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Validation of residual SYNTAX score with second-generation drug-eluting stents: one-year results from the prospective multicentre SEEDS study

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KEYWORDS

- drug-eluting stent
- everolimus
- long lesion
- multivessel disease
- residual SYNTAX score
- small vessel

Abstract

Aims: The SYNTAX score has been proposed as a valuable tool to characterise coronary anatomy prospectively based on its complexity. This study evaluated the prognostic value on adverse outcomes of the residual SYNTAX score (rSS) in patients with complex lesions treated with an everolimus-eluting stent (EES).

Methods and results: One thousand eight hundred and fifty-one patients with small vessel (reference diameter <2.75 mm), long lesion (length >25 mm), or multivessel (>2 target vessels) disease who underwent percutaneous coronary intervention (PCI) with EES in the prospective SEEDS (A Registry To Evaluate Safety And Effectiveness Of Everolimus Drug Eluting Stent For Coronary Revascularization) trial were categorised into low (<6), mid (>6-<12) and high (>12) baseline SYNTAX score (bSS) groups, and into low (=0), mid (>0-<5) and high (>5) rSS groups. Mean bSS and rSS were 10.87±7.26 and 2.18±3.97, respectively; 64% of patients had complete revascularisation (rSS=0). At 12 months the primary outcome of ischaemia-driven target vessel failure (TVF, composite of cardiac death, target vessel myocardial infarction and ischaemia-driven target vessel revascularisation) was significantly higher in the high bSS and rSS groups than in the respective lower groups (p<0.01 for both). In multivariable analysis, rSS was an independent predictor of TVF (hazard ratio: 1.403, 95% confidence interval: 1.081 to 1.820, p=0.01).

Conclusions: Twelve-month TVF was significantly higher in the highest rSS group; rSS with a cut-off of 5 might therefore allow the risk stratification of patients with complex lesions treated with a second-generation drug-eluting stent (ClinicalTrials.gov identifier: NCT 01157455).

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Abbreviations

ARC	Academic Research Consortium
bSS	baseline SYNTAX score
CABG	coronary artery bypass graft
CI	confidence interval
EES	everolimus-eluting stent
MI	myocardial infarction
PCI	percutaneous coronary intervention
rSS	residual SYNTAX score
SS	SYNTAX score
ST	stent thrombosis
TVF	target vessel failure
TVMI	target vessel myocardial infarction
TVR	target vessel revascularisation
VIF	variance inflation factor

Introduction

The SYNTAX score (SS) has been examined as an angiographic tool to grade complexity of coronary lesions based on their location and characteristics[1]. Baseline SS (bSS), a surrogate marker of disease burden before revascularisation, has demonstrated value in the treatment selection for patients with complex coronary lesions and the prediction of clinical outcomes after percutaneous coronary intervention (PCI)[2,3]. Residual SS (rSS), recently proposed as an index of completeness of revascularisation after PCI, has additionally been validated as an independent predictor for adverse events[4-6]. However, studies examining the impact of rSS were primarily performed using first-generation drug-eluting stents (DES, namely paclitaxel- or sirolimus-eluting stents) while the use of second-generation DES has been more common in recent years.

Patients with lesions with complex anatomic characteristics (lesions in small vessels, long lesions, and multivessel disease), who experience worse clinical outcomes after PCI[7-9], are very common in "real-world" practice, probably more so in China than in the West[10]. We therefore investigated the prognostic value of SS, particularly rSS, in Chinese patients with complex anatomic lesions treated with an everolimus-eluting stent (EES), a second-generation DES.

Methods

STUDY PROTOCOL, POPULATION AND PROCEDURE

The SEEDS was a prospective, multicentre, open-label registry trial that complied with the Declaration of Helsinki and whose protocol was approved by the institutional ethics committee at each participating site. From June 2010 to December, 2011, 1,900 eligible patients treated with EES (XIENCE V; Abbott Vascular, Santa Clara, CA, USA) were enrolled in 45 sites in mainland China, two in Taiwan and one in Macao. All patients signed a written informed consent. Inclusion criteria were: i) patients aged 18 to 75 years old with symptomatic ischaemic heart disease and/or objective evidence of myocardial ischaemia; and ii) by visual estimation, target vessel diameter <2.75 mm (small vessel disease), target lesion length >25 mm (long lesion), or number of target vessels >2 and at least one target lesion with >70% diameter stenosis in one epicardial target vessel (multivessel disease). Patients were assigned to each anatomic group based on the presence or absence of these anatomic characteristics, and therefore patients could belong to multiple groups. For example, if a patient's lesion length was >25 mm and RVD <2.75 mm, this patient was assigned to both the long lesion and the small vessel groups. Exclusion criteria were: i) acute myocardial infarction (MI) within a week; ii) congenital heart disease, severe valve dysfunction, bypass graft lesions, severe heart failure (NYHA ≥III level) or left ventricular ejection fraction ≤30%; iii) previous stent implantation within one year; iv) renal dysfunction (serum creatinine >2.0 mg/dl); v) bleeding disorder contraindicating antiplatelet and/or anticoagulant therapy; vi) hypersensitivity or allergy to drugs and devices related to the PCI procedure; vii) illness limiting life expectancy; viii) participation in other clinical trials; ix) heart transplant; and x) incapacity to complete the study.

