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EDITORIAL COMMENT: Expert Article Analysis for:
Predicting mortality after percutaneous coronary intervention: The need for improved risk models

Predicting 2-year all-cause mortality after contemporary PCI: Updating the logistic clinical SYNTAX score

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Abstract

Aims: We aimed to update the logistic clinical SYNTAX score to predict 2 year all-cause mortality after contemporary percutaneous coronary intervention (PCI).

Methods and results: We analyzed 15,883 patients in the GLOBAL LEADERS study who underwent PCI. The logistic clinical SYNTAX model was updated after imputing missing values by refitting the original model (refitted original model) and fitting an extended new model (new model, with, selection based on the Akaike Information Criterion). External validation was performed in 10,100 patients having PCI at Fu Wai hospital.

Chronic obstructive pulmonary disease, prior stroke, current smoker, hemoglobin level, and white blood cell count were identified as additional independent predictors of 2 year all-cause mortality and included into the new model.

The c-indexes of the original, refitted original and the new model in the derivation cohort were 0.74 (95% CI 0.72–0.76), 0.75 (95% CI 0.73–0.77), and 0.78 (95% CI 0.76–0.80), respectively. The c-index of the new model was lower in the validation cohort than in the derivation cohort, but still showed improved discriminative ability of the newly developed model (0.72; 95% CI 0.67–0.77) compared to the refitted original model (0.69; 95% CI 0.64–0.74). The models overestimated the observed 2 year all-cause mortality of 1.11% in the Chinese external validation cohort by 0.54 percentage points, indicating the need for calibration of the model to the Chinese patient population.

Conclusions: The new model of the logistic clinical SYNTAX score better predicts 2 year all-cause mortality after PCI than the original model. The new model could guide clinical decision making by risk stratifying patients undergoing PCI.

KEYWORDS
coronary artery disease, percutaneous coronary intervention, risk score, risk stratification

1 | INTRODUCTION

The logistic clinical SYNTAX score was developed from a pooled database of seven stent trials to predict all-cause mortality within 1 year after percutaneous coronary intervention (PCI).[1] The core model of the score consists of the anatomic SYNTAX score and the components of the age, creatinine, ejection fraction (ACEF) score.[2] The extended model—which added six variables to the core model—improved its discriminative ability. The logistic clinical SYNTAX score better predicted and stratified long-term mortality compared to the anatomic SYNTAX score alone in patients undergoing PCI.[1,3] Later on, the logistic clinical SYNTAX score was revised using the derivation cohort to predict 2 and 3 year all-cause mortality after PCI.[4]

New-generation drug-eluting stents (DES), physiology and image-guided revascularization, and guideline-directed medical therapy are all increasingly used in contemporary PCI[5-8] and have contributed to improvements in patient outcomes.[9] Of note, at the time of the development of the logistic clinical SYNTAX score, guidance of PCI with pressure-wire assessment and stent optimization using intravascular imaging were not fully endorsed by revascularization guidelines and the majority of patients were still receiving bare-metal or first-generation DES. Furthermore, the usage of statins and potent antiplatelet therapy post-PCI was lower than current practice. In addition, several important predictors for all-cause mortality after PCI such as a history of chronic obstructive pulmonary disease (COPD), previous coronary artery bypass graft (CABG), and anemia were not available in the developmental cohort. Many studies have demonstrated the impact of these variables on the outcomes after PCI.[10,11]

Prespecified validation of the existing logistic clinical SYNTAX score in 3,271 patients of the GLOBAL LEADERS study population showed moderate discrimination and calibration.[12] The significant change in PCI practice and the substantial improvement in patient outcomes have made the logistic clinical SYNTAX score essentially obsolete and in desperate need of updating in order to keep its performance relevant to contemporary practice. Therefore, we aimed to update the logistic clinical SYNTAX score for the prediction of 2 year all-cause mortality after PCI in the GLOBAL LEADERS study, and to validate this new model in a large PCI cohort.

2 | METHODS

2.1 | Study design and population

The GLOBAL LEADERS study (NCT01813435) was a randomized clinical trial evaluating two strategies of antiplatelet therapy in 15,968 all-comers patients undergoing PCI.[13] The patients were enrolled at 130 sites (secondary or tertiary hospital) in 18 countries worldwide between July 2013 and November 2015. Inclusion, exclusion criteria of the GLOBAL LEADERS study and details of the antiplatelet strategy are in the Appendix (Supporting Information). In brief, patients were enrolled to the study in an all-comers concept; no restrictions to the number, severity, location of lesions or the number of stents used. Key exclusion criteria were the planned need for surgery within 6 months after the index procedure or need for chronic anticoagulation therapy. PCI was done uniformly with biodegradable polymer biolimus A9-eluting stents and bivalirudin was administered whenever feasible.

The institutional review board at each participating center approved the study and all patients provided informed consent. The study complied with the Declaration of Helsinki and Good Clinical Practice.

