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Establishing a predictive model for aspirin resistance in elderly Chinese patients with chronic cardiovascular disease

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Abstract

Background Resistance to anti-platelet therapy is detrimental to patients. Our aim was to establish a predictive model for aspirin resistance to identify high-risk patients and to propose appropriate intervention. **Methods** Elderly patients (n = 1130) with stable chronic coronary heart disease who were taking aspirin (75 mg) for > 2 months were included. Details of their basic characteristics, laboratory test results, and medications were collected. Logistic regression analysis was performed to establish a predictive model for aspirin resistance. Risk score was finally established according to coefficient B and type of variables in logistic regression. The Hosmer–Lemeshow (HL) test and receiver operating characteristic curves were performed to respectively test the calibration and discrimination of the model. **Results** Seven risk factors were included in our risk score. They were serum creatinine (> 110 μmol/L, score of 1); fasting blood glucose (> 7.0 mmol/L, score of 1); hyperlipidemia (score of 1); number of coronary arteries (2 branches, score of 2; ≥ 3 branches, score of 4); body mass index (20–25 kg/m^2, score of 2; > 25 kg/m^2, score of 4); percutaneous coronary intervention (score of 2); and smoking (score of 3). The HL test showed $P \geq 0.05$ and area under the receiver operating characteristic curve ≥ 0.70. **Conclusions** We explored and quantified the risk factors for aspirin resistance. Our predictive model showed good calibration and discriminative power and therefore a good foundation for the further study of patients undergoing anti-platelet therapy.

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Keywords: Aspirin resistance; Cardiovascular disease; Predictive model; Risk score

1 Introduction

Platelet activation plays a vital role in the development of cardiovascular disease (CAD). Anti-platelet therapy inhibits platelet aggregation and prevents thrombogenesis and can be used in primary and secondary prevention of CAD. However, according to clinical observations, not all patients are equally sensitive to anti-platelet therapy. Some patients still have different types of ischemic events during therapy, which is defined as anti-platelet therapy resistance.[1]

Anti-platelet therapy resistance is detrimental to patients. According to the Heart Outcomes Prevention Evaluation (HOPE) Study, patients with aspirin resistance had a 1.8-fold higher risk of the composite outcome of myocardial infarction (MI), stroke, or cardiovascular death, a two-fold higher risk of myocardial infarction, and a 3.5-fold higher risk of cardiovascular death, when compared with patients who were sensitive to aspirin.[2] A multivariate analysis revealed that aspirin resistance is an independent predictor of myonecrosis after percutaneous coronary intervention (PCI) [odds ratio (OR): 2.9; 95% confidence interval (CI): 1.2–6.9; P = 0.015].[3] In another, during follow-up, aspirin resistance was associated with an increased risk of death, myocardial infarction, or cerebrovascular accident (24% *vs.* 10%, hazard ratio: 3.12).[4]

Many factors may be involved in the development of anti-platelet therapy resistance. Age, diabetes and acute coronary syndrome are also predictors of anti-platelet therapy resistance.[5,6] Thus, there might be an association between risk factors and anti-platelet therapy resistance.

In our study, we established a predictive model for aspirin resistance in elderly Chinese patients, and discussed its calibration and discrimination in identifying high-risk populations.

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2 Methods

2.1 Ethical approval of the study protocol

Informed consent was obtained from each patient. The study protocol conformed to the Ethical Guidelines of the 1975 Declaration of Helsinki and approved by the Scientific and Ethics Review Board of Chinese PLA General Hospital (Beijing, China).