All eligible patients underwent PCI with EES available at 2.25-4.0 mm in diameter and 8-28 mm in length. PCI procedures were completed in accordance with the established standard of care at each site, although predilatation of the target lesion was preferred. Aspirin 300 mg was given orally within 24 hours before the procedure. Clopidogrel was given at a dose of 300 mg six hours before or 75 mg/day three days before the procedure. After the procedure, dual antiplatelet therapy (aspirin 100 mg/day indefinitely and clopidogrel 75 mg/day for at least 12 months) was recommended.

ENDPOINTS AND DEFINITIONS

Clinical follow-up was scheduled at 1, 6, 12 and 24 months via clinical visit or phone contact. The primary endpoint was ischaemia-driven target vessel failure (TVF), defined as the composite of cardiac death, target vessel myocardial infarction (TVMI), and ischaemia-driven target vessel revascularisation (TVR), at 12 months post procedure. Secondary endpoints included: i) TVF at 1, 6 and 24 months; ii) each component of TVF at 1, 6, 12 and 24 months; and iii) Academic Research Consortium (ARC) defined definite/probable stent thrombosis (ST)[11]. Device success was defined as the attainment of <50% residual stenosis of the target lesion using only the assigned device. Lesion success was defined as the attainment of <30% residual stenosis, TIMI 3 flow, and no residual dissection and thrombosis of the target lesion using any percutaneous method. Clinical success was defined as attainment of lesion success in all target lesions and no in-hospital major adverse cardiac event. All major adverse events were adjudicated by an independent clinical events committee.

SYNTAX SCORE ASSESSMENT

The SS, bSS and rSS were assessed visually by three experienced imaging analysts from an independent core laboratory (CCRF, Beijing, China). Each lesion with >50% diameter stenosis in vessels ≥1.5 mm in diameter was scored using the SS algorithm described previously[1]. The rSS was calculated based on the remaining obstructive coronary disease after PCI.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±SD and were compared using the Student's t-test or the Mann-Whitney test depending on

data distribution. Categorical variables are presented as frequencies and were compared using the chi-square or Fisher's exact test. Time-to-event variables were analysed using Kaplan-Meier methodology, and compared using the log-rank test and Cox proportional hazards regression. Multivariable analyses of covariates associated with TVF were conducted with a Cox regression model using a stepwise selection method, and a variance inflation factor (VIF) was used to detect collinearity. Two separate multivariable models were constructed because of the high correlation between bSS and rSS. The bSS was stratified into low (<6), mid (>6-<12), and high (>12) tertiles. Bootstrap methodology[12] was used to evaluate different rSS thresholds (rSS>4, >5, >6 or >8) for the prediction of one-year TVF among patients without complete revascularisation. For each bootstrap run, 80% of the total population was sampled; a total of 1,000 bootstrap runs was performed to assess the performance of each rSS cut-off point. Comparison between bSS and rSS (when added to baseline covariates) was performed using the likelihood ratio test. All analyses were conducted using SAS system software, version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

PATIENT DEMOGRAPHICS, LESION CHARACTERISTICS AND PROCEDURAL RESULTS

Among the 1,900 patients with coronary small vessel, long lesion or multivessel disease who were enrolled and implanted with EES in the SEEDS study, 1,851 patients **(Table 1)** had a residual SYNTAX score calculated (49 patients lacked bSS or rSS for technical reasons). As shown in **Table 2**, among the enrolled, 1,065, 1,291 and 708 patients had small vessel, long lesion and multivessel disease, respectively. Patients had a mean age of 60 years, 27% were diabetic and 84% presented with unstable angina. After PCI **(Table 2)**, mean diameter stenosis was reduced from 69.60±15.57% to 13.30±8.26%. Device and clinical success rates were 99.95% and 96.76%, respectively. Mean bSS was 10.87±7.26 before PCI, ranging from 1 to 44.5 with a median of 9. Mean rSS following PCI was 2.18±3.97, ranging from 0 to 29.5 with a median of 0. Complete revascularisation (rSS=0) was achieved in 64% of patients.

Patients were stratified into low, mid and high tertile groups based on bSS (≤6, >6-≤12, and >12, respectively). In bootstrap analyses, the threshold of rSS >5 among incomplete revascularisation patients was the most predictive for one-year TVF, with the highest mean hazard ratio (HR) of 1.53±0.21 (HR of rSS threshold >4, >6 and >8 was 1.47±0.22, 1.19±0.17 and 1.01±0.18, respectively). Accordingly, patients were stratified by rSS into low (=0), mid (>0-≤5) and high (>5) groups. There was a strong correlation between bSS and rSS (correlation coefficient=0.533, p<0.001) **(Figure 1)**.