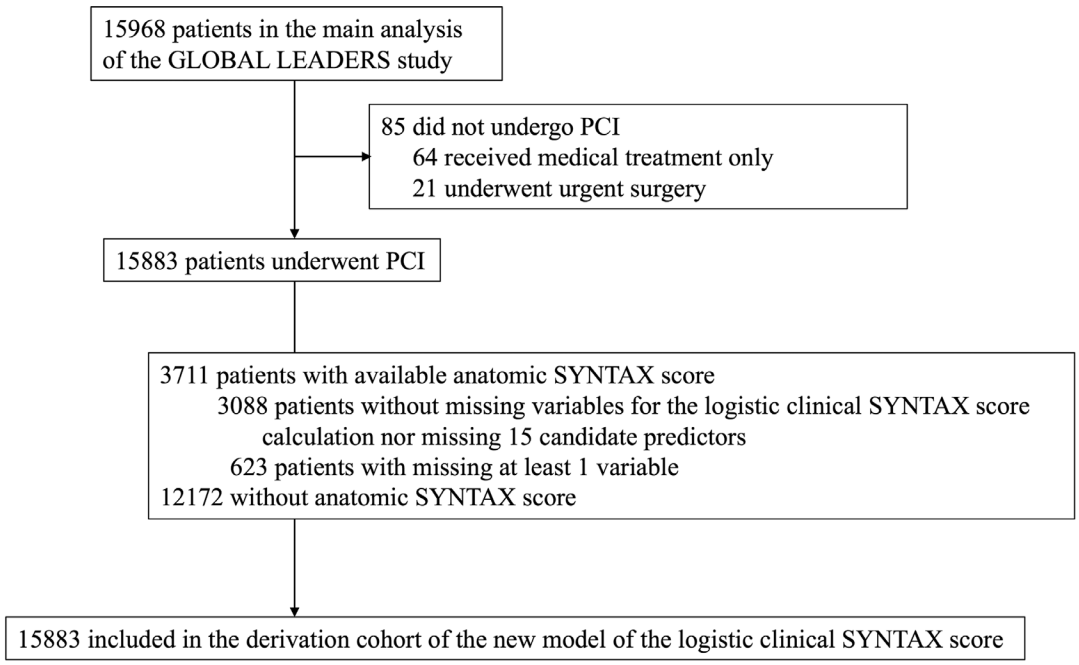
2.2 | Outcomes

The endpoint of the present study was 2 year all-cause mortality, a hard endpoint, which required no adjudication or blind assessment. The survival status of those patients lost to follow-up was obtained through public civil registries such that more than 99.95% of the vital status at 2 years were available in the study.[13]

2.3 | The logistic clinical SYNTAX score for 2 year all-cause mortality

The logistic clinical SYNTAX score for 2 year all-cause mortality after PCI combined the anatomic SYNTAX score with seven clinical characteristics and comorbidities; age (years), creatinine clearance (ml/min), left ventricular ejection fraction (LVEF, %), body mass index (BMI, kg/m^2), diabetes, peripheral vascular disease and SYNTAX-like characteristics (left main disease in isolation or associated with one, two or three-vessel disease or three-vessel disease alone).[4]

In the GLOBAL LEADERS study, the anatomic SYNTAX score analysis was prespecified in the protocol for the first 4,000 consecutive patients enrolled between July 1, 2013 and April 22, 2014. The anatomic SYNTAX score was analyzed off-line by an independent core lab blinded to the treatment allocation.[14] In cases of ST segment elevation MI, the anatomic SYNTAX score was calculated using the angiogram performed prior to wiring as described previously.[15] In patients with CABGs, the anatomic SYNTAX score of the native coronary arteries were deducted based on the segment weighting of the coronary segment supplied by the bypassed graft as described previously.[16]



*including age, creatinine clearance, LVEF, diabetes, peripheral vascular disease, body mass index, anatomic SYNTAX score and SYNTAX-like characteristics
**15 candidate predictors are sex, hypertension, hypercholesterolemia, previous major bleeding, current smoker, COPD, previous stroke, previous MI, previous PCI, previous CABG, clinical presentation, heart failure at presentation, cardiac arrest at presentation, hemoglobin level, and WBC level

FIGURE 1 Flow of the patients in the derivation cohort of the new model of the logistic clinical SYNTAX score. PCI, percutaneous coronary intervention

A total of 15 variables (sex, hypertension, hypercholesterolemia, previous major bleeding, current smoker, COPD, previous stroke, previous MI, previous PCI, previous CABG, clinical presentation, heart failure at presentation, cardiac arrest at presentation, hemoglobin level, and white blood cell count) in the GLOBAL LEADERS study database were identified as candidate predictors to improve the score's performance. These variables were selected based on the existing clinical knowledge of their potential correlation with adverse outcomes after PCI.[17]

2.4 | Statistical methods

We handled missing data in the GLOBAL LEADERS study database with multivariable imputation by chained equations creating 10 complete datasets.[18] This approach included the imputation of the anatomic SYNTAX score in patients for whom the anatomic SYNTAX scores was not available.