2.2 Establishment of predictive model

We enrolled 1130 patients with chronic CAD and aspirin therapy (> 75 mg) for > 2 months from Wanshoulu community, Beijing, China. All the cases had complete clinical and follow-up records. All patients had prior history of cardiovascular disease as defined by previous documented coronary stenosis on cardiac catheterization of ≥ 60%, previous history of MI or stroke, or previous invasive cardiovascular revascularization procedure. All of them received a regular aspirin therapy (100 mg/day) before platelet function assays. Exclusion criteria were; thrombocytopenia (< 100,000/mm^3) or thrombocytosis (> 400,000/mm^3), anemia (hemoglobin < 10 g/dL), polycythemia (hematocrit > 50%), end stage renal disease, acute or chronic liver disease, hematologic diseases, malignancies and history of major surgical procedure within the last month.

Baseline characteristics were collected including age, sex, race, marital status, educational level, smoking, physical activity, body weight, blood pressure, medications and co-morbidities.

Exclusion criteria were as follows: (1) use of heparin, low molecular heparin or other anti-platelet agents within four weeks; (2) surgery within one week before study enrollment; (3) personal or family history of bleeding disorders; (4) platelet count < 150×10^9/L or > 450×10^9/L; (5) hemoglobin level < 80 g/L; (6) history of myeloproliferative diseases; (7) history of drug-induced thrombocytopenia; and (8) history of allergy to aspirin.

2.3 Sample collection

Venous blood (15 mL) was collected following overnight fasting for at least 12 h for routine blood testing, blood biochemistry, homocysteine, coagulation function, anti-thrombin III, high sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), platelet aggregation, and thrombelastography (TEG).

2.4 Light transmittance aggregometry (LTA)

Blood samples were centrifuged at 800 r/min for 5 min to obtain native platelet-rich plasma and further centrifuged at 4000 r/min for 8 min to obtain platelet-poor plasma. The platelet count was assessed using a standard cell counter. Aggregation was performed using arachidonic acid (AA, 0.5 mmol/L) and adenosine diphosphate glucose pyrophospheralase (ADP, 10 μmol/L) with a ChronoLog Aggregometer (Chronolog, Havertown, PA, USA).[7]

2.5 TEG

The TEG platelet mapping assay (Haemoscope, Niles, IL, USA) relies on the measurement of platelet function through clot strength. We used AA (1 mmol/L) as a platelet agonist to measure the degree of thromboxane (TX)A_2-induced platelet aggregation, as previously described.[8]

2.6 Definition of laboratory aspirin resistance

LTA, aspirin resistance was defined as both ≥ 20% AA (0.5 mmol/L) and ≥ 70% ADP (10 μmol/L) induced aggregation. Aspirin semi-resistance was defined as either ≥ 20% AA (0.5 mmol/L) or ≥ 70% ADP (10 μmol/L) induced aggregation, but not both of them.[9,10] TEG, aspirin resistance was defined as platelet inhibition ≤ 50% induced by AA (1 mmol/L).[8]

2.7 Establishment of risk score and stratification

Risk score were finally established according to the regression coefficient and type of variables in the logistic regression model as follows: (1) definition of weight coefficient. Logistic regression coefficients of each included parameter were converted into an integer risk score by the quotient of the corresponding regression coefficient and the lowest one. The weight coefficient of the parameter with the lowest regression coefficient was defined as 1. (2) Definition of ranked score. When the parameter was binary, if the value = 0, the ranked score = 0; if the value = 1, the ranked score = 1. When the parameter was ordinal, in the lowest grade, ranked score = 0; in the second lowest grade, ranked score = 1, etc. (3) Calculation of risk score. The final score was the product of weight coefficient and ranked score. The predicted risk score for aspirin resistance was estimated by the sum of final scores.

2.8 Evaluation of predictive model

A total of 310 cases with chronic stable CAD were recruited from Chinese PLA General Hospital and enrolled in the study. All subjects received a regular aspirin therapy (100 mg/day). Baseline characteristics were collected including age, sex, race, marital status, educational level, smoking, sports, body weight, blood pressure, platelet aggregation, medications and comorbidities.

