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Development and Validation of a Risk Prediction Model for Angina Recurrence after Percutaneous Coronary Intervention in Elderly Patients with Acute ST-Segment Elevation Myocardial Infarction Based on CYP2C19-Related Genetic Markers: A Postprint

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Abstract

Background: Acute ST-segment elevation myocardial infarction (STEMI) is associated with high mortality and disability rates. Percutaneous coronary intervention (PCI) is an important revascularization method that can improve prognosis. However, angina recurs in some patients after PCI, affecting quality of life and long-term prognosis. Genetic polymorphisms of drug-metabolizing enzymes influence drug efficacy and adverse reactions. Cytochrome P450 2C19 (CYP2C19) is involved in the metabolism of multiple drugs, and its genetic polymorphisms can alter enzyme activity and affect drug metabolism. The correlation between different CYP2C19 metabolic levels and angina recurrence in STEMI patients after PCI warrants investigation.

Objective: To investigate the correlation between different CYP2C19 metabolic levels and angina recurrence in STEMI patients after PCI.

Methods: A total of 128 patients who underwent emergency PCI for acute coronary occlusion at the Chest Pain Center of the First Affiliated Hospital of Inner Mongolia Medical University in 2022 were selected as study subjects. Patient case data and CYP2C19 gene detection results were collected. Patients were followed up by telephone or outpatient visit at 1, 3, 6, and 12 months after PCI, with follow-up ending on December 31, 2023. The endpoint event was angina attack. Lasso regression analysis was used to screen variables associated with angina attack events, followed by multivariate Logistic regression analysis to construct a prediction model and draw a nomogram. Bootstrap was used for internal validation of the model. The training set and validation set models

were evaluated by receiver operating characteristic (ROC) curve, goodness-of-fit test, calibration curve, and decision curve analysis (DCA) to construct a risk prediction model for angina recurrence after PCI in elderly STEMI patients.

Results: A total of 128 patients were included, including 92 males (71.9%) and females (27.1%), with a median age of 63.5 (61.0, 66.0) years. During follow-up, 45 patients (35.2%) had angina recurrence, and 83 patients (74.8%) did not experience angina recurrence. There were statistically significant differences in gender, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and CYP2C19 genotype between patients without and with angina recurrence (P<0.05). Lasso regression analysis identified 7 independent predictor variables, including gender, LDL-C, HDL-C, homocysteine (Hcy), apolipoprotein B (ApoB), D-dimer, and CYP2C19 genotype. Multivariate Logistic regression analysis showed that female gender (OR=3.4929, 95%CI=-1.2888–15.0662), elevated LDL-C (OR=3.1237, 95%CI=1.6859–6.3484), and elevated Hcy (OR=1.0614, 95%CI=1.0288–1.1036) were risk factors for angina recurrence after STEMI intervention, while elevated HDL-C (OR=0.0167, 95%CI=0.0009–0.2091), CYP2C19 intermediate metabolizer type (OR=0.2734, 95%CI=0.0747–0.9237), and CYP2C19 normal metabolizer type (OR=0.0867, 95%CI=0.0255–0.2561) were protective factors against angina recurrence after STEMI intervention. Bootstrap resampling was repeated 1,000 times for internal validation of the model, and the Hosmer-Lemeshow calibration curve showed good model fit. ROC curves were plotted for the training set and validation set, and the area under the ROC curve (AUC) was calculated. The AUCs were 0.869 (95%CI=0.796–0.943) and 0.789 (95%CI=0.701–0.877) in the training set and validation set, respectively, indicating that the prediction model had good discriminative ability in both the modeling and validation populations. Further DCA showed that the model had good clinical utility.

Conclusion: CYP2C19 intermediate metabolizer type and normal metabolizer type are protective factors against angina recurrence after STEMI intervention. This study established a risk prediction model for angina recurrence comprising 5 clinical indicators including gender (female), LDL-C, Hcy, HDL-C, and CYP2C19, which can be used to predict and screen high-risk patients for angina recurrence. The model demonstrates good fit, discriminative ability, and clinical application value.

