Prognostic usefulness of residual SYNTAX score combined with clinical factors for patients with acute coronary syndrome who underwent percutaneous coronary intervention from the SHINANO Registry

Daisuke Kashiwagi[1)], Soichiro Ebisawa[1)], Hisanori Yui[1)], Shusaku Maruyama[1)], Ayumu Nagae[1)], Takahiro Sakai[1)], Tamon Kato[1)], Tatsuya Saigusa[1)], Ayako Okada[1)], Hirohiko Motoki[1)], Koichiro Kuwahara[1)]

1) Shinshu University School of Medicine

Corresponding author: Daisuke Kashiwagi, MD

Department of Cardiovascular Medicine, Shinshu University School of Medicine

3-1-1 Asahi, Matsumoto-shi 390-8621, Japan

Tel: +81-263-37-3486/Fax: +81-263-37-3489

dkashiwag@shinshu-u.ac.jp

Abstract

The optimal strategy for percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) with multi-vessel disease (MVD) is still controversial. Residual anatomical features alone are not sufficient to appropriately stratify patient risk. Our aim was to assess the effectiveness of the residual Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (rSS) combined with clinical factors to predict long-term clinical outcomes in ACS patients. A total of 120 patients with ACS and MVD undergoing PCI were recruited from the SHINANO 5-year registry: a prospective, multi-center, cohort study. The rSS combined with clinical factors (Combined Score) were calculated based on the residual coronary angiogram and each clinical feature after primary PCI. The Combined Score was calculated by replacing SS with rSS using the SYNTAX score II (SSII) calculator. We grouped the Combined Score in two groups according to the cut-off value calculated by the ROC curve (the C-statistic was 0.82 [95% CI: 0.74–0.91]) for all-cause mortality. The primary endpoint was all-cause mortality during the 5-year follow-up. The Combined Score was associated with long-term mortality in Cox-regression analysis (HR 1.08, 95% CI 1.05–1.11, P<0.001). The mortality rate was significantly higher in the high-score group compared with the low-score group (5.7% vs 38.0%; P<0.001). In

ACS with MVD, the Combined Score might be considered an important tool to predict long-term mortality following PCI.

Key words

Percutaneous coronary intervention, Acute coronary syndrome, Multi-vessel coronary disease, Residual SYNTAX score

Introduction

The favorable effect of complete revascularization on multivessel coronary disease (MVD) has been established. However, the possibility of complete revascularization depends on many factors including the lesion and the systemic background of the patient. In particular, in acute coronary syndrome (ACS) cases complicated with multi-vessel disease (MVD) [1, 2], the decision for performing an invasive procedure is very difficult because the clinical background and current status of each ACS case varies.

Recent randomized clinical trials have shown preferable clinical outcomes were associated with complete revascularization performed in a primary procedure compared to culprit lesion-only percutaneous coronary intervention (PCI) [3–5]. However, there is no consensus available regarding the management of non-culprit lesions, unless the patient is in cardiogenic shock or has persistent ischemia.

The residual Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (rSS) [6, 7] was developed to quantitatively assess the degree and complexity of residual stenosis, based on the recalculation of the SYNTAX score from coronary angiography after PCI [8, 9, 11]. Furthermore, the rSS is useful in patients with ACS complicated with MVD [10].

The rSS was not considered as a clinical factor that can appropriately stratify the risk of patients undergoing PCI. Therefore, in order to account for the variability of clinical parameters affecting long-term outcomes and hence better classification of patients' risk, the SSII was developed by complementing the SS with 7 prognostic variables [12].

However, currently there is no established stratification tool combining both angiographical and clinical information, useful for decision-making strategies for

primary PCI in ACS patients with MVD.

The aim of the present study was to assess the predictive value of rSS combined with clinical variables (named the "Combined Score") in patients with ACS undergoing PCI.

