

Prediction Score Project for the Incidence of Cerebrovascular Events in Patients With Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Research

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Abstract

Background

We sought to develop and validate a novel marker-based risk score to improve stroke prognostication in patients with myocardial infarction (MI) undergoing primary percutaneous coronary intervention (PCI).

Methods

A retrospective study was conducted and internally validated a new biomarker-based risk score for the incidence of stroke in 4103 patients with MI undergoing primary PCI who were randomized into a derivation and a validation cohort. Predictive values of markers and clinical variables were evaluated using Cox regression models and least absolute shrinkage and selection operator regression. The most important variables were included in the score, with weight proportional to the model coefficients.

Results

Significant predictors of the incidence of cerebrovascular events were age, history of atrial fibrillation, history of hypertension, Killip class, blood pressure group, target lesion involving branches, percutaneous transluminal coronary angioplasty, and thrombus aspiration. The models had good calibration and discrimination in derivation and internal validation. The areas under the curve (AUC) of the receiver operating characteristic (ROC) curve analysis for predicting cerebrovascular events were 0.773 and 0.766 for the derivation and validation cohorts, respectively, at 5-year follow-up. Survival ROC curves exported the best cut-off values and divided them into low-risk and high-risk groups using the R language. We conducted Kaplan–Meier survival analysis for the two groups. Both groups displayed significant difference in the derivation and validation cohorts ($P=0.00003$ and $P=0.009$, respectively). We compared the new prediction model to the CHADS-VASc score; the AUCs were 0.773 and 0.754, respectively.

Conclusion

The prediction model was internally validated and calibrated in large cohorts of patients with MI receiving primary PCI therapy. This risk score incorporates allows re-evaluation of the risk of cerebrovascular events after undergoing primary PCI.

Introduction

Primary percutaneous coronary intervention (PCI) for patients with acute myocardial infarction (MI) is regarded as the optimal method for achieving reperfusion and has been shown to increase the survival rate [1]. Although the long-term outcome event rates were low, stroke has carried high short- and long-term mortality and has significantly adversely affected quality of life after undergoing PCI. Conclusive data on the exact incidence and consequences of long-term stroke following primary PCI remain insufficient thus far [2–6]. Whereas relatively simple patients were treated in the initial period, the complexity of lesion and patients has developed and can reach 30% of their patient load. Intervention of octogenarians with

diffuse atherosclerosis, multi-vessel disease and left main lesion is a matter of course as well as the routine treatment. Therefore, healthcare decisions, practices, and interventions should be adapted to individuals based on their predicted risk of diseases. We sought to develop and validate a novel marker-based risk score to evaluate the long-term (5-year risk) probability of stroke in patients with MI who had undergone primary PCI. We present the following article in accordance with the TRIPOD reporting checklist (supplementary file)¹.

¹The authors have completed the TRIPOD reporting checklist

Materials And Methods

Study design and participants

A total of 4151 consecutive patients with acute MI who underwent primary PCI at Fuwai Hospital (Beijing, China) between January 2010 and June 2017 were enrolled. We excluded subjects without follow-up data from the study and 4103 remained (3582 STEMI and 521 NSTEMI). The outcome of this study included only initial stroke. The diagnosis of the outcome was confirmed by local neurologists when patient moved to another center and source documents were obtained via follow-up. The R software was used to randomly and proportionally divide the patients into derivation and validation cohorts (70%:30%). All patients were referred to a coronary catheterization center with a diagnosis of MI fulfilling the criteria for primary PCI according to the guidelines (ESC and ACCF/AHA guideline) [7, 8]. The study was approved by the Ethics Committee of Fuwai Hospital (2016-I2M-1-009), and all patients provided informed consent for coronary angiography and primary PCI. Patient records, including demographics, medical history, physical examination, blood test results, electrocardiography, echocardiographic data, and discharge medication regimen, were reviewed. Blood testing was performed in a clinical laboratory at Fuwai Hospital. The study flow chart is shown in Supplementary Fig. 1.

Definitions

Hypertension was defined as blood pressure (BP) $\geq 140/90$ mmHg at rest in three measurements or a previous diagnosis of hypertension and current use of antihypertensive drugs. Diabetes mellitus (DM) was defined according to the 75-g oral glucose tolerance test (OGTT). Specifically, patients were diagnosed with DM if they met one of the following criteria: (i) fasting plasma glucose level of ≥ 7.0 mmol/L, (ii) 2-h value of ≥ 11.1 mmol/L in the 75-g OGTT, and (iii) casual plasma glucose level of ≥ 11.1 mmol/L. Dyslipidemia was defined by any of the following parameters: total cholesterol level of ≥ 5.0 mmol/L, low-density lipoprotein cholesterol level of ≥ 3.0 mmol/L, triglyceride level of ≥ 1.7 mmol/L, high-density lipoprotein cholesterol level of ≥ 1.2 mmol/L (in women) or ≥ 1.0 mmol/L (in men). Trained medical staff measured height and weight; body mass index was calculated by dividing weight (kg) by the square of height (m^2). No-reflow phenomenon was described as Thrombolysis in Myocardial Infarction flow grade < 3 after primary PCI. Stroke was determined according to the World Health

Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases standard [9].

Follow-up was conducted via phone calls or their health status was confirmed from their health records with permission from the Review Board of Fuwai Hospital and patients were followed-up for at least 1 year after discharge. Stroke, as diagnosed by a neurologist, included subarachnoid hemorrhage, intracranial hemorrhage, cerebral thrombosis, and cerebral embolism. Stroke is defined as a rapidly developing focal or widespread brain dysfunction that lasts for more than 24 hours or causes death, excluding nonvascular causes (e.g., trauma, metabolic disorders, tumors, and any neurological abnormalities due to central nervous system infection). Hemorrhagic stroke included subarachnoid hemorrhage and intracranial hemorrhage, whereas ischemic stroke included cerebral thrombosis and cerebral embolism. Transient ischemic attack and chronic cerebrovascular disease were not included. Investigators collected data from head computed tomography, head magnetic resonance imaging, and hospital records of patients during their hospitalization.

Statistical analysis

The normal distribution of outcome variables was confirmed using the Kolmogorov–Smirnov test. Baseline parameters and major adverse events at follow-up were expressed as median (standard error) for continuous variables and as frequency and percentage for categorical variables in the table presenting the characteristics of the derivation and validation cohorts. All variables included in the new prediction model were prespecified. Univariate Cox regression analysis was conducted to initially screen candidate factors for predicting stroke with a P value of < 0.2 . These included variables required for calculating the risk of major adverse cardiovascular events (i.e., sex, age, history of hypertension, atrial fibrillation [AF], history of coronary artery bypass grafting, history of PCI, diabetes status, BP, estimated glomerular filtration rate, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, lipase activator, and coronary angiography results). The least absolute shrinkage and selection operator (LASSO) method was employed to further screen the independent variables included in the Cox regression model so as to realize the reduction and simplification of the model and prevent the occurrence of overfitting. Variable filtering using the LASSO tends to be “harsh” because of the use of lambda minse; however, the effect is also significant. Therefore, it is more suitable for large-scale, ultra-high dimensional data. On the premise of not affecting the accuracy, the range of dimension reduction is relatively large. The selection of parameters was based on previous clinical practice experience, with reference to relevant literature [10–11] and in combination with the results of univariate Cox regression analysis. We used the multiple imputation with automated variable selection to account for missing values.

