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ORIGINAL STUDIES

Usefulness of the updated logistic clinical SYNTAX score after percutaneous coronary intervention in patients with prior coronary artery bypass graft surgery: Insights from the GLOBAL LEADERS trial

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Abstract

Objectives: We aimed to investigate the prognostic utility of the anatomical CABG SYNTAX and logistic clinical SYNTAX scores for mortality after percutaneous coronary intervention (PCI) in patients with prior coronary artery bypass grafts (CABG).

Background: The anatomical SYNTAX score evaluated the anatomical complexity of coronary artery disease and helped predict the prognosis of patients undergoing PCI. The anatomical CABG SYNTAX score was derived from the anatomical SYNTAX score in patients with prior CABG, whilst the logistic clinical SYNTAX score was developed by incorporating clinical factors into the anatomical SYNTAX score.

Methods: We calculated the anatomical CABG SYNTAX score and logistic clinical SYNTAX score in 205 patients in the GLOBAL LEADERS trial. The predictive abilities of these scores for 2-year all-cause mortality were evaluated.

Results: Using the median scores as categorical thresholds between low and high score groups, the logistic clinical SYNTAX score was able to discriminate the risk of 2-year mortality, unlike the anatomical CABG SYNTAX score. The logistic clinical SYNTAX was significantly better at predicting 2-year mortality, compared to the anatomical CABG SYNTAX score, as evidenced by AUC values in receiver-operating characteristic curve analysis (0.806 vs. 0.582, $p < .001$) and integrated discrimination improvement (0.121, $p < .001$).

Conclusions: The logistic clinical SYNTAX score was superior to the anatomical CABG SYNTAX score in predicting 2-year mortality.

KEYWORDS
coronary bypass grafts, drug eluting, percutaneous coronary intervention (PCI), risk stratification, stent

1 | INTRODUCTION

The anatomical SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score[1] is recommended to evaluate the anatomical complexity of coronary artery disease and can also help predict medium-term prognosis in patients undergoing percutaneous coronary intervention (PCI).[2-4] The anatomical CABG SYNTAX score, which takes into account the extent of revascularization by bypass grafts, was proposed in 2012 for the patients who had undergone coronary artery bypass graft (CABG) surgery.[5] However, the prognostic value of this specific score has not yet been further evaluated in patients with prior CABG undergoing PCI.[6]

To enable individualized risk estimation for all-cause mortality after PCI, the clinical SYNTAX score and logistic clinical SYNTAX score was developed by combining the anatomical SYNTAX score and clinical factors, and the logistic clinical SYNTAX score has been recently updated and validated.[7-10] The performance of the logistic clinical SYNTAX score has been assessed in patients with left main coronary artery disease and acute coronary syndromes,[11,12] but not in patients with prior CABG undergoing PCI.

We aimed to investigate and compare the prognostic performance of the anatomical CABG SYNTAX score, clinical SYNTAX score and logistic clinical SYNTAX score in predicting 2 years all-cause mortality after PCI in patients with prior CABG using the GLOBAL LEADERS trial database.[13]

2 | METHODS

2.1 | Study design and participants

The GLOBAL LEADERS trial (NCT01813435) was a prospective randomized, open-label trial, designed to compare 23-month ticagrelor monotherapy following one-month dual antiplatelet therapy and 12-month dual antiplatelet therapy followed by 12-month aspirin monotherapy after PCI in a total of 15,991 all-comers patients.[13]

The anatomical SYNTAX score analysis was prespecified in the protocol for the first 4,000 consecutive patients in the GLOBAL LEADERS trial.[14] Among the first 4 000 consecutive patients, 275 patients had a prior CABG. Of these 275 patients, one patient did

not receive PCI, and coronary arteries and bypass grafts were not fully assessed in 48 patients (e.g., native right coronary artery was not assessed since a bypass graft to right coronary artery was patent). Therefore, 226 had coronary angiograms for which the anatomical CABG SYNTAX score could be calculated by an independent core lab (ART, Academic Research Team, Rotterdam, The Netherlands),[5] by analysts unaware of the patient's treatment assignment or clinical outcome.

The anatomical CABG SYNTAX score[5] derived from Leaman score[15] was calculated by determining the standard anatomical SYNTAX score in the "native" coronary vessels (native SYNTAX score) and deducting points based on the weighting of the diseased coronary artery segment that have a functioning bypass graft anastomosed distally. Therefore, the anatomical CABG SYNTAX score could reflect anatomical complexity and extent of revascularization, as well as the anatomical SYNTAX score after PCI. An example of the calculation is presented in Figure 1.

Of these 226 patients, at least one variable for the logistic clinical SYNTAX score calculation was missing in 21 patients, thus, all baseline characteristics for the updated logistic clinical SYNTAX score[9] calculation including age, creatinine clearance (CrCl), left ventricular ejection fraction (LVEF), body mass index (BMI), diabetes, peripheral vascular disease (PVD), and SYNTAX-like characteristics, were available in 205 patients. SYNTAX-like characteristic was defined as unprotected left main coronary artery disease and/or three vessel disease without patency of grafts.

The clinical SYNTAX score is one of the historical and developmental SYNTAX-derived scores and includes only three patient characteristics: age, CrCl, and LVEF and was inspired by the ACEF score.[16-19] This score was calculated using the following formula; (the anatomical CABG SYNTAX score) × (age/EF + 1 point for every 10 reduction in CrCl below 60 mL/min).[7] In this calculation, a CrCl of between 50 and 59 mL/min, 40 and 49 mL/min, 30 and 39 mL/min, 20 and 29 mL/min, 10 and 19 mL/min, and 0 and 9 mL/min would receive 1, 2, 3, 4, 5, and 6 points, respectively.