Full Text

Construction and Validation of a CYP2C19-Related Genetic Marker-Based Risk Prediction Model for Recurrent Angina After Percutaneous Coronary Intervention in Elderly Patients with STEMI

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Abstract

Background Acute ST-segment elevation myocardial infarction (STEMI) has high mortality and disability rates. Percutaneous coronary intervention (PCI) is a crucial revascularization method that improves prognosis, yet some patients experience recurrent angina after PCI, affecting their quality of life and long-term outcomes. Polymorphisms in drug-metabolizing enzyme genes influence drug efficacy and adverse reactions. Cytochrome P450 2C19 (CYP2C19) participates in the metabolism of multiple drugs, and its genetic polymorphisms can alter enzyme activity and affect drug metabolism. The correlation between different CYP2C19 metabolic levels and recurrent angina after PCI in STEMI patients warrants investigation.

Objective To investigate the correlation between different CYP2C19 metabolic levels and recurrent angina after PCI in STEMI patients.

Methods A total of 128 patients who underwent emergency PCI for acute coronary occlusion at the Chest Pain Center of the First Affiliated Hospital of Inner Mongolia Medical University in 2022 were selected as study subjects. Patient medical records and CYP2C19 gene test results were collected. Follow-up was conducted via telephone or outpatient visits at 1, 3, 6, and 12 months after PCI, ending on December 31, 2023. The endpoint event was angina attack. Lasso regression analysis was used to screen variables related to angina events, followed by construction of a predictive model using multivariate logistic regression analysis and development of a nomogram. Bootstrap resampling was used for internal model validation. The training and validation sets were evaluated using receiver operating characteristic (ROC) curves, goodness-of-fit tests, calibration curves, and decision curve analysis (DCA) to construct a risk prediction model for recurrent angina after PCI in elderly STEMI patients.

Results Among 128 included patients (92 males [71.9%] and 36 females [28.1%]), the median age was 63.5 (61.0, 66.0) years. During follow-up, 45 patients (35.2%) experienced recurrent angina, while 83 patients (64.8%) did not. Statistically significant differences were observed between patients with and without recurrent angina in gender, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and CYP2C19 genotype ($P<0.05$). Lasso regression analysis identified seven independent predictive variables: gender, LDL-C, HDL-C, homocysteine (Hcy), apolipoprotein B (ApoB), D-dimer, and CYP2C19 genotype. Multivariate logistic regression analysis

showed that female gender (OR=3.4929, 95%CI=1.2888–15.0662), elevated LDL-C (OR=3.1237, 95%CI=1.6859–6.3484), and elevated Hcy (OR=1.0614, 95%CI=1.0288–1.1036) were risk factors for recurrent angina after STEMI intervention, while elevated HDL-C (OR=0.0167, 95%CI=0.0009–0.2091), intermediate CYP2C19 metabolism (OR=0.2734, 95%CI=0.0747–0.9237), and normal CYP2C19 metabolism (OR=0.0867, 95%CI=0.0255–0.2561) were protective factors. Bootstrap resampling with 1,000 replications was used for internal validation, and the Hosmer-Lemeshow calibration curve showed good model fit. ROC curves for the training and validation sets yielded AUCs of 0.869 (95%CI=0.796–0.943) and 0.789 (95%CI=0.701–0.877), respectively, indicating good discrimination in both populations. Further DCA demonstrated good clinical utility.

Conclusion Intermediate and normal CYP2C19 metabolic types are protective factors against recurrent angina after STEMI intervention. This study established a risk prediction model for recurrent angina comprising five clinical indicators: female gender, LDL-C, Hcy, HDL-C, and CYP2C19. The model can be used to predict the risk of recurrent angina for early screening of suspicious patients and demonstrates good fit, discrimination, and clinical application value.