The corresponding nomogram model was drawn depending on the regression coefficient of selected independent variables. For variables selected in the nomogram model, the values of different variables could correspond to different scores on the integral line at the top of the nomogram (score range: 0–300 points) through the projection of the vertical line, and the total score could be obtained by adding up the scores corresponding to the values of each variable. The cumulative probability of the occurrence of

cerebrovascular events in 5 years could be obtained from the total score on the prediction line at the bottom of the nomogram. To reduce overfitting bias, the self-sampling method was used to verify the nomogram model. Model discrimination was quantified by Harrell's c-statistic and calibration chart. The receiver operating characteristic (ROC) curve was drawn using MedCalc for Windows version 18.2.1 (MedCalc Software, Mariakerke, Belgium). Survival ROC curves exported the best cut-off values and divided them into low-risk and high-risk groups using the R language. We conducted Kaplan–Meier (K-M) survival analysis for the two groups and exported the discrepancy result of the analysis. The LASSO method adopts the “glmnet” package of the R language for variable selection, as well as the “rms” package of the R language for drawing and internal validation of the nomogram (calibration chart). Cox regression analysis was performed using the survival package. R language version 3.6.2 was used as the main statistical analysis software throughout this study. Other analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY). The accuracy of the new prediction model and CHADS-VASc score in predicting cerebrovascular events was evaluated according to the area under the curve (AUC) of the ROC curve and was compared with a nonparametric test developed by DeLong et al [12] using MedCalc for Windows version 18.2.1 (MedCalc Software, Mariakerke, Belgium). All *P* values were two-tailed, and statistical significance was set at $P < 0.05$.

Performance and internal validation of new risk prediction equations

Baseline survival probabilities of each model were obtained using R language (version 3.6.2) commands that were utilized to fit the models. Calibration performance was graphically assessed to predict the 3-year and 5-year risk of cerebrovascular events and plot the predicted 3-year and 5-year risk against the observed 3-year and 5-year risk. A diagonal line with a slope of 1 represents perfect calibration. The observed 3-year and 5-year risk was obtained via the K-M method, and the slopes of regression lines comparing the predicted 5-year risk to the observed 5-year risk were calculated. Standard statistical metrics of the model and discrimination performance (R^2 , Harrell's c-statistic) were calculated. The calibration and discrimination performance of equations developed in the derivation subcohort was assessed in the validation subcohort and compared with the performance of models developed in the entire cohort; baseline survival functions and hazard ratios were also compared. Indicators of internal validation include the degree of calibration, which represents the prediction accuracy and prediction consistency of the nomogram prediction model. The degree of calibration was represented by a calibration graph. ROC plotting was used for the survival ROC package.

Results

Demographics of patients in the derivation and validation cohorts

The study population comprised 4151 men and women aged 24–97 years at the time of their first predicted risk assessment between January 1, 2010, and June 30, 2017 (Supplementary Fig. 1). Forty-

eight patients without follow-up data were excluded from the study and 4103 remained (3582 STEMI and 521 NSTEMI). A total of 2875 and 1228 individuals were randomly allocated to the derivation and validation cohorts, respectively. Furthermore, 66 (2.30%) participants in the derivation cohort and 17 (1.38%) participants in the validation cohort experienced a cerebrovascular event during follow-up. The characteristics of participants are outlined in Table 1.

Table 1
the characteristic of derivation cohort and validation cohort

Variables	Derivation cohort N = 2875	Validation cohort N = 1228	P value
Age (years)	59.0424 ± 11.9442	59.8070 ± 11.7523	0.0593
Male [% (n)]	2273 (79.06%)	949 (77.28%)	0.2033
Height (cm)	168.2712 ± 7.3622	168.4220 ± 7.2347	0.5569
Weight (kg)	73.7956 ± 12.9157	73.6671 ± 12.9013	0.7773
BMI (kg/m ²)	25.9684 ± 3.6923	25.8750 ± 3.7083	0.4728
Heart rate (beats per minute)	77.4973 ± 15.3686	78.1033 ± 30.6300	0.4083
SBP (mmHg)	124.3189 ± 18.3940	124.1268 ± 18.1244	0.7621
DBP (mmHg)	74.1744 ± 12.8245	74.5756 ± 13.1307	0.3703
History of disease			
Hypertension [% (n)]	1765 (61.39%)	742 (60.42%)	0.5603
Diabetes [% (n)]	941 (32.73%)	406 (33.06%)	0.8360
Hyperlipidemia [% (n)]	2661 (92.56%)	1127 (91.78%)	0.3893
Previous PCI [% (n)]	401 (13.95%)	164 (13.36%)	0.6138
Previous CABG [% (n)]	30 (1.04%)	18 (1.47%)	0.2493
Atrial fibrillation [% (n)]	186 (6.47%)	67 (5.46%)	0.2165
CKD [% (n)]	227 (7.90%)	101 (8.22%)	0.7219
Laboratory examinations			
HDL-cholesterol (mg/dl)	1.6919 ± 1.1720	1.7115 ± 1.1004	0.6186
LDL-cholesterol (mg/dl)	2.7317 ± 0.9467	2.7624 ± 0.9236	0.3422
Triglycerides (mg/dl)	1.0511 ± 0.2843	1.0558 ± 0.2785	0.6253
LPA (g/L)	265.9897 ± 245.6388	269.3142 ± 250.4794	0.6932
hs-CRP	7.5879 ± 5.0006	7.5390 ± 4.9117	0.7751

Continuous data are presented as mean ± SD (standard deviation), categorical variables are presented as % (n). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; LPA, lipase activator; hs-CRP, high sensitive C-reactive protein; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IABP, Intra-Aortic Balloon Pump