2.9 Statistical analyses

Categorical variables are presented as frequencies and

percentages. For the categorical variables, patient demographics between groups were compared using chi-square tests or, if expected cell frequencies were small, exact tests. Continuous variables are presented as means ± SD. Logistic regression was adopted to establish the predictive model. Variables entered into the model include: age, smoking, body mass index (BMI), blood pressure, coagulation function, serum homocysteine, anti-thrombin III, hs-CRP and NT-proBNP, history of tobacco use, diabetes, hypertension, hyperlipidemia, revascularization, MI, hemoglobin, platelet count, creatinine.

We compared the predicted percentages of aspirin resistance with the actual percentages to evaluate the calibration and discrimination of the predictive model. Calibration was tested by the Hosmer-Lemeshow (HL) test. $P > 0.05$ was regarded as satisfactory. Discrimination was reflected by the [area under the receiver operating characteristic (ROC) curve, AUC]. As AUC approached 1, the better was the discriminative power. All of the statistical analyses were performed by SPSS version 17.0.

3 Results

3.1 Patient characteristics

According to the results of both LTA and TEG, patients were grouped into aspirin resistant (AR) ($n = 119$), semi-AR ($n = 449$), and aspirin sensitive (AS) ($n = 562$) groups. Basic characteristics of patients are shown in Table 1. The distributions of quantitative data are shown in Table 2. For the

Table 1. Basic characteristics of patients.

Variables	AR ($n = 119$)	Semi-AR ($n = 449$)	AS ($n = 562$)	*P* value
Age, yrs	79.2 ± 10.1	79.8 ± 9.1	79.3 ± 9.4	0.557
Smoking	21	114	123	0.002
Female	19	82	91	0.018
BMI, kg/m^2	24.98 ± 3.56	24.74 ± 3.40	24.88 ± 3.31	0.664
Homocysteine, μmol/L	13.49 ± 4.69	14.03 ± 6.09	14.56 ± 7.43	0.475
NT-proBNP, pg/mL	155.90 ± 151.80	205.61 ± 255.72	199.34 ± 257.10	0.429
hs-CRP, mg/dL	6.55 ± 1.69	5.67 ± 1.31	5.77 ± 2.24	0.001
Creatinine, μmol/L	85.29 ± 26.26	89.41 ± 39.72	94.65 ± 52.44	0.032
Fasting serum glucose, mmol/L	6.23 ± 1.57	5.74 ± 1.63	5.69 ± 1.24	0.328
HbA1c, %	6.23 ± 1.33	5.89 ± 1.04	5.84 ± 1.07	0.643
TC, mmol/L	4.38 ± 0.99	4.40 ± 1.01	4.38 ± 2.12	0.026
TG, mmol/L	1.90 ± 1.17	1.70 ± 1.20	1.53 ± 0.80	0.098
HDL, mmol/L	1.17 ± 0.32	1.21 ± 0.43	1.28 ± 0.74	0.328
LDL, mmol/L	2.50 ± 0.83	2.51 ± 0.78	2.46 ± 0.78	0.061
Uric acid, μmol/L	334.51 ± 95.92	336.87 ± 92.09	329.79 ± 86.75	0.168
Platelet, /μL	182.69 ± 56.3	185.72 ± 51.76	188.45 ± 48.41	0.031
Hypertension	32 (26.9%)	162 (36.1%)	277 (49.3%)	0.000
Diabetes	50 (42%)	52 (11.6%)	52 (9.3%)	0.009
PAOD	21 (17.6%)	56 (12.5%)	45 (8%)	0.337
Hyperuricemia	10 (8.4%)	34 (7.6%)	28 (5%)	
1	50 (42.0%)	177 (39.6%)	242 (43.1%)	0.069
2	37 (31.1%)	127 (28.3%)	185 (32.9%)	0.058
≥ 3	32 (26.9%)	145 (32.3%)	135 (24.0%)	0.007
Left coronary artery involved	9 (7.6%)	24 (5.3%)	18 (3.2%)	0.079
Medications				
Statins	88 (73.9%)	326 (72.6%)	486 (86.5%)	0.299
ACEIs/ARBs	97 (81.5%)	292 (65.0%)	382 (68.0%)	0.068
β-blockers	95 (79.8%)	305 (61.1%)	467 (83.1%)	0.871
Nitrates	29 (24.4%)	133 (29.6%)	184 (32.7%)	0.462
PCI	23 (19.3%)	85 (18.9%)	79 (14.1%)	0.000
CABG	19 (16.0%)	37 (32.7%)	51 (9.0%)	0.001