The logistic clinical SYNTAX model was updated in the imputed GLOBAL LEADERS study dataset by refitting the original model and by fitting an extended new model.[19]

For the "original model," we used the original formula of the score without any update (Supplementary Figure S1). The "refitted original model" was derived by fitting the eight predictors of the original logistic clinical SYNTAX score to all-cause mortality in the GLOBAL LEADERS study population using Cox regression analysis. The "new model" was developed by fitting the eight original predictors and the 15 candidate predictors in a Cox regression analysis. Restricted cubic splines were used to test the nonlinear associations between continuous variables and all-cause mortality. The original predictors of the logistic clinical SYNTAX score were retained in the multivariable model irrespective of predictive ability. Backwards selection was used to select additional predictors in the new model by using the Akaike Information Criterion as stopping rules to compare the fit of the models and to avoid the model complexity.[19]

Discriminative ability was assessed using Harrell's concordance index (c-index).[20] The c-index estimates the probability for two randomly selected patients that the one who has lower predicted risk will outlive the one who has higher predicted risk. The c-index ranges from 0.5 (no discrimination) to 1.0 (theoretically maximal value). An overfitting of the model may lead to an optimistic impression of the model performance in which the model may perform differently in the population outside the developmental cohort. The difference between true and apparent performance of the model is defined as optimism. We used the internal bootstrap validation (200 samples with replacement)[19] to estimate the optimism and correct the c-index. We used Kaplan–Meier curves of 2 year all-cause mortality in fifths of the predicted risk score to assess the ability of the score to differentiate between low-risk and high-risk patients. Calibration was assessed by calibration plots of 2 year all-cause mortality. Net reclassification improvement (NRI) was assessed using the survival outcome reclassification method.[21]

TABLE 1 Clinical characteristics of the derivation cohort of the new model of the logistic clinical SYNTAX score

	Derivation cohort (N = 15,883)
Age (years)	64.5 ± 10.3 (N = 15,883)
Women	23.3 (3,696/15,883)
Hypertension	73.6 (11,656/15,829)
Hypercholesterolemia	69.6 (10,706/15,381)
Current smoking	26.2 (4,153/15,883)
Diabetes	25.3 (4,018/15,872)
Peripheral vascular disease	6.3 (996/15,737)
Chronic obstructive pulmonary disease	5.1 (812/15,812)
LVEF (%)	54.9 ± 10.6 (N = 15,008)
Body mass index (kg/m^2)	28.2 ± 4.6 (N = 15,881)
Prior MI	23.3 (3,691/15,837)
Prior PCI	32.7 (5,196/15,869)
Prior CABG	5.9 (939/15,870)
Prior stroke	2.6 (418/15,860)
Prior bleeding	0.6 (98/15,862)
Clinical presentation	
Stable coronary artery disease	53.1 (8,426/15,883)
Unstable angina	12.7 (2,011/15,883)
NSTEMI	21.2 (3,362/15,883)
STEMI	13.1 (2,084/15,883)
Heart failure at presentation	2.4 (374/15,883)
Cardiac arrest at presentation	0.6 (93/15,883)
Laboratory data	
Creatinine clearance (ml/min)	91.7 ± 32.8 (N = 15,740)
Hemoglobin (g/dl)	14.2 ± 1.5 (N = 15,081)
White blood cell count (10^9 cells/L)	8.3 ± 2.7 (N = 14,505)
Anatomic SYNTAX score	12.7 ± 9.0 (N = 3,711)
SYNTAX-like characteristics	25.4 (941/3,711)

Note: Values are mean ± *SD* (N) or % (n/N).
Abbreviations: CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

As a sensitivity analysis, we assessed the predictive performances of the two models in the subsample of the derivation cohort with available anatomic SYNTAX scores (3,711 patients).

2.5 | External validation

The external validation was performed by Cardiovascular Imaging Core Laboratory for Interventional Diagnosis and Therapy, National Center for Cardiovascular Diseases, Beijing, China. The original model, the refitted original model and the new model of the logistic clinical SYNTAX score were validated in 10,724 patients who underwent PCI in Fu Wai hospital from January 2013 to December 2013. We excluded

patients with incomplete information for the calculation of both models of the logistic clinical SYNTAX score, which resulted in 10,100 patients in the external validation cohort. Discrimination and calibration were assessed using similar methods as in the derivation cohort.

All analyses were performed with R version 3.4.2 (R Foundation, Vienna, Austria).

