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SYNTAX II SCORE AS A PREDICTOR OF MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE) IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY (CABG) DURING TREATMENT AT HAJI ADAM MALIK HOSPITAL (RSUP HAM) MEDAN

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Abstract

Background: Acute Coronary Syndrome is still the main cause of death in Indonesia with a mortality rate of 384.9 per 100,000 population. Syntax score is a risk stratification modality for patients undergoing revascularization and can predict mortality and morbidity rates.

Objective: Assessing the accuracy of Syntax II Score in predicting Major Adverse Cardiovascular Events (MACE) in patients undergoing CABG.

Methods: ACS patients who underwent CABG at Haji Adam Malik Hospital Medan in August 2019, which was observed for MACE that occurred during in-hospital treatment. The sample who experienced MACE will be assessed for Syntax scores II which are grouped into 2 groups, moderate Syntax scores (<32) and high Syntax scores (≥ 33). ROC curve analysis will get the cut-off point.

Results: From 60 subjects, 10 patients (16.7%) experienced MACE. ROC curve analysis showed that the Syntax II Score was able to predict the incidence of Total MACE with cut-off points was 29.85 (AUC=0.869, p<0.001, sensitivity 90%, specificity 68%) and cut-off point for Heart failure was 37.05 (AUC) = 0.935, p=0.004, sensitivity 75%, specificity 83.9%).

Conclusion: Syntax II Score can be used as a valid scoring system to predict the incidence of MACE in ACS patients who underwent CABG.

Introduction

Acute coronary syndromes (ACS) are a large group of acute ischemic heart disease consisting of ST-segment elevation acute myocardial infarction (STEMI) and non-ST-segment elevation acute myocardial infarction (NSTEMI) (Chan *et al.*, 2016). ACS is still the leading cause of death worldwide, with 7 million deaths every year. In addition, SKA is still a burden because it causes a high number of hospitalizations (Amsterdam *et al.*, 2014). The risk factors for coronary heart disease are broadly divided into two, namely traditional and non-traditional risk factors. Traditional risk factors are smoking, hypertension, diabetes mellitus (DM), high serum cholesterol and aging (Grover-Páez and Zavalza-Gómez, 2009). The pathophysiology of ACS syndrome is an imbalance between the supply and demand of the myocardium for oxygen due to the rupture of atheromatous plaques in the coronary arteries, followed by platelet aggregation and activation of the coagulation pathway which then forms a thrombus, resulting in partial blockage of the coronary artery lumen (Hedayati, Yadav and Khanagavi, 2018).

The process of atherosclerotic plaques formation in arteries occurs in 8 stages, including (1) endothelial barrier disruption occurs causing lipoproteins (especially LDL) to easily enter the initima layer, then there will be an accumulation of LDL which will undergo oxidation or glycation; (2) the presence of oxidative stress, including the presence of antibody modified LDL that induces the elaboration of cytokines; (3) these cytokines will increase the expression of adhesion molecules that bind leukocytes and chemoreactant molecules; (4) Macrophages will enter the arterial wall in response to chemoreactants; (5) scavenger receptors will mediate the uptake of modified lipoprotein particles and promote the formation of foam cells; (6) smooth muscle cells migrate from media layer to intima layer. This migration will cause thickening of the intima layer; (7) smooth muscle cells that have migrated to the intima layer will stimulate the extracellular matrix and cause matrix accumulation which eventually leads to the development of atherosclerotic plaques; (8) calcification occurs and fibrosis process will continue (Storm and Libby, 2011).

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

A scoring system was created to quantitatively assess the severity of coronary lesions angiographically, one of the most widely used is the Syntax Score. The Syntax score assesses the characteristics of the coronary vasculature by assessing the overall number, location, complexity, and functional impact of obstructive lesions on angiography (Sianos *et al.*, 2005). Each significant lesion (defined as 50% diameter stenosis of vessels with a minimum diameter of 1.5 mm) was visually assessed and analyzed according to the ACC/AHA lesion classification system (Thygesen *et al.*, 2018). The Syntax score is calculated using a computer program consisting of several interrelated questions. This algorithm consists of 12 main questions which are divided into 2 groups. The first 3 questions will determine the dominant system, the total number of lesions, and the coronary artery segments involved per lesion. There is no limit to the number of segments involved in each lesion. Syntax scores can be categorized into three groups, low scores 22, moderate scores 23-32, and high scores 33. It was found that the higher the Syntax score, the clinical outcome of CABG patients was better than PCI patients (Sianos *et al.*, 2005).