The updated logistic clinical SYNTAX score in patients with prior CABG was calculated using the following formula; 0.0187 × (the anatomical CABG SYNTAX score) + 0.1667 × (SYNTAX-like characteristic) + 0.0425 × (age) + 0.0174 × (90-CrCl) + 0.0522 × (50-EF) + 0.0312 × (BMI) + 0.57 × (PVD) + 0.3463 × (diabetes)−4.521.

All patients provided informed, written consent. The study complied with the Declaration of Helsinki and Good Clinical Practices.

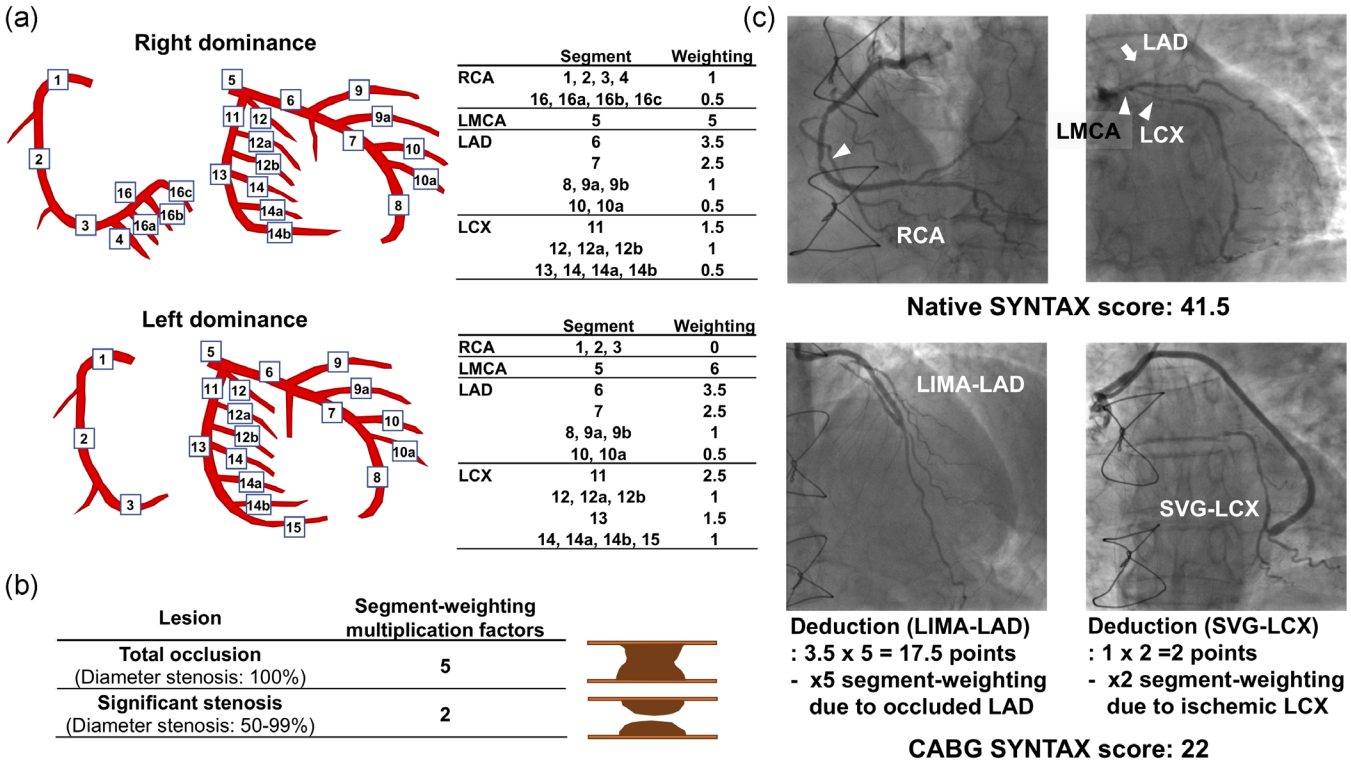

FIGURE 1 An example of the calculation of the anatomical CABG SYNTAX score. (a and b) Coronary segment-weighting derived from Leaman score[5,15] (a), and segment-weighting multiplication factors depending on severity of the lesion[15] (b). These were used to calculate points for deduction from the native SYNTAX score. (c) The native SYNTAX score was 41.5 due to left main and three-vessel disease (upper images). A patent left internal mammary artery (LIMA) to left anterior descending artery (LAD) with no intervening obstructive disease (lower left image) led to the deduction of 3.5 × 5 points (×5 segment-weighting due to occluded LAD) from the native SYNTAX score. A patent saphenous vein graft (SVG) to left circumflex (LCX) with no intervening obstructive coronary disease (lower right image) led to 1 × 2 points (×2 segment-weighting due to ischemic LCX) deduction. Therefore, the CABG SYNTAX score was 41.5–17.5–2 = 22 points. RCA, right coronary artery; LMCA, left main coronary artery; an arrow indicates occlusion; arrow heads indicate stenosis [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patient characteristics

