



## Original Article

# The association of the Syntax score II with carotid intima media thickness and epicardial fat tissue<sup>☆</sup>



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## ABSTRACT

**Aim:** Syntax score II (SSII) is a highly predictive scoring system, which is used to improve individualized assessment of patients with complex coronary artery disease and facilitates clinical decision making. Surrogate markers [carotid intima-media thickness (CIMT), epicardial fat tissue (EFT)] are also used for risk assessment, but their relation with SSII is not well established.

**Method:** We enrolled 543 consecutive patients, who underwent coronary angiography for stable angina pectoris and acute coronary syndrome, in the study. SSII was calculated for each patient and the patients were divided into two groups as low SSII group and high SSII group according to their median SSII.

**Results:** The average age of the patients was 61.4 years and 75% of the patients were male. The multivariate analysis indicated that only EFT (p: 0,035), CIMT (p:0,04) and Hypertension (HT) (p: 0,014) were independently associated with high SSII.

**Discussion:** EFT and CIMT, the surrogate markers which can be simply and non-invasively determined, are of the independent predictors of high SSII. The inclusion of these parameters in the risk classification may provide additional clinical benefit.

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## 1. Introduction

Syntax score II (SSII) is a derivative of previously established Syntax score and incorporates clinical variables (age, creatinine clearance, left ventricular ejection fraction, sex, chronic obstructive pulmonary disease, and peripheral arterial disease) to the original, purely anatomic classification. SSII has shown to be a more powerful prediction tool than SS. <sup>1–3</sup> Since 2013, various reports have described alternative markers, which can be potentially used for the improvement of this scoringsystem. <sup>4–6</sup>

Carotid intima-media thickness (CIMT) is a widely used non-invasive surrogate marker for subclinical or early atherosclerosis and found to be an independent predictor for cardiovascular

events. <sup>7,8</sup> It is an easy-to-use test with negligible operator dependence. Previous studies have also demonstrated that several therapies for cardiovascular risk factors could also regress CIMT, which effect to decrease atherosclerotic process via various mechanism. Kim et al. showed thyroid hormone replacement resulted in regression of the increased CIMT, which was attributed to the improvement in the lipid profile and Mita et al showed that sitagliptins were associated with the regression of carotid atherosclerosis.

Epicardial fat tissue (EFT) is a quantitative measure of epicardial fat deposit, which is directly related with myocardium. Epicardial fat can stimulate atherosclerosis via various pro-inflammatory cytokines, and increased EFT is associated with cardiovascular risk. <sup>9,10</sup>

Most of the literature regarding surrogate markers focus on their correlation with older scoring modalities, such as Gensini or syntax scoring system. <sup>10,11</sup> In this article, we aimed to assess the relationship between SSII and possible surrogate cardiovascular risk factors, which have the potential to be included in the system.

<sup>☆</sup> Preliminary results of this study were presented at 11th International Congress of Update in Cardiology and Cardiovascular Surgery in Antalya (TR), 2015.

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## 2. Method

### 2.1. Patient characteristics

We included 586 consecutive patients, who underwent coronary angiography due to stable angina pectoris or acute coronary syndrome, in the study. All patients had a clear indication for coronary angiography such as increased levels of cardiac biomarkers, positive treadmill test or myocardial perfusion scintigraphy.

All patients were enrolled in the study after the provision of informed consent forms and the approval of Institutional Ethics Committee. Patients with severe aortic stenosis ( $n = 7$ ), history of myocardial infarction (MI) in the prior week ( $n = 10$ ), history of coronary artery bypass graft (CABG) surgery or prior percutaneous coronary intervention (PCI) ( $n = 7$ ) and those, who were unsuitable for ultrasonography ( $n = 19$ ), were excluded from the study. A total of 543 patients were included in the final analysis. The mean age of the patients was  $61.4 \pm 11.1$  years.