Keywords ST elevation myocardial infarction; Angina pectoris; CYP2C19; Percutaneous coronary intervention; Prediction model; Nomogram

Introduction

Acute myocardial infarction (AMI) is a major cardiovascular disease with high mortality and disability rates worldwide [1-2]. In China, the incidence of AMI has been increasing annually with the acceleration of population aging. Although AMI onset is gradually becoming younger, the formulation of prevention and postoperative personalized plans is particularly important [3]. Despite percutaneous coronary intervention (PCI) significantly improving prognosis in patients with ST-segment elevation myocardial infarction (STEMI), recurrent angina after PCI remains a key issue affecting long-term survival and quality of life [4]. In recent years, with advances in medical technology and data analysis methods, the construction and validation of genetic marker-based risk prediction models have become research hotspots [5-7]. These models identify key prognostic factors by analyzing clinical, laboratory, and imaging data, thereby reducing adverse events [8]. The role of the CYP2C19 gene in clopidogrel metabolism has been extensively studied, as CYP2C19 polymorphisms affect clopidogrel metabolism speed and consequently its antiplatelet effect. Rapid metabolizers maintain normal clopidogrel metabolism speed with stable active metabolite levels, typically achieving expected antiplatelet effects. Intermediate metabolizers have slower metabolism, reduced active metabolite generation, weakened antiplatelet effects, and potentially increased cardiovascular risk. Poor metab-

olizers have extremely slow metabolism, minimal active metabolite generation, nearly lost antiplatelet effects, and significantly increased cardiovascular risk. Different metabolic levels lead to significant variations in patient response to clopidogrel, thereby affecting prognosis after PCI in AMI patients [9-10].

Existing prediction models for recurrent angina after PCI have limitations in genetic considerations, personalization, prediction accuracy, and dynamic assessment. Therefore, constructing more comprehensive and precise risk prediction models is necessary to better guide clinical decision-making and improve long-term patient prognosis. The risk prediction model based on CYP2C19-related genetic markers proposed in this study aims to address these limitations. By retrospectively analyzing clinical data from STEMI patients, screening independent predictors, and establishing a risk model through Lasso-Logistic regression analysis, this study seeks to accurately assess patients' risk of recurrent angina. This research compensates for deficiencies in existing studies that combine genetic markers with clinical indicators for personalized risk assessment, providing new insights and tools for long-term prognosis management in elderly STEMI patients with important clinical practice value.

Methods

Study Design and Population This retrospective study selected 128 patients who underwent emergency PCI for acute coronary occlusion at the Chest Pain Center of the First Affiliated Hospital of Inner Mongolia Medical University in 2022. The study was approved by the Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University (approval number: YKD2024021019), with informed consent waived for this retrospective design.

Inclusion criteria: (1) Admission diagnosis of STEMI with age >60 years; (2) Coronary angiography showing acute single-vessel occlusion; (3) Ability to adhere to oral antiplatelet therapy such as aspirin and ticagrelor; (4) Post-PCI restoration of TIMI grade 3 flow in the culprit vessel.

Exclusion criteria: (1) Coronary lesions: non-native large vessel disease, left main disease, chronic total occlusion, severe calcification, graft lesions, or multivessel disease; (2) Prior history of coronary heart disease; (3) History of coronary artery bypass grafting or previous PCI in the target vessel; (4) >50% stenosis in coronary arteries other than the culprit vessel; (5) Expected survival <1 year; (6) Procedure failure; (7) Poor compliance with follow-up.

PCI Perioperative Management All procedures were performed by operators with coronary intervention training certification. STEMI patients received oral aspirin 300 mg loading dose, clopidogrel 300 mg loading dose (or ticagrelor 180 mg loading dose), followed by maintenance doses. Atorvastatin 20 mg/d was administered. Preoperative examinations were completed urgently, including blood routine, urine routine, stool routine, coagulation function, liver and kidney function, electrocardiogram, and echocardiography. Patients and their

families were informed of procedural risks and complications, and informed consent was obtained.

CYP2C19 Genetic Testing Sample collection: EDTA-anticoagulated whole blood (2 mL in purple-top tube) was collected for genomic DNA extraction. Samples were sent for testing promptly to ensure DNA quality and integrity.