Farooq et al developed the Syntax II Score to predict mortality in patients with complex lesions undergoing PCI and CABG. The Syntax II Score consists of 8 variables, namely 6 clinical variables (age, gender, creatinine clearance, peripheral vascular disease, COPD, and Left Ventricular Ejection Fraction (LVEF)) and 2 anatomical variables (SS anatomical and Unprotected Left Main Coronary Artery (ULMCA)). It can perform an individualized assessment of the mortality rate of patients with Left Main CAD or Multivessel CAD undergoing either PCI or CABG (Yadav *et al.*, 2013).

Major Adverse Cardiovascular Events (MACE) is a combination of clinical events consisting of in-hospital mortality or death during treatment, cardiogenic shock, acute heart failure, and malignant arrhythmias. The study by Carnero-Alcázar stated that after 1 year of monitoring, there was no significant correlation between Syntax Score and the incidence of acute MACE in CABG patients (p=0.38), inversely there was a significant relationship with acute MACE (p=0.007) in PCI patients. A study by Manuel et al of 716 patients with Three-vessel disease or LMCA disease showed that there was a significant relationship between Syntax Score and early acute CVC (Carnero-Alcázar *et al.*, 2011).

Methods

Study Population

This research is an observational analytical study with a retrospective sampling method, conducted in August 2019. The research sample was patients with ACS and undergoing CABG at Haji Adam Malik Hospital Medan who were willing to participate in this study. Medical record data for all samples were recorded (consisting of patient history, physical examination, ECG, echocardiography, and laboratory results), then the MACE events that occurred during treatment at Haji Adam Malik Hospital in Medan will be observed. The patients with incomplete medical record data and undergoing PCI were excluded.

Skor Syntax II

The severity of coronary artery lesions will be assessed using the Syntax II Score. Syntax II scores will be assessed by two different observers. The results of the calculation of the Syntax II Score will then be grouped into 2 groups, namely the group with the moderate Syntax Score (<32) and high Syntax Score (≥ 33).

Tabel 1. Syntax II Score Algorithm

No	Parameter
1.	Dominance
2.	Number of lesions
2.	Segments involved per lesion *Lesion Characteristics*
3.	Total occlusion
	I. Number of segments involved
	II. Age of the total occlusion (>3 months)
	III. Blunt Stump
	IV. Bridging collaterals
	V. First segment beyond the occlusion visible by antegrade or retrograde filling vi. Side branch involvement
4.	Trifurcation

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Number of segments diseased
5. Bifurcation
   I. Type
   II. Angulation between the distal main vessel and the side branch <70°
6. Aorto-ostial lesion
7. Severe tortuosity
8. Length >20mm
9. Heavy calcification
10. Thrombus
11. Diffuse disease/small vessels
    Number of segments with diffuse disease/small vessels

Statistical analysis

The data were analyzed using SPSS version 25. Categorical variables are presented by frequency (n) and percentage (%). The analysis between Syntax II Score and MACE will be using the Chi square test or Fisher exact test. P-value <0.05 is said to be statistically significant.

Results

Characteristics of Research Subjects

The subjects who participated in this study were 60 patients who underwent Coronary Artery Bypass Graft (CABG) surgery. A total of 10 patients (16.7%) experienced a major adverse cardiovascular event (MACE) and 50 other patients (83.3%) did not experience MACE. The mean age of the patients in this study was 56.26 years. Based on the basic characteristics of the subjects, there were significant differences only in the characteristics of age (p value = 0.05) and ureum levels (p value = 0.05). Characteristics and baseline parameter data are presented in table 1.

Table 1. Characteristics and baseline parameters of patients undergoing CABG

Parameter	MACE		Total	P value
	Yes (n=10)	No (n=50)		
Age (years old))	61,8±4,93	55,16±4,94	56,26	0,05
Weight (kg)	64,3±6,3	62,5 ±5,66	62,85	0,57
Height (cm)	160,8 ±3,88	160,9±2,83	160,93	0,65
BP Systolic (mmHg)	125±14,33	125,2±10,54	125,16	0,41
BP Diastolic (mmHg)	74±8,43	74.2±7,58	74,16	0,65
Heart rate (x/m)	75,5±7,82	74,0±9,28	74,25	0,28
Respiratory rate (x/m)	20,8±1.68	20,08±0,56	20,2	0,06
Haemoglobin	13,16±2,05	13,63±1,62	13,55	0,45
Haematocrite	39,85±6,14	40,5±5,05	40,44	0,60
Leukocyte	10.753±2.349	8.855±2.460	9.172,15	0,81
Platelet	271.500±107.257	249.540±60.120	252.300	0,56
Ureum	41,57±20,99	30,89±13,09	32,67	0,05
Creatinine	1,59±0,44	1,17±0,38	1,24	0,55
Creatinine clearence	45,80±12,86	71,46±38,94	67,18	0,38
Sodium	139,40±7,02	138,76±4,95	138,86	0,17
Potassium	4,52±4,94	4,15±0,42	4,2±0,43	0,55
Chloride	108,92±6,60	106,34±6,74	106,7±6,73	0,67

Syntax II score in predicting MACE of patients undergoing CABG

In the analysis test, it was found that there was a statistically significant difference in each point of the Syntax II Score between MACE patients and those who did not experience MACE. There are three variables in Syntax II Score that have statistically significant mean differences, including age (p value = 0.000), creatinine clearance (p value = 0.045), and LVEF (p value = 0.005).