Baseline characteristics	All patients *n* = 205	CABG SYNTAX score			Clinical SYNTAX score			Logistic clinical SYNTAX score		
		Low: *n* = 105	High: *n* = 100	*p* value	Low: *n* = 103	High: *n* = 102	*p* value	Low: *n* = 103	High: *n* = 102	*p* value
Age (years)	68.8 ± 8.73	68.3 ± 8.41	69.4 ± 9.05	.346	65.8 ± 8.67	71.9 ± 7.71	<.001	64.2 ± 7.90	73.5 ± 6.81	<.001
Male	171/205 (83.4)	81/105 (77.1)	90/100 (90.0)	.015	84/103 (81.6)	87/102 (85.3)	.574	87/103 (84.5)	84/102 (82.4)	.711
Body mass index (kg/m^2)	28.2 ± 4.74	28.3 ± 4.83	28.0 ± 4.66	.647	28.7 ± 4.59	27.6 ± 4.85	.112	28.6 ± 4.52	27.7 ± 4.92	.159
CrCl (ml/min)	81.0 ± 28.8	83.5 ± 29.9	78.4 ± 27.6	.201	92.5 ± 27.5	69.4 ± 25.3	<.001	95.9 ± 26.2	66.0 ± 23.0	<.001
LVEF (%)	52.3 ± 12.6	53.8 ± 11.5	50.7 ± 13.4	.080	56.8 ± 9.71	47.8 ± 13.6	<.001	56.3 ± 9.31	48.3 ± 14.1	<.001
Hypertension	170/205 (82.9)	85/105 (81.0)	85/100 (85.0)	.464	80/103 (77.7)	90/102 (88.2)	.063	78/103 (75.7)	92/102 (90.2)	.009
Hypercholesterolemia	177/203 (87.2)	91/104 (87.5)	86/99 (86.9)	1.000	89/102 (87.3)	88/101 (87.1)	1.000	88/103 (85.4)	89/100 (89.0)	.531
Diabetes mellitus	75/205 (36.6)	36/105 (34.3)	39/100 (39.0)	.562	36/103 (35.0)	39/102 (38.2)	.665	26/103 (25.2)	49/102 (48.0)	.001
Previous MI	94/204 (46.1)	47/105 (44.8)	47/99 (47.5)	.779	42/103 (40.8)	52/101 (51.5)	.160	44/102 (43.1)	50/102 (49.0)	.483
Previous PCI	108/205 (52.7)	58/105 (55.2)	50/100 (50.0)	.486	52/103 (50.5)	56/102 (54.9)	.577	46/103 (44.7)	62/102 (60.8)	.025
Previous stroke	10/205 (4.88)	3/105 (2.86)	7/100 (7.00)	.206	3/103 (2.91)	7/102 (6.86)	.214	2/103 (1.94)	8/102 (7.84)	.058
Established PVD	41/205 (20.0)	13/105 (12.4)	28/100 (28.0)	.008	12/103 (11.7)	29/102 (28.4)	.003	7/103 (6.80)	34/102 (33.3)	<.001
COPD	20/205 (9.76)	13/105 (12.4)	7/100 (7.00)	.242	11/103 (10.7)	9/102 (8.82)	.814	6/103 (5.83)	14/102 (13.7)	.063
Previous bleeding	3/205 (1.46)	1/105 (0.95)	2/100 (2.00)	.614	1/103 (0.97)	2/102 (1.96)	.621	1/103 (0.97)	2/102 (1.96)	.621
Currently smoking	26/205 (12.7)	14/105 (13.3)	12/100 (12.0)	.836	17/103 (16.5)	9/102 (8.82)	.141	17/103 (16.5)	9/102 (8.82)	.141
Heart failure at presentation	3/205 (1.46)	3/105 (2.86)	0/100 (0.00)	.247	1/103 (0.97)	2/102 (1.96)	.621	0/103 (0.00)	3/102 (2.94)	.121
Cardiac arrest at presentation	1/205 (0.49)	1/105 (0.95)	0/100 (0.00)	1.000	0/103 (0.00)	1/102 (0.98)	.498	0/103 (0.00)	1/102 (0.98)	.498
Clinical presentation										
Stable angina	138/205 (67.3)	69/105 (65.7)	69/100 (69.0)	.657	69/103 (67.0)	69/102 (67.7)	1.000	64/103 (62.1)	74/102 (72.6)	.137
Acute coronary syndrome	67/205 (32.7)	36/105 (34.3)	31/100 (31.0)	.657	34/103 (33.0)	33/102 (32.4)	1.000	39/103 (37.9)	28/102 (27.5)	.137
Unstable angina	20/205 (9.76)	12/105 (11.4	8/100 (8.00)	.484	14/103 (13.6)	6/102 (5.88)	.098	12/103 (11.7)	8/102 (7.84)	.481
NSTEMI	43/205 (21.0)	24/105 (22.9)	19/100 (19.0)	.607	19/103 (18.5)	24/102 (23.5)	.400	23/103 (22.3)	20/102 (19.6)	.732
STEMI	4/205 (1.95)	0/105 (0.00)	4/100 (4.00)	.055	1/103 (0.97)	3/102 (2.94)	.369	4/103 (3.88)	0/102 (0.00)	.121
CABG SYNTAX score	23.4 ± 11.7	14.4 ± 4.87	32.8 ± 9.03	<.001	16.1 ± 6.86	30.7 ± 10.9	<.001	20.3 ± 10.7	26.5 ± 11.8	<.001
Clinical SYNTAX score	44.1 ± 36.3	25.0 ± 18.3	64.2 ± 39.7	<.001	19.3 ± 7.46	69.1 ± 36.7	<.001	24.5 ± 14.3	64.0 ± 40.8	<.001
Logistic clinical SYNTAX score	0.454 ± 0.862	0.146 ± 0.725	0.777 ± 0.879	<.001	−0.107 ± 0.555	1.020 ± 0.738	<.001	−0.204 ± 0.449	1.119 ± 0.640	<.001
SYNTAX-like patient	9/205 (4.39)	1/105 (0.95)	8/100 (8.00)	.017	3/103 (2.91)	6/102 (5.88)	.332	6/103 (5.83)	3/102 (2.94)	.498

Note: Continuous variables were expressed as mean ± *SD*, and categorical variables were reported as numbers and percentages. CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

