Original Article

The Association between *CYP2C19* Genetic Polymorphism and Prognosis in Patients Receiving Endovascular Therapy

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Abstract

Background: Potentially substantial impacts on the prognosis have been observed in individuals undergoing endovascular treatment due to cytochrome P450 2c19 (C*YP2C19*) polymorphism. In an attempt to improve prognosis and lower the recurrence rate, this study investigated the *CYP2C19* polymorphism in acute ischemic stroke patients. **Materials and Methods:** A retrospective analysis was performed on 292 patients with cerebral infarction who had acute endovascular recanalization at the Department of Neurology of Chongqing Hospital of Traditional Chinese Medicine between May 2017 and 2019. The patients were categorized into rapid-, medium-, and slow-metabolism groups based on *CYP2C19* gene polymorphism, and their prognosis was monitored. In addition, the prognosis of 188 patients selectively receiving carotid artery stenting at a selected time was also observed. **Results:** Among the 292 cerebral infarction cases receiving acute endovascular recanalization, the patients in the *CYP2C19* rapid-metabolism group regularly took clopidogrel and aspirin combined with antiplatelet therapy and suffered from reoccurrence of apoplexy and cerebral hemorrhage; the 90-day good prognosis had a statistical difference ($P < 0.05$, prognostic assessment includes hospitalization and 6 months after discharge) and the other adverse events had no statistical difference (including mortality). The 188 patients selectively receiving carotid artery stenting had a recurrence of apoplexy, cerebral hemorrhage, and restenosis rate with a statistical difference ($P < 0.05$), and the other adverse events had no statistical difference. **Conclusions:** In conclusion, the findings of the current study indicate that irrespective of whether patients are undergoing selective carotid artery stenting or acute endovascular recanalization, those with rapid *CYP2C19* metabolism have a significantly lower likelihood of experiencing adverse prognostic events compared to those with intermediate and slow metabolism. Furthermore, this group also has a more favorable prognosis than the other two groups.

Keywords: Clopidogrel, *CYP2C19*, endovascular, stroke

Introduction

Cerebral infarction is a prevalent ailment characterized by elevated rates of mortality and disability. Environmental and hereditary factors influence cerebral infarction. Endovascular therapy is currently the most efficacious treatment for severe stenosis and intracranial and extracranial vascular occlusion.[1-4] Clinicians frequently prescribe clopidogrel, an antiplatelet drug, particularly in patients with atherosclerosis who have undergone endovascular therapy and where its combination with aspirin effectively prevents ischemic events.[5,6] An association has been established between cytochrome P450 2c19 (*CYP2C19*) gene polymorphisms and clopidogrel's antiplatelet activity, although the precise mechanism by which this relationship operates is still unknown.[7] The present method for categorizing the *CYP2C19* genotype involves the administration of probe drugs, specifically mephenytoin and omeprazole. Rapid, medium, and slow metabolism are the classifications attributed to *CYP2C19* polymorphisms based on the distinct effects of *CYP2C19* on substrates and, consequently, metabolism. Genetic analysis has shown that the CYP2C19*17/*17, CYP2C19*1/*17, and CYP2C19*1/*1 polymorphisms belong to the rapid-metabolism group, CYP2C19*2/*17, CYP2C19*3/*17, CYP2C19*1/*2, and CYP2C19*1/*3 belong to the medium-metabolism group, and CYP2C19*2/*2, CYP2C19*2/*3, and CYP2C19*3/*3 belong to the slow-metabolism group.[8] Antiplatelet medication can effectively reduce the risk of stroke recurrence in patients who have experienced cerebral infarction subsequent to brain endovascular therapy. The catalytic activity of *CYP2C19* significantly influences the antiplatelet activity of clopidogrel. Research has revealed that *CYP2C19* genetic polymorphisms may impact the efficacy of the drug in patients undergoing vertebral artery stent implantation.[9,10] Nevertheless, there is a lack of research examining the impact of *CYP2C19*

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Submitted: 25-Jun-2023 **Revised:** 22-Jul-2023 **Accepted:** 25-Jul-2023
Published: 01-Feb-2024