### 2.2. Definitions

Hypertension (HT) was defined either as history of chronic antihypertensive medication use or blood pressure  $> 140/90$  mmHg obtained in two consecutive measurements. The patients, whose fasting blood glucose was  $> 126$  mg/dL or who were on oral antibiotics/insulin medication, were accepted as patients with diabetes mellitus (DM). Chronic renal insufficiency was determined using the Glomerular filtration rate (GFR)  $< 60$  ml/min/1.73m<sup>2</sup>. GFR was calculated with the Cockcroft Gault Formula. Body mass index (BMI) value was calculated based on the height and weight of each patient.

Peripheral arterial disease (PAD) was classified as the state of having undergone angioplasty or surgery or having diagnostic lesions in Doppler ultrasound or angiography. Chronic obstructive pulmonary disease (COPD) was defined through the GOLD criteria.<sup>12</sup> Low-density lipoprotein (LDL) and high-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG), and fasting glucose were measured before coronary angiography, and chronic medications were noted.

### 2.3. Coronary angiography and Syntax score II

All patients underwent coronary angiography (Toshiba Infinix, Toshiba Japan) using the Judkins technique through femoral artery. Non-ionic contrast agent was used at a dose of 6–10 ml for each manual injection. Coronary angiograms were performed by two invasive cardiologists, who were blinded to the patient's data. Syntax score (SS) was developed to assess the complexity of coronary artery disease and the latest online version was used in the calculation of the syntax scores. All lesions with  $> 1.5$  mm segment length and  $> 50\%$  stenosis was taken into consideration in scoring. Two orthogonal views were obtained for evaluations. After the calculation of the SS score, we used a nomogram to evaluate SSII including two anatomical variables (anatomical SS and unprotected left main coronary artery disease) and six clinical variables (age, creatinine clearance, left ventricular ejection fraction, sex, COPD and PAD), which was previously described.<sup>3</sup> Two experienced cardiologists, who were blinded to the procedural data and the clinical outcome, calculated both SS and SSII. In the case of disagreement, another blinded clinician's opinion was asked for the resolution of the agreement.

### 2.4. Ultrasonography

Transthoracic Echocardiography (TTE) was performed with Vivid 7 Dimension (General Electric, Fairfield, CT, USA) machine

using a 7.5 MHz transducer probe in line with the guidelines of the American Society of Echocardiography. One cardiologist, who was also blinded to the patient data, carried out all TTE procedures.

CIMT was measured as the distance between the lumen-intima and the media-adventitia interfaces starting approximately 1 cm proximal to the bifurcation area of the common carotid artery (CCA) which was free from plaque, as previously described.<sup>13</sup> At least, three measurements were performed bilaterally and averaged. The average of the measurements obtained from both CCAs was taken as CIMT and included in the final analysis.

EFT was measured from a hypoechoic space between the outermost border of right ventricle myocardium and the visceral layer of the pericardium. The largest diameter of epicardial fat located on the right ventricular (RV) free wall was determined, as previously described.<sup>14</sup> Then, EFT was measured in the parasternal long axis view at end-diastole in three cardiac cycles. The average of three cardiac cycles was used for statistical analysis.

### 2.5. Statistical analysis

The study data was analyzed using the SPSS 20 for Mac (IBM, Armonk, NY, USA). Continuous variables were expressed with the mean  $\pm$  standard deviation or median (interquartile range) values, whereas categorical variables were presented in percentages. The Independent Student *t*-test or the Mann-Whitney *U* test was used for the comparison of continuous variables while the Chi-square test was used for the comparison of categorical variables. The Bland–Altman test and intraclass correlation coefficient (ICC) were used to evaluate interobserver and intraobserver variability for SS and SSII variables. Multivariate logistic regression analysis was performed to identify the independent predictors of high SSII. All variables that showed the significance value  $< 0.05$  on univariate analysis were included in the regression model. Variables that used to calculate SSII were not included in final analysis. Two groups were created according to the median SSII values (Low SSII group, High SSII group). Receiver–operating characteristic (ROC) analysis was used to determine the cutoff value of CIMT and EFT in the prediction of high SSII. Two-tailed *p* values  $< 0.05$  were considered as statistically significant.

## 3. Results

The final analysis was performed using the data of 543 patients and 75.7% of the study population was male. Baseline clinical, biochemical, and angiographic characteristics relative to the SSII group are shown in Table 1.