TABLE 2 Procedural characteristics

Procedural characteristics	All patients *n* = 205	CABG SYNTAX score			Clinical SYNTAX score			Logistic clinical SYNTAX score		
		Low: *n* = 105	High: *n* = 100	*p* value	Low: *n* = 103	High: *n* = 102	*p* value	Low: *n* = 103	High: *n* = 102	*p* value
Target vessels										
Left anterior descending	38/205 (18.5)	24/105 (22.9)	14/100 (14.0)	.110	21/103 (20.4)	17/102 (16.7)	.590	18/103 (17.5)	20/102 (19.6)	.722
Left circumflex artery	74/205 (36.1)	37/105 (35.2)	37/100 (37.0)	.885	30/103 (29.1)	44/102 (43.1)	.042	34/103 (33.0)	40/102 (39.2)	.385
Right coronary artery	55/205 (26.8)	32/105 (30.5)	23/100 (23.0)	.270	31/103 (30.1)	24/102 (23.5)	.344	32/103 (31.1)	23/102 (22.6)	.208
Left main coronary artery	19/205 (9.27)	6/105 (5.71)	13/100 (13.0)	.092	8/103 (7.77)	11/102 (10.8)	.481	11/103 (10.7)	8/102 (7.84)	.631
Bypass graft	50/205 (24.4)	18/105 (17.1)	32/100 (32.0)	.018	22/103 (21.4)	28/102 (27.5)	.333	22/103 (21.4)	28/102 (27.5)	.333
Saphenous vein graft	47/50 (94.0)	18/18 (100.0)	29/32 (90.6)	.545	21/22 (95.5)	26/28 (92.9)	1.000	20/22 (90.9)	27/28 (96.4)	.576
Mammary artery bypass graft	4/50 (8.00)	0/18 (0.00)	4/32 (12.5)	.282	2/22 (9.09)	2/28 (7.14)	1.000	3/22 (13.6)	1/28 (3.57)	.308
Multi vessel treatment	37/205 (18.0)	16/105 (15.2)	21/100 (21.0)	.364	15/103 (14.6)	22/102 (21.6)	.208	18/103 (17.5)	19/102 (18.6)	.858
Number of lesions treated	1.29 ± 0.54	1.22 ± 0.44	1.36 ± 0.63	.065	1.20 ± 0.53	1.37 ± 0.53	.026	1.30 ± 0.56	1.27 ± 0.53	.728
Number of stents	1.52 ± 0.86	1.39 ± 0.71	1.65 ± 0.98	.032	1.38 ± 0.64	1.66 ± 1.02	.021	1.49 ± 0.80	1.55 ± 0.92	.599
Total stent length	29.6 ± 20.2	28.6 ± 19.8	30.7 ± 20.6	.448	26.9 ± 15.4	32.3 ± 23.8	.054	28.7 ± 18.4	30.5 ± 21.9	.504

Note: Continuous variables were expressed as mean ± *SD*, and categorical variables were reported as numbers and percentages.

TABLE 3 Medications at discharge

Medications at discharge	All patients	CABG SYNTAX score			Clinical SYNTAX score			Logistic clinical SYNTAX score		
	n = 205	Low: *n* = 105	High: *n* = 100	*p* value	Low: *n* = 103	High: *n* = 102	*p* value	Low: *n* = 103	High: *n* = 102	*p* value
Experimental antiplatelet therapy	104/205 (50.7)	48/105 (45.7)	56/100 (56.0)	.163	54/103 (52.4)	50/102 (49.0)	.676	56/103 (54.4)	48/102 (47.1)	.329
ACE-inhibitor/ARB	163 /203 (80.3)	81/104 (77.9)	82/99 (82.8)	.385	83/103 (80.6)	80/100 (80.0)	1.000	82/103 (79.6)	81/100 (81.0)	.861
Beta-blocker	163 /203 (80.3)	83/104 (79.8)	80/99 (80.8)	1.000	85/103 (85.2)	78/100 (78.0)	.482	80/103 (77.7)	83/100 (83.0)	.380
Statin	187/203 (92.1)	93/104 (89.4)	94/99 (95.0)	.194	93/103 (90.3)	94/100 (94.0)	.436	97/103 (94.2)	90/100 (90.0)	.307
Other lipid lowering drugs	19/203 (9.4)	8/104 (7.7)	11/99 (11.1)	.474	9/103 (8.7)	10/100 (10.0)	.813	9/103 (8.7)	10/100 (10.0)	.813
Optimal medical therapy	125/203 (61.6)	62/104 (59.6)	63/99 (63.6)	.567	66/103 (64.1)	59/100 (59.0)	.474	65/103 (63.1)	60/100 (60.0)	.668

Note: Continuous variables were expressed as mean ± *SD*, and categorical variables were reported as numbers and percentages. ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker. Optimal medical therapy was defined as the combination of at least one antiplatelet, ACE-inhibitor/ARB, beta-blocker, and statin.