DOI: 10.4103/aian.aian_564_23

polymorphism on the prognosis of antiplatelet activity in patients who have experienced cerebral infarction subsequent to acute endovascular recanalization. Two hundred ninety-two patients were the subjects of the retrospective cohort analysis in the present study. An analysis of 292 patients who had undergone acute endovascular recanalization for cerebral infarction at our institution was conducted to determine the incidence of adverse prognostic events during hospitalization and 6 months after discharge, in addition to a prognostic assessment 3 months after discharge. Furthermore, 188 patients who had received selective carotid artery stenting were also analyzed, and the incidence of adverse events and prognostic predictions was assessed. The primary purpose of the thromboelasticity chart is to assess the platelet inhibition induced by various antiplatelet drugs. The inhibition rate of arachidonic acid (AA) primarily signifies the patient's reaction to aspirin, while the inhibition rate of adenosine diphosphate (ADP) primarily signifies the body's reaction to clopidogrel and other inhibitors. An ADP% of <50% is regarded as indicative of sensitivity to the antiplatelet effect. Through an examination of the correlation between the platelet inhibition rate in the thromboelastogram and *CYP2C19*, we proceeded to investigate whether a genetic variant of *CYP2C19* with a rapid metabolism is comparatively sensitive to clopidogrel. The primary objective of this research endeavor was to investigate the correlation between *CYP2C19* polymorphism and the prognosis of patients undergoing endovascular therapy. In addition, the study aimed to ascertain the optimal antiplatelet regimen for patients who experienced cerebral infarction while undergoing endovascular therapy and contribute to the mitigation of adverse prognostic events among patients with cerebral infarction.

Patients and Methods

Patients

A retrospective investigation was conducted. The data were collected from patients who underwent endovascular therapy and selective carotid artery stenting between May 2017 and 2019 at the Department of Neurology, University of Traditional Chinese Medicine in Chongqing, China.

Inclusion criteria: The inclusion criteria were as follows: (1) a total of 292 patients who received emergency endovascular recanalization in accordance with the Chinese acute ischemic stroke diagnosis and treatment guidelines 2018;[11] (2) patients with large vessel occlusion (LVO) in the anterior circulation (internal carotid artery and middle cerebral artery [M1/M2]); (3) Of the 188 patients who received carotid stents:those with internal carotid artery stenosis ≥50% and the presence of clinical symptoms, or if asymptomatic, stenosis ≥70%, all displayed good medical compliance[12]; (4) patients older than18 years old; (5) patients with complete and accurate clinical data. Every patient or family member signed an informed consent form after providing their approval.

Exclusion criteria: The study exclusion criteria were as follows: (1) patients with cardiogenic apoplexy caused by heart diseases such as atrial fibrillation; (2) other cerebral infarction caused by nonatherogenesis of the great arteries; (3) patients using anticoagulant agents, either oral or intravenous, and patients with platelet dysfunction; (4) patients with malignant tumors; (5) patients with mental disorders or family history of psychosis; (6) patients allergic to contrast agents; (7) patients or family members who refused to be included; (8) patients with incomplete case data; and (9) those with corresponding contraindications.

Methods

Acute endovascular recanalization

Computed tomography angiography (CTA) and cerebral perfusion angiography (CTP) of the head and neck blood vessels were performed preoperatively in patients with acute cerebral infarction. Advanced vessel analysis (AVA) and Extended Brilliance Workspace (EBW; Phillips) image postprocessing workstation perfusion software were utilized for CTP and head and neck CTA reconstruction following the patient's scan. The interventional physician assessed the endovascular therapy in light of the findings from CTA and CTP. Following the family members' conclusion of the assessment and approval of the consent form for the operation, a brain digital subtraction angiography (DSA) was conducted. Acute endovascular recanalization was executed based on the unique characteristics of each patient, as determined by preoperative assessment and intraoperative angiography. Various techniques were utilized, such as balloon dilation and stent thrombus removal.

Selective internal carotid artery stenosis stenting

A total of 188 eligible patients underwent head and neck CTA examination to determine the location and degree of stenosis. Subsequently, the operating surgeon conducted an evaluation.[13] If the patient met the criteria for carotid artery stenting, a metal stent was placed at the site of the stenosis to improve the patient's ischemic symptoms.

Monitoring of CYP2C19

All blood samples utilized for genetic investigations were collected subsequent to hospital admission. Genomic DNA was isolated from blood samples and subsequently amplified using the polymerase chain reaction (PCR) technique. The amplified DNA was then subjected to hybridization for color development. The data obtained from the biochip was examined using BaiO gene chip image processing software after being read by a biochip reader. Subsequently, the genetic information was transported.[14-16] The genotypes of the 292 patients who received endovascular therapy were classified into rapid-metabolism group (Group A_1, 105 cases), medium-metabolism group (Group B_1, 111 cases), and slow-metabolism group (Group C_1, 76 cases). The same *CYP2C19* gene classification was conducted on 188 patients with selective internal carotid artery stenosis stenting, namely, rapid-metabolism group (Group A_2, 77 cases), medium-metabolism group (Group B_2, 69 cases), and slow-metabolism group (Group C_2, 42 cases).

