.064

Mann Whitney-U test

DISCUSSION

The number of deaths due to coronary artery disease rank first across the globe (3). As AMI has high mortality and morbidity, it is essential to make its diagnosis and to begin its treatment as soon as possible. In practice, however, this is not always the case due to factors related to both patients and physicians (7). Tanrıkulu et al. detected that 23.7% of all patients presenting to the emergency department had cardiovascular disorders (8). Novel diagnostic methods and markers are constantly developed in an attempt to facilitate early diagnosis of ACS.

It is recognized that interactions between thrombocytes, monocytes, and endothelial cells play a role in the pathogenesis of thrombotic events leading to myocardial ischemia (9-11).

According to an experimental study by Türkmen et al., a significant rise in SCUBE 1 level is associated with thrombocyte adhesion; SCUBE 1 level significantly rises within the first two hours in pulmonary thromboembolism (PTE), and the test offers promise in PTE (12). Dai et al. reported that SCUBE 1 level significantly rose in patients with acute ischemic stroke whereas it remained normal in patients with chronic coronary artery disease, with the maximum level being attained at 6th hour. They attributed a stable SCUBE 1 level in chronic arterial diseases to a more stable plaque structure, less severe inflammation, a lesser rate of plaque rupture, and plaque coverage by thick fibrous caps (5). Although SCUBE 1 level was higher in the patient group, it showed no significant difference from that of the control group. We believe that low median CKMB and troponin levels simultaneously

studied with SCUBE 1 indicate that blood samples were taken at the early hours of AMI. Therefore, we believe that blood samples may have been taken before the SCUBE 1 level started to rise. SCUBE 1 level may have started to rise due to increased thrombocyte activity during plaque rupture, the release of SCUBE 1 containing granules within thrombocytes, and incorporation of SCUBE 1 into the thrombus structure. Former studies have reported that AMI typically affects individuals aged 55-75 years, and there is a negative, albeit statistically non-significant, the correlation between SCUBE 1 level and age (5,13-15). Ulusoy et al. did not detect any significant correlation between SCUBE 1 level and age among hemodialysis patients (16). It has been reported that SCUBE 1 level is significantly affected by various physiological factors such as increased oxidant levels, exercise, and hydration (6). In agreement with the current literature, our study did not show any significant correlation between age and SCUBE 1 level in AMI patients. We believe that the incidence of AMI increases in advanced age due to a shift of physiological processes from an anabolic state to a catabolic state, increased prevalence of atherosclerosis, and impaired vascular anatomic structures. We also of the opinion that, apart from age, the SCUBE 1 response to AMI is proportional to the affected myocardial area, the extent of necrosis, and the amount of reactive oxygen radicals.

Prior studies have shown that AMI is more common in women (13-15). Ulusoy et al. detected lower SCUBE 1 levels in female patients in a hemodialysis population and attributed that finding to an increased risk for cardiovascular disorders in men (16). Our study was in agreement with the literature data because 68.8.% of its population were male, and SCUBE 1 was significantly higher in women. We are of the opinion that women had a higher SCUBE 1 level owing to having AMI later in life, and atherosclerosis and ischemic events being more prevalent at an advanced age in women.

WBC and its subtypes are known as the classical markers of inflammation in cardiovascular disease (17). Neutrophil/lymphocyte ratio is more valuable than neutrophil, and lymphocyte counts alone and has been shown to be potentially useful for long-term mortality prediction among patients with STEMI undergoing PCI (percutaneous coronary intervention (18,19). Leukocytosis is usually associated with necrosis size in STEMI, glucocorticoid level, and coronary arterial inflammation (18,19). Although RDW is usually used for the differential diagnosis of anemia, it has been recently found to correlate to increased risk of mortality and adverse cardiovascular events among individuals with heart failure, stable coronary artery disease, ACS, AMI, and cardiovascular disease (14,20). Our study detected a positive correlation between WBC and SCUBE 1 level whereas no

significant correlation was found between SCUBE 1 level and neutrophil, lymphocyte, neutrophil/lymphocyte ratio, and RDW. We believe that extensive necrosis increases WBC count and the amount of oxygen radicals, causing a rise in SCUBE 1 level simultaneously with WBC; we also believe that other parameters would have risen in blood samples obtained at more appropriate time intervals.

Dai et al. reported that soluble plasma SCUBE 1 is obtained from activated platelets and may play a pathological role by facilitating platelet adhesion/agglutination and later thrombus formation (5). Ulusoy et al., in a study on patients undergoing dialysis, reported no relationship between SCUBE 1 level and the thrombocyte count (16). Günaydın et al. stated that they found no significant correlation between thrombocyte count and SCUBE 1 level (21). Our study detected a negative but statistically non-significant correlation between SCUBE 1 level and thrombocyte count. This might be explained by SCUBE 1 release into the bloodstream as a result of thrombocyte chemotaxis to rupture area and disruption after plaque rupture.

Our study failed to show any relationship between liver transaminases and angiographically determined cardiovascular diseases (22). Baahrs et al. reported a correlation between stenosis severity and AST, troponin level but not ALT level in AMI (23). So far, the relationship between cardiac troponin concentrations and microvascular obstruction has been reported by many studies (15,24,25). Other studies have failed to show any significant correlation between troponin and SCUBE 1 levels in patients with ischemia (5,21). No study in the literature has yet shown any correlation between SCUBE 1 level and liver enzymes, CK-MB, and CK. Our study showed that AST, ALT, and CK levels showed no correlation with SCUBE 1 level while CK-MB and troponin levels showed a positive correlation with SCUBE 1

level. Considering the pathophysiology of AMI, we believe that SCUBE 1, which takes part in thrombocyte aggregation, is released following plaque rupture, but that event rather locally affects the lesion area. Thus, we think that, although AST, ALT, and CK did not rise, SCUBE 1 level rose in proportion to thrombus aggregation and necrosis size. Additionally, the simultaneous rise of CK-MB, troponin, and SCUBE 1 over time may have caused a joint increase in those markers. The low number of patients in this study and the fact that the SCUBE 1 parameter studied is not in routine use creates potential limitations.

CONCLUSION

SCUBE 1 is not a promising cardiac marker early in the ACS process. Its lower sensitivity and specificity limit its use. Although there was no significant correlation between age and SCUBE 1 level, women had a significantly higher SCUBE 1 level. Our study demonstrated a positive correlation between SCUBE 1 level and WBC, CKMB, and troponin levels but not neutrophil, lymphocyte, neutrophil /lymphocyte ratio, RDW, platelet, AST, ALT, or CK. This may have been related to necrosis size and blood sampling time. No correlation was found between the infarction type and SCUBE 1 level.

In conclusion, no significant rise in SCUBE 1 level could be shown in patients with AMI. As the test had lower sensitivity and specificity than the other markers, we are of the opinion that it is not suitable for practical use, and multi-center studies with a larger population size about this test should be conducted.

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