Variables	Derivation cohort	Validation cohort	P value
	N = 2875	N = 1228	
D-dimer	1.1072 ± 2.4913	0.9541 ± 2.0669	0.1042
Crea	82.2265 ± 24.3151	82.2354 ± 27.0233	0.9918
eGFR	88.5384 ± 71.4704	92.4513 ± 102.6954	0.1622
Discharge medication regimen			
Statin[%(n)]	2609 (93.58%)	1113 (93.69%)	0.8993
Aspirin[%(n)]	2762 (99.07%)	1174 (98.82%)	0.4770
ACEI[%(n)]	1725 (61.87%)	731 (61.53%)	0.8398
ARB[%(n)]	248 (8.90%)	102 (8.59%)	0.7526
Beta-Blockers[%(n)]	2419 (86.76%)	1050 (88.38%)	0.1612
Diuretic[%(n)]	822 (88.38%)	328 (27.61%)	0.2329
Spironolactone[%(n)]	612 (21.95%)	253 (21.30%)	0.6468
P2Y12 inhibitors	2770 (99.35%)	1174 (98.82%)	0.0852
Endpoint events			
Stroke [% (n)]	66 (2.30%)	17 (1.38%)	0.0576
Triple-vessel lesions	1201 (43.08%)	505 (42.51%)	0.7400
PTCA	2444(85.01%)	1053(85.75%)	0.564
Continuous data are presented as mean ± SD (standard deviation), categorical variables are presented as % (n). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; LPA, lipase activator; hs-CRP, high sensitive C-reactive protein; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IABP, Intra-Aortic Balloon Pump			

Outcome events were obtained exclusively from follow-up databases between August 3, 2010, and March 11, 2019. No statistical differences in age, sex, heart rate, body mass index, BP, history of the disease, laboratory examination, discharge medication regimen, and incidence of endpoint events were noted between the two groups. There was a considerable difference in the number of patients with an intra-aortic balloon pump, left main lesion, and no-reflow phenomenon between the two groups ($P < 0.0001$).

Primary screening by the univariate Cox regression analysis and LASSO method

We chose both continuous and categorical values of age, history of hypertension, DM, AF, Killip classification, stent implantation, triple-vessel lesions, thrombus aspiration, target lesion involving branches, creatinine, BP group, and other 13 variables as candidate parameters with $P < 0.8$ in the univariate Cox regression model (Supplementary Table 1). These 24 variables were filtered using the LASSO regression method (Supplementary Fig. 2). It is necessary to make the classification variables into factorization and subsequently use the `as.matrix()` function to convert data from the non-matrix format to the matrix format before the R language “glmnet” package can call the data. The filtering and cross-validation processes for independent variables are presented in Supplementary Fig. 2A and 2B, respectively. Lambda.min is the lambda value of the optimal efficiency model in the standard error range that provides a model with excellent performance. At this time, a total of 8 independent variables, namely, age, history of AF, history of hypertension, Killip classification, BP group, target lesion involving branches, percutaneous transluminal coronary angioplasty (PTCA), and thrombus aspiration, were included in the prediction model.

Establishment of the risk prediction score project

At this time, a total of 8 independent variables, namely, subgroup of age, history of AF, history of hypertension, Killip classification, BP group, target lesion involving branches, PTCA, and thrombus aspiration, were included in the prediction model. For variables selected in the nomogram model, the values of different variables could correspond to different scores on the integral line at the top of the nomogram (score range: 0–300 points) through the projection of the vertical line, and the total score could be obtained by adding up the scores corresponding to the values of each variable. Points for the score (range: 0–300) were assigned as follows: for age < 40 years, 100 points; for age of 40–49 years, 80 points; for age of 50–59 years, 60 points; for age of 60–69 years, 40 points; for age of 70–79 years, 20 points; for age \geq 80 years, 0 point; for having a history of hypertension, 25.7 points; for Killip class I, 21.23 points; for Killip class II, 14.16 points; for Killip class III, 7.08 points; for multivessel lesion, 17.2 points; for not undergoing PTCA, 5.09 points; for thrombus aspiration, 20.8 points; for optimal BP, 0 point; for normal BP, 14 points; for high normal BP, 28 points; for hypertension stage I, 42 points; and for hypertension stage II, 56 points.

Nomogram drawing and evaluation of the risk prediction model

Model and discrimination metrics indicated that the risk equations performed excellent in predicting cerebrovascular events. According to the nomogram model (Fig. 1), the score predicting project included age, history of AF, history of hypertension, Killip classification, BP group, target lesion involving branches, PTCA, and thrombus aspiration. Patients were categorized into six groups according to age (age \leq 40 years, 40 years < age \leq 50 years, 50 years < age \leq 60 years, 60 years < age \leq 70 years, 70 years < age \leq 80 years, age > 80 years) referred to similar published study on the risk of stroke after MI and PCI [13], and these were assigned with 100, 80, 60, 40, 20, and 0 points, respectively, in the nomogram model. The scores for a history of hypertension, AF, target lesion involving branches (the presence of a target lesion involving branches was assigned with 1, whereas its absence was assigned with 0), not undergoing PTCA

(PTCA was a protective factor), and thrombus aspiration during hospitalization were 25.7, 58.5, 17.2, 5.09, and 20.8 points, respectively. Furthermore, the prediction scores for Killip classes I–IV were 21.23, 14.16, 7.08, and 0 points, respectively. BP at admission was divided into the following 5 groups: for optimal BP (diastolic BP [DBP] < 80 mmHg and systolic BP [SBP] < 120 mmHg), assign 1; for normal BP (DBP ranging from 80 to 84 mmHg or SBP ranging from 120 to 129 mmHg), assign 2; for high normal BP (DBP ranging from 85–89 mmHg or SBP ranging from 130 to 139 mmHg), assign 3; for hypertension stage I, (DBP ranging from 90 to 99 mmHg and SBP ranging from 140 to 159 mmHg), assign 4; and for hypertension stage II (DBP \geq 100 mmHg and SBP \geq 160 mmHg), assign 5. The prediction scores were 0, 14, 28, 42, and 56 points, respectively. With the increase in the total score of the nomogram model, the corresponding 5-year risk of stroke increased (Fig. 1).

Evaluating the reliability and validity of the C-index provides a reliable tool for assessing the model. The C-index was 0.717 for the derivation cohort (SD, 0.09; $P < 0.0001$) and 0.454 for the validation cohort (SD, 0.189; $P = 0.4923$).

Supplementary Fig. 3 shows the ROC curves for the discriminatory value of the 5-year evaluation performance of the risk prediction model in the derivation and validation cohorts. The AUCs were 0.773 and 0.766 in the ROC curves for the derivation and validation cohorts, respectively (Supplementary Fig. 3).

Model discrimination was quantified by Harrell's c-statistic and calibration chart. The predicted versus observed 3-year and 5-year risk plots for cerebrovascular events using the risk prediction model showed excellent calibration performance (Fig. 2A and 2B).

Survival ROC curves exported the best cut-off values and divided them into low-risk and high-risk groups using the R language. We conducted K-M survival analysis (Fig. 3) for the two groups and exported the discrepancy result of the analysis. Both groups showed a significant difference in the derivation and validation cohorts ($P = 0.00003$ and $P = 0.009$, respectively). We compared the new prediction model and CHADS-VASc score. The AUC of the new model is 0.773, whereas the AUC of CHADS-VASc is 0.754. Pairwise comparison of ROC curves: difference between areas, 0.191; standard error, 0.0239; 95% confidence interval, -0.0278 to 0.0661; z-statistic, 0.800; significance level, $P = 0.4239$. (Fig. 4)

Discussion

We have analyzed over 4000 patients undergoing primary PCI in Fuwai Hospital and National Center for Cardiovascular Diseases PCI database. Patients undergoing primary PCI frequently have a worse risk profile than elective patients. Therefore, the management and assessment of this particular patient population should be individualized and precise to ensure the sustainable development of contemporary healthcare system. To our knowledge, our study is the first to develop and validate a risk model for stroke prediction that is suitable for patients with acute MI who had undergone primary PCI from a large-scale national perspective. The robustness of our results was confirmed through rigorous statistical analysis: LASSO regression, ROC curve analysis, nomogram model, calibration graph, and K-M survival analysis.