The clinical and angiographic characteristics of patients stratified by rSS are shown in **Table 1** and **Table 2**. Compared with patients with complete revascularisation (rSS=0), those in the highest rSS tertile (rSS >5) were more likely to have had previous CABG, stable angina, lower TIMI flow, and more complex coronary lesions resulting in a higher SS at baseline (p<0.01), including higher proportions of longer lesions, total occlusions, severe calcified lesions, type C lesions and left main disease.

CLINICAL OUTCOMES

Among all 1,900 enrolled patients, the primary endpoint of TVF rate at one year was 5.95%. All-cause death and components of

Table 1. Baseline demographics according to rSS tertiles.

	All patients n=1,851	Low rSS (=0) n=1,190	Mid rSS (>0-<5) n=403	High rSS (>5) n=258	*P**
Patient demographics					
Age, years	59.58±9.50	59.39±9.44	59.48±9.47	60.64±9.79	0.15
Male gender	74.23 (1,374)	73.78 (878)	77.42 (312)	71.32 (184)	0.18
Diabetes	27.23 (504)	25.80 (307)	28.29 (114)	32.17 (83)	0.09
Hypertension	64.02 (1,185)	61.43 (731)	68.73 (277)	68.60 (177)	0.02
Hypercholesterolaemia	33.98 (629)	33.87 (403)	36.72 (148)	30.23 (78)	0.47
Current smoker	41.49 (768)	41.51 (494)	40.94 (165)	42.25 (109)	0.97
Family history of CAD	12.53 (232)	12.94 (154)	12.16 (49)	11.24 (29)	0.74
Prior MI	24.85 (460)	22.69 (270)	27.54 (111)	30.62 (79)	0.05
Previous PCI	8.27 (153)	8.99 (107)	6.70 (27)	7.36 (19)	0.61
Previous CABG	1.13 (21)	0.76 (9)	0.99 (4)	3.10 (8)	0.01
Angina pectoris					0.02
Stable angina	6.21 (115)	6.13 (73)	4.96 (20)	8.53 (22)	
Unstable angina	84.39 (1,562)	85.46 (1,017)	83.37 (336)	81.01 (209)	
Silent ischaemia	4.48 (83)	4.62 (55)	3.72 (15)	5.04 (13)	
LVEF, %	61.00±8.57	61.43±8.34	60.43±9.18	60.01±8.56	0.03

Note: all data are presented as % (n) or mean±SD. **p* among the three rSS groups. CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

Table 2. Lesion characteristics and procedural results according to rSS tertiles.