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

Table 2. Eight-point Risk Scoring System with Syntax II Score in patients undergoing CABG

Syntax Score	MACE		Total	P value
	Yes (n=10)	No (n=50)		
Syntax Score I	21,05±8,82	16,9±8,21	17,6±8,39	0,156
Age (years old)	61,80±4,93	55,16±4,91	56,2±5,49	<0,001
Creatinine clearence (ml/minute)	45,80±12,81	71,46±38,91	67,1±37,12	0,045
LVEF (%)	41,70±11,00	53,76±12,08	51,75±12,66	0,005
Left Main	45,5±27,61	34,8±32,20	36,60±31,55	0,333
Sex				
Man	10 (18,21%)	45 (81,81%)	55(100%)	0,578
Woman	0 (0,00%)	5 (100,00%)	5(100%)	
COPD				
Yes	6 (28,61%)	15 (71,42%)	21(100%)	0,143
No	4 (10,31%)	35 (89,72%)	39 (100%)	
PVD				
Yes	2 (40,00%)	3 (60,00%)	5 (100%)	0,190
No	8 (14,52%)	47 (85,52%)	55 (100%)	
Syntax II Score	37 (29,8 – 53)	23 (10,2 – 41)	25 (10,2 – 53)	<0,001

Bivariate analysis was used to determine which factors were predictors of MACE incidence in patients undergoing CABG, presented in table 3 below.

Table 3. Bivariate analysis of Syntax II Score in predicting MACE in patients undergoing CABG

MACE	Syntax II Score		P value
	Moderate	High	
Mortality			
Yes (n=3)	1 (2,63%)	2 (9,09%)	0,548
No (n=57)	37 (97,36%)	20 (90,90%)	
Malignant arrhythmia			
Yes (n=1)	0	1 (4,54%)	0,367
No (n=59)	38 (100 %)	21 (95,45%)	
Cardiogenic Shock			
Yes (n=2)	0	2 (9,09%)	0,131
No (n=58)	38 (100 %)	20 (90,90%)	
Heart Failure			
Yes (n=4)	0	4 (18,18%)	0,015
No (n=56)	38 (100 %)	18 (81,81%)	

Cut-off point, sensitivity, and specificity of Syntax II score in predicting MACE of patients undergoing CABG

ROC curve analysis showed that the Syntax II score was able to predict the incidence of Total MACE and MACE Heart failure with the cut-off points of 29.85 (AUC = 0.869, p<0.001) and 37.05 (AUC=0.935, p=0.004), as the picture below (Fig.1). The Syntax II score was significantly able to predict Total MACE with a sensitivity value of 90% and a specificity value of 68%, and was able to predict MACE in the form of heart failure with a sensitivity value of 75% and a specificity value of 83.9%.

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

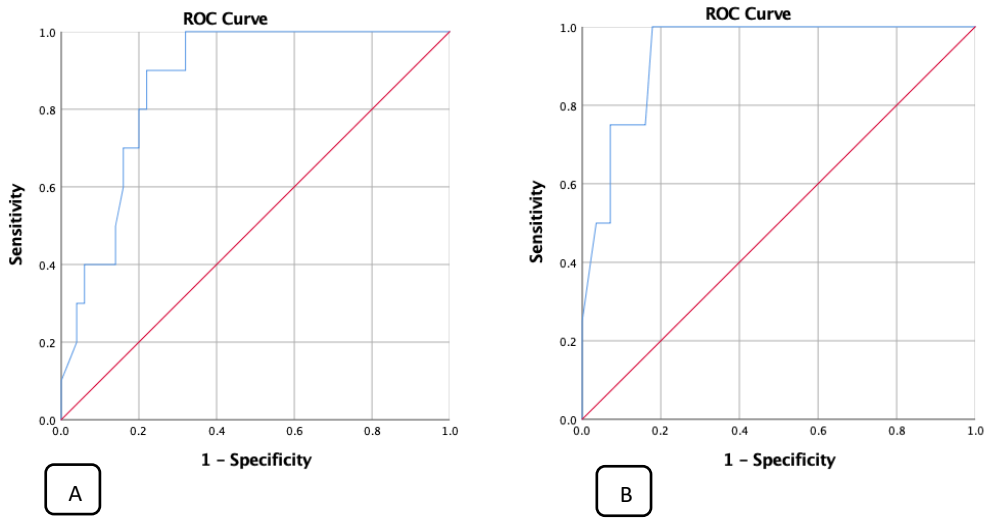

Fig.1. A) ROC Curve Syntax II Score on the incidence Total MACE; B) ROC Curve Syntax II Score on the incidence of MACE Heart Failure