To evaluate the further 5-year risk probability of stroke in patients with MI who had undergone primary PCI, we developed a risk prediction score project that could be used by primary and specialist healthcare professionals to enhance risk assessment and management. This risk score incorporates routine clinical data, inflammatory factor in the serum, and coronary angiography results. By incorporating the time since an event, it allows re-evaluation of the risk of major adverse cardiovascular events at ≥ 5 years after undergoing primary PCI. The established risk score may be used to inform decisions about novel therapies and be trialed in the context of changes in quantifiable risk. This is the most appropriate type of study population to develop or validate a risk prediction model suitable for patients with acute MI who had undergone primary PCI.

The strategy for thrombectomy during PCI has been reported to be correlated with an elevated risk of cerebrovascular events, including ischemic and hemorrhagic strokes within 30 days, leading to degrees of disability [3]. The TOTAL meta-analysis concluded that there is a general tendency for increased stroke incidence with thrombectomy [14]. Moreover, consequences of stroke after primary PCI in the setting of ST-elevation myocardial infarction (STEMI) are similar among clinical trials. A large, contemporary, prospective, international randomized controlled trial assessing pexelizumab showed that all hemorrhagic strokes occurred after PCI [15]. In the present study, we found that thrombus aspiration during primary PCI was a factor for the prediction model, which is consistent with the findings of previous studies, and contributed to a score of 22.1 points for the effects. The feasible interpretation of the rising incidence of ischemic stroke might not be excepting the thromboembolism occurred in the cerebrovascular from the coronary vasculature. Furthermore, traversing the coronary lesions with radical catheter guidewire manipulation could result in the translocation of atheroma from the aorta. This might elucidate the incidence of ischemic stroke after primary PCI. A report from a Japanese multicenter registry concluded that compared with a transfemoral intervention, a transradial intervention was correlated with a decrease in the risk of stroke, which is a life-threatening complication [16].

Luke et al. [17] previously reported that risk factors such as age, AF, female sex, Killip classification, and chronic disease could predict stroke incidence after PCI, which is generally in accordance with the classic risk variables in the general population [18, 19]. Furthermore, previous analyses identified that the presence of valvular heart disease, which mostly results in AF, is one of the most principal predictive factors for ischemic stroke complications [20], which is in keeping with the conclusion of our study. Diseases such as AF-related cardiogenic embolism and a pro-inflammatory status have extended to the vasculature of cerebrovascular from coronary artery [21]. A prior survey of APEX research data [22] concluded that new-onset AF was independently correlated with mortality and was an index of adverse endpoints in subjects undergoing primary PCI. They make the conclusion that patients with AF are feeble and usually have more complications during (external) hospitalization. Hence, it is crucial to account for confounding elements when evaluating the relevance of AF with respect to long-term outcomes. Furthermore, we identified age, particularly an age of less than 40 years and age ranging from 40 to 50 years, as a risk factor for cerebrovascular events following primary PCI. In the present study, patients were categorized into six groups according to age (age ≤ 40 years, 40 years $<$ age ≤ 50 years, 50 years $<$ age ≤ 60 years, 60 years $<$ age ≤ 70 years, 70 years $<$ age ≤ 80 years, age > 80 years), and these were assigned

with 100, 80, 60, 40, 20, and 0 points, respectively, in the nomogram model. The results of our analysis suggest that age is among the strongest predictors of stroke complications. Additionally, our results are consistent with those of the study by Luke et al. [17], who reported a maximum incidence rate ratio of 28.1 for age ranging from 35 to 39 years, as compared to an incidence rate ratio of 0.65 for age of more than 85 years. Previous studies [23, 24] also illustrated that patients receiving primary PCI therapy have characteristics that are distinct from those of other subjects with stroke in the general population. Patients aged > 80 years were more commonly females and showed lower rates of dyslipidemia and smoking, which are risk factors for stroke, than non-elderly patients. Fuchs et al. suggested the potential association between a history of hypertension and stroke [25]. Administration of contrast medium during PCI may be complicated by transient or ongoing deterioration in renal function. The pathogenesis of kidney injury is not yet completely understood, and multiple mechanisms may be involved, including sustained intra-renal vasoconstriction, direct cytotoxic effect of the contrast medium, renal medullary hypoxia, ischemic injury, oxidative stress, and inflammation [26, 27].

Mukolwe et al. had determined that Killip classification has prognostic importance in non-ST-segment elevation acute coronary syndromes using multivariate Cox proportional hazards models [28]. In previous studies [29–31], Killip classification was an independent risk factor for long-term major adverse cardiac and cerebrovascular events in female patients with acute STEMI and was a predictor of short and long term mortality, which is consistent with our finding. Furthermore, we identified that bifurcation lesion of the target artery was a predictor of the risk of cerebrovascular events, which has also been confirmed by several studies [32, 33]. Chen et al. enrolled 212 patients with 230 true bifurcation lesions treated by crush stenting with drug-eluting stents and concluded that the location of bifurcation lesions correlated with the clinical outcome [34]. In the present study, BP at admission was divided into 5 groups and the risk coefficient increased with BP. Data on the relationship between BP at admission and long-term and short-term outcomes in patients with acute MI who had undergone primary PCI have been well-documented [35, 36], which is similar to the conclusion of the present study.

Mechanism of stroke after PCI

1) Embolization of air bubble or thrombi due to inadequate back-flushing or anticoagulation; 2) Use of specific devices including intra-aortic balloon pump, manual thrombectomy catheters; 3) Hypotension leading to cerebral ischemia; 4) Hypertension, aortic dissection and atrial fibrillation; 5) Dislodgement of atherosclerotic debris from the aorta; 6) Adverse effect to antiplatelet and anticoagulant medications. 7) Aggressive anticoagulant and/or antiplatelet treatment regimens may increase the risk of hemorrhagic stroke by acting on the platelet-mediated process of thrombus [37]. Defining the both acute and long term risk of stroke and its clinical implications is of paramount importance in an era where fully informing patients of the treatment options and including them in the decision-making process actively.

Strengths and limitations

Our study has several strengths. The models incorporated variables such as routine clinical data, inflammatory factor in the serum, coronary angiography results, and other relevant clinical parameters

that are commonly considered in clinical assessment. The Fuwai Hospital and National Center for Cardiovascular Diseases PCI database contains an overwhelming majority of primary PCI procedures performed in Beijing and reflects real-world experience. Therefore, the present study included high-risk subjects encountered in daily interventional practice who were frequently excluded from randomized controlled trials. These variables are routinely recorded in electronic health records; hence, collection of data on these variables does not entail additional cost.