		All patients n=1,851	Low rSS (=0) n=1,190	Mid rSS (>0-<5) n=403	High rSS (>5) n=258	*p**
Target lesion assessment	Target lesion number	2,767	1,732	648	387	
	Target lesion location					<0.01
	LM	2.20 (61)	1.85 (32)	1.85 (12)	4.39 (17)	
	LAD	46.69 (1,292)	48.56 (841)	46.60 (302)	38.50 (149)	
	LCX	26.49 (733)	26.67 (462)	26.70 (173)	25.32 (98)	
	RCA	24.61 (681)	22.92 (397)	24.85 (161)	31.78 (123)	
	ACC/AHA lesion classification					<0.01
	A	1.70 (47)	2.42 (42)	0.46 (3)	0.52 (2)	
	B1	19.15 (530)	21.07 (365)	18.52 (120)	11.63 (45)	
	B2	35.81 (991)	36.03 (624)	36.42 (236)	33.85 (131)	
	C	43.33 (1,199)	40.47 (701)	44.60 (289)	54.01 (209)	
Lesion characteristics	Small vessel	57.4 (1,065)	57.90 (689)	58.06 (234)	55.04 (142)	0.68
	Long lesion	69.75 (1,291)	67.73 (806)	72.70 (293)	74.42 (192)	0.04
	Multivessel	38.25 (708)	35.55 (423)	45.41 (183)	39.53 (102)	<0.01
	Total occlusion	8.75 (242)	7.91 (137)	9.10 (59)	11.89 (46)	0.04
	Bifurcation lesion	26.96 (746)	23.27 (403)	33.64 (218)	32.30 (125)	<0.01
	Severe tortuosity	0.47 (13)	0.58 (10)	0.46 (3)	0.00 (0)	0.43
	Heavy calcification	2.10 (58)	1.10 (19)	2.93 (19)	5.17 (20)	<0.01
	Thrombus-containing lesion	0.54 (15)	0.52 (9)	0.46 (3)	0.78 (3)	0.75
	TIMI flow pre-procedure					<0.01
	0	8.85 (245)	7.91 (137)	9.41 (61)	12.14 (47)	
	I	1.01 (28)	0.69 (12)	1.08 (7)	2.33 (9)	
	II	2.82 (78)	2.48 (43)	4.48 (29)	1.55 (6)	
	III	87.31 (2,416)	88.91 (1,540)	85.03 (551)	83.98 (325)	
Pre-procedural QCA	Reference vessel diameter, mm	2.64±0.48	2.66±0.48	2.62±0.46	2.63±0.47	0.11
	Lesion length, mm	19.07±12.26	18.07±11.62	20.03±12.65	22.09±13.83	<0.01
	Minimal luminal diameter, mm	0.81±0.45	0.84±0.46	0.77±0.43	0.73±0.44	<0.01
	Diameter stenosis, %	69.60±15.57	70.83±15.17	72.56±15.81	69.60±15.57	<0.01
Procedural results	Predilatation	82.31 (2,284)	79.55 (1,373)	87.50 (574)	85.75 (337)	<0.01
	Stent per patient	2.05±1.09	1.92±1.02	2.31±1.19	2.26±1.16	<0.01
	Stent per lesion	1.37±0.62	1.32±0.58	1.42±0.63	1.49±0.71	<0.01
	Stent diameter, mm	2.90±0.44	2.91±0.44	2.88±0.41	2.89±0.45	0.57
	Post-dilatation	41.15 (1,142)	41.60 (718)	40.24 (264)	40.71 (160)	0.82
	Study device, n	3,800	2,286	930	584	
Post-procedural QCA	Reference vessel diameter, mm	2.63±0.45	2.64±0.46	2.61±0.43	2.64±0.45	0.25
	Minimal luminal diameter, mm					
	In-stent	2.46±0.41	2.48±0.42	2.43±0.40	2.43±0.42	<0.01
	In-segment	2.28±0.44	2.29±0.45	2.25±0.42	2.28±0.43	0.12
	Diameter stenosis, %					
	In-stent	8.93±6.08	8.68±6.00	9.11±6.13	9.78±6.32	<0.01
	In-segment	13.30±8.26	13.19±8.19	13.62±8.41	13.26±8.34	0.52
	Acute gain, mm					
	In-stent	1.65±0.48	1.64±0.49	1.66±0.45	1.70±0.49	0.09
	In-segment	1.47±0.52	1.45±0.53	1.48±0.48	1.56±0.51	<0.01
Successful rates	Device success	99.95 (3,800)	99.96 (2,286)	100 (930)	99.83 (584)	0.34
	Lesion success	99.93 (2,773)	99.94 (1,725)	100 (656)	99.75 (392)	0.32
	Clinical success	96.76 (1,791)	97.65 (1,162)	96.03 (387)	93.80 (242)	<0.01
SYNTAX scores	Baseline SYNTAX score	10.87±7.26	8.29±5.68	12.85±6.25	19.68±7.39	<0.01
	Residual SYNTAX score	2.18±3.97	0.00±0.00	3.39±1.36	10.32±4.43	<0.01

Note: all data are presented as % (n) or mean±SD. *p among the three rSS groups. LAD: left anterior descending artery; LCX: left circumflex; LM: left main; QCA: quantitative coronary angiography; RCA: right coronary artery

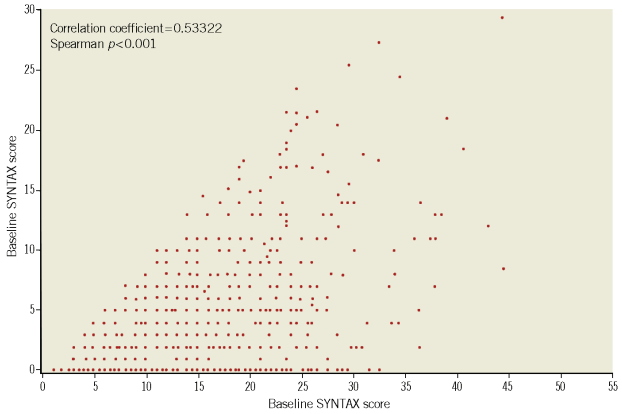

Figure 1. *Correlations between baseline and residual SYNTAX scores. Residual SYNTAX score (rSS) correlated strongly with baseline SYNTAX score (bSS). However, rSS varied within a considerable range for each level of bSS.*

TVF, namely cardiac death, TVMI, and TVR occurred in 0.68%, 0.47%, 3.42% and 2.47% of patients at 12 months after PCI, respectively. The rate of ARC-defined definite/probable ST was 0.58%.

One-year rates of TVF were significantly higher among patients in the highest bSS or rSS tertile. Cumulative TVF rates at one year were 9.14%, 4.31% and 2.69% in patients in the high, mid and low bSS groups, respectively (log-rank p<0.01). After stratification by rSS, TVF rates were 10.08%, 6.95% and 4.37% in patients in the high, mid and low rSS groups, respectively (log-rank p<0.01). In terms of individual TVF components, patients in the highest tertiles of bSS and rSS were more likely to suffer cardiac death, TVMI and/or TVR **(Table 3, Figure 2, Figure 3)**.