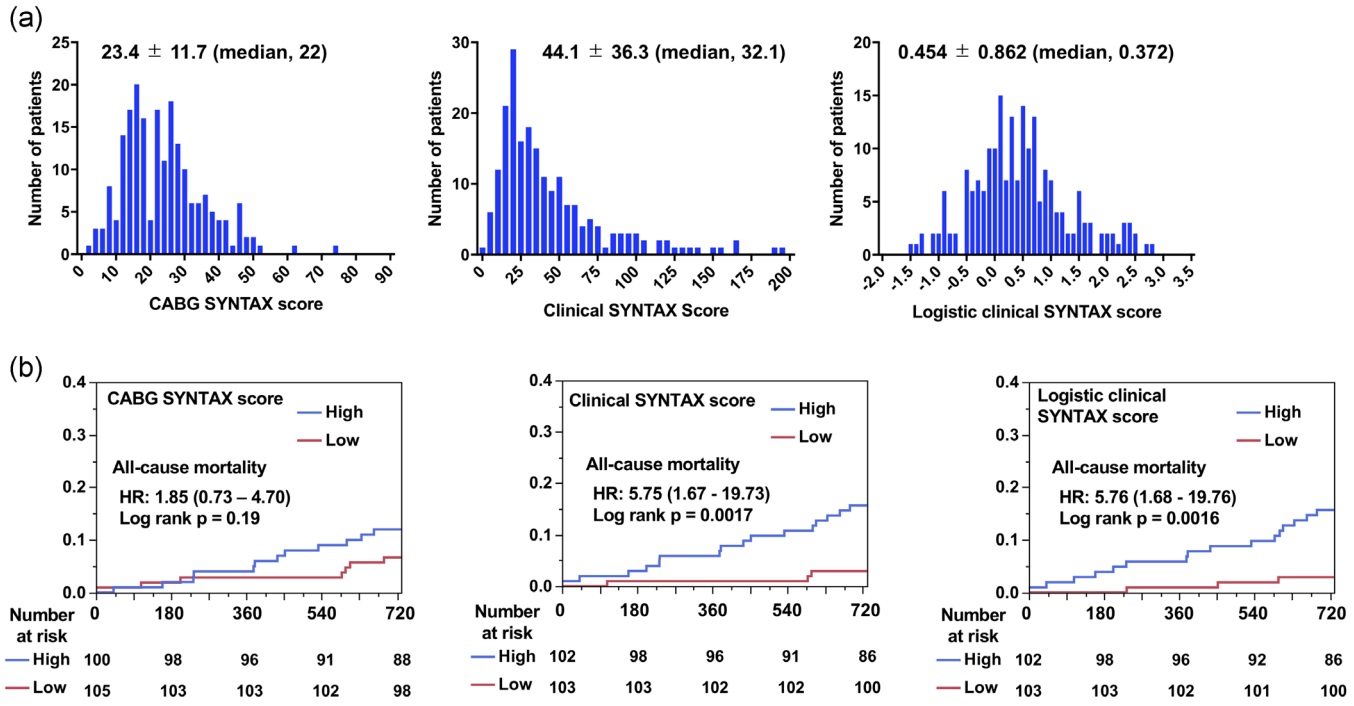

FIGURE 2 (a) Distribution of the anatomical CABG SYNTAX scores, clinical SYNTAX scores and logistic clinical SYNTAX scores. Scores are shown as mean ± *SD* (median). (b) Cumulative incidence of all-cause mortality at 2 years [Color figure can be viewed at wileyonlinelibrary.com]

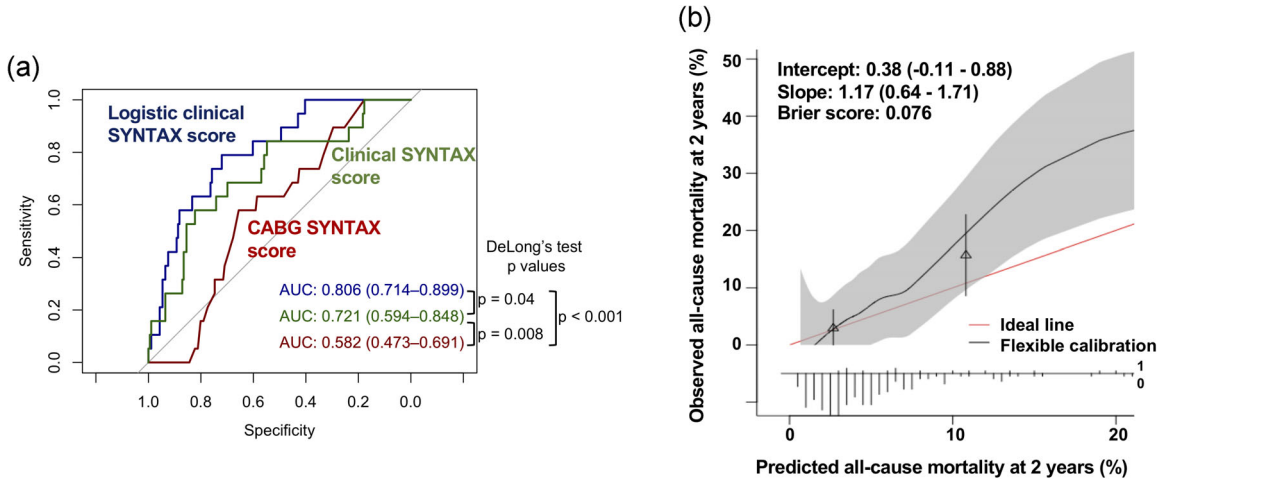

FIGURE 3 (a) Receiver-operating characteristic curves for the anatomical CABG SYNTAX score, clinical SYNTAX score and logistic clinical SYNTAX score predicting 2-year all-cause mortality. *p* values were obtained using DeLong's test. (b) Calibration plot for the updated logistic clinical SYNTAX score for 2-year all-cause mortality. Triangles represent two groups of patients with mean predicted probability and mean observed all-cause mortality rate with 95% confidence interval. The distribution of patients is indicated with spike at the bottom of the graph, stratified by outcomes (deaths above the *x*-axis and survivors below the *x*-axis) [Color figure can be viewed at wileyonlinelibrary.com]

2.2 | Endpoint

This study is a non-prespecified post-hoc analysis of the GLOBAL LEADERS trial. The primary endpoint of this study was 2-year all-cause mortality. The causes of death were classified to cardiovascular death, noncardiovascular death and undetermined according to the Academic Research Consortium (ARC)-2 definition.[20] As defined in the ARC-2 definition, undetermined death was classified as cardiovascular death for end point determination. Patient-oriented composite endpoint (POCE) of all-cause mortality, any stroke, any myocardial infarction or any revascularization, net adverse clinical events (NACE) of POCE or Bleeding Academic Research Consortium (BARC) grade 3 or 5 bleeding, and their components were also assessed with the scores that have been specifically designed to predict all-cause

mortality.[9,10] The survival status of the patients lost to follow up was obtained through public civil registry and more than 99.95% of the vital status at 2 years were available in the GLOBAL LEADERS trial.[13] The vital status at 2 years were available in all 205 patients.

