The Predictive Value of Coronary Artery Disease Complexity for Adverse Clinical Events and Myocardial Injury in Patients with Acute Coronary Syndrome

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Abstract

Objective: The complexity of coronary artery disease (CAD) poses a challenge during percutaneous coronary interventions. Although it is well-defined in patients with stable ischemic heart disease, its prognostic implication and effect on myocardial injury are not demonstrated well in patients with acute coronary syndrome (ACS).

Methods: We enrolled 313 patients with ACS (149 ST-elevated myocardial infarction and 164 ACS without ST elevation) in this study. The complexity of CAD was decided using SYNTAX score (SxS). Amount of myocardial injury was determined according to high-sensitive troponin and creatine-kinase levels. Clinical outcomes were reinfarction, revascularization, and cardiac death.

Results: Thrombolysis in myocardial infarction and global registry of acute coronary events risk scores were significantly higher in patients with high SxS (p=0.007 and p<0.001, respectively). There was no significant difference in cardiac biomarkers (p=0.429 for troponin and p=0.253 for creatinine kinase myocardial band). Ejection fraction was significantly lower in patients with high SxS (p=0.006). Clinical endpoints were similar between syntax groups (p=0.402 for reinfarction and p=0.342 for cardiac death) except revascularization. Revascularization was higher in patients with high SxS (p=0.007). When patients in ST-segment elevated myocardial infarction and non–ST-segment elevated myocardial infarction/unstable angina pectoris groups were examined together, clinical endpoints were significantly higher in the high SxS group.

Conclusion: Our study demonstrated that the complexity of CAD in patients with ACS is associated with adverse clinical outcomes but not with myocardial injury.

Keywords: Acute coronary syndrome, coronary artery disease, myocardial injury

Akut Koroner Sendrom Hastalarında Koroner Arter Hastalığı Kompleksliğinin Istenmeyen Klinik Olaylar ve Miyokardiyal Hasar İçin Öngördürücü Değeri

Öz

Amaç: Koroner arter hastalığının (KAH) kompleksliği perkütan koroner girişimler sırasında zorluk teşkil etmektedir. Her ne kadar stabil koroner arter hastalığında bu kompleksliğin prognoza ve miyokardiyal hasara etkisi gösterilmiş olsa da akut koroner sendrom (AKS) hastalarında bu etki açıkça tanımlanamamıştır.

Yöntemler: Bu çalışmada retrospektif olarak 313 hasta dahil edildi (149 ST elevasyonlu miyokard infarktüsü ve 164 ST yükselmesiz AKS). KAH'nın kompleksliği Syntax skoru ile deüerlendirildi. Miyokardiyal hasar düzeyi yüksek duyarlıklı troponin ve kreatin-kinaz MB düzeylerine göre karar verildi. Klinik sonlanım noktaları re-infarktüs, revaskülarizasyon ve kardiyak ölüm olarak belirlendi.

Bulgular: TIMI ve Grace skorları Syntax skoru yüksek olan grupta anlamlı olarak yüksekti (p=0,007 ve p<0,001, sırasıyla). Gruplar arasında kardiyak biyobelirteçler açısından fark saptanmadı (troponin için p=0,429 ve CK-MB için p=0,253). Syntax skoru yüksek olan hastalarda ejeksiyon fraksiyonu anlamlı olarak düşük saptandı (p=0,006). Revaskülarizasyon dışındaki klinik sonlanım noktaları gruplar arasında benzer saptandı (re-infarktüs için p=0,402 ve kardiyak ölüm için p=0,342). Revaskülarizasyon Syntax skoru yüksek olan grupta istatistiksel olarak anlamlı bir şekilde daha yüksek saptandı (p=0,007). STEMI ve N-STEMI grupları birlikte değerlendirildiğinde klinik sonlanım noktaları Syntax skoru yüksek grupta daha sık izlendi.

Sonuç: Çalışmamızın sonucu koroner arter hastalığının kompleksliği istenmeyen klinik sonlanım noktaları ile ilişkilidir ancak çalışmamızda miyokardiyal hasarın miktarı ile ilişkisi gösterilememiştir.

Anahtar kelimeler: Akut koroner sendromlar, koroner arter hastalığı, myokardial hasar

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Acute coronary syndromes (ACS) are the most critical and catastrophic presentations of ischemic heart disease. Therefore, in-hospital and long-term risk estimation of ACS patients have gained more interest in recent years [1]. Existing data indicate that cardi-

ac biomarkers, especially cardiac troponins, directly demonstrate myocardial cell damage and are highly associated with prognosis [2].

Although several angiographic predictors for adverse outcomes after revascularization, such as SYNTAX score (SxS), have been validated in patients with stable coronary artery disease (CAD), using these predictors for patients with ACS is not universally accepted. However, the power of angiographic predictors for prediction of adverse cardiovascular events in patients with ACS is not well-defined because of conflicting results of these studies [3].