MULTIVARIABLE ANALYSIS AND ROC ANALYSIS

In Cox multivariable analyses, rSS was a strong independent predictor of TVF, all-cause death, cardiac death and TVMI, but not of

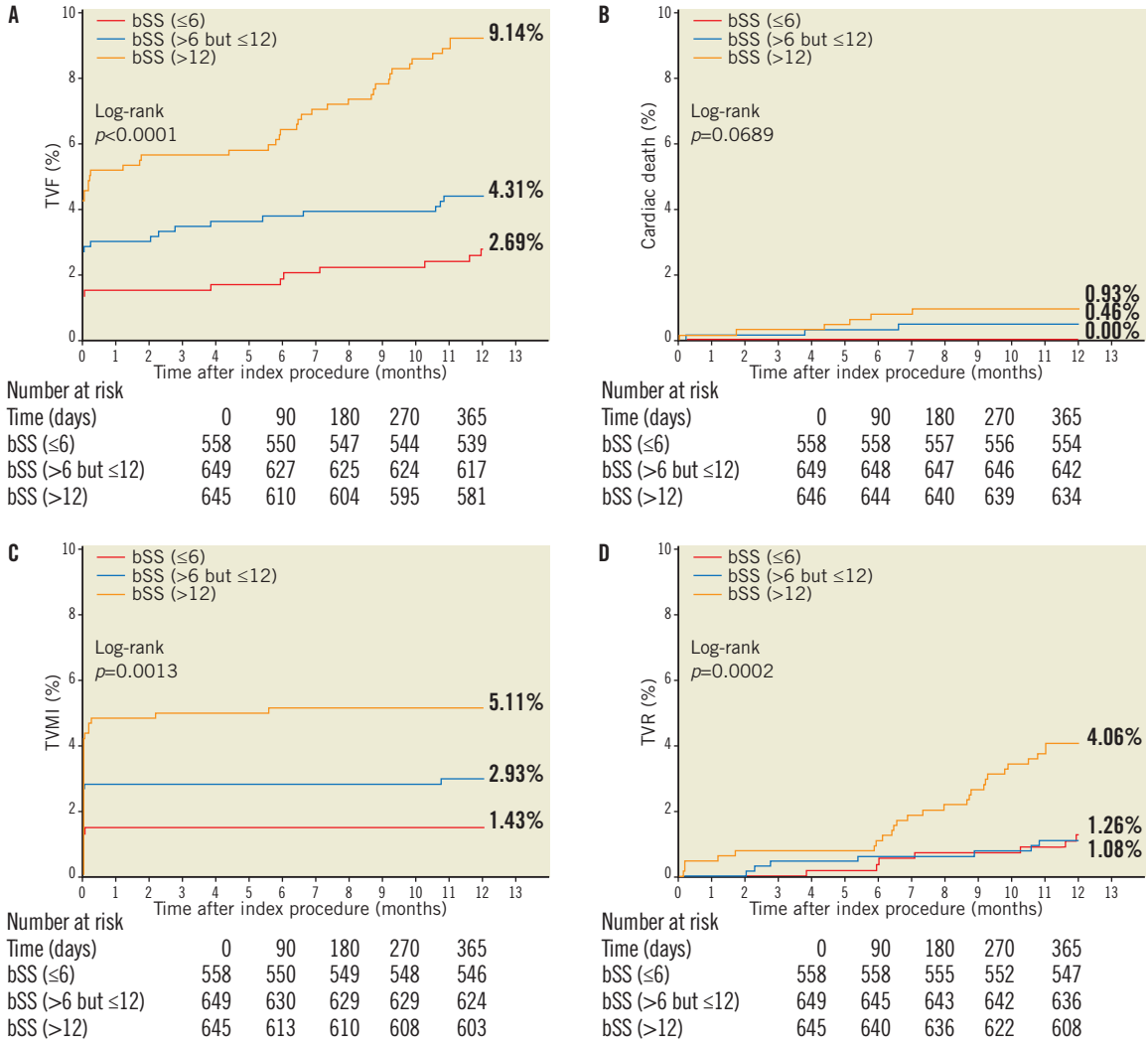

Figure 2. *Kaplan-Meier estimates of cumulative event rates up to one year stratified by bSS. A) TVF; B) cardiac death; C) TVMI; and D) TVR, stratified by tertiles of baseline SYNTAX score (bSS). Patients were categorised based on bSS into low (≤6), mid (>6-≤12) and high (>12) bSS groups. The high bSS group had the worst clinical outcomes. TVF: ischaemia-driven target vessel failure, defined as the composite of cardiac death, TVMI, and TVR; TVMI: target vessel myocardial infarction; TVR: ischaemia-driven target vessel revascularisation*