Materials and methods

Patient population

This study was a subanalysis of data extracted from the SHINANO registry, a Shinshu prospective 13-site study of elderly patients with coronary artery disease undergoing PCI, at the 5-year follow-up time point. We studied a cohort of 1665 consecutive patients undergoing primary PCI for any coronary artery disease from the registry between August 2012 and July 2013. We included 728 patients with ACS (ACSs were defined according to guidelines at the time of registration [13]). We excluded 608 patients with no evidence of MVD and with previous coronary artery bypass graft (CABG), and no necessary clinical laboratory data. A total of 120 patients were available at the 5-year follow-up for analysis, and we calculated the Combined Score after primary PCI (Figure 1).

This registry was approved by the ethics committee of each hospital and the study was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant.

The decision of the primary PCI strategy and stenting were left to the discretion of the operator. Dual-antiplatelet therapy with aspirin and P2Y12 receptor inhibitor were recommended for 6–12 months. All patients were followed up routinely as outpatients or by phone.

Definitions of the Combined Score

The SS was calculated based on coronary angiogram before primary PCI, and the rSS was calculated based on the residual coronary angiogram after primary PCI by experienced interventional cardiologists at each hospital. Each coronary lesion with >50% diameter stenosis in a vessel >1.5 mm in diameter were scored using the SS algorithm [14]. The Combined Score was calculated using the PCI SYNTAX score II calculator (simply switching SS to rSS) based on the previously published nomogram [12]. Clinical factors included age, creatinine clearance, left ventricular ejection fraction (LVEF), presence of unprotected left main coronary artery disease, peripheral vascular disease (PVD), female sex, and chronic obstructive pulmonary disease (COPD). Patients were then classified into 2 groups according to the cut-off value (the Combined Score was 38.0) calculated by receiver operating characteristic (ROC) curve analysis for all-cause mortality (Figures 1, 2, 3).

Clinical Outcome

The primary endpoint was all-cause mortality at the 5-year follow-up. The secondary endpoint was major adverse cardiovascular events (MACE) defined as the composite of all-cause mortality, clinically indicated revascularization, or MI at the 5-year follow-up. These outcomes were ascertained through medical records and follow-up questionnaires sent to the patients' primary physician.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation or medians with interquartile range (IQR) and were compared using the Student's t-test or

Mann-Whitney test as appropriate. Categorical variables are expressed as frequency (percentages) and were compared using the Fisher's exact or the chi-square test. The cumulative incidences were estimated based on the Kaplan-Meier method, and differences were assessed using the log-rank test. For our analysis, we stratified patients according to our cut-off value of the Combined Score. The ROC curves were generated to assess the cut-off value and the ability of prognostic prediction in patients with ACS subjected to PCI at the 5-year follow-up. Interaction analyses were performed using the Cox proportional hazards model. Multivariate Cox analysis was used to determine the significance of the Combined Score as a predictor of all-cause mortality in forward stepwise multivariable model. The variables included were SS, rSS, SSII, the Combined Score, sex, the body mass index (BMI), previous myocardial infarction (MI), previous heart failure (HF), diabetes mellitus and hemoglobin levels. The adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated. All analyses were performed with SPSS version 26.0 software (SPSS Inc., Chicago, Ill, USA).

Results

Baseline characteristics

The mean follow-up time was 1548 days. Overall, the mean age was 72.4 ± 10.3 years and 84 (70.0%) patients were male, 35.8% had diabetes mellitus, and 63.3% presented with STEMI. Multivessel PCI was performed in 56.7% patients (n= 68), which was similar to the number performed during the one stage procedure during primary PCI (n= 24, 20.0%) and the staged procedure (n= 44, 36.7%) performed during the hospital stay. For the entire cohort, the mean rSS was 7.3 (IQR: 4.0 to 14.4) and the Combined Score

was 35.8 (IQR: 25.7 to 46.1). According to ROC analysis of the Combined Score, the cut-off value of the Combined Score was set at 38.0 and patients were divided into low (≤38.0) and high (>38) rSS groups. The comparison of the baseline characteristics of the low Combined Score group (n=70) and high score group (n=50) is shown in Table 1. The High score group patients had lower BMI, and were more likely to have a prior history of atrial fibrillation (AF) and HF. Compared to patients with the high Combined Score group, patients with low score group had a lower Killip class. With regard to angiographical parameters (Table 2), the number of pre-procedure diseases was similar for each group of the Combined Score (2.1 [±0.8] vs 2.1 [±0.9], p=0.924). The residual diseases occurred more frequently in patients within the high score group, however, there were no significant differences in residual disease location. There were also no differences in oral medical therapy including anticoagulation drug use between the two groups (Table 2).