Data are presented as mean ± SD, *n* or *n* (%). ACEIs: angiotensin-converting enzyme inhibitors; AR: aspirin resistant; ARBs: angiotensin receptor blockers; AS: aspirin sensitive; BMI: body mass index; CABG: coronary artery bypass graft; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: Hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PAOD: peripheral arterial occlusive disease; PCI: percutaneous coronary intervention; TC: total cholesterol; TG: triglyceride.

Table 2. Distributions of quantitative data.

Variables	*n* (%)	Value
Age, yrs		
41–50	1 (0.08%)	1
51–60	46 (4.07%)	2
61–70	156 (13.8%)	3
71–80	335 (29.6%)	4
81–90	440 (38.9%)	5
> 90	152 (13.5%)	6
BMI, kg/m^2		
< 20	52 (4.6%)	0
20–25	531 (47.0%)	1
> 25	547 (48.4%)	2
Homocysteine, μmol/L		
< 13.9	638 (56.5%)	0
≥ 13.9	492 (43.5%)	1
NT-proBNP, pg/mL		
< 95	494 (43.7%)	0
95–220	391 (34.6%)	1
221–460	136 (12.0%)	2
> 460	109 (9.6%)	3
hs-CRP, mg/dL		
< 5	506 (44.8%)	0
5–10	447 (39.6%)	1
> 10	177 (15.6%)	2
Creatinine, μmol/L		
≤ 110	952 (84.2%)	0
> 110	178 (15.8%)	1
Fasting serum glucose, mmol/L		
< 6.0	767 (67.9%)	0
6.1–7.0	212 (18.8%)	1
> 7.0	151 (13.4%)	2
HbA1c		
< 6.0	612 (54.16%)	0
6.0–7.0	369 (32.65%)	1
> 7.0	149 (13.2%)	2
Uric acid, μmol/L		
< 390	843 (74.6%)	0
≥ 390	287 (25.4%)	1
Platelet count, /μL		
< 100	14 (1.2%)	0
100–200	751 (66.5%)	1
201–300	330 (29.2%)	2
> 300	35 (3.1%)	3
Number of involved coronary arteries		
1	469 (41.5%)	1
2	349 (30.9%)	2
≥ 3	312 (27.6%)	3

BMI: body mass index; HbA1c: Hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

qualitative data (female, smoking, hypertension, diabetes, dyslipidemia, myocardial infarction, cerebral embolism, and peripheral arterial occlusive disease), if there is, value = 1; otherwise, value = 0.

3.2 Establishment of predictive model

According to logistic regression analysis, elevated serum creatinine levels, elevated fasting serum glucose levels, dyslipidemia, large number of involved coronary arteries, high BMI, PCI, and smoking were risk factors for aspirin resistance (Table 3).

$$\text{Odds value} = e^{(0.107\times1+0.207\times2+0.211\times3-0.241\times4+0.253\times5+0.302\times6+0.361\times7-0.884)}$$

The percentages of aspirin resistance incidence = $\frac{\text{Odds}}{1+\text{Odds}}\times100\%$.

3.3 Risk score and stratification

We converted all the quantitative data into ordinal data. Risk score was finally established according to regression coefficient and type of variables in the logistic regression model (Table 4). Scores 0–5, 6–10 and > 10 were classified into low, intermediate and high-risk groups, respectively.