Nonetheless, our study has several limitations that should be noted. Imaging of cerebral hemorrhage and cerebral ischemia to comprehend the mechanism of stroke and identify what induces cerebrovascular events was insufficient. Cerebrovascular events were determined by contacting subjects, followed by validation through medical records. While this had probably covered almost all hemorrhagic and ischemic strokes, it might have undervalued stroke incidence if the patients were asymptomatic and not admitted to the hospital. Finally, the incidence of cerebrovascular events was not very high, which might have resulted in the LASSO method being not stable to some extent. However, the present study provides some inspirations for the development of PCI-related models, and the predictive score should be used with circumspection until further large-scale external validation is carried out.

Conclusion

In summary, we present risk prediction models for estimating the risk of stroke based on clinical parameters that are commonly available in all individuals with MI who had undergone primary PCI. These models can be implemented alongside further medical investigations to support therapeutic decision making. However, as with any new risk prediction model, further independent evaluation is required in different settings including geographic locations and healthcare organizations to guide its application in clinical management and practice.

Declarations

Acknowledgements

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Data Availability

Data will be provide by any resonable reason.

Sources of funding

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Ethics approval and consent to participate

It is from the ethics committee of the department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, China.

Consent for publication

Written informed consent for publication was obtained from all participants.

Declaration of competing interest

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Conflict of Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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References

1. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*, 2018; 39: 119-77.
2. Mohamad Alkhouli, Fahad Alqahtani, Abdulrahman Tarabishy, et al. Incidence, Predictors, and Outcomes of Acute Ischemic Stroke Following Percutaneous Coronary Intervention. *J Am Coll Cardiol Intv* 2019;12:1497–506.
3. Rishi Chandiramani, Huazhen Chen, Shunsuke Aoi, et al. Incidence, predictors and impact of stroke on mortality among patients with acute coronary syndromes following percutaneous coronary intervention—Results from the PROMETHEUS registry. *Catheter Cardiovasc Interv*. 2020;95:885–892.
4. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008; 358: 557–567.
5. Vlaar PJ, Svilaas T, van der Horst IC, et al. Cardiac death and reinfarction after 1 year in the thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet* 2008; 371:1915–1920.
6. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33:2569–2619
7. [Steg PG](#), [James SK](#), [Atar D](#), et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; 33:2569-2619.
8. [O'Gara PT](#), [Kushner FG](#), [Ascheim DD](#), et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation* 2013; 127: 529-55.
9. Zhao D, Liu J, Wang W, et al. Epidemiological transition of stroke in China: twenty-one-year observational study from the Sino-MONICA-Beijing Project [J]. *Stroke*, 2008, 39(6): 1668-1674.
10. Head S J, Milan M, Joost D, et al. Stroke Rates Following Surgical Versus Percutaneous Coronary Revascularization [J]. *J. Am. Coll. Cardiol*, 2018, 72(4):386-398.
11. Jolly S S, Cairns J A, Yusuf S, et al. Stroke in the TOTAL trial: A randomized trial of routine thrombectomy vs. percutaneous coronary intervention alone in ST elevation myocardial infarction [J]. *Eur Heart J*, 2015, 36(35).
12. DeLong, E.R.; DeLong, D.M.; Clarke-Pearson, D.L. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988, 44, 837–845.
13. Shmuel Fuchs, Eugenio Stabile, Timothy D. Kinnaird, et al. Stroke Complicating Percutaneous Coronary Interventions Incidence, Predictors, and Prognostic Implications. *Circulation*. 2002;106:86-91
14. Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. *Eur Heart J* 2008; 29:2989–3001.

15. Guptill JT, Mehta RH, Armstrong PW, et al. Stroke after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction: timing, characteristics, and clinical outcomes. *Circ Cardiovasc Interv* 2013;6:176–183.
16. Shoji S , Kohsaka S , Kumamaru H , et al. Stroke After Percutaneous Coronary Intervention in the Era of Transradial Intervention[J]. *Circulation Cardiovascular Interventions*, 2018, 11(12).
17. Luke P Dawson, Justin A Cole, Terase F, et al. Lancefield Incidence and risk factors for stroke following percutaneous coronary intervention. *International Journal of Stroke*, 2020(0) 1–14.
18. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 2017; 135: e146–e603.
19. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (interstroke): a case-control study. *Lancet* 2016; 388: 761–775.
20. Kwok Chun Shing, Kontopantelis Evangelos, Myint Phyo K, et al. Stroke following percutaneous coronary intervention: type-specific incidence, outcomes and determinants seen by the British Cardiovascular Intervention Society 2007–12[J]. *European Heart Journal* (25):25.
21. Guptill, J. T, Mehta, R. H, Armstrong, P. W, et al. Stroke After Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction: Timing, Characteristics, and Clinical Outcomes[J]. *Circulation Cardiovascular Interventions*, 2013, 6(2):176-183.
22. Lopes RD, Elliott LE, White HD, et al. Antithrombotic therapy and outcomes of patients with atrial fibrillation following primary percutaneous coronary intervention: results from the APEX-AMI trial. *Eur Heart J*. 2009;30:2019–2028.
23. Arboix A, Cartanya A, Lowak M, Garcia-Eroles L, Parra O, Oliveres M, et al. Gender differences and woman-specific trends in acute stroke: results from a hospital-based registry (1986-2009). *Clin Neurol Neurosurg* 2014; 127: 19–24.
24. Arboix A, Garcia-Eroles L, Massons J, Oliveres M and Targa C. Lacunar infarcts in patients aged 85 years and older. *Acta Neurol Scand* 2000; 101: 25–29.
25. S, Fuchs. Stroke Complicating Percutaneous Coronary Interventions: Incidence, Predictors, and Prognostic Implications [J]. *Circulation*. 2002; 106:86-91
26. McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol*. 2008;51:1419-28.
27. James MT, Ghali WA, Tonelli M, et al. Acute kidney injury following coronary angiography is associated with a long-term decline in kidney function. *Kidney Int*. 2010;78:803-9.
28. Mukolwe, Newton. Introduction to Psychology & Educational Statistics Books [J]. *JAMA*, 2012, 290(16):32.
29. Miyachi H , Takagi A , Miyauchi K , et al. Current characteristics and management of ST elevation and non-ST elevation myocardial infarction in the Tokyo metropolitan area: from the Tokyo CCU network registered cohort[J]. *Heart and Vessels*, 2016, 31(11):1740-1751.