3 | RESULTS

In the GLOBAL LEADERS study, 15,883 patients received PCI and 474 patients died of any cause within 2 years after PCI (2.99%). Figure 1 demonstrates the flow of patients in the derivation cohort of the new model of the logistic clinical SYNTAX score. Table 1 shows characteristics of the derivation cohort. Number of missing observation per candidate predictor are shown in Supplementary Table S1. In multivariable regression analysis, beside the eight original predictors that were forced into the model, the backward selection procedure identified five additional variables that were strongly associated with 2 year all-cause mortality: history of COPD, prior stroke, current smoker, hemoglobin level, and white blood cell count (Table 2). The associations between all-cause mortality and the anatomic SYNTAX score, age, creatinine clearance and white blood cell count were almost linear (Supplementary Figure S2). The nonlinear associations between all-cause mortality and LVEF and BMI were modeled using additional quadratic terms while hemoglobin level was capped at values above 15 g/dl. The models developed to predict 2 year all-cause mortality after PCI are show in full in Figure 2.

The c-indexes of the original model, the refitted original model and the new model in the derivation cohort—after correction for optimism—were 0.74 (95% CI 0.72–0.76), 0.75 (95% CI 0.73–0.77), and 0.78 (95% CI 0.76–0.80), respectively. The Kaplan–Meier curves of all-cause mortality in quintiles showed that the new model discriminated mortality among the first, second, and third quintiles better than the refitted original model (Figure 3). The original model overestimated 2 year all-cause mortality in the derivation cohort with 0.77

TABLE 2 Multivariable associations of the components of the refitted original and the new model of the logistic clinical SYNTAX score with 2 year all-cause mortality

	Refitted original model				New model			
Variables	Coefficient	HR (95% CI)[a]	Chi-square	p-value	Coefficient	HR (95% CI)[a]	Chi-square	p-value
Anatomic SYNTAX score (for each increase of 1 point)	0.0388	1.04 (1.02–1.06)	13.4	.0003	0.041	1.04 (1.02–1.06)	15.6	<.0001
SYNTAX-like characteristics	−0.5103	0.60 (0.33–1.10)	2.8	.0964	−0.5314	0.59 (0.33–1.04)	3.3	.0697
Age (for each increase of 10 years)	0.3161	1.37 (1.22–1.55)	26.1	<.0001	0.3945	1.48 (1.30–1.69)	33.8	<.0001
Creatinine clearance (for each increase of 10 ml/min)	−0.1999	0.82 (0.77–0.87)	37.7	<.0001	−0.0755	0.93 (0.89–0.97)	10.1	.0015
Left ventricular ejection fraction (per 1%)	−0.0579	0.94 (0.93–0.95)	104.3	<.0001	−0.0991	0.81 (0.72–0.91)[b]	83	<.0001
LVEFaLVEF	–	–	–	–	0.0007	–	12.6	.0004
BMI (per 10 kg/m2)	0.1456	1.16 (0.93–1.44)	1.7	.1946	−0.883	1.06 (0.93–1.20)[b]	7.7	.0958
BMIaBMI	–	–	–	–	0.1762	–	4.3	.0379
Established peripheral vascular disease	0.5932	1.81 (1.38–2.38)	17.9	<.0001	0.4174	1.52 (1.15–2.00)	8.8	.003
Diabetes mellitus	0.2583	1.29 (1.06–1.58)	6.3	.0121	0.1579	1.17 (0.95–1.44)	2.3	.1326
Chronic obstructive pulmonary disease	–	–	–	–	0.7829	2.19 (1.69–2.84)	34.6	<.0001
Previous stroke	–	–	–	–	0.607	1.83 (1.23–2.73)	9	.0027
Hemoglobin (for each increase of 1 g/dl)	–	–	–	–	−0.244	0.78 (0.73–0.84)	54.8	<.0001
White-blood-cell count (for each increase of 10^9 cells per L)	–	–	–	–	0.0771	1.08 (1.05–1.11)	23.7	<.0001
Current smoker	–	–	–	–	0.3729	1.45 (1.15–1.83)	9.81	.0017

Note: Creatinine clearance was capped at the value above 90 ml/min in the refitted original model. LVEF was capped at the value above 50 in the refitted original model. BMI was modeled linearly in the refitted original model. In the new model, for easy calculation of individual risk predictions, the nonlinear associations between all-cause mortality and LVEF and BMI were modeled using quadratic terms, and between all-cause mortality and hemoglobin level by capping hemoglobin values above 15 g/dl. Hemoglobin level was capped at values above 15 g/dl.

Abbreviation: LVEF, left ventricular ejection fraction.

[a]Hazard ratio and 95% confidence interval was derived from the imputed dataset.

[b]Hazard ratio for LVEF and BMI at the median value are reported for the new model.

percentage points (2.99 vs. 3.76%). Calibration plots of the refitted original model and the new model in the derivation cohort showed good agreement between predicted and Kaplan–Meier estimates of 2 year all-cause mortality in all quintiles (Figure 4). The sensitivity analysis of the performance of both models in 3711 patients with available anatomic SYNTAX score showed consistent results with the analysis in the full-imputed datasets (Supplementary Figure S3).

Compared to the refitted original model, the new model improved reclassification by 10.6% in patients who died and 4.5% in patients who survived resulting in NRI of 15.1% (Supplementary Table S2). Compared with the original model, the new model improved reclassification by 12.5% in patients who died and 2.6% in patients who survived resulting in the NRI of 15.1%.