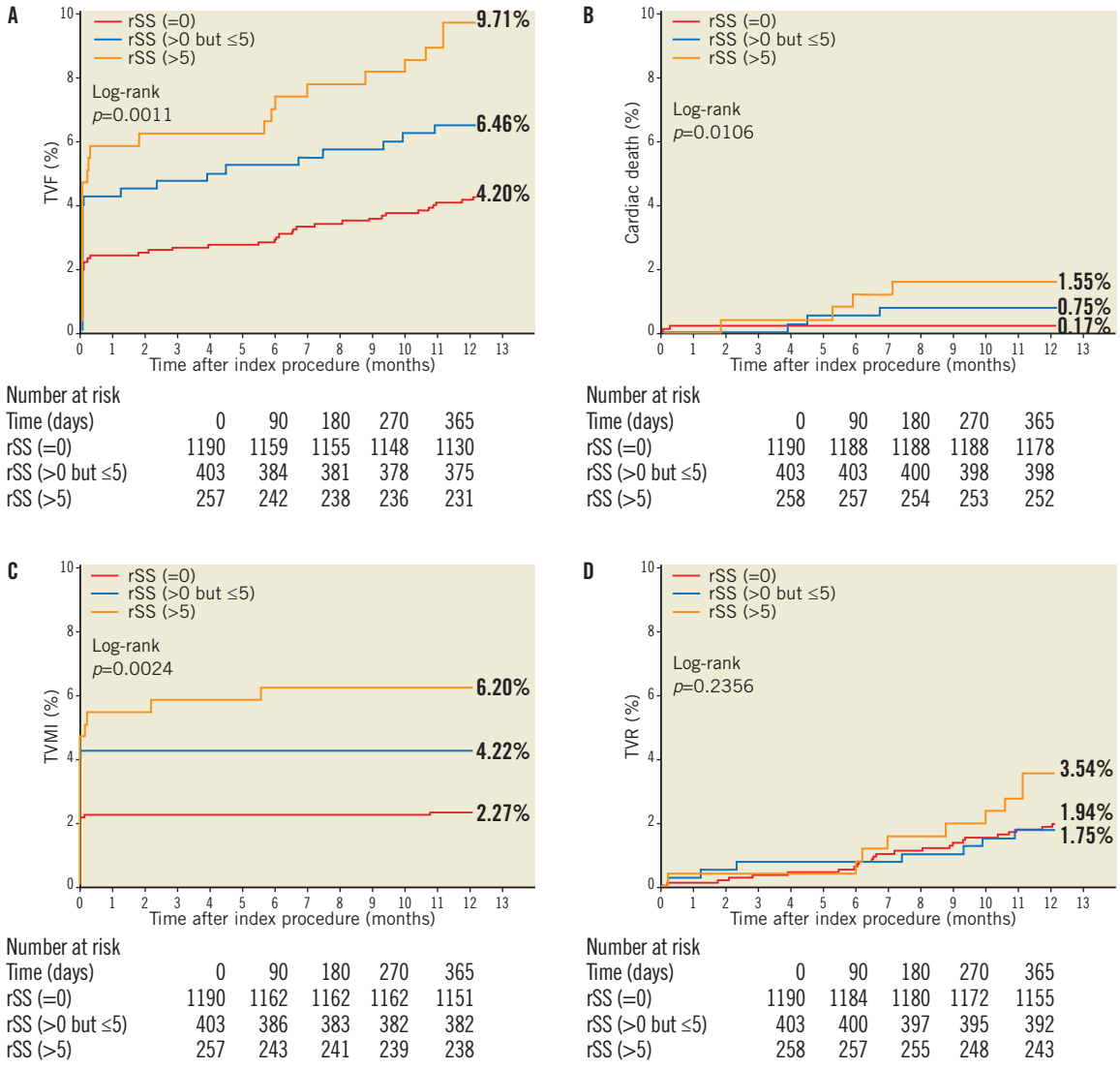

Figure 3. *Kaplan-Meier estimates of cumulative event rates up to one year stratified by rSS. A) TVF; B) cardiac death; C) TVMI; and D) TVR, stratified by tertiles of residual SYNTAX score (rSS). Patients were categorised based on rSS into low (=0), mid (>0-≤5) and high (>5) bSS groups. The high rSS group had the worst clinical outcomes. TVF: ischaemia-driven target vessel failure, defined as the composite of cardiac death, TVMI, and TVR; TVMI: target vessel myocardial infarction; TVR: ischaemia-driven target vessel revascularisation*

TVR, at one year **(Table 4)**. VIF contributes to collinearity diagnosis in multivariate analysis and showed low collinearity for all variables (all VIF <2) **(Online Table 1)**. ROC curve analyses also demonstrated a significant association between rSS and one-year TVF (p=0.02), all-cause death (p=0.01), cardiac death (p<0.01) and TVMI (p=0.04) **(Table 5)**. Compared with bSS, rSS had

Table 3. Clinical outcomes at 12 months stratified according to rSS.