Long-term outcomes

Figure 4 shows the comparison of long-term outcomes between the low and high Combined Scores. The incidence of all-cause mortality was significantly higher in the high score group compared to the low score group (38.0% versus 5.7%, p<0.01). The incidence of MACE was also higher in the high score group compared to the low score group (60% versus 38.6%, p=0.017) (Figure 5). Conversely, the incidence of any clinically indicated revascularizations and MI were not significantly different for the two groups (30.0% versus 16.0%, p=0.339, 2.9% versus 6.0%, p=0.241, respectively) (Figure 6, 7).

Usefulness of the novel predictive score: Combined Score

The independent predictors for all-cause mortality identified by multivariate Cox analyses are presented in Table 3. In the multivariate analysis, independent predictors of all-cause mortality were serum hemoglobin level (HR 0.75, 95% CI [0.61–0.93], p=0.008), previous myocardial infarction (HR 3.13, 95% CI [1.04–9.49], p=0.043), and the Combined Score (HR 1.08, 95% CI [1.04–1.12], P<0.001). The comparison between the traditional rSS and the Combined Score were performed by ROC analysis (Figure 3). For the prediction of all-cause mortality, the area under the curve (AUC) of the Combined Score was 0.82 (95% CI: 0.74–0.91) and was preferable over that of the rSS (AUC=0.54, 95% CI: 0.1–0.67, P < 0.001) (Figure 3). Compared with SSII, the Combined Score had a higher AUC (AUC 0.82 [0.74–0.91] vs. 0.80 [0.71–0.90], P=0.089), although the increase was not statistically significant.

Discussion

The findings of the present study can be summarized as follows: (1) combination of the anatomical residual disease, calculated by the rSS, and clinical factors, introduced by the SSII, could predict all-cause mortality and MACE during the 5-year follow-up in patients with ACS and MVD undergoing PCI; (2) our Combined Score provided superior discrimination of risk for all-cause mortality and MACE than the conventional rSS.

The decision-making strategy for the residual not-culprit lesions after primary PCI for an ACS patient complicated by MVD is still difficult. The residual burden of anatomical coronary disease can worsen clinical events in patients with ACS and MVD. Therefore,

the rSS is an effective tool for prognostic evaluation, and aiming to lower the rSS can lead to a better prognosis. In clinical practice, however, complete revascularization is often difficult to achieve for a variety of reasons. Thus, we should assess appropriate strategies by considering both residual anatomical disease and clinical features. We aimed to establish a novel Combined Score because neither the rSS nor the SS Ⅱ was sufficient to represent the prognosis of ACS patients with MVD.

Our study demonstrates that adding clinical factors to the rSS can help to identify patients with ACS and MVD who are at increased risk for long-term clinical adverse events. A sub-study of the COURAGE trial demonstrated that besides the degree of ischemia, the extent of anatomic obstruction of the coronary arteries predicted death and ACS [14]. Another study found that the rSS retains its value as a measure of the residual coronary atherosclerotic disease that may cause adverse clinical outcomes in the long-term [15]. However, the rSS is based solely on angiographic variables and cannot account for the interindividual variability associated with clinical factors that are widely acknowledged to effect long-term outcomes of PCI, such as age, renal impairment, or left ventricular dysfunction.

There are several risk stratifications for adverse outcomes in patients with ACS, of which the GRACE risk score is commonly used to stratify the risk in patients with ACS [16–18]. This score includes several clinical variables into its models; however, it lacks some important predictors of mortality, such as the LVEF, as well as classifiers of complex coronary anatomy [19–22]. The recently developed SSII has been supplemented with clinically significant prognostic variables, known to be independent predictors of mortality at 4 years in patients with stable coronary artery disease (CAD) enrolled in the SYNTAX trial [23–24]. The SSII has been indicated as a better

discriminator of risk for long-term mortality in patients with stable CAD [12]. A further study showed that the SSII independently predicts all-cause mortality and MACE during the 1-year follow-up also in patients with ACS undergoing PCI when compared to the GRACE risk score [25]. The findings showed that the SSII could also independently predict all-cause mortality and MACE during 1-year follow-up and provides superior discrimination of risk for all-cause mortality and MACE than the GRACE risk score.