The extent of CAD defined by SxS is not the sole predictor of myocardial injury in patients with ACS, because when ACS occur, mechanisms such as augmented inflammatory status, generalized vasospasm, and enhanced thrombogenicity may extend myocardial damage beyond infarct-related artery (IRA) territory via their effects on lesions in non–infarct-related arteries. In contrary, myocardial adaptation to ischemia, which may be observed in patients with extensive CAD, may reduce myocardial damage after prolonged acute ischemic episodes, which is known as ischemic preconditioning [4]. Owing to contrary and complex mechanism during ACS, disadvantages of having a complex coronary disease may be balanced with advantages of extensive coronary disease. Therefore, although theoretically the extent and complexity of the CAD could be considered as a risk predictor in patients with ACS, this suggestion demands evidence in terms of in-hospital and long-term adverse events.

This study primarily aimed to compare the predictive value of SxS for in-hospital and 2-year major adverse cardiovascular events (MACE) in patients with ACS. Our secondary aim was to evaluate the relationship between the complexity of CAD and the extent of myocardial injury in terms of cardiac biomarkers.

Material and Methods

A total of 313 patients with ACS (149 patients with ST-segment elevated myocardial infarction [STEMI] and 164 patients without persistent STEMI or unstable angina pectoris [non-ST-segment elevated myocardial infarction (NSTEMI)/unstable angina pectoris) were enrolled. Written informed consent was obtained from patients who participated in this study. The amount of myocardial cell damage was measured according to blood creatinine kinase myocardial band (CK-MB) fraction and troponin T levels. Demanding technical issues and ethical considerations restrict the use of functional or imaging methods to determine myocardial damage in STEMI setting and in patients with hemodynamic and electrical instability. The inclusion criteria were as follows: (1) patients with a diagnosis of type 1 myocardial infarction (MI), (2) patients treated with percutaneous coronary intervention (PCI) during the index hospitalization, and (3) patients over the age of 18 years. Patients were excluded from the study if the (1) patient refused to give informant consent, (2) patient had non-obstructive CAD, or (3) patient had chronic renal failure.

SxS is a method of quantitative measurement of complexity and severity of CAD. SxS was calculated retrospectively by scoring all coronary lesions with a diameter stenosis of >50% in vessels >1.5 mm. SxS was calculated by two cardiologists using the algorithm that is available on the SxS website [5]. In the event of disagreement, a third cardiologist calculated SxS and then a final decision was made in consensus. In patients with STEMI, SxS was calculated after the recanalization of the culprit artery via a guidewire or balloon inflation. In NSTEMI patients, SxS was calculated before any coronary intervention unless the vessel was totally occluded. In case of total occlusion, SxS was calculated soon after recanalization of the culprit artery.

Myocardial reinfarction, revascularization, and cardiac death were evaluated as primary endpoints and all-cause mortality as the secondary endpoint. The endpoints were decided using data from patient files, and available patients were contacted by telephone. Patients with STEMI were divided in tertiles according to their SxS. Patients with NSTEMI were divided into three tertiles in line with the substudy of Acute Catheterization and Urgent Intervention Triage Strategy trial, which divided SYNTAX tertiles as low (SxS <7), intermediate (7 <SxS <13), and high (SxS >13) [6, 7].

Statistical analysis

Statistical analysis was made by using Statistical Packag for the Social Sciences software version 15.0 (SPSS Inc., Chicago, IL, USA). We used Pearson test for correlation, Chi-squared test, Fischer test, Student *t* test, and Mann-Whitney U test for comparison of continuous and categorical variables. Multivariate logistic regression analysis was also used for predictors of MACE. P value less than 0.05 was accepted as statistically significant.

Results

There were no significant differences between groups in terms of sex when NSTEMI/USAP patients in both groups were evaluated with regard to their SxS tertiles (p=0.468) (Table 1). Patients were older in the high SxS tertile (p=0.036). There were no statistically significant differences with respect to concomitant hypertension, diabetes, dyslipidemia, and smoking.