2.3 | Statistical analysis

Continuous variables were expressed as mean ± *SD*, and were compared using Student's *t* test or Mann–Whitney *U* test. Categorical variables were reported as numbers and percentages, and were compared using chi square or Fisher's exact test as appropriate. The cumulative event rates at 2 years were estimated by Kaplan–Meier method and comparisons of outcomes were performed with log-rank test. The all-cause mortality risk reclassification was assessed using the net reclassification index (NRI). The predictive capability of the anatomical CABG SYNTAX score, clinical STNTAX score and logistic clinical SYNTAX score for the 2-year outcomes was assessed using receiver-operating characteristic (ROC) curve analysis with area under the curve (AUC). DeLong's test was used to analyze the differences between AUC values of the anatomical CABG SYNTAX score, clinical SYNTAX score and logistic clinical SYNTAX score and the corresponding *p* values. The predictive value was also assessed by integrated discrimination improvement (IDI). Agreement between observed and predicted all-cause mortality was assessed by calibration plot. Two groups based on the updated logistic clinical SYNTAX score were depicted in the calibration plot augmented by a locally weighted scatterplot smoothing.[21] Calibration-in-the-large (model intercept) and calibration slope were evaluated by fitting the calculated linear predictor in all patients with all-cause mortality as the outcome in the logistic regression model. Intercept of 0 and slope of 1 indicate perfect prediction. Negative and positive intercepts indicate overestimation and underestimation, respectively. Brier score was reported as an overall measure of performance, which ranges from 0 (perfect model) to 0.25 (non-informative model).[21]

A two-sided *p* value <.05 was considered statistically significant. Analyses were performed using JMP Pro14 (SAS Institute Inc., Cary, NC) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 4 Causes of death

Causes of death	All patients *n* = 205	Logistic clinical SYNTAX score	
		Low: *n* = 103	High: *n* = 102
Cardiovascular death	11/205 (5.37)	0/103 (0.00)	11/102 (10.8)
Noncardiovascular death	7/205 (3.37)	2/103 (1.94)	5/102 (4.90)
Undetermined	1/205 (0.48)	1/103 (0.97)	0/102 (0.00)

Note: Variables were reported as numbers and percentages.

TABLE 5 Predictive ability of the logistic clinical SYNTAX score for outcomes at 2 years

Outcomes at 2 years	AUCs
All-cause death	0.806 (0.714–0.899)
Cardiovascular death	0.825 (0.717–0.934)
Stroke	0.668 (0.354–0.982)
Myocardial infarction	0.674 (0.487–0.861)
Revascularization	0.537 (0.430–0.645)
BARC 3 or 5	0.574 (0.369–0.779)
POCE	0.590 (0.496–0.685)
NACE	0.592 (0.500–0.685)

Abbreviations: AUC, area under the curve; BARC, bleeding academic research consortium; POCE, patient-oriented composite endpoint; NACE, net adverse clinical events.

3 | RESULTS

Patient characteristics, procedure characteristics, and medications at discharge are shown in Tables 1–3, respectively. Distributions of the anatomical CABG SYNTAX Scores, clinical STNTAX scores and logistic clinical SYNTAX scores are shown in Figure 2a. Patients were divided into two groups based on the median of the scores, as previously reported[5] (anatomical CABG SYNTAX score; ≦22 [low group, *n* = 105], >22 [high group, *n* = 100], clinical SYNTAX score; ≦32.13 [low group, *n* = 103], >32.13 [high group, *n* = 102] and logistic clinical SYNTAX score; ≦0.372 [low group, *n* = 103], >0.372 [high group, *n* = 102]). The rate of all-cause mortality at 2 years in the high anatomical CABG SYNTAX score group tended to be numerically higher than in the low anatomical CABG SYNTAX score group, although they were not significantly different (low = 6.7% vs. high = 12.0%, *p* = .19, Figure 2b). On the other hand, there were significant differences in all-cause mortality at 2-year between patients in the high versus low clinical SYNTAX score group (low clinical SYNTAX score, 2.9%; high clinical SYNTAX score, 15.7%; *p* = .0017) and those in the high versus low logistic clinical SYNTAX score group (low logistic clinical SYNTAX score, 2.9%; high logistic clinical SYNTAX score, 15.7%; *p* = .0016, Figure 2b). The logistic clinical SYNTAX score tended to improve risk classification for the 2-year all-cause mortality, compared to the anatomical CABG SYNTAX score (NRI, 0.221 [–0.068–0.511], *p* = .134) But there was no difference between the logistic clinical SYNTAX score and clinical SYNTAX score (NRI, 0.000 [–0.217–0. 217], *p* = 1.000). The ROC curves of the anatomical CABG SYNTAX score, clinical SYNTAX score and logistic clinical SYNTAX score for the 2-year all-cause mortality are shown in Figure 3a, with significantly different AUC values of 0.582 (0.473–0.691), 0.721 (0.594–0.848), and 0.806 (0.714–0.899), respectively. This superior predictive ability of the logistic clinical SYNTAX score, compared to the anatomical CABG SYNTAX score and clinical SYNTAX score, was also demonstrated by the fact that IDI was 0.121 (0.052–0.190, *p* < .001) and 0.052 (0.010–0.094, *p* = .017), respectively.