Two groups were created depending on the median SSII value (the mean SSII was found 35). As 49.9% of the patients was in the low SSII group, 50.1% was of in the high SSII group, respectively. In univariate analysis Age ( $p < 0.001$ ), Sex ( $p < 0.001$ ), HT ( $p < 0.009$ ), PAD ( $p < 0.001$ ), COPD ( $p < 0.001$ ), Glucose ( $p < 0.035$ ), GFR ( $p < 0.001$ ), TC ( $p < 0.001$ ), LDL ( $p < 0.04$ ), HDL ( $p < 0.015$ ), EFT ( $p < 0.001$ ), CIMT ( $p < 0.001$ ) and EF ( $p < 0.001$ ) were associated with high SSII.

In the multivariate analysis, EFT ( $p < 0.001$ ), CIMT ( $p < 0.001$ ) and HT ( $p < 0.001$ ) were independently associated with high SSII (Table 2). For SS and SSII values, both interobserver and intraobserver variability shows perfect agreement. The ICC values of the intra-observer variability were 0.84 and 0.82 for SS and SSII calculations. The ICC values of the inter-observer variability were 0.76 and 0.80 for SS and SSII calculations, respectively.

ROC analysis was used to detect the cutoff value of CIMT and EFT in the prediction of the high SSII to establish the optimal cutoff value to be used in clinical decision-making. CIMT value  $> 9.5$  yielded an AUC value of 0.64 (95% CI 0.59–0.68;  $P < 0.001$ ) and EFT value  $> 7$  yielded an AUC value of 0.69 (95% CI 0.62–0.72;  $P < 0.001$ ).

**Table 1**  
Baseline clinical and laboratory characteristics according to SSII groups.

Variables	Low SSII N=271	High SSII N=272	P Value
Age (years)	58,66 ± 11,34	64,14 ± 12,16	<0,001
Male (%)	85,2	66,2	<0,001
PCI (%)	45	46,7	0,7
Weight (cm)	78,75 ± 13,93	77,41 ± 14,6	0,281
Height (kg)	167 ± 10,57	166 ± 11,27	0,310
DM (%)	21,8	23,9	0,55
HT (%)	43,2	54,4	0,009
ACS (%)	16,2	22,4	0,068
PAD (%)	22,5	44,9	<0,001
COPD (%)	44,6	59,2	0,001
Smoking (%)	39,9	37,9	0,635
Glucose (mg/dl)	106(95–131)	95(71–125)	0,005
GFR (mL per min/1.73 m <sup>2</sup> )	97,8(80–122,54)	72(57–93)	<0,001
TC (mg/dl)	158(44,7–186)	174(47,76–203)	0,002
HDL (mg/dl)	40,2(13,2–37)	44,31(33–50,2)	0,01
LDL (mg/dl)	91,78(37,25–87)	85,1(55–109)	0,029
TG (mg/dl)	125,35(69,9–116)	133,8(80,25–156)	0,754
CIMT (mm)	0,83 ± 0,26	0,97 ± 0,3	<0,001
EFT (mm)	5,78 ± 2,37	7,26 ± 2,38	<0,001
EF (%)	51,93 ± 9,69	47,9 ± 10,56	<0,001
BMI (kg/m <sup>2</sup> )	28,32 ± 5,42	28,16 ± 5,6	0,848
Medications			
ACEI (%)	25,1	25,7	0,863
BB (%)	6,6	7,7	0,62
CCB (%)	8,5	9,9	0,56
ASA (%)	17,7	16,5	0,71
Statin (%)	16,2	17,6	0,66

Abbreviations: DM, diabetes mellitus; HT, hypertension; ACS, acute coronary syndrome; PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; CIMT, carotid intima-media thickness; EFT, epicardial fat thickness; EF, ejection fraction; BSA, body surface area; BMI, body mass index; ACE, angiotensin-converting enzyme; BB, beta blocker; CCB, calcium channel blocker; ASA, acetyl salicylic acid; GFR, glomerular filtration rate; SS II, SYNTAX score II.