The three models were externally validated in 10,100 patients in the PCI dataset of Fu Wai hospital. Characteristics of patients in the validation cohort are shown in Supplementary Table S3. In the validation cohort, mean age, mean anatomic SYNTAX score, mean WBC count, prevalence of PVD, and COPD were lower while the prevalence of diabetes, previous stroke and current smoker were higher than in the derivation cohort. The rate of 2 year all-cause mortality in the external validation cohort was 1.11%. Mean predicted 2 year all-cause mortality of the refitted original model and the new model was 1.63 and 1.64% respectively. Both the refitted original model and the new model overestimated the observed 2 year all-cause mortality particularly in the fifth quintile (Figure 4 lower panel). Hence, an overall calibration—only adjusting the 2 year baseline hazard (intercept)—may be necessary to calibrate the model to the Chinese patient population (Figures 2 and 4). The c-indexes of the three models were lower in the validation cohort than in the derivation cohort, but still showed improved discriminative ability of the newly developed model (0.72; 95% CI 0.67–0.77) as compared to the refitted original model (0.69; 95% CI 0.64–0.74) or to the original model (0.70; 95% CI 0.65–0.75). The new model discriminated outcome among the first, second, and third quintiles better than the refitted original model (Figure 3). As an indication of the maximum achievable discriminative ability of our new model, we refitted the model to the validation cohort, resulting in a c-index of 0.74 (95% CI 0.69–0.78).

The NRI of the new model compared with the original model and the refitted original model in the validation cohort was 7.2 and 14.7% respectively (Supplementary Table S4).

New model of the logistic clinical SYNTAX score

LN Hazard (Death) = 0.0410* SXscore – 0.5314*SYNTAX-like + 0.0394 *Age – 0.0076* CrCl – 0.0991*LVEF + 0.0007 *(LVEF*LVEF) - 0.0883 *BMI + 0.0018*(BMI*BMI) + 0.4174*PVD+ 0.1579*DM + 0.7829*COPD + 0.6070*stroke + 0.2440*$(15\text{-}Hb)_+$ + 0.0771*WBC + 0.3729*Smoke – 3.0766†

† intercept in validation cohort was -3.4763 instead of -3.0766

Re-fitted original model of the logistic clinical SYNTAX score

LN Hazard (Death) = 0.0388 * SXscore – 0.5103*SYNTAX-like + 0.0316*Age + 0.0200*$(90\text{-}CrCl)_+$ + 0.0579*$(50\text{-}LVEF)_+$ + 0.0146*BMI + 0.5932*PVD + 0.2583*DM – 7.1152

Risk of 2-year death = 1- exp[-exp(LN Hazard(Death))]

Key

SXscore	= Anatomic SYNTAX score
SYNTAX-like	= SYNTAX-like characteristics: three vessel disease or left main stem disease (Yes = 1/No = 0)
Age	= Age (years)
LVEF	= Left Ventricular Ejection Fraction
CrCl	= Creatinine clearance by Cockcroft-Gault Equation (ml/min)
BMI	= Body Mass Index (kg/m2)
PVD	= Peripheral Vascular Disease (Yes = 1/No = 0): Extracardiac arteriopathy – one or more of the following: 1) claudication,2) carotid occlusion or >50% stenosis, 3) amputation for arterial disease, 4) previous or planned intervention on the abdominal aorta, limb arteries or carotids)
DM	= Diabetes Mellitus, either non-insulin treated or insulin-treated
COPD	= Chronic Obstructive Pulmonary Disease: Chronic lung disease, long-term use of bronchodilators or steroids for lung disease
Stroke	= Previous stroke
Hb	= Hemoglobin (g/dL)
WBC	= White Blood Cell (10^9 cells/L)
Smoke	= Current smoker
$(15\text{-}Hb)_+$	indicates 15-Hb for positive values, 0 for negative values
$(90\text{-}CrCl)_+$	indicates 90-CrCl for positive values, 0 for negative values
$(50\text{-}LVEF)_+$	indicates 50-LVEF for positive values, 0 for negative values

FIGURE 2 Regression formula of the refitted original model and the new model of the logistic clinical SYNTAX score to predict 2 year all-cause mortality after PCI. PCI, percutaneous coronary intervention [Color figure can be viewed at wileyonlinelibrary.com]

