Impacts of Residual SYNTAX Score on The Clinical Outcomes Following Percutaneous Coronary Intervention in Chronic Coronary Syndrome Patients

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ARTICLE INFO

Keywords:
Percutaneous Coronary Intervention; Chronic Coronary Syndrome; Residual Syntax Score.

ABSTRACT

Background: The residual SYNTAX score (RSS) can be used to measure the residual stenosis severity and complexity. The prognostic role of RSS in CCS patients is still unknown. We purposed to investigate the impact of RSS on the clinical outcomes following PCI in CCS patients.

Methods: A prospective cohort study was performed. Based on the residual SYNTAX score, patients were divided into three groups: RSS 0, RSS 0 to 9.5, and RSS >9.5. The primary outcome was patient-oriented composite endpoint (POCE), including repeat revascularization, myocardial infarction, and all-cause mortality.

Results: After 1-year follow-up period, patients in RSS >9.5 group revealed the greater POCE (4.3% vs. 6.4% vs. 23.9%; p = 0.016) than others. The repeat revascularization rate also was greater in the RSS >9.5 group (0.0% vs. 6.4% vs. 19.6%; p = 0.012). However, the hospitalization due to angina rates in all groups was not significantly different (4.3% vs. 4.2% vs. 4.3%; p = 1.000). The multivariate analysis revealed that RSS >9.5 was the strong predictor for repeat revascularization during 1 year follow-up (Odds ratio [OR] = 9.605; 95% confidence interval [CI] = 1.207 - 76.458; p = 0.033).

Conclusion: The greater RSS was associated with the higher 1-year POCE and repeat revascularization rate in CCS patients. The high RSS was also the strong predictor for 1-year repeat revascularization for CCS patients.

1. Introduction

Coronary artery disease (CAD) is a chronic disease due to atherosclerotic plaque generation in the epicardial coronary arteries.¹,² Globally, CAD has been recognized as the number one cause of death.²,³ Every year, at least 470,000 Indonesian people are estimated to die due to stroke or CAD.⁴ The dynamic nature of CAD manifests as the various clinical presentation. Acute coronary syndromes (ACS) and chronic coronary syndromes (CCS) are the clinical manifestations of CAD.¹ The CCS is a new terminology that replaces “stable CAD.” It is a progressive atherosclerotic plaque accumulation process accompanied by functional changes in the epicardial coronary artery.¹ Myocardial revascularization through coronary bypass graft (CABG) or percutaneous coronary intervention (PCI) are the cornerstones of the CCS treatment strategy.¹,⁵ Complete revascularization has to be achieved during conducting PCI or CABG. However, in a particular circumstance, complete revascularization cannot be achieved by PCI because of several reasons.⁶

The severity and complexity of coronary artery lesions can be assessed using the SYNTAX score.⁷ The residual SYNTAX score (RSS) can be used to measure the residual stenosis severity and complexity by calculating the SYNTAX score from post-PCI angiography.⁸ The ACUITY trial revealed that in non-ST elevation myocardial infarction (NSTEMI), the RSS >8 could independently predict 1-year ischemic events and mortality.⁹ A study from Altekin et al. demonstrated that in ST-elevation myocardial infarction (STEMI), the higher RSS was associated with the greater ischemic cardiac events.¹⁰ The prognostic role of RSS in CCS patients is still unknown. In this prospective study, we purposed to investigate the impact of RSS on the clinical outcomes following PCI in CCS patients.

2. Methods

2.1 Study design and participants

We conducted a prospective cohort study in dr. Saiful Anwar General Hospital Malang, East Java, Indonesia in 2016. This cohort study conformed with the declaration of Helsinki principles and was recognized by the local research ethics board. Before collecting data,
patients or their family members had signed the informed consent.

In this study, we included: (1) all CCSs patient who underwent PCI, (2) aged >40 years; (3) previous history of myocardial infarction (MI) or positive exercise stress test result; (4) treated with optimal medical treatment based on guideline; and (5) good adherence to the medication. The exclusion criteria were: (1) lost to follow-up; (2) incomplete data; (3) disability to conduct physical activities; (4) myocardial infarction within two weeks following PCI procedure; and (5) psychiatric disorders. All essential data regarding clinical, angiographic, and procedural characteristics data were collected from the direct interview and medical record. Our study flowchart was displayed in figure 1

2.2 Residual SYNTAX score assessment

The RSS was determined from coronary angiogram reading by using the online calculator. Residual SYNTAX is estimated based on these following parameters: (1) the dominant vessel; (2) number of coronary lesions; (3) segment involved; (4) aorto-ostial lesion; (5) bifurcation; (6) trifurcation; (7) total occlusion; (8) lesion length; (9) tortuosity; (10) thrombus; (11); calcification and (12) diffuse disease.7,12 Two investigators conducted the RSS assessment. The suggestion from the third investigator resolved the discrepancy in the RSS assessment between the two investigators. Based on the residual SYNTAX score, patients were divided into three groups: RSS 0, RSS 0 to 9.5, and RSS >9.5.