Table 1. Characteristics of patients with NSTEMI/USAP

Variables	SxS <8	SxS 8-13	SxS >13	p
Sex, n (%)				
Male	27 (23.7)	31 (27.2)	56 (49.1)	0.468
Female	14 (28.6)	9 (18.4)	26 (53.1)	
Age	55.59	58.18	60.76	0.036
Hypertension	23	27	46	0.347
Dyslipidemia	16	15	82	0.946
Diabetes mellitus	11	15	37	0.131
Smoking	25	16	33	0.137
Creatinine levels, mg/dL	0.95	1.11	1.07	0.488
Ejection fraction, %	53.09	48.68	45.07	0.007
TIMI score	2.65	3.03	3.36	0.007
GRACE score	102.5	121.8	127.3	<0.01

SxS: syntax score; TIMI: thrombolysis in myocardial infarction; GRACE: global registry of acute coronary events

Table 2. Characteristics of patients with STEMI

Variables	SxS <9	SxS 9-16	SxS >16	p
Sex, n (%)				
Male	24 (32)	21 (28)	30 (40)	0.922
Female	7 (28.6)	5 (26.3)	7 (36)	
Age	57.84	57.54	62.46	0.176
Hypertension	13	8	16	0.773
Dyslipidemia	8	1	5	0.65
Diabetes mellitus	8	3	7	0.394
Smoking	24	20	25	0.587
Creatinine (mg/dL)	0.88	0.9	0.96	0.440
Ejection fraction	47.23	41.50	39.57	0.008
TIMI score	3.1	3.08	3.84	0.300
GRACE score	116.32	124.24	129.54	0.009
Killip class	1.16	1.23	1.46	0.239

SxS: syntax score; TIMI: thrombolysis in myocardial infarction; GRACE: global registry of acute coronary events

Table 3. Cardiac biomarkers in patients with STEMI and NSTEMI/USAP

Variables	SxS: low	SxS: intermediate	SxS: high	p
NSTEMI/USAP				
Troponin	13.29	19.60	15.55	0.429
CK-MB	64.28	93.71	88.4	0.252
ST depression	1.1	1.3	1.2	0.213
STEMI				
Troponin	52.45	60	62.84	0.409
CK-MB	189.55	328.15	221.14	0.221
ST elevation	2.00	2.96	3.01	0.028

SxS: syntax score; NSTEMI/USAP: non–ST-segment elevated myocardial infarction/unstable angina pectoris; CK-MB: creatinine kinase myocardial band; STEMI: ST-segment elevated myocardial infarction

Table 4. Clinical endpoints for both groups respectively

Variables	SxS: low	SxS: intermediate	SxS: high	p
NSTEMI/USAP				
Reinfarction	7	12	21	0.005
Revascularization	2	6	40	0.003
Cardiac death	1	1	12	NS
MACCE	10	19	73	<0.001
STEMI				
Reinfarction	5	7	8	0.402
Revascularization	1	3	7	0.007
Cardiac death	2	3	1	0.342
MACCE	8	13	16	0.201

SxS: syntax score; NSTEMI: non–ST-segment elevated myocardial infarction; MACCE: major adverse cerebro-cardiac event; STEMI: ST-segment elevated myocardial infarction

Table 5. All patients' clinical endpoints

Variables	SxS: low	SxS: intermediate	SxS: high	p
Reinfarction	12	19	29	0.002
Revascularization	3	9	47	0.002
Cardiac death	3	4	13	0.003
MACCE	16	32	89	<0.001

SxS: syntax score; MACCE: major adverse cerebro-cardiac event

Thrombolysis in MI (TIMI) and global registry of acute coronary events (GRACE) risk scores were significantly higher in patients with high SxS (p=0.007 and p<0.001 respectively for TIMI and GRACE). There were no significant differences with respect to cardiac biomarkers (p=0.429 for troponin and p=0.253 for CK-MB). ST-segment deviation was similar between groups (p=0.213). Ejection fraction was significantly lower in patients with high SxS (p=0.006). Clinical endpoints such as reinfarction, revascularization, and MACE were significantly higher in patients with high SxS (p=0.005, p=0.003, and p<0.001, respectively) (Table 1).

In patients with STEMI, there were no statistically significant differences between SxS tertiles with respect to age, gender, and risk factors for CAD. TIMI risk score and Killip class were also similar between groups (p=0.3 for TIMI score and p=0.239 for Killip class). Ejection fraction was significantly lower in patients with high SxS (p=0.008) (Table 2).

There were no significant differences with respect to cardiac biomarkers among SxS tertiles (p=0.409 and p=0. 221 for troponin and CK-MB, respectively). ST-segment elevation was higher for patients with high SxS (p=0.028) (Table 3).

Clinical endpoints were similar between SYNTAX groups (p=0.402 for reinfarction and p=0.342 for cardiac death) except revascularization. Revascularization was higher in patients with high SxS (p=0.007) (Table 4).

When patients in STEMI and NSTEMI/USAP groups were examined together, clinical endpoints were significantly higher in the high SxS group (Table 5).

Discussion

Our study demonstrated that complexity of CAD, which was assessed by SxS, is closely associated with the clinical endpoints in patients with ACS. Although this statistically significant difference was evident only for revascularization in STEMI patients, it was significant for all clinical endpoints in patients without persistent STEMI. This finding is compatible with our findings, revealing that GRACE Score was also significantly high in the high SxS tertile group in comparison with other SxS tertiles.