The updated logistic clinical SYNTAX score systematically underestimated 2-year all-cause mortality as demonstrated by the positive

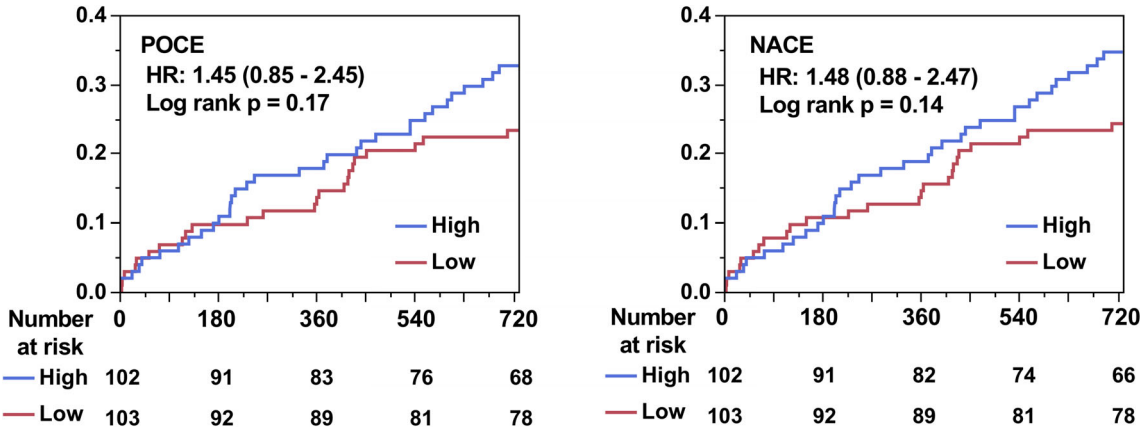

FIGURE 4 Cumulative incidence of patient-oriented composite endpoint (POCE) and net adverse clinical events (NACE) at 2 years [Color figure can be viewed at wileyonlinelibrary.com]

intercept (Figure 3b). Predicted probabilities of 2-year all-cause mortality in the two groups were close to the ideal line. The Brier score of the updated logistic clinical SYNTAX score for 2-year all-cause mortality was 0.076.

Definite cardiovascular deaths were more frequently observed than noncardiovascular death (n = 11 [5.37%] vs. n = 7 [3.37%], respectively, Table 4). Of note, no patient died from definite cardiovascular cause in low logistic clinical SYNTAX score group (Table 4), and the predictive ability for the 2-year cardiovascular death of the logistic clinical SYNTAX score was high (AUC: 0.825 [0.717–0.934], Table 5).

Applying the logistic clinical SYNTAX score to the 2-year POCE and NACE, the rates of POCE and NACE in 2 years was not significantly different in low and high score groups (POCE: 23.3% vs. 32.7%, p = .17; NACE: 24.2% vs. 34.6%, p = .14, respectively, Figure 4). The AUC values for the 2-year POCE and NACE were 0.590 (0.496–0.685) and 0.592 (0.500–0.685), respectively. AUC values of components of these composite endpoints are shown in Table 5.

4 | DISCUSSION

The main finding of this study is that compared to the anatomical CABG SYNTAX score, the logistic clinical SYNTAX score is more effective in predicting 2 years all-cause mortality after PCI in patients with prior CABG. Furthermore, to the best of our knowledge, this analysis is the first to evaluate the predictive value of the logistic clinical SYNTAX score in patients with prior CABG.

Initially, we evaluated the performance of the anatomical CABG SYNTAX score in predicting 2-year all-cause mortality. An anatomical SYNTAX score ≦22 is generally accepted as a low score,[22] and even in patients with prior CABG, patients with a low anatomical CABG SYNTAX score (≦22) tended to be at low risk for death (Figure 2b). The anatomical CABG SYNTAX score in patients with prior CABG at the time of PCI reflects on one hand the anatomical complexity of coronary artery disease and on the other hand the extent and functionality of the surgical revascularization previously performed, but apparently cannot predict the 2 year vital prognosis of the planned percutaneous revascularization post CABG. Therefore, this score may not have a sufficient discriminative ability to predict 2 year mortality. At variance with the anatomical CABG SYNTAX score, the native anatomical SYNTAX score in patients with prior CABG reflects the overall atherosclerosic burden but does not reflect the extent and functionality of revascularization.

But, when patients were divided into two groups based on the median of the native anatomical SYNTAX score in the present study population (native anatomical SYNTAX score; ≦34 [low group, n = 105], >34 [high group, n = 100], Figure S1a), there was no significant difference in the rate of all-cause mortality at 2 years between patients in the low and high native anatomical SYNTAX score groups (low = 8.6% vs. high = 10.0%, p = .73, Figure S1b).

Patients with equivalent anatomical SYNTAX scores sometimes have very different outcomes after revascularization, depending on the presence of comorbidities.[23] To overcome this limitation, comorbidities derived from surgical scores such as the ACEF[16,17] or EuroSCORE[24] were incorporated into the anatomical SYNTAX score (Clinical SYNTAX score[7] or Global risk classification,[25] respectively). Following this, the logistic clinical SYNTAX score was developed, updated and validated by combining the anatomical SYNTAX score with clinical factors selected on the basis of logistic regression coefficients.[8-10] Reflecting the logistic evolution of SYNTAX-derived scores, the predictive value for the 2-year all-cause mortality of the logistic clinical SYNTAX score was superior to the clinical SYNTAX score in this study (Figure 3a). Although the updated logistic clinical SYNTAX score systematically underestimated 2-year all-cause mortality in patients with prior CABG, predicted probabilities of 2-year all-cause mortality of the two groups were close to the identity line between the predicted and observed mortality (Figure 3b).