Moreover, a CIMT value >9.5 demonstrated a sensitivity of 70% and a specificity of 54% for the prediction of SS II >35 (Fig. 1). Additionally, an EFT value >7 demonstrated a sensitivity of 66% and a specificity of 56% for the prediction of SSII >35 (Fig. 2).

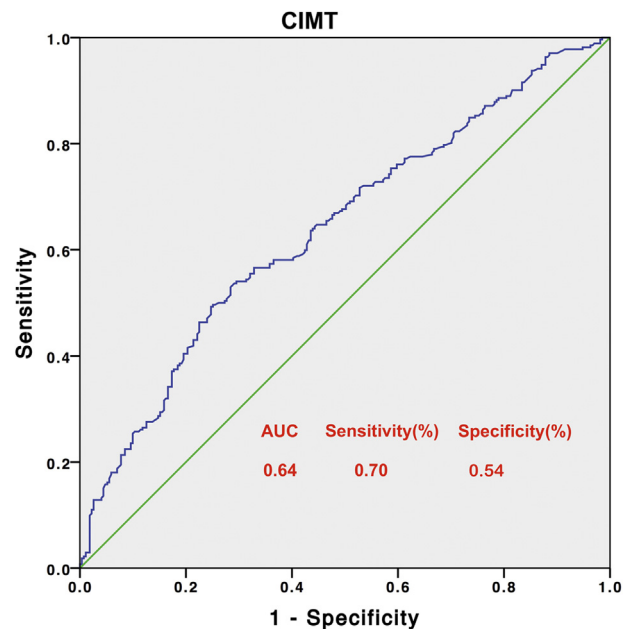
#### 4. Discussion

Various studies have showed that coronary complexity is associated with surrogate markers, which may have a role on coronary atherosclerosis pathophysiology via the paracrine or autocrine effect. However, those previous studies employed either the Gensini scoring system or older risk classification systems.<sup>15–23</sup> Also, the association between SSII and surrogate markers had not been proven, yet. Therefore, this is the first study in the literature to elucidate the association of CIMT and EFT with SSII based coronary complexity. If these parameters could be dichotomized according to the cut-off values and included in the scoring systems such as age, sex, COPD, diagnostic power would increase and providing additional clinical benefit.

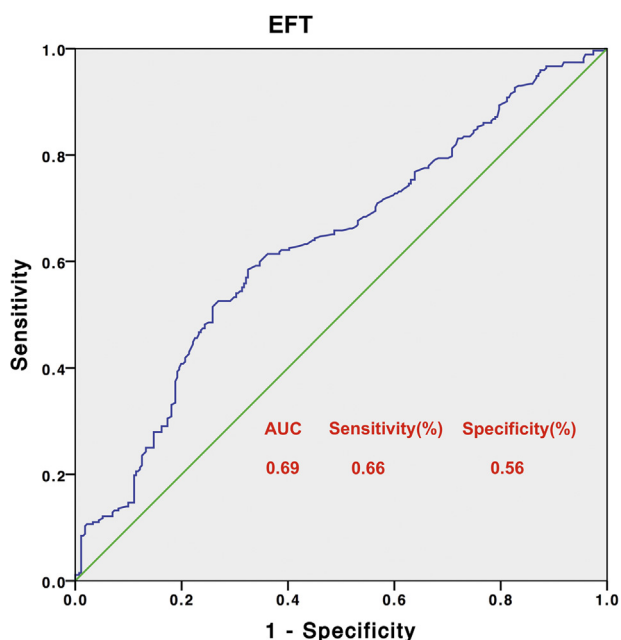
**Table 2**  
Independent Predictors of high SSII in logistic regression analysis.

Variables	Univariate OR, 95%CI	Univariate P value	Multivariate OR, 95%CI	Multivariate P value
EFT (mm)	1.29 (1.19–1.39)	<0,001	1,48(1,02–2,15)	0,035
CIMT (mm)	6,04 (3,16–11,53)	<0,001	3,4(1,16–6,2)	0,04
LDL (mg/dl)	0,995 (0,99–1)	0,029	0,96(0,93–1,03)	0,125
HDL (mg/dl)	1018(1003–1032)	0,01	0,984(0,92–1,04)	0,61
Glucose (mg/dl)	0,994(0,98–1)	0,005	0,99(0,96–1,01)	0,41
HT (%)	1,5(1,12–2,2)	0,009	1,49(1,03–4,62)	0,014

Abbreviations: EFT, epicardial fat thickness; CIMT, carotid intima-media thickness; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HT, hypertension; CI, confidence interval; OR, odds ratio.