3.4 Evaluation of predictive model

Three hundred and ten cases with chronic stable CAD in a hospital in Beijing were collected to evaluate the predictive model. HL test and ROC curve were performed to test calibration and discrimination of the model, respectively. The HL test *P* value was 0.84. AUC was 0.741 (0.712–0.771) (Figure 1). Due to HL test values of $P > 0.05$ and AUC > 0.70, our model showed good calibration and discriminative power.

4 Discussion

We established a predictive model for aspirin resistance in the present study. According to logistic regression analysis, elevated serum creatinine levels, elevated fasting serum glucose levels, dyslipidemia, large number of involved coronary arteries, high BMI, PCI, and smoking were risk factors for aspirin resistance. The risk score was finally established according to the regression coefficient and type of variables in the logistic regression model.

For example, in a 65-year-old man after PCI, with two branches of involved coronary arteries, BMI: 27 kg/m^2, normal serum lipid levels, fasting serum glucose: 7.4 mmol/L, and smoking, the steps of stratification were as follows: (1) after PCI = 2, fasting glucose levels 7.4 mmol/L = 1, BMI

Table 3. A predictive model for aspirin resistance in the elderly patients with cardiovascular disease (logistic regression analysis).

Variables	B	Wald	*P*	OR	95% CI
Creatinine	0.107	6.672	0.001	1.316	1.172–1.826
Fasting serum glucose	0.207	13.533	< 0.0001	1.230	1.121–1.402
Dyslipidemia	0.211	12.326	< 0.0001	1.273	1.005–1.664
Number of involved coronary arteries	0.241	9.688	0.002	1.427	1.205–1.668
BMI	0.253	10.411	0.003	1.594	1.257–1.774
PCI	0.302	7.124	< 0.0001	1.621	1.296–1.852
Smoking	0.361	5.568	0.018	1.438	1.178–1.609
Constant	–0.884	3.680	< 0.0001		

BMI: body mass index; PCI: percutaneous coronary intervention.

Table 4. Risk score for the predictive model for aspirin resistance.

Risk factors	Weight coefficient	Ranked score	Final score
Creatinine (> 110 μmol/L)	1	1	1
Fasting serum glucose > 7.0	1	1	1
Dyslipidemia	1	1	1
Number of involved coronary arteries			
2	2	1	2
≥ 3	2	2	4
BMI, kg/m^2			
20–25	2	1	2
> 25	2	2	4
After PCI	2	1	2
Smoking	3	1	3

BMI: body mass index; PCI: percutaneous coronary intervention.

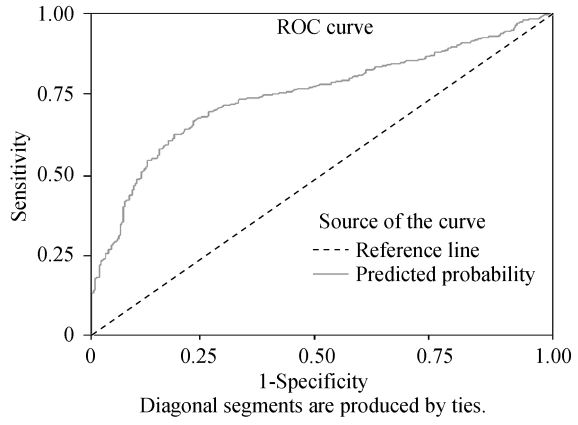

Figure 1. ROC curve for the evaluation of the predictive model. ROC: receiver operating characteristic.

27 kg/m^2 = 2 × 2 = 4, smoking = 3; (2) 2 + 1 + 4 + 3 = 10; and (3) this patient should be classified into the intermediate-risk group.