30. Rott D , Behar S , Gottlieb S , et al. Usefulness of the Killip Classification for Early Risk Stratification of Patients With Acute Myocardial Infarction in the 1990s Compared With Those Treated in the 1980s[J]. American Journal of Cardiology, 1997, 80(7):859-864.
31. El-Menyar A , Zubaid M , Almahmeed W , et al. Killip classification in patients with acute coronary syndrome: insight from a multicenter registry[J]. american journal of emergency medicine, 2012, 30(1):0-103.
32. Suzuki K , Tsurumi Y , Fuda Y , et al. Postprocedural resistance of the target lesion is a strong predictor of subsequent revascularization: assessment by a novel lesion-specific physiological parameter, the epicardial resistance index[J]. Heart & Vessels, 2007, 22(3):139-145.
33. Siono T , Saito S , Miyashita Y , et al. PE-048 Two Years Results of Crush Stenting for the Left Main True Bifurcation Lesion(Coronary revascularization, PCI(07)(IHD),Poster Session(English),The 72nd Annual Scientific Meeting of the Japanese Circulation Society)[J]. Circulation Journal Official Journal of the Japanese Circulation Society, 2008, 72.
34. Chen S L , Zhang J J , Ye F , et al. Crush Stenting With Drug-Eluting Stents: Relevance of Coronary Bifurcation Lesion Location on Angiographic and Clinical Outcomes[J]. Clinical cardiology, 2010, 33(12):0-0.
35. Diana B , Florina C , Cristian M , et al. Prognostic impact of blood pressure and heart rate at admission on in-hospital mortality after primary percutaneous intervention for acute myocardial infarction with ST-segment elevation in western Romania[J]. Therapeutics & Clinical Risk Management, 2017, 13:1061-1068.
36. Jun Shiraishi, Takeshi Nakamura, Akira Shikuma, et al. Relationship Between Mean Blood Pressure at Admission and In-Hospital Outcome After Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction [J]. International heart journal, 2016, 57(5).
37. Mario Gaudino, Dominick J. Angiolillo, Antonino Di Franco, et al. Stroke After Coronary Artery Bypass Grafting and Percutaneous Coronary Intervention: Incidence, Pathogenesis, and Outcomes. J Am Heart Assoc. 2019;8:e013032.

Figures

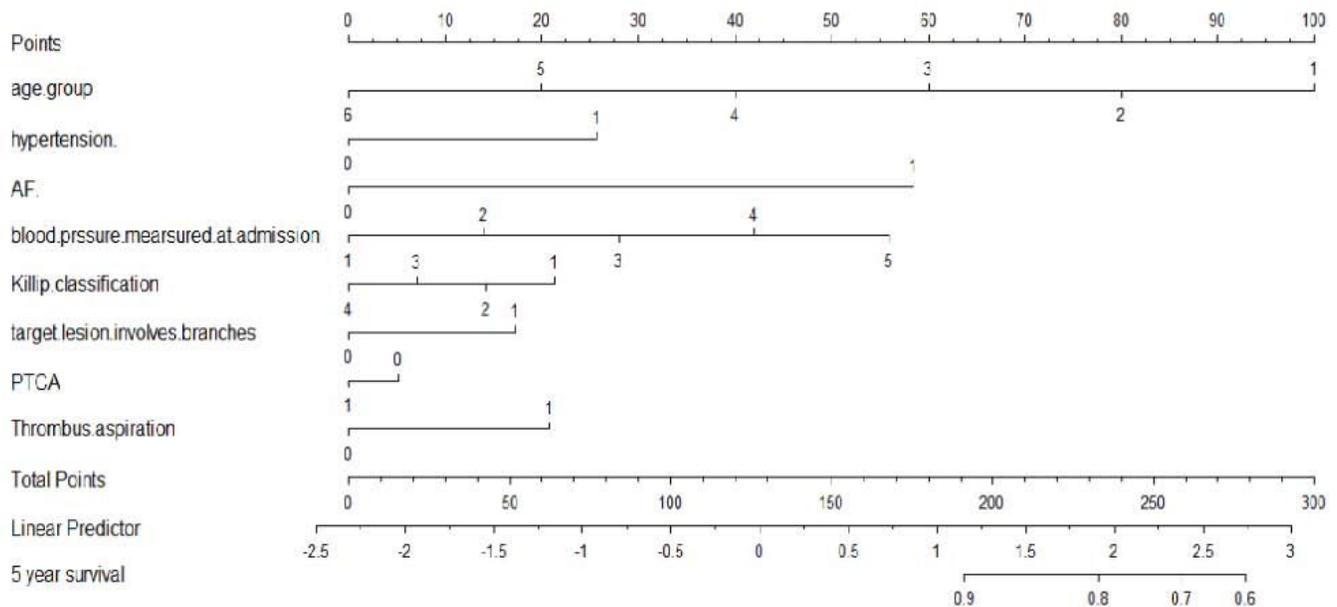
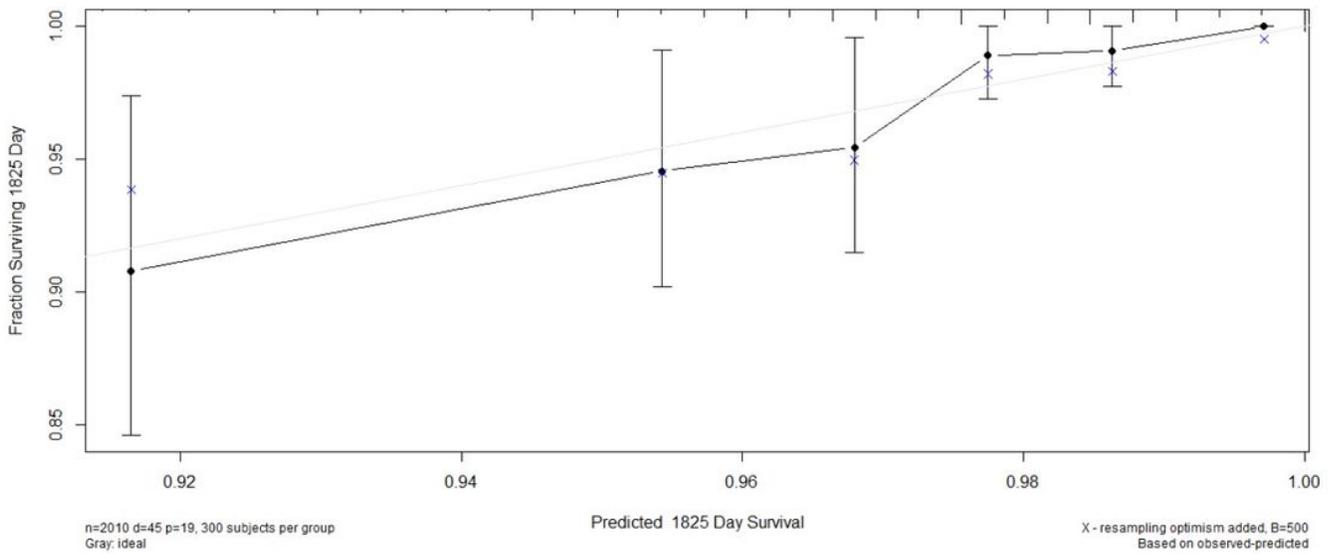