**Fig. 1.** Receiver-operator characteristic (ROC) curve analysis for CIMT in the prediction of high SSII.

CIMT and EFT are non-invasively and reliably measured parameters that are shown to be closely related to coronary atherosclerosis.<sup>24,25</sup> These parameters can be measured with negligible operator dependence, and their reproducibility is excellent.<sup>26–28</sup> That is the reason why we hypothesized that CIMT and EFT are good candidates for further improvement of SSII. CIMT has been frequently assessed as a marker of cardiovascular risk in various studies, which yielded conflicting results. This association is very strong in the case of end point cerebrovascular event as in the study of Kitamura et al. Moreover, when the CIMT cut-off value is  $\geq 1.07$  mm, the risk for stroke dramatically increases.<sup>8</sup> However, the meta-analysis by Lorenz et al. demonstrated this correlation to become weaker when combined with the cardiovascular end-points (myocardial infarction, vascular death, stroke etc.). The aforementioned meta-analysis found that the presence of CIMT was strongly correlated with cardiovascular risk, but the progression of CIMT did not lead to increased incidence of suggested endpoints.<sup>7</sup> Many studies reported weak association between CIMT and low/high SSII for the patients receiving their first coronary angiogram; however, our study focused on a specific subset of the patients, who had a clear indication for the assessment with a first-time coronary angiogram and the CIMT results strongly correlated accordingly within each group. This fact can explain the absence of the correlation between increased risk and CIMT progression, as relatively earlier assessment might leave a wider margin for observation of progression in time. It can be concluded considering the information given below that CIMT is a



**Fig. 2.** Receiver-operator characteristic (ROC) curve analysis for EFT in the prediction of high SSII.

good candidate to be considered for the inclusion into the SSII system.

EFT has been linked with various diseases that either result in maladaptive cardiac changes (COPD, obstructive sleep apnea)<sup>29</sup> or directly harm cardiovascular structure (metabolic syndrome, diabetes mellitus, coronary artery disease). EFT is an active tissue including lymphoid aggregates and responsible for secretion of adipokines, lymphokines and other markers.<sup>9,10,30</sup> The presence of increased EFT is associated with subclinical and clinical atherosclerosis and it has been also indicated to be correlated with the extent and severity of coronary artery disease as classified using the Gensini and Syntax scoring system.<sup>9,10,30,31</sup> The data obtained in this study regarding EFT demonstrates a clear correlation with SSII based CAD complexity and is consistent with previously reported observational studies considering population and study data. Additionally, despite not being a routine clinical assessment like CIMT, EFT has higher reproductivity and provides better correlation in high-risk patients. Therefore, EFT is also a good candidate to be incorporated into the risk scoring systems for coronary artery disease complexity.

#### 4.1. Limitations

Our study has several limitations. First, the cohort of the patients involved a relatively small number of patients, and moreover, we had to exclude the patients with previous PCI and CABG from the study. On the other hand, as we included the patients with stable angina pectoris in the study and did not set a lower age limit as an inclusion criterion, the cohort was able to closely represent a population, which is cumulatively seen in the clinical practice. Second, HT definition could be considered as a limitation. Because two consecutive measurements could not enough to define HT. Optic coherence tomography or intravascular ultrasound could not be applied due to the inavailability of the required equipment.

#### 5. Conclusion

CIMT and EFT non-invasively and reliably measured parameters, which may also have a pathogenetic relationship with the

initiation and progression of coronary artery disease through biochemical processes. Both markers have greatly promising potential for incorporation into the established scoring systems for a stronger prediction and more individualized tailoring of the clinical course of a disease.

#### Conflict of interest

There is no conflict of interests.

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