Many evidence-based studies have shown that clinical risk factors, such as age, diabetes, hypertension, smoking, acute MI, and cardiac insufficiency, can predict thrombotic events in patients with coronary heart disease. Meanwhile, patients with aspirin resistance also have elevated risk for thrombotic events. Case–control studies also show that age, diabetes, and acute coronary syndrome are predictive factors for aspirin resistance.[5–7,11–13] Among these risk factors, elevated serum creatinine level,[14,15] elevated serum glucose level,[16,17] dyslipidemia,[4,18,19] high BMI,[20,21] and smoking,[22,23] are consistent with the results from other countries. Large number of involved coronary arteries was not a consistent risk factor.[24,25]

Smoking is a major risk factor for cardiovascular diseases. Our study indicates that smoking is also a risk factor for aspirin resistance. In men with coronary heart disease, pre-administration of aspirin failed to prevent smoking-induced platelet aggregation and release of the contents of platelet α granules.[26] Multivariate analysis also demonstrated a strong and significant association between smoking and aspirin resistance (relative risk: 11.47, 95% CI: 6.69–18.63, $P < 0.0001$).[27] The corresponding mechanism may be involved in the elevated platelet activity by smoking.[28]

Dyslipidemia is closely related to chronic inflammation and prothrombotic state. We found that dyslipidemia is a risk factor for aspirin resistance, which is consistent with other studies.[11,19,29,30] In a study exploring platelet responsiveness to aspirin in patients with hyperlipidemia, nine of 13 (69%) patients with hyperlipidemia had poor responsiveness to aspirin. Significant correlations were seen between the degree of platelet aggregation and the levels of total cholesterol ($r = 0.35$, $P = 0.009$).[29] Recent studies have also implicated that the immunomodulatory dyad CD40/CD40L is also found on endothelial cells, smooth muscle cells, macrophages, T lymphocytes, and platelets in human atheroma. Both membrane-bound and soluble CD40L (sCD40L) interact with CD40 on vascular cells and result in inflammatory and prothrombotic responses.[31] *In vitro*, oxidized-LDL promotes expression of CD40 and CD40L in human vascular cells with atheroma.[32] *In vivo*,

patients with hypercholesterolemia had increased levels of sCD40L, which was also positively correlated with *in vivo* platelet activation, as reflected by 11-dh thromboxane B_2 and P-selectin.[31] Therefore, CD40L–CD40 interaction may play a vital role in the development of aspirin resistance in patients with hyperlipidemia. Whether drugs to treat dyslipidemia are effective for aspirin resistance need further studies.

DiMinno, *et al*.,[33] found that dosing schedules for aspirin that may suffice in normal circumstances are not effective in patients with diabetic angiopathy. This phenomenon may be due to a high rate of new platelets in the circulation in these patients. Many later studies have also demonstrated the close relationship between elevated serum glucose and aspirin resistance, which is consistent with our results. A correlation analysis showed that aspirin resistance was positively associated with fasting serum glucose levels (r = 0.224, $P < 0.001$) and hemoglobin A1c (HbA1c) levels (r = 0.297, $P < 0.0001$), which indicates that glycemic control influences aspirin resistance in patients with diabetes.[21] In patients with diabetes, there is a significant correlation between TXB_2 production and fasting serum glucose and HbA1c. This association suggests that hyperglycemia is a determinant of the reduced sensitivity to aspirin in diabetes.[34] According to our study, high BMI also increased the risk of aspirin resistance. The positive correlation between BMI and aspirin resistance (r = 0.190, $P < 0.01$) has also been shown in another study.[21] One possibility is attributed to the increase in leptin in patients with obesity, which induces hypercoagulability. Another reason is the low concentration of drug distribution. Many later studies have also demonstrated the close relationship between elevated serum glucose and aspirin resistance, which is consistent with our results.

We also examined an independent group of people involving 310 cases with chronic, stable coronary heart disease in a Beijing hospital to evaluate our predictive model. The model showed good calibration and discriminative power in which the HL test $P > 0.05$ and AUC > 0.70. Ac-cording to the inclusion and exclusion criteria, this predictive model was applicable to cases with chronic, stable coronary heart disease and receiving oral aspirin medication.

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