2.3 Clinical outcomes

The primary outcome in this study was patient-oriented composite endpoint (POCE). The definition of POCE was the composite of repeat revascularization, myocardial infarction, and all-cause mortality.13 vs. 21.3% vs. 63.0%; p <0.001) from the angiographic characteristics. The baseline SYNTAX score (8.00 [7.00 - 12.00] vs. 16.00 [10.00 - 20.50] vs. 25.50 [19.13 - 32.13]; p <0.001) and residual CTO proportion (0.0% vs. 12.8% vs. 43.5%; p <0.001) were greater in RSS >9.5 group. However, SYNTAX score reduction was greater in RSS 0 to 9.5 group (8.00 [7.00 - 12.00] vs. 11.00 [7.00 - 18.00] vs. 6.50 [2.00 - 12.00]; p <0.001) (Table 1).

2.4 Statistical analysis

The IBM Statistical Package for Social Science (SPSS version 25.0) was used in processing data. The number and percentage were used to show the categorical data. Mean and standard deviation (SD) were used to describe continuous data with normal distribution. On the other hand, median and interquartile range (IQR: the 25th percentile [0.25 quantile] and the 75th percentile [0.75 quantile]) were used to show continuous data with the abnormal distribution. We used the Shapiro-Wilk test and the Kolmogorov-Smirnov test to evaluate continuous data normality. The analysis of variance (ANOVA) or Kruskal Wallis tests were used to compare continuous data with or without normal distribution, respectively. The Chi-squared test and Kolmogorov-Smirnov test were used to compare categorical data. The p-value was less than 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics

At the beginning of the study, we registered and assessed RSS in 145 CCS patients. We excluded 29 patients because of loss to follow-up (n = 14) and incomplete data (n =15). A total of 116 patients were included in the data analysis (RSS 0 [n = 23]; RSS 0 to 9.5 [n = 47], and RSS >9.5 [n = 46]). Overall, the baseline characteristics among the three groups were not significantly different. Patients in RSS >9.5 group revealed a greater proportion of three-vessel disease (8.7% vs. 59.6% vs. 76.1%; p <0.001), left main disease (0.0% vs. 0.0% vs. 13%; p = 0.003), and chronic total occlusion (CTO) (17.4% vs. 12.00%; p <0.001) vs. 63.0%; p <0.001) from the angiographic characteristics. The baseline SYNTAX score (8.00 [7.00 - 12.00] vs. 16.00 [10.00 - 20.50] vs. 25.50 [19.13 - 32.13]; p <0.001) and residual CTO proportion (0.0% vs. 12.8% vs. 43.5%; p <0.001) were greater in RSS >9.5 group. However, SYNTAX score reduction was greater in RSS 0 to 9.5 group (8.00 [7.00 - 12.00] vs. 11.00 [7.00 - 18.00] vs. 6.50 [2.00 - 12.00]; p <0.001) (Table 1).

3.2 Clinical outcomes

All patients for whom the loss of follow-up was not included in the data analysis. After 1-year follow-up period, patients in RSS >9.5
This prospective cohort study represented the real-world data in Indonesian population with no loss of follow-up. We evaluated the severity of incomplete revascularization using RSS and its effect on the clinical outcomes in CCS patients. Several essential findings were obtained from this prospective cohort study. First, the greater RSS was associated with the higher 1-year POCE and repeat revascularization obtained from this prospective cohort study. First, the greater RSS was associated with the higher 1-year POCE and repeat revascularization.

### 4. Discussion

This prospective cohort study represented the real-world group revealed the greater POCE (4.3% vs. 6.4% vs. 23.9%; p = 0.016) than others. The repeat revascularization rate also was greater in the RSS >9.5 group (0.0% vs. 6.4% vs. 19.6%; p = 0.012). However, the hospitalization due to angina rates in all groups was not significantly different (4.3% vs. 4.2% vs. 4.3%; p = 1.000). Only one patient in RSS >9.5 group passed away during the follow-up period. The summary of the outcomes is presented in Table 2. The multivariate analysis revealed that RSS >9.5 was the strong predictor for repeat revascularization during 1 year follow-up (Odds ratio [OR] = 9.605; 95% confidence interval [CI] = 1.207 - 76.458; p = 0.033).