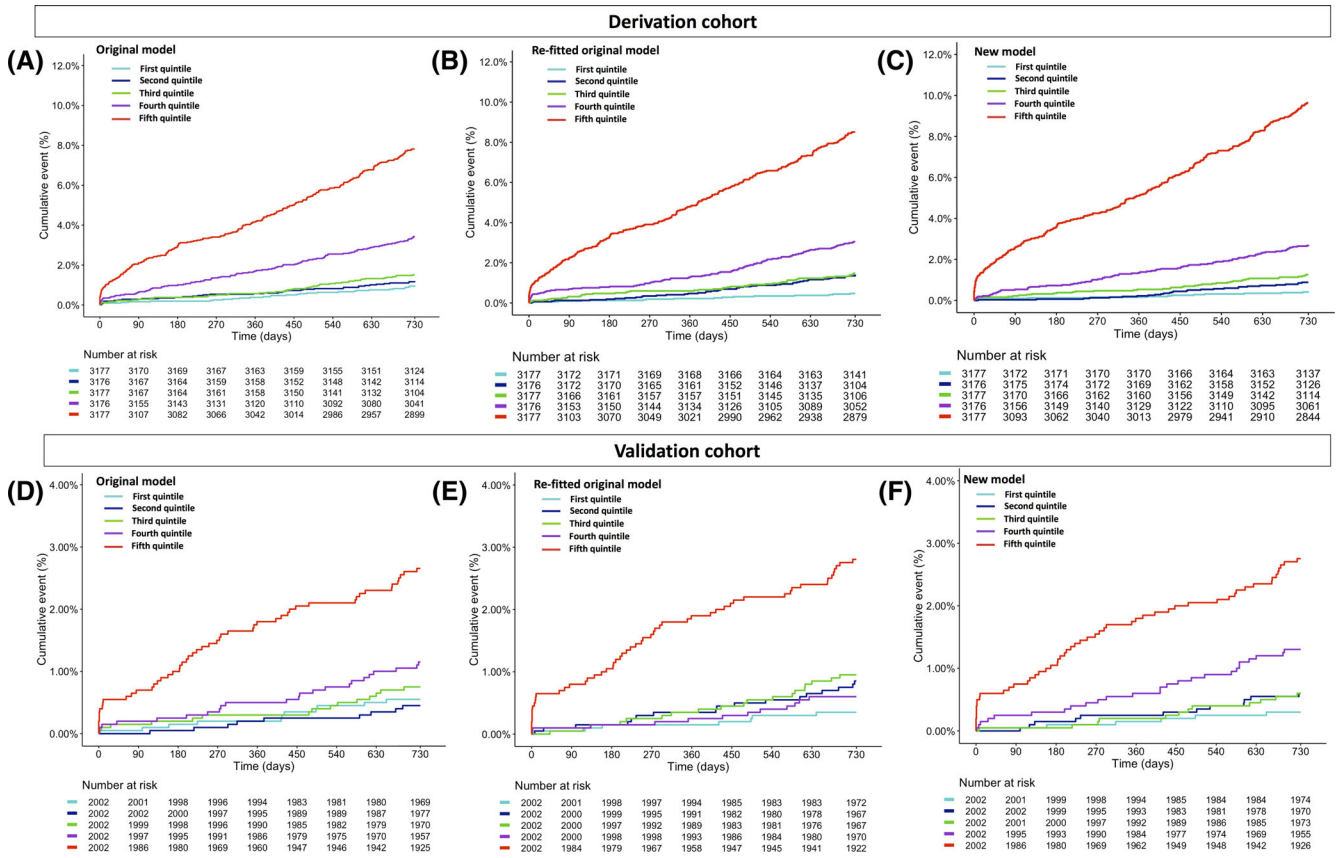


FIGURE 3 Kaplan–Meier curves of 2 year all-cause mortality among the logistic clinical SYNTAX score quintiles in derivation and validation cohort. Panel A and B shows the Kaplan–Meier curves for 2 year all-cause mortality among the refitted original model and the new model of the logistic clinical SYNTAX score respectively in the derivation cohort. Panel C and D shows the Kaplan–Meier curves for 2 year all-cause mortality among the refitted original model and the new model of the logistic clinical SYNTAX score respectively in the validation cohort [Color figure can be viewed at wileyonlinelibrary.com]