GRACE risk score is a well-established and guideline-recommended risk score predicting early and post-discharge mortality in patients with ACS, especially in NSTEMI patients [8]. In our study, patients with high GRACE risk score had more complex CAD in both STEMI and NSTEMI groups. In accordance with our findings, Nayel et al. [8] also demonstrated a good correlation between the GRACE risk score and SxS in patients with NSTEMI. The relationship between TIMI

risk score and SxS was also investigated in our study; however, no significant relationship was observed. This discrepancy between GRACE and TIMI risk scores may be explained with utilization of different variables. GRACE risk score is based mainly on patients' clinical data and hemodynamic data. In contrast, TIMI risk score is based on clinical data and does not include hemodynamic variables.

As atherosclerosis is an extensive disease, most patients with ACS also have atherosclerotic plaques in territories other than IRA [9]. Existing data suggest that subclinical plaque rupture of plaques other than the culprit lesion occurs simultaneously along with IRA during ACS. Rioufol et al. [10] found 50 plaque ruptures in 24 patients with ACS by using intracoronary ultrasound. Besides, plaque rupture–generalized coronary vasospasm occurs during the acute phase of ACS, which can impede coronary flow and microcirculation [11]. When data regarding concomitant plaque rupture in non–infarct-related arteries and coronary vasospasm in ACS are considered, it is safe to assume that patients with extensive coronary disease will have poorer prognosis [12, 13]. In contrast, extensive atherosclerosis produces ischemia via endothelial dysfunction and/or disturbance in coronary flow. Previous studies revealed that ischemic preconditioning as a result of long periods of ischemia protects the myocardium from acute ischemic insult of ACS. Murry et al. [4] demonstrated that myocardial benefits of repetitious episodes of reversible ischemia result in reduced myocardial injury after prolonged ischemia. Therefore, although theoretically the extent and complexity of the CAD could be considered as a risk predictor in patients with ACS, this suggestion demands to be proved with solid evidence in terms of clinical outcomes.

After ensuring patency of IRA, the main purpose should be to aim for risk stratification and post-MI care. Previous studies strongly demonstrate that patients with more myocardial damage are more prone to adverse cardiovascular events [14]. Because of myocardial stunning during ACS, imaging techniques such as echocardiography are not conclusive to determine myocardial damage. Troponins and CK-MB are biochemical markers of myocardial cell damage and strongly related to the amount of injured myocardium. In our study, we found the complexity of CAD to be highly associated with GRACE risk score, but we could not find any association between the severity of coronary atherosclerosis and the degree of myocardial injury after ACS. Myocardial injury may be expected to be high in patients with extensive CAD owing to existing endothelial dysfunction, high thrombogenicity, and generalized vasospasm in all vessels; however, the development of myocardial adaptation to ischemia may balance the adverse effects of acute damage.

We found that ejection fraction was lower in patients with high SxSs, which indicates a more deleterious effect of ischemic insult in patients with extensive CAD owing to myocardial stunning. Van Der Schaaf et al. [3] demonstrated that multivessel disease in patients with ACS results in higher mortality than single-vessel disease. In this trial, higher mortality rates have been driven primarily by death caused by heart failure.

Palmerini et al. [15] showed that SxS is valuable in risk stratification for patients with NSTEMI. Our study also demonstrated that patients with high SxS possess more risk for coronary revascularization, reinfarction, and MACE. The effect of SxS on MACE was significant between upper tertile and intermediate-lower tertile. There were no significant differences with regard to MACE between intermediate and lower tertile. Scherff et al. [2] demonstrated the value of SxS and clinical SxS in patients undergoing primary PCI who are over the age of 75 years. In this trial, SxS accurately predicted 30-day mortality but did not predict 1-year mortality. After adding clinical variables, the predictive value of SxS was increased. We could not find any association between SxS and clinical endpoints except revascularization. As expected, coronary revascularization was higher in patients with complex CAD. Previous studies demonstrated the usefulness of SxS in risk stratification of patients with STEMI [15]. These studies are in contrast to our findings. Patients with STEMI have very different anatomical characteristics compared with patients with a stable disease, which was the object of study in the original SYNTAX trial [16]. Chronic occlusion of the vessel has high impact on SxS; however, in STEMI, chronic total occlusion of the culprit artery is not commonly expected. Coronary artery stenosis should be over 50% to calculate the SxS; however, in STEMI setting, most patients have a culprit artery with a baseline narrowing less than 50%. The SYNTAX trial included patients with left main or tree vessel CAD; therefore, mean SxS was extremely higher than that in our study, which included all-comers.

In conclusion, complexity of CAD in terms of SxS is associated with adverse outcomes in patients with NSTEMI/USAP but not in patients with STEMI. Myocardial injury assessed with cardiac biomarkers is more extensive in patients with higher SxS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University-Cerrahpaşa (July 10/2013, 18225).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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