Figure 1

The risk score nomogram for bedside application. Age group: 1 = age <40 years; 2 = age ranging from 40 to 50 years; 3 = age ranging from 50 to 60 years; 4 = age ranging from 60 to 70 years; 5 = age ranging from 70 to 80 years; 6 = age >80 years. Hypertension: 1 = with a history hypertension; 0 = without a history of hypertension. Atrial fibrillation (AF): 1 = with a history of AF; 0 = without a history of AF. BP measured at admission: 1 = optimal BP (DBP <80 mmHg and SBP <120 mmHg); 2 = normal BP (DBP ranging from 80 to 84 mmHg or SBP ranging from 120 to 129 mmHg); 3 = high normal BP (DBP ranging from 85 to 89 mmHg or SBP ranging from 130 to 139 mmHg); 4 = hypertension stage I (DBP ranging from 90 to 99 mmHg and SBP ranging from 140 to 159 mmHg); 5 = hypertension stage II (DBP ≥100 mmHg and SBP ≥160 mmHg). Killip classification: 1 = Killip I; 2 = Killip II; 3 = Killip III; 4 = Killip IV. Target lesion involving branches: 1 = present; 0 = absent. Percutaneous transluminal coronary angioplasty (PTCA): 0 = without undergoing PTCA; 1 = undergoing PTCA. Thrombus aspiration: 1 = with thrombus aspiration; 0 = without thrombus aspiration. Histogram refers to the score distribution in the derivation cohort. For variables selected in the nomogram model, the values of different variables could correspond to different scores on the integral line at the top of the nomogram (score range: 0–300 points) through the projection of the vertical line, and the total score could be obtained by adding up the scores corresponding to the values of each variable. The cumulative probability of the occurrence of cerebrovascular events in 5 and 7 years could be obtained from the total score on the prediction line at the bottom of the nomogram.

2A



2B

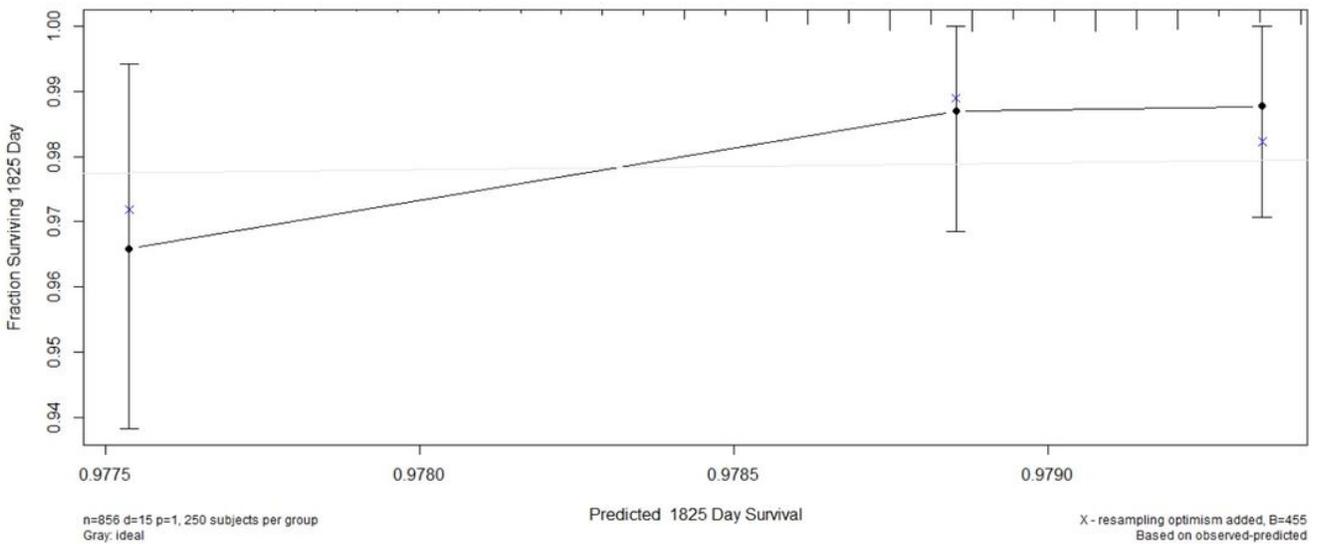
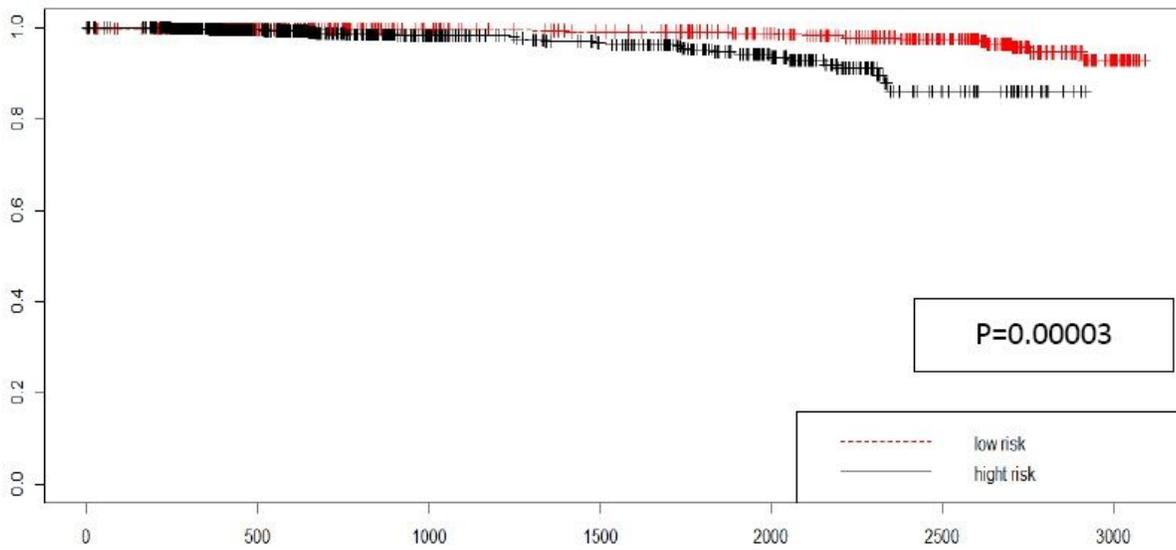


Figure 2

Risk score calibration in the derivation cohort and internal validation cohort. The stroke event risk score at 5 years in the (A) derivation cohort and (B) validation cohort. Calibration is indicated as the estimated risk against survival in the Kaplan-Meier analysis. Gray line represents perfect calibration.