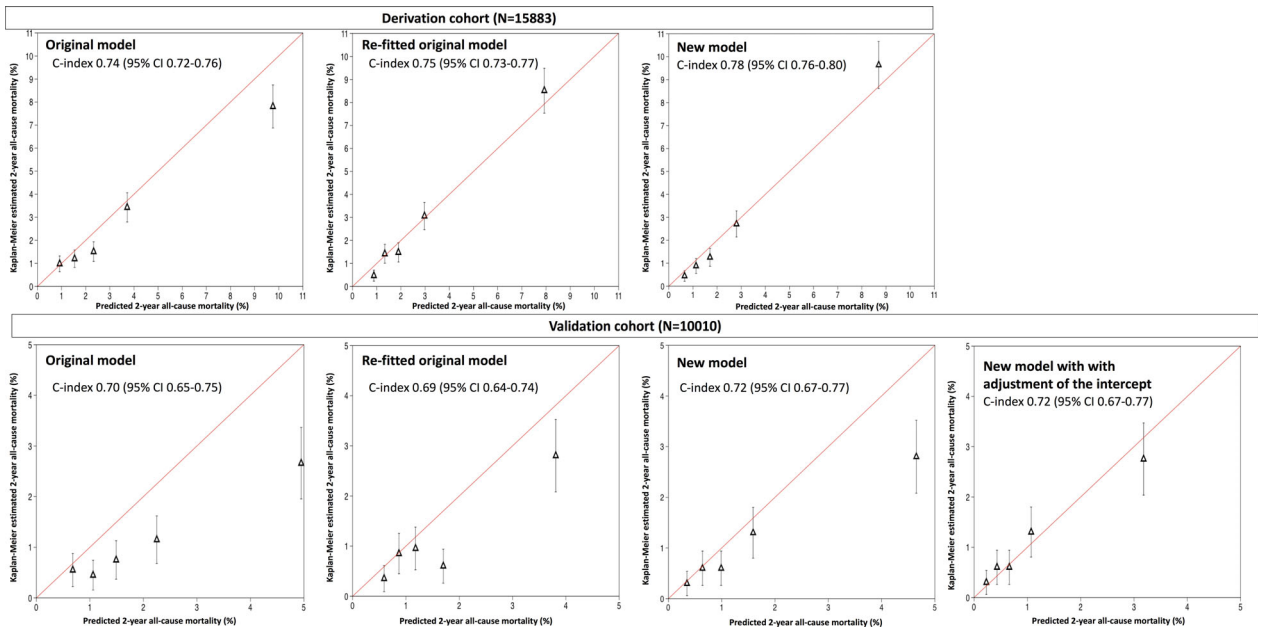


FIGURE 4 Calibration plot of the original, refitted original and new model of the logistic clinical SYNTAX score in derivation and validation cohort. Triangles represent five quintiles of patients with mean predicted probability derived from the logistic clinical SYNTAX score and Kaplan–Meier estimate of 2 year all-cause mortality with 95% confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In the present study, the logistic clinical SYNTAX score was updated using a large population treated with contemporary PCI nested in a randomized controlled trial. The models were also externally validated in a large PCI cohort in which the characteristics and outcomes were substantially different from the derivation cohort. The main findings are as follows: (1) The new model of the logistic clinical SYNTAX score included five additional predictors, which are relatively simple and easy to measure. (2) The 95% confidence interval of C-indexes of the three models overlap considerably; however, the discriminative ability of the new model is useful according to a generally accepted approach.[22] Discriminative ability of the new model was acceptable in external validation and better than the refitted original model in differentiating the risk between groups. (3) Although the new model overestimated 2 year all-cause mortality in the highest risk group of the external validation cohort, calibration was reasonable in the majority of the patients.

Risk stratification and prediction are essential in the clinical care of patients with coronary artery disease undergoing revascularization.[23] To serve this purpose, clinical prediction models have been developed to predict prognosis after PCI. These models combine several predictors in the multivariable regression model and give a risk estimation for each patient.[24]

Two risk models were established to predict medium- to long-term outcomes after PCI and were previously recommended in the European Society Cardiology guideline for myocardial revascularization.[1,25,26] The ASCERT-PCI model, which was developed from a large PCI registry between 2004 and 2009,[26] identified 2 anatomical and 17 clinical variables which could be used to predict mortality up to 3 years after PCI. The logistic clinical SYNTAX score, which was developed from a pooled database of stent trials which enrolled patients between 2005 and 2007,[1,4] used fewer variables (one anatomical and seven clinical variables). The logistic clinical SYNTAX score was initially developed to predict 1 year mortality after PCI, however it was subsequently revised to predict mortality at 2 and 3 years.[4] Both scores share common shortcomings due to the fact that they were derived when potent antiplatelet inhibitors, newer-generation DES or guideline-directed optimal medical therapy were not available or widely implemented. In addition, the risk profile of PCI patients such as the prevalence of advanced age or other comorbidities has changed over time. Consequently, established risk scores may not be up to date and their predictive performance may be suboptimal in contemporary practice.[12,27]

In the present analysis, instead of developing a new score, we updated the logistic clinical SYNTAX score by re-estimation and extension using the data of a large contemporary randomized trial to predict 2 year all-cause mortality. This approach avoids losing the information from the previous developmental study and allows for robust combination of this information with data from the new settings.[28] We found five additional predictors, which independently predict 2 year all-cause mortality. These predictors included COPD, prior stroke, current smoker, hemoglobin level and white blood cell count—that are relatively simple, easy to measure and do not require any sophisticated testing. Our findings are in line with previous studies, which have demonstrated the association of these variables with long-term adverse events and mortality.[29-33] Noticeably, clinical presentation (chronic vs. acute coronary syndrome) did not emerge as a strong predictor for mortality. A possible explanation is that clinical presentation may be strongly correlated with WBC counts or LVEF and the predictive effect of clinical presentation may have been captured by these two variables.