### Table 1. Baseline characteristics

| Variables | Residual SYNTAX Score 0 (n = 23) | 0 to 9.5 (n = 47) | >9.5 (n = 46) | P-value |
|-----------|----------------------------------|------------------|--------------|---------|
| Clinical characteristics | | | | |
| Age, years | 59.00 ± 8.26 | 59.68 ± 8.65 | 59.78 ± 8.08 | 0.930 |
| Male | 16 (69.6) | 37 (78.7) | 40 (87.0) | 0.221 |
| Body weight, kg | 66.13 ± 9.06 | 68.72 ± 11.25 | 67.76 ± 9.73 | 0.611 |
| Diabetes mellitus | 5 (21.7) | 18 (38.3) | 14 (30.4) | 0.363 |
| Hypertension | 18 (78.3) | 31 (66.0) | 24 (52.2) | 0.091 |
| Dyslipidemia | 13 (56.5) | 23 (48.9) | 25 (54.3) | 0.798 |
| Active smoker | 3 (13.0) | 13 (27.7) | 18 (39.1) | 0.077 |
| Myocardial infarction | 5 (21.7) | 6 (12.8) | 12 (26.1) | 0.264 |
| PCI | 5 (21.7) | 19 (40.4) | 18 (39.1) | 0.270 |
| Family history of CAD | 4 (17.4) | 8 (17.0) | 10 (21.7) | 0.826 |
| Stroke | 1 (4.3) | 5 (10.6) | 7 (15.2) | 0.397 |
| Serum creatinine, mg/dl | 1.02 (0.83 - 1.31) | 1.03 (0.92 - 1.26) | 1.05 (0.92 - 1.18) | 0.938 |
| Creatinine clearance, ml/min | 61.15 (43.77 - 91.08) | 67.81 (46.18 - 87.70) | 70.08 (60.94 - 85.67) | 0.515 |
| RWMA | 9 (39.1) | 16 (34.0) | 23 (50.0) | 0.475 |
| Ejection fraction, % | 52.75 ± 14.44 | 53.94 ± 13.37 | 47.51 ± 17.62 | 0.326 |
| Aspirin | 23 (100.0) | 47 (100.0) | 45 (97.8) | 0.856 |
| Clopidogrel | 23 (100.0) | 47 (100.0) | 44 (95.7) | 0.449 |
| β-blocker | 15 (65.2) | 29 (61.7) | 29 (63.0) | 0.960 |
| ACEi | 6 (26.1) | 13 (27.7) | 22 (47.8) | 0.074 |
| ARB | 11 (47.8) | 17 (36.2) | 17 (37.0) | 0.609 |
| Statin | 22 (95.7) | 46 (97.9) | 45 (97.8) | 0.838 |
| Calcium channel blocker | 2 (8.7) | 13 (27.7) | 5 (10.9) | 0.052 |
| Nitrate | 18 (78.3) | 40 (85.1) | 40 (87.0) | 0.635 |

### Angiographic characteristics

| Number of diseased vessels | 0 (n = 23) | 0 to 9.5 (n = 47) | >9.5 (n = 46) | P-value |
|----------------------------|------------|------------------|--------------|---------|
| 1 vessel disease | 17 (73.9) | 7 (14.9) | 1 (2.2) | <0.001 |
| 2 vessels disease | 4 (1.4) | 12 (25.5) | 10 (21.7) | 0.003 |
| 3 vessels disease | 2 (8.7) | 28 (59.6) | 35 (76.1) | 0.003 |
| Left main disease | 0 (0.0) | 0 (0.0) | 6 (13.0) | 0.003 |
| CTO | 4 (17.4) | 10 (21.3) | 29 (63.0) | <0.001 |
| Baseline SYNTAX score | 8.00 (7.00 - 12.00) | 16.00 (10.00 - 20.50) | 25.50 (19.13 - 32.13) | <0.001 |
| Reference vessel diameter | 2.83 ± 0.39 | 2.87 ± 0.45 | 2.81 ± 0.53 | 0.805 |

### Procedural characteristics

| LAD alone revascularization | 16 (69.6) | 22 (46.8) | 23 (50.0) | 0.182 |
| RCA alone revascularization | 3 (13.0) | 7 (14.9) | 9 (19.8) | 0.740 |
| Ostial lesion revascularization | 2 (8.7) | 4 (8.3) | 8 (17.4) | 0.283 |
| In-stent restenosis treatment | 1 (4.3) | 1 (2.1) | 0 (0.0) | 0.906 |
| Number of implanted stents | 1.30 ± 0.47 | 1.59 ± 0.95 | 1.37 ± 0.80 | 0.480 |
| Type of stent (total = 156) | 0.00 (0.00 - 0.00) | 6 (12.8) | 20 (43.5) | <0.001 |

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMS = bare metal stent; CAD = coronary artery disease; CTO = chronic total occlusion; DES = drug-eluting stent; LAD = left anterior descending; PCI = percutaneous coronary intervention; RCA = right coronary artery; RWMA = regional wall motion abnormality.