The discriminative ability of the logistic clinical SYNTAX score for 2-year all-cause mortality in 3271 patients without prior CABG has been already reported using the GLOBAL LEADERS database.[10] Notably in this population, the prognostic value of the logistic clinical

SYNTAX score was much higher in patients with prior CABG (AUC, 0.806; Figure 3a) than in patients without (0.71).[10]

This differential performance can be partially explained by considering the clinical characteristics and event rates in patients with and without prior CABG. The rate of all-cause mortality in the present study (Figure 2b) was 9.27%, whereas in the 3,271 patients without prior CABG in the validation cohort it was 2.66%.[10] Patients with prior CABG also tended to be older, have lower CrCl and LVEF, and had more comorbidities, such as diabetes mellitus and peripheral vascular disease, compared to those without (Table 6).[10] Furthermore, the rates of hypertension, hypercholesterolemia, previous MI, previous PCI, previous stroke, and COPD were also higher in patients with prior CABG, compared to those without (Table 6). Taken together, the difference between the predictive values of the logistic clinical SYNTAX score in patients with prior CABG compared to those without might be largely dependent on major differences in clinical characteristics.

The predictive values of the logistic clinical SYNTAX score for POCE and NACE were poor mainly due to the poor predictive value for revascularization, although those for any stroke and myocardial infarction were possibly helpful.[26] The logistic clinical SYNTAX score was updated to predict all-cause mortality in 6304 patients enrolled in seven contemporary coronary stent trials (SIRTAX, ARTS-II, STRATEGY, MULTISTRATEGY, LEADERS, SYNTAX, RESOLUTE All-Comers), and was not accurate enough to predict outcomes other than mortality. However, of note, in the present study, all definite cardiovascular deaths occurred in the high logistic clinical SYNTAX score group (Table 4).

Pharmacological therapy and lifestyle changes for risk factor modification has been strongly recommended for secondary prevention (Ia).[22] In the SYNTAX trial started in 2005, optimal medical therapy (OMT), defined as the combination of at least 1 antiplatelet, angiotensin-converting-enzyme (ACE)-inhibitor/ angiotensin II receptor blocker (ARB), beta-blocker, and statin was given in only 50.2% of patients at the time of discharge after PCI.[27] The GLOBAL LEADERS trial was started in 2013. Regardless of the strong OMT recommendation, OMT was prescribed in 61.6% at discharge and even in the high logistic clinical SYNTAX score patients, the rate of OMT was almost the same and only 60% (Table 3). The logistic clinical SYNTAX score can predict the individual mortality rate after PCI, and should be a strong incentive to an aggressive adjunctive pharmacological treatment and a closer monitoring of these patients at high risk.

In the future, further iterations of the logistic clinical SYNTAX score may be needed due to improvement of mortality after PCI. However, at present, the logistic clinical SYNTAX score has a high predictive ability for 2-year all-cause mortality after PCI in patients with prior CABG.

TABLE 6 Patient characteristics in patients with and without prior CABG

	Present study		
Baseline characteristics	**Patients with prior CABG *n* = 205**	**Patients without prior CABG *n* = 3,271**	***p* value**
Age (years)	68.8 ± 8.73	64.3 ± 10.5	<.001
Male	83.4%	76.4%	.021
Body mass index (kg/m^2)	28.2 ± 4.73	28.1 ± 4.46	.923
CrCl (ml/min)	81.0 ± 28.8	92.8 ± 32.7	<.001
LVEF (%)	52.3 ± 12.6	54.8 ± 10.7	.007
Hypertension	82.9%	69.7%	<.001
Hypercholesterolemia	87.2%	66.9%	<.001
Diabetes mellitus	36.6%	22.9%	<.001
Previous MI	46.1%	20.9%	<.001
Previous PCI	52.7%	28.6%	<.001
Previous stroke	4.88%	2.33%	.034
Established PVD	20.0%	6.14%	<.001
COPD	9.76%	5.61%	.020

Note: Continuous variables were expressed as mean ± *SD*, and categorical variables were reported as percentages. CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease.

4.1 | Limitation

The present study is based on a non-prespecified post hoc analysis. In view of the post hoc nature of the analysis, the results have to be interpreted strictly as hypothesis-generating. The sample size (*n* = 205) was small as a subanalysis of the large GLOBAL LEADERS trial (*n* = 15,991). The number of deaths was 19 in the present study, and external validation of a prognostic model generally requires a minimum of 100 events.[28] Therefore, the sample size might be insufficient to demonstrate the efficacy of the anatomical CABG SYNTAX score. From the 275 patients with prior CABG included in the first 4,000 consecutive patients with corelab analysis of the SYNTAX score (prespecified analysis), We excluded patients without anatomical CABG SYNTAX score and patients who had at least one missing variable for the calculation of the logistic clinical SYNTAX score. Therefore, selection bias might exist. The results need to be confirmed in dedicated large-scale trials. In terms of extent of revascularization, the higher prognostic value of the post-PCI (residual) CABG SYNTAX score in patients with prior CABG, compared to the CABG SYNTAX score, has been previously reported.[6] In the GLOBAL LEADERS trial, only diagnostic angiograms for index PCI were collected and post procedural angiograms were not available, therefore, the predictivity of the residual CABG SYNTAX score could not be evaluated. In addition, detailed information about prior CABG surgery, such as the number of bypass grafts performed and the completeness of revascularization, was missing in this trial which enrolled patients exclusively for PCI.

5 | CONCLUSION

The logistic clinical SYNTAX score was superior to the anatomical CABG SYNTAX score for predicting 2-year all-cause mortality after PCI.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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