Residual SYNTAX score	Low (rSS=0) n=1,190	Mid (rSS>0 but ≤5) n=403	High (rSS>5) n=258	*p*			
				*Low vs. Mid	*Mid vs. High	*Low vs. High	All groups
TVF	4.37 (52)	6.95 (28)	10.08 (26)	0.04	0.15	<0.01	<0.01
Cardiac death	0.17 (2)	0.74 (3)	1.55 (4)	0.11	0.44	0.01	<0.01
TVMI	2.27 (27)	4.22 (17)	6.59 (17)	0.04	0.18	<0.01	<0.01
TVR	2.10 (25)	2.23 (9)	3.88 (10)	0.87	0.22	0.09	0.23
ST	0.34 (4)	0.50 (2)	1.55 (4)	0.65	0.22	0.04	0.05

Note: all data are presented as % (n). rSS: residual SYNTAX score; ST: stent thrombosis; TVF: ischaemia-driven target vessel failure, defined as the composite of cardiac death, TVMI, or TVR; TVMI: target vessel myocardial infarction; TVR: ischaemia-driven target vessel revascularisation

Table 4. Independent predictors of 1-year clinical outcomes.

Variables	p	Hazard ratio [95% CI]
Target vessel failure		
Multivessel disease	<0.01	2.05 [1.33,3.15]
Lesion length before PCI, mm	<0.01	1.02 [1.01,1.04]
Minimum lumen diameter after PCI, mm	<0.01	0.45 [0.25,0.80]
Residual SYNTAX score (low =0, mid >0-<5, high >5)	0.01	1.40 [1.08,1.82]
All-cause death		
Residual SYNTAX score (low =0, mid >0-<5, high >5)	0.02	2.23 [1.11,4.46]
Cardiac death		
Residual SYNTAX score (low =0, mid >0-<5, high >5)	0.02	2.65 [1.17,6.02]
Target vessel myocardial infarction		
Age	0.04	1.77 [1.04,3.03]
Multivessel disease	<0.01	2.21 [1.28,3.83]
Lesion length before PCI, mm	<0.01	1.03 [1.01,1.05]
Residual SYNTAX score (low =0, mid >0-<5, high >5)	0.01	1.51 [1.09,2.09]
Target vessel revascularisation		
Previous CABG	0.02	5.63 [1.35,23.51]
Multivessel disease	0.02	2.29 [1.13,4.64]
Minimum lumen diameter after PCI, mm	<0.01	0.22 [0.09,0.56]

CI: confidence interval; PCI: percutaneous coronary intervention

a similar predictive value and discrimination for cardiac death (p=0.97) and TVMI (p=0.14) at one year, whereas bSS was a slightly stronger predictor of TVF and TVR (both p<0.01) **(Online Table 2)**.

Discussion

The current study, drawn from a large cohort of patients with complex anatomic characteristics, is the first to investigate the predictive value on clinical outcomes of rSS in EES-treated patients with complex disease (small vessels, long lesions, and multivessel disease). The major findings of this analysis are as follows: 1) the 12-month rates of TVF and its individual components (cardiac death, TVMI and TVR) as well as those of ARC-defined definite/probable ST were low in patients with complex lesions after PCI with EES; and 2) rSS >5 were associated with increased rates of adverse clinical outcomes after EES implantation, including TVF, all-cause death and TVMI.

Table 5. ROC curve analysis of rSS on 1-year clinical outcomes.

Variables	AUC	p	Optimal cut-off	Sensitivity (%)	Specificity (%)
TVF	0.5890	0.02	3	44	73
All-cause death	0.7211	0.01	2	77	65
Cardiac death	0.7476	<0.01	2	78	66
TVMI	0.6075	0.04	4	45	76
TVR	0.5425	0.12	4	36	75

AUC: area under the curve; rSS: residual SYNTAX score; TVF: target vessel failure, defined as the composite of cardiac death, TVMI, or TVR; TVMI: target vessel myocardial infarction; TVR: ischaemia-driven target vessel revascularisation

Recently, rSS has been proposed as an index of revascularisation completeness with rSS=0 defined as complete revascularisation[4]. Indeed, since its first introduction[1], SS has been evaluated for treatment selection and prediction of clinical outcomes after coronary revascularisation[2-6,13-15]. However, most previous assessments of SS, particularly rSS, were conducted with early-generation DES. Moreover, no studies have been performed to determine whether the rSS is meaningful in patients with complex anatomic characteristics (lesions in small vessels, long lesions, and multivessel disease), who are known to experience worse clinical outcomes after PCI[7-9]. In the present study, we have shown that quantification of the extent and complexity of coronary stenosis with bSS and rSS provide substantial prognostic information among patients undergoing PCI with EES.

In this study, median bSS was 9 (mean±SD: 10.87±7.26), which is comparable to that of patients with moderate-risk and high-risk acute coronary syndrome from the ACUITY trial (mean±SD: 12.8±6.7)[4]. At one year after EES implantation, patients in the high bSS and rSS tertiles had greater rates of TVF, cardiac death, TVMI and TVR.