The models were assessed using the two core measures for model performance, discrimination, and calibration.[22] The discriminative ability of the new model was acceptable[34] or helpful[22] and better than the refitted original model in the internal validation. In the external validation cohort, the discriminative ability of the new model was still robust since the c-index was in the range of acceptable. The calibration of the new model was not perfect and actually overestimated the mortality in the third and the fifth quintile. This imperfect calibration during external validation is not totally unexpected considering the substantial differences in patient characteristics between the derivation and validation cohorts (Supplementary Table S3). In particularly, the 2 year all-cause mortality in the validation cohort was almost three times lower than in the derivation cohort (2.99% in the GLOBAL LEADERS study vs. 1.11% in the Fu Wai PCI cohort). Nevertheless, whether poor calibration among patients at higher risk is actually a problem, depends on the threshold for decision-making.[22] In our case, although there is no widely acceptable threshold for mortality at 2 years after PCI, it is reasonable to say that a predicted 2 year all-cause mortality in the order of 4.9% and an observed mortality in the order of 2.7% in the very high-risk quintiles would be still a clinically relevant threshold for the same clinical decisions. Importantly, the new model was externally validated in a large PCI cohort with a reasonable number of patients with 2 year all-cause mortality (more than 100 patients).[35] The new model had an acceptable performance even in the validation cohort that had risk factor profiles, patient presentation, and gender bias at variance with the developmental cohort. Hence, the results of the external validation in the present study confirm the improved performance of the new model compared with the original model and ensure its generalizability to routine practice.

5 | CLINICAL IMPLICATION OF THE LOGISTIC CLINICAL SYNTAX SCORE

The informed consent process in individual patients before PCI is essential and recommended by guidelines.[36] The field of precision medicine is growing and patients increasingly want to know what their long-term risk will be. The objective information on individual risk derived from the new model of the logistic clinical SYNTAX score will help serve this purpose.

Risk models can be used to guide management of specific group of the patients.[37] For example, patients at very high risk may benefit from more intensive therapy in term of adjunctive pharmacological therapy or risk factor modification. Another aspect of the clinical

impact of the risk score is related to clinical trials, for example, in the development of transcatheter aortic valve replacement when a patient underwent a valve procedure, the Society of Thoracic Surgery score was used to classify patients into low, intermediate, and high risk.[38] This is an example of using a predictive model to assess the risk and then conducting a trial with progressively decreasing risk: from nonoperable to high, intermediate and to low-risk patients. These topics are beyond the scope of the present study. Nevertheless, we believe that the updated logistic clinical SYNTAX score is fundamental for dedicated impact studies of therapeutic decisions in PCI patients.

6 | LIMITATIONS

First, the use of randomized control trial data for prognostic score development may raise a concern on the representativeness of the population.[24] However, the GLOBAL LEADERS study enrolled patients using the concept of all-comers trial in which there was minimal exclusion criteria. In addition, the good quality of data in the GLOBAL LEADERS study in which the variables were prospectively collected using well-defined definitions and the 99.95% availability of the 2 year vital status in the study patients may outbalance these concerns. Nevertheless, some exclusion criteria of the study such as the need for oral anticoagulant therapy, the history of overt major bleeding or severe hepatic impairment would limit the use of the logistic clinical SYNTAX score in these patients. Second, the logistic clinical SYNTAX score was developed and updated to predict only all-cause mortality after PCI and does not predict other outcomes such as stroke, MI or revascularization. It could be argued that these outcomes are also relevant to patients and affect the quality of life. However, all-cause mortality needs no clarification and is similarly perceived by patients and physicians as the hardest endpoint for cardiovascular disease. Third, due to the design of the GLOBAL LEADERS study, the anatomic SYNTAX score was available in 3711 patients in the derivation cohort. However, we used the multiple imputation, which is a standard method to handle missing data and allow efficient use of the available data to update the score.[18,24] In addition, the sensitivity analysis in 3711 patients with available anatomic SYNTAX score shows consistent results (Supplementary Figure S3). Fourth, we did not consider the effect of antiplatelet strategy in the updating of the model given that no significant difference in 2 year all-cause mortality between the two treatment arms was demonstrated. Nonetheless, the treatment effect is usually small compared with the effect of other prognostic factors when the derivation of the risk score focuses on the absolute risk prediction.[24] Physiology-guided PCI may affect long-term outcomes in patients undergoing PCI, unfortunately, the GLOBAL LEADERS study database did not capture this information. However, this issue may not affect mortality prediction since the landmark studies of physiology-guided PCI did not show mortality benefit of this strategy compared with angiographic-guided PCI.[39] Finally, although the new model has shown acceptable discrimination and reasonable calibration in the present study, the studies evaluating the impact of using the score to guide patient care in the clinical practice are required.

7 | CONCLUSIONS

The logistic clinical SYNTAX score was validated in a large contemporary PCI population for predicting 2-year all-cause mortality and updated to include five additional predictors, which are simple and easy to measure. The new model performs better than the refitted original model, as observed in both internal and external validation studies. In the context of precision and individualized medicine, the new model could guide clinical decision making by better risk stratification of patients undergoing PCI.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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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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