Detection sites: Included CYP2C19*2 (c.681G>A), CYP2C19*3 (c.636G>A), and CYP2C19*17 (c.-806C>T).

Result interpretation: Based on melting curve Tm value changes or microarray hybridization signal intensity, CYP2C19 gene polymorphism types were determined. CYP2C19*1/*1 was normal metabolizer; CYP2C19*2/*2 or CYP2C19*2/*3 were poor metabolizers (slow metabolism); CYP2C19*1/*2 or CYP2C19*1/*3 were intermediate metabolizers (metabolism speed between normal and slow).

Data Collection Modeling data included patient basic information, laboratory tests, and examination indicators. Basic information comprised age, gender, marital status, smoking (defined as regular smoking within the past year), alcohol consumption (defined as >3 times/week with average >50 mL/time within the past year), and history of hypertension and diabetes. Laboratory indicators included blood lipids, homocysteine (Hcy), apolipoproteins (Apo), cardiac enzymes, troponin, D-dimer, international normalized ratio (INR), N-terminal pro-brain natriuretic peptide (NT-proBNP), and liver function. Examination indicators included echocardiography and angiography findings such as target lesion location and length. Data were entered into R 4.4.1 after organization. Missing values <10% were handled using multiple imputation with the mice package, while missing values >10% led to data exclusion. Bootstrap resampling was used for validation. CYP2C19 metabolic levels (normal, intermediate, and poor) were compared pairwise: normal vs. intermediate recorded as 1, intermediate vs. poor as 2, and normal vs. poor as 3, then included as multicategorical variables in the dataset.

Follow-up Follow-up was conducted via telephone or outpatient visits at 1, 3, 6, and 12 months after PCI, ending on December 31, 2023. The endpoint event was angina attack, characterized by crushing pain or chest tightness in the precordial or retrosternal area, possibly accompanied by palpitations, fatigue, and diaphoresis. Pain was primarily located in the retrosternal region, potentially radiating to the precordial area, left upper limb, neck, and jaw. Angina typically occurred with exertion or emotional stress, lasting several minutes and rapidly relieved by rest or nitrates.

Statistical Analysis Data analysis was performed using SPSS 26.0 and R 4.4.1. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and

compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as M(P25, P75) and compared using Wilcoxon test. Categorical variables were expressed as n(%) and compared using ^{2} test or Fisher's exact test. Lasso regression analysis was used to screen variables related to angina events, followed by multivariate logistic regression to construct the prediction model and draw a nomogram. Bootstrap resampling was used for internal validation. Model performance in training and validation sets was evaluated using ROC curves, goodness-of-fit tests, calibration curves, and decision curve analysis (DCA). P<0.05 was considered statistically significant.

Results

Patient Baseline Characteristics A total of 128 patients were included (92 males [71.9%] and 36 females [28.1%]), with a median age of 63.5 (61.0, 66.0) years. During follow-up, 45 patients (35.2%) experienced recurrent angina, while 83 patients (64.8%) did not. Statistically significant differences were observed between patients with and without recurrent angina in gender, LDL-C, HDL-C, and CYP2C19 genotype (P<0.05). No significant differences were found in age, smoking, alcohol consumption, marital status, lesion location, lesion length, total cholesterol, triglycerides, Hcy, complement C1q, ApoA, ApoB, creatine kinase-MB, creatinine, D-dimer, hypersensitive troponin T, NT-proBNP, INR, fasting glucose, uric acid, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, left ventricular ejection fraction, PCI methods, or medication history (P>0.05) (Table 1).

Variable Selection by Lasso Regression Lasso regression analysis was performed on selected variables. Vertical lines were drawn at the minimum criterion and 1 standard error of the minimum criterion at the optimal value. Based on 10-fold cross-validation, the optimal model was achieved at $ $1se = 0.0710, log($ $)$=-2.6450, screening out seven independent predictive variables: gender, LDL-C, HDL-C, Hcy, ApoB, D-dimer, and CYP2C19 genotype (Figure 1 [Figure 1: see original paper], Figure 2 [Figure 2: see original paper]).