Residual SYNTAX score was correlated with bSS, which is consistent with previous studies[4,6] **(Figure 1)**. Because complete coronary revascularisation has been shown to result in improved clinical outcomes[16,17], rSS, an index of completeness of coronary revascularisation after PCI, may provide better prognostic information. Indeed, the highest rSS tertile (rSS >5) had higher rates of TVF, TVMI and cardiac death at one year post PCI **(Figure 3)**. Also, rSS was found by multivariate analysis in this study to be an independent predictor of TVF, all-cause death, cardiac death and TVMI, but not TVR, at one year **(Table 4)**. Not surprisingly, a strong correlation was observed between baseline severity of coronary artery disease and revascularisation completeness. Compared with patients with complete revascularisation (rSS=0), those with incomplete revascularisation in the upper rSS tertile were more likely to have had previous CABG, stable angina, lower TIMI flow, and more complex coronary disease with higher proportions of longer lesions, total occlusions, calcified lesions, type C lesions and left main disease **(Table 1, Table 2)**. These findings suggest that patients with the latter characteristics are least likely to benefit from PCI.

In the past, there have been no standard thresholds to stratify rSS. Généreux et al stratified rSS into 0, 0-2, 2-8 and >8[4], and Farooq et al stratified rSS into 0, 0-4, 4-8 and >8[6]. In the present study, bootstrap methodology was used to determine an optimal rSS cut-off value; rSS >5 among patients with incomplete revascularisation was the best predictor of one-year TVF (HR for threshold of 5 and 8 was 1.53±0.23 and 1.01±0.18, respectively, p<0.01). The fact that the best threshold of 5 in this study is different from that in other studies might be due to the lower post-PCI mean rSS of 2.18 in this study, in contrast to that between 4 and 6 in others. Moreover, the rate of complete revascularisation (rSS=0) was higher in our study (64%) than in other real-world studies (40 to 43%)[4-6]. Therefore, it is possible that the lower cut-off point determined in this study is

a result of the greater degree of complete revascularisation in this patient cohort **(Table 2)**. This study suggests that a cut-off of 5 appears reasonable to stratify rSS.

Study limitations

Several limitations of the present study should be discussed. First, there was no "conventional" control group for head-to-head comparisons of stent efficacy or safety. However, it is worth noting that this study was aimed to investigate the safety and efficacy of EES among patients with complex anatomic characteristics in China, a largely unstudied patient population. Second, as in other studies[4-6], cut-off values of bSS and rSS were generated within the present dataset, and as such remain exploratory. Future prospective studies are needed to assess the predictive value of rSS at pre-set cut-off values.

Conclusions

EES is safe and effective in the treatment of Chinese patients with complex coronary small vessels, long lesions, and multivessel disease. The rSS has a good discriminatory power for risk prediction of one-year TVF in this population, with an rSS >5 being associated with an increased risk of one-year TVF.

Impact on daily practice

Residual SS (rSS) has been validated as an independent predictor for adverse events. However, studies examining the impact of rSS were primarily performed using first-generation drug-eluting stents (DES) while the use of second-generation DES has been more common in recent years. Moreover, patients with lesions with complex anatomic characteristics (small vessels, long lesions, and multivessel disease), who experience worse clinical outcomes after PCI, are very common in "real-world" practice, probably more in China than in the West. Our study revealed that everolimus-eluting stents are safe and effective in the treatment of Chinese patients with those complex anatomic characteristics. Furthermore, rSS >5, which is associated with an increased risk of one-year target vessel failure, could be considered as a good risk predictor in this population.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Online data supplement

Appendix. SEEDS study organisation.

Online Table 1. Collinearity analysis for all variables.

Online Table 2. ROC curve analysis of bSS and rSS on 1-year clinical results.

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Online data supplement

Appendix. SEEDS study organisation

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Online Table 1. Collinearity analysis for all variables.

Variables	Variance inflation factor (VIF)
Age (1=older than 65 years, 0=less than 65 years)	1.05
Gender (1=male, 0=female)	1.05
Diabetes (1=yes, 0=no)	1.02
Lesion type (1=multivessel, 0=non-multivessel)	1.16
Diameter stenosis before PCI (%)	1.14
Previous CABG (1=yes, 0=no)	1.01
Lesion length before PCI (mm)	1.06
Minimal lumen diameter after PCI (mm)	1.07
rSS (0=0, 1=0-≤5, 2=5)	1.05

Note: VIF >10 indicates high collinearity.

Online Table 2. ROC curve analysis of bSS and rSS on 1-year clinical results.

Variables		AUC	95% CI	*p*
TVF	bSS	0.659	[0.605, 0.713]	0.01
	rSS	0.589	[0.535, 0.643]	
Cardiac death	bSS	0.751	[0.568, 0.934]	0.97
	rSS	0.748	[0.576, 0.919]	
TVMI	bSS	0.659	[0.589, 0.729]	0.14
	rSS	0.608	[0.539, 0.676]	
TVR	bSS	0.663	[0.580, 0.746]	<0.01
	rSS	0.543	[0.456, 0.629]	

AUC: area under the curve; bSS: baseline SYNTAX score; CI: confidence interval; rSS: residual SYNTAX score; TVF: target vessel failure, defined as the composite of cardiac death, TVMI, or TVR; TVMI: target vessel myocardial infarction; TVR: ischaemia-driven target vessel revascularisation