3A



3B

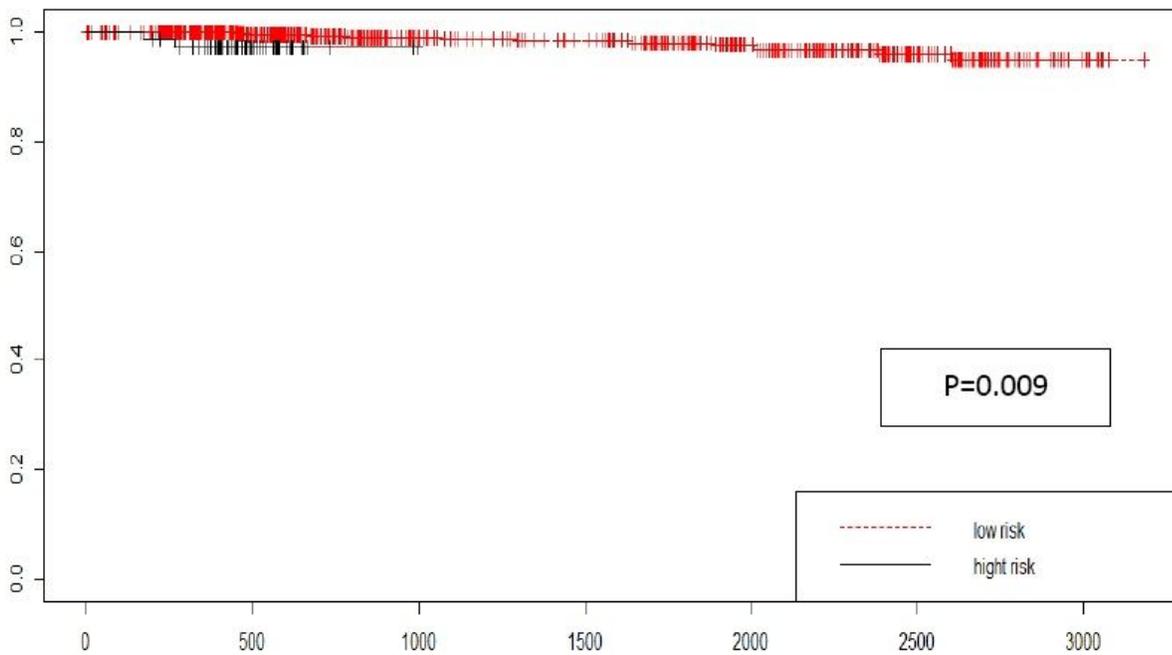


Figure 3

Kaplan-Meier (K-M) survival analysis. (A) K-M survival curve for the derivation cohort. (B) K-M survival curve for the validation cohort. Both groups showed a significant difference in the derivation and validation cohorts (P=0.00003 and P=0.009, respectively).

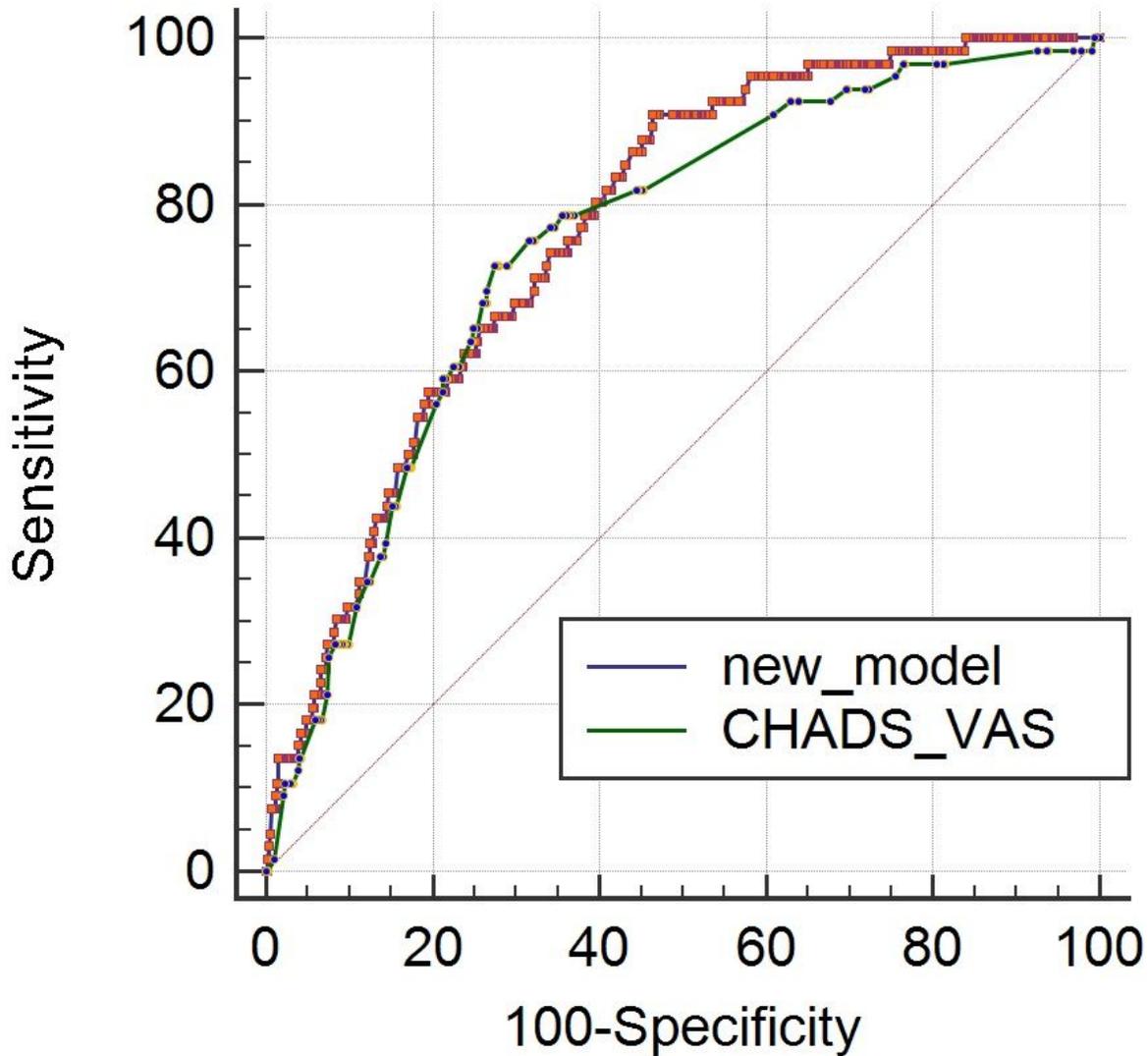


Figure 4

Comparison of the new prediction model and CHADS-VASc score. The AUC of the new model is 0.773, whereas the AUC of CHADS-VASc is 0.754. Pairwise comparison of ROC curves: difference between areas, 0.191; standard error, 0.0239; 95% confidence interval, -0.0278 to 0.0661; z-statistic, 0.800; significance level, $P=0.4239$.

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