Atherosclerosis formation is the key pathogenesis in CAD. It is slowly progressing for several decades. The atherosclerosis risk factors including, male sex, genetics, dyslipidemia, obesity, hypertension, diabetes mellitus, or sedentary lifestyle induce a low-grade inflammation. That low-grade inflammation has the critical role in the atherosclerosis process acceleration. In CCS, this slowly progressive...
recognized to be beneficial because it can significantly improve myocardial infarction and cardiovascular death. However, around 59% of patients have incomplete revascularization following PCI procedure.21 In the EXCELLENT registry, the high SYNTAX was a strong predictor for major adverse cardiovascular events (MACE) or mortality.22,23 The residual SYNTAX score can be calculated from post-PCI angiology to assess the complexity and severity of the residual stenotic lesion.2 It is important to stratify the patients and prepare the next revascularization strategy.

SYNTAX score has been developed to determine coronary artery lesions’ complexity or severity. The higher SYNTAX score represents a more complex and more severe coronary artery lesion. It is also correlated with bad prognosis in CAD patients receiving PCI. However, until now, the CAG is still the gold standard tool in evaluating coronary artery stenosis severity.15 In determining the vessel wall and atherosclerotic plaque morphology, other imaging modalities including, optical coherence tomography (OCT) and intravascular ultrasound (IVUS), are required.16,17 In certain conditions, myocardial ischemia occurs because the stenotic blood vessels fail to compensate the raised myocardial oxygen demand.18,19 The compensatory vasodilation is not helpful if the coronary artery lumen stenosis is greater than 80% of lumen diameter. Endothelial dysfunction, microvessel disease, or vascular spasm may increase the ischemia.20 Complete revascularization with PCI is recognized to be beneficial because it can significantly improve myocardial infarction and cardiovascular death.21 However, around 59% of patients have incomplete revascularization following PCI procedure.22

The SYNTAX score was found to be an effective tool to stratify patients at high risk of adverse outcomes following PCI.23 The SYNTAX score is a clinical and angiographic score that is calculated to assess the complexity and severity of the residual stenotic lesion.2 It is important to stratify the patients and prepare the next revascularization strategy.

Our results support the findings of the prior studies. In the EXCELLENT registry, the higher RSS (RSS >7) was associated with increased 1-year POCE and repeat revascularization. Moreover, in that study, the high RSS was recognized as the significant predictor for 1-year POCE. A study from Yan et al. revealed that incomplete revascularization (RSS >8) increased the risk of MACE, MI, cardiac mortality, all-cause mortality, repeat revascularization, and stroke. Both studies included all ACS and CCS patients. However, our current study only included CCS patients. In the ACS setting, two previous studies revealed that RSS had an excellent performance in predicting the poor prognosis. The ACUITY trial revealed that in NSTEMI, the RSS >8 could independently predict 1-year ischemic events and mortality. Altekin et al. demonstrated that the higher RSS (RSS >7) was associated with the greater ischemic cardiac events in STEMI patients. This study demonstrated that higher RSS was not associated with higher rehospitalization because of angina. This finding was not reported in the prior studies. In theory, complete revascularization (RSS 0) can provide better clinical outcomes regarding angina or rehospitalization because of angina. However, our finding failed to prove it. It could be caused by several reasons: (1) small number of study participants; (2) not long enough follow-up period; and (3) the optimal use of antianginal drugs.

Some important lessons can be drawn from our current research. First, our research provided the data about the benefit of complete revascularization (RSS 0) in reducing 1-year POCE and repeat revascularization in CCS patients who underwent PCI. Second, incomplete revascularization with high RSS was the strong predictor for 1-year repeat revascularization. However, our current research had some limitations. First, this study was a single-center study. Second, our present study included small number of patients compared to the previous studies. Third, even though we conducted multivariate analysis to overcome significant confounders, we cannot manage the other confounders that may bring the significant impact on the study results. Fourth, we did not compare the prognostic value of RSS with the novel SYNTAX-II score, which includes clinical and angiographic parameters. Because of those several drawbacks, a randomized controlled trial (RCT) with better design, larger study population, and longer follow-up is required.

5. Conclusion

Our study demonstrated that the greater RSS was associated with the higher 1-year POCE and repeat revascularization rate in CCS patients. The high RSS was the strong predictor for 1-year repeat revascularization for CCS patients. The RSS can be used to guide the level of revascularization determination and the next revascularization strategy.
We thank to Brawijaya Cardiovascular Research Center.

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