Prediction Model Construction Using recurrent angina (assignment: no=0, yes=1) as the dependent variable and the seven predictive variables screened by Lasso regression as independent variables, multivariate logistic regression analysis identified five predictive variables. Female gender (OR=3.4929, 95%CI=1.2888–15.0662), elevated LDL-C (OR=3.1237, 95%CI=1.6859–6.3484), and elevated Hcy (OR=1.0614, 95%CI=1.0288–1.1036) were risk factors for recurrent angina after STEMI intervention, while elevated HDL-C (OR=0.0167, 95%CI=0.0009–0.2091), intermediate CYP2C19 metabolism (OR=0.2734, 95%CI=0.0747–0.9237), and normal CYP2C19 metabolism (OR=0.0867, 95%CI=0.0255–0.2561) were protective factors (Table 2).

Nomogram Development A dynamic nomogram was constructed to demonstrate the influence of Hcy, LDL-C, gender, HDL-C, and CYP2C19 on total points. The horizontal axis represents point values for each variable, while the vertical axis shows cumulative total points. A red dot marks the specific threshold (0.493), with total points exceeding this threshold considered high risk. Hcy point values ranged from 0–100, showing a large influence range. LDL-C point values ranged from 0–50, showing moderate contribution. The gender variable boxplot showed point distribution differences between males and females, with outliers marked. HDL-C point values were concentrated, showing small variation. The CYP2C19 variable boxplot showed point distributions across different genotypes, with red dots marking significant genotype effects. The total points axis at the bottom showed overall distribution after considering all variables. The predictive model nomogram is shown in Figure 3 [Figure 3: see original paper].

Model Performance Evaluation The net reclassification improvement index (NRI) and integrated discrimination improvement index (IDI) were used to evaluate the new model (including CYP2C19 genotype) versus the baseline model (excluding CYP2C19 genotype). For categorical variables, NRI=0.1759 (95%CI=0.0075–0.3443, P=0.041), indicating significant improvement in classification performance. For continuous variables, NRI=0.7550 (95%CI=0.4175–1.0926, P<0.001), indicating significant improvement in continuous variable prediction. IDI=0.1458 (95%CI=0.0793–0.2124, P<0.001), indicating significant improvement in discrimination ability.

Bootstrap resampling with 1,000 replications was used for internal validation. The Hosmer-Lemeshow calibration curve showed good model fit (Figure 4 [Figure 4: see original paper]). ROC curves for training and validation sets yielded AUCs of 0.869 (95%CI=0.796–0.943) and 0.789 (95%CI=0.701–0.877), respectively, indicating good discrimination in both populations (Figure 5 [Figure 5: see original paper]). Further DCA showed good clinical utility (Figure 6 [Figure 6: see original paper]).

Discussion

Major adverse cardiovascular events (MACE) remain a serious adverse outcome in AMI patients, with previous studies reporting MACE incidence of approximately 4.2%–51% [1]. In recent years, AMI cases have increased annually with a trend toward younger onset. Elderly patients have more comorbidities and higher PCI treatment risks, with higher postoperative angina recurrence risk. WANG et al. [2] conducted a comparative study of myocardial infarction in young and elderly patients, including 114 young AMI patients ($ 42*years*)*and*179*elderlyAMIpatients*($60 years). Results showed a higher proportion of males in the young AMI group (94.7% vs. 64.2%, P<0.05), with young patients having higher rates of smoking history and positive family history but lower rates of hypertension and diabetes. Elderly AMI patients were

more likely to have various clinical manifestations and multivessel disease, while young AMI patients had fewer symptoms and more limited lesions. Clinical manifestations of AMI differ between young and elderly patients. This study constructed and validated a risk model for recurrent angina after PCI in elderly AMI patients based on multiple indicators. Results showed that female gender, LDL-C, Hcy, HDL-C, and CYP2C19 genotype had high value in identifying recurrent angina after STEMI.