Discussion

Initially, the Syntax Score was used to predict the clinical outcome of patients with stable coronary artery disease or left main disease undergoing PCI or CABG. The Syntax II score is known to be a risk stratification of patients with complex coronary artery disease where the Syntax II score is superior to the Syntax score in predicting 2-year mortality. The cohort study by Ana et al, showed the long-term prognostic value of the Syntax II Score on all-cause mortality and MACE and the Syntax II Score had a predictive accuracy of all-cause mortality that was superior to the GRACE score (The Global Registry of Acute Coronary Events) and Syntax score (Cid Alvarez *et al.*, 2019).

This study aims to determine the role of Syntax II Score (SS II) in predicting major adverse cardiovascular events (MACE) in patients after undergoing CABG, where the results are predictive values for the components "age", "creatinine clearance", "Left Ventricular Ejection Fraction or LVEF" can significantly predict the occurrence of MACE (p value = 0.000; p = 0.045; p = 0.005, respectively). This study was in line with the study by Mert et al, which showed that the variables of age, creatinine clearance, and LVEF had significant differences in low, moderate, and high Syntax II scores (p value < 0.001, p < 0.001, p < 0.001, respectively) (Cid Alvarez *et al.*, 2019).

The ROC curve analysis of this study showed that the Syntax II score was significantly able to predict the incidence of Total MACE with a cutoff value of 29.85 (AUC = 0.869, p<0.001, sensitivity 90%, specificity 68%) and MACE Heart Failure with the cut-off point was 37.05 (AUC=0.935, p=0.004, sensitivity 75%, specificity 83.9%). These results indicate that the Syntax II score is better in ruling-in the MACE Total because it has a higher sensitivity value than the specificity value, while the Syntax II score is better in ruling-out the MACE Heart Failure because it has a lower sensitivity value than its specificity. Correspondingly, the study by Windecker et al, showed that the Syntax II score with a cutoff value of 29.5 is the optimal value in predicting MACE with a sensitivity value of 82.4% and a specificity value of 65.6% (Girasis *et al.*, 2011). Likewise, the study of Mert et al, stated that the best cut-off point of the Syntax II Score in predicting MACE mortality was 45.5 (AUC = 0.78, p = <0.001, sensitivity 74%, specificity 71%) (Cid Alvarez *et al.*, 2019).

Arsalan et al showed that the incidence of intrahospital MACE in the high Syntax II score group was greater than in the moderate Syntax II score group. The study by Serruys et al showed that a high Syntax II score was more sensitive in predicting MACE in PCI patients than CABG (p = 0.001). Wang et al conducted a study of 477 STEMI patients undergoing PCI showed that SS-II was a significant independent predictor of in-hospital mortality (OR: 2,151, 95% CI: 1,281-3.613, p<0.001)(Wang *et al.*, 2016). Juskova et al's study of 1965 STEMI patients

INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

with PCI also confirmed it (in-hospital mortality was significantly higher in the high Syntax II Score group compared to the low and medium categories (85.7% vs 38.9% vs 24.4%, p<=0.001)) (Juskova *et al.*, 2020).

Similarly, our study found that patients with a high Syntax II score (SS II ≥33) experienced a higher incidence of MACE than the moderate score (SS II < 32), both in MACE mortality, malignant arrhythmias, cardiogenic shock, and heart failure, although only MACE in heart failure was shown to be significantly different. Several studies that analyzed the relationship between preoperative Syntax II scores and PoAF (Postoperative Atrial Fibrillation; malignant arrhythmias) in patients undergoing CABG stated that PoAF significantly correlated with cut-off Syntax II scores between 22.65 to 33.7 (Rencüzoğulları, 2017; Ozsin *et al.*, 2019).

Conclusion

From a total of 60 post-CABG patients at Haji Adam Malik Hospital Medan, the components of the Syntax II (SS II) score that can predict MACE are the "age", "Left Ventricular Ejection Fraction (LVEF)" and "creatinine clearance". The cut-off point for the Syntax II Score (SS II) for Total MACE was 29.85 with a sensitivity of 90% and a specificity of 68%, and the cut-off point for MACE in heart failure was 37.05 with a sensitivity of 75% and specificity of 83.9. %.

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INTERNATIONAL JOURNAL OF RESEARCH SCIENCE & MANAGEMENT

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