From our findings, the Combined Score showed preferable prognostic accuracy in both all-cause mortality and MACE in patients with ACS and MVD undergoing PCI. Although the Combined Score provided no incremental risk stratification for long-term adverse outcomes compared with the SSII, our score was a stronger prognostic indicator of patient outcomes.

This could be explained by the fact that Combined Score included residual anatomical coronary diseases unlike the SSII. The burden of anatomic coronary atherosclerosis, either obstructive or nonobstructive, is likely to be associated with more subclinical atherosclerotic lesions that may rupture and cause adverse clinical events [26, 27]. To predict the prognosis of patients with ACS, it is necessary to assess not only clinical factors, but also residual anatomical lesions.

In our study, the Combined Score simply substituted SS with rSS using on the SSII calculator (Figure 2). As described in Table 2, overall, the rSS was lower than the SS (7.3 [IQR: 4.0 to 14.4] versus 18.8 [IQR: 12.6 to 24.0]). Thus, we might consider whether it was better to substitute rSS to SS as the same points. It might be better to divide the rSS to new distribution and recalculate according to new formula. However, the Combined Score formula defined in this study was a simple and convenient tool

because it could be easily calculated using the novel SSII calculator.

Although in this study, the described the usefulness of Combined Score to predict long-term mortality compared with rSS, in clinical practice, individual operators should determine whether performing complete revascularization or not based on clinical background. This, an assessment tool based on 'Combined Score' for the ACS patient with MVD may be required.

In current trend of multivessel intervention, the majority of studies suggesting the complete revascularization for ACS patients [3–5, 28]. However, complete revascularization is sometimes not possible due to the specific background factors of each patient. Seeking an appropriate therapeutic goal using a logical approach for each patient is important. The Combined Score may help to decide the best management strategies to improve prognosis of patients with ACS and MVD after PCI.

Limitations

Our study has several additional important limitations. First, this study was a retrospective observational and non-randomized sub-analysis of a prospective study, and thus presents inherent limitations and bias. Second, interpretation of angiograms and assessment of the SS and rSS was not determined by a core laboratory; although each interventional cardiologist was experienced and well trained to calculate the score. Third, the strategy of revascularization after primary-PCI was dependent on each physician's discretion, consequently, it was not possible define a standard approach to patients with ACS and MVD. In fact, some patients have been revascularized for residual coronary disease after enrollment in this study. But there were no significant differences in revascularizations across Combined Scores for each group during the

follow-up period. Fourth, we did not collect data on the functional assessment of coronary stenosis. Finally, our study lacked a surgical arm, although the SS was developed to determine whether the PCI was appropriate over CABG in complex lesions.

Conclusion

In the present study, we demonstrate a clinically relevant superiority of combining the residual SYNTAX score and clinical factors when compared to the anatomical residual SYNTAX score in risk stratification of patients with ACS and MVD undergoing PCI. Our data suggest that combining residual SYNTAX score and clinical factors might be an important tool to predict long-term mortality following PCI in patients with ACS and MVD.

Conflicts of interest

The authors report no financial relationships or conflict of interest regarding the content herein.

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Figure legends

Figure 1. Patient flow chart

Figure 2. Formula of the Combined Score.

Figure 3. ROC curve for rSS with clinical factors, rSS and SS Ⅱ in predicting 5-year all-cause mortality

Figure 4. Kaplan-Meier survival curves at the 5-year follow-up for freedom from all-cause mortality

Figure 5. Kaplan-Meier survival curves at the 5-year follow-up for freedom MACE

Figure 6. Kaplan-Meier survival curves at the 5-year follow-up for freedom any revascularization

Figure 7. Kaplan-Meier survival curves at the 5-year follow-up for freedom MI