Female patients had higher recurrent angina risk than males, possibly due to reduced estrogen-mediated vascular protection after menopause [3], warranting further clinical research. LDL-C was an independent risk factor and HDL-C an independent protective factor for recurrent angina, consistent with clinical understanding. The core component of coronary plaque formation is lipid plaque [4]. The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines [5] emphasized that coronary disease progression risk positively correlates with blood lipid levels, particularly LDL-C. HDL-C can transport cholesterol from peripheral tissues for conversion to bile acids or direct intestinal excretion, reducing total cholesterol levels and readmission risk [6]. LDL-C has opposite effects. Early endothelial dysfunction in atherosclerosis involves monocyte-macrophage phagocytosis of oxidized LDL-C to form foam cells, the core process of atherosclerosis [7]. WU et al. [8] conducted a nested case-control study of 3,438 CHD patients (1,719 pairs), including 1,084 US Caucasians (542 pairs), 1,244 US Blacks (622 pairs), and 1,110 Chinese adults (555 pairs), emphasizing that several lipoprotein biomarkers including ApoB/ApoA1, ApoB, and LDL-C were closely related to CHD occurrence. Hcy is a predictor of cardiovascular and cerebrovascular diseases and can reflect early cardiac injury. WU et al. [9] conducted a study on Hcy and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels in coronary heart disease diagnosis, including 232 patients in a retrospective study divided into AMI, unstable angina, and stable angina groups, with 75 healthy adults as controls. Univariate and multivariate logistic regression analysis identified Hcy, Lp-PLA2, hypertension, and hyperlipidemia as important risk factors for coronary heart disease.

The CYP2C19 enzyme plays a crucial role in drug metabolism, particularly for clopidogrel. Clopidogrel is a prodrug requiring CYP2C19-mediated conversion to active metabolites for antiplatelet effects. Therefore, CYP2C19 polymorphisms significantly affect clopidogrel efficacy. In contrast, ticagrelor is a novel antiplatelet agent whose activity does not depend on CYP2C19 metabolism and is thus unaffected by CYP2C19 polymorphisms.

CYP2C19 encodes a cytochrome P450 family protein that primarily exists in the liver and participates in metabolizing multiple important drugs including proton pump inhibitors, antidepressants, antiepileptics, and antiplatelet agents such as clopidogrel. CYP2C19 gene variants can significantly affect enzyme activity, leading to different metabolic phenotypes. CYP2C19 genotyping differences can influence drug efficacy and safety, holding important significance in personalized medicine by allowing adjustment of drug treatment based on

individual genetic backgrounds [10]. This study showed that high metabolic level CYP2C19 genotypes reduced recurrent angina risk. ZHANG et al. [11] investigated the relationship between CYP2C19*2/CYP2C19*3 polymorphisms and coronary heart disease development and their impact on adverse clinical events, including 231 PCI patients genotyped for CYP2C19*2 and CYP2C19*3 with 14-month follow-up. Results showed CYP2C19*2 carriers had significantly higher cardiovascular event rates than non-carriers (21.6% vs. 6.3%, P=0.019). Cox proportional hazards model indicated CYP2C19*2 was an independent predictor of MACE (OR=3.65, 95%CI=1.09–12.25, P=0.036). CYP2C19*2 polymorphism increased coronary heart disease and MACE risk, while CYP2C19*3 showed no similar effect in Chinese Han population.

This study has several limitations, including single-center design, retrospective methodology, and relatively small sample size, which may introduce confounding factors. Additionally, external validation is lacking. To further confirm the reliability of conclusions, future prospective, multicenter studies are needed. In summary, female gender, LDL-C, Hcy, HDL-C, and CYP2C19 genotype are key factors affecting 1-year recurrent angina after PCI in STEMI patients. The prediction model constructed based on these factors shows high predictive efficacy and may facilitate clinical decision-making and early intervention.

Author Contributions

JIA Gaopeng was responsible for data collection and manuscript writing. CHEN Qiuyu was responsible for statistical analysis guidance and manuscript writing guidance.

Conflict of Interest

The authors declare no conflict of interest.

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