Thromboelastogram and platelet inhibition rate (ADP%)

Thrombelastograms were acquired for all patients before therapy and 6 months posttreatment using the TEG C5000 thermoscope from Weimei Company. The platelet aggregation function test kit, employing the coagulation method, was utilized to assess the antiplatelet effect, with ADP% ≥50% considered as an indicator of sensitivity.[17]

Observational indicators and evaluation of effects

The patients' basic medical history comprised their age, sex, history of diabetes, hypertension, hyperlipidemia, and smoking. Adverse events occurring during hospitalization were observed, including recurrent apoplexy, cerebral hemorrhage, and other adverse events such as skin hemorrhage, gingival hemorrhage, hematochezia, and mortality. Following their discharge from the hospital, patients underwent a 90-day evaluation of their good prognosis using the modified Rankin scale (mRS).[18,19] Patients who had undergone acute endovascular recanalization had their adverse events assessed 6 months after discharge, primarily through outpatient visits and assessments by phone and video. Following a 6-month period, patients who underwent selective internal carotid artery implantation underwent a CTA assessment to determine the degree of vascular stenosis (normal diameter of the distal end of the stenosis - minimum diameter of the vascular stenosis site)/normal diameter of the distal end of the stenosis × 100%). The vascular stenosis was defined as ≥50% in this study.

Statistical analysis

For the analysis of continuous variables, which are reported as mean ± standard deviation (SD), the Student's *t*-test or the Mann–Whitney U test was employed. Categorical variables were examined using the χ^2 test or Fisher's exact test, and they are expressed as frequency (%). The association between group membership and categorical outcomes (blood vessel restenosis, cerebral hemorrhage, mRS ≤2, recurrence of acute ischemic stroke) was examined using logistic regression analysis. Statistical Package for the Social Sciences (SPSS) 20.0 software was used to analyze the data, and *P* values <0.05 were regarded as statistically significant.

Results

An examination of the primary clinical data of the patients revealed no notable disparities in age, gender, history of diabetes, history of smoking, hyperlipidemia, hypertension history, or admission status. The text refers to the National Institutes of Health Stroke Scale (NIHSS), the Alberta Stroke Program Early CT Score (ASPECTS), the occlusion site, and the modified Thrombolysis in Cerebral Infarction (mTICI) scale for reperfusion before intervention [Tables 1a and b].

Comparison of thromboelastogram platelet inhibition rate (ADP%) between the two groups of patients before and after treatment

There were no statistically significant differences in the ADP% ≥50% values before treatment between patients who underwent endovascular therapy and those who received selective carotid artery stenting ($P_1 > 0.05$, $P_2 > 0.05$). However, the ADP% ≥50% values were found to be significantly different 6 months after discharge ($P_1 < 0.05$, $P_2 < 0.05$). The findings demonstrated a substantial rise in platelet inhibition rate (ADP%) ≥50% among patients classified as belonging to the *CYP2C19* rapid-metabolism group compared to those in

Table 1a: Baseline demographics of acute endovascular recanalization [$\bar{x}\pm s$, *n* (%)]

	Group A_1	Group B_1	Group C_1	*P*
n	105	111	76	
Age	56.2±2.6	61.3±4.7	57.2±2.8	0.15
Male	52 (49.5%)	57 (51.3%)	39 (47.3%)	0.08
Hypertension history	57 (54.2%)	55 (49.5%)	42 (55.2%)	0.70
Smoking history	30 (28.6%)	29 (26.1%)	17 (22.3%)	0.46
Hyperlipidemia	18 (17.1%)	22 (19.8%)	10 (13.2%)	0.19
Diabetes history	18 (17.1%)	19 (17.1%)	11 (14.4%)	0.15
Admission NIHSS	13.1±1.3	14.5±2.6	12.7±1.8	0.71
ASPECTS	9.2±2.1	9.6±1.2	9.2±1.7	0.23
Occlusion site				0.49
ICA	57 (54.2%)	47 (42.3%)	35 (46.0%)	0.13
MCA	48 (45.8%)	64 (57.7%)	41 (54.0%)	0.17
Reperfusion before intervention (mTICI)				0.45
0	96 (91.4%)	100 (90%)	65 (85.5%)	0.41
1	5 (4.8%)	6 (5.4%)	4 (5.2%)	0.17
2a	2 (1.9%)	3 (2.8%)	3 (4.1%)	0.37
2b	2 (1.9%)	1 (0.9%)	4 (5.2%)	0.48
3	0 (0)	1 (0.9%)	0 (0)	0.71

A_1: Rapid-metabolism group of endovascular therapy; B_1: Medium-metabolism group of endovascular therapy; C_1: Endovascular therapy slow-metabolism group. ASPECTS=Alberta Stroke Program Early CT Score, ICA=Internal carotid artery, MCA=Segment of middle cerebral artery, mTICI=Modified thrombolysis in cerebral infarction, NIHSS=National Institutes of Health Stroke Scale. Age, admission NIHSS and ASPECTS were represented as mean±SD. All others were as *n* (%)

Table 1b: Baseline demographics of patients selectively receiving carotid artery stenting [$\bar{x}\pm s$, *n* (%)]

	Group A_2	Group B_2	Group C_2	*P*
n	77	69	42	0.23
Age	54.2±1.6	60.1±2.5	58.2±1.1	0.41
Male	42 (54.5%)	36 (52.1%)	21 (50.0%)	0.71
Hypertension history	34 (44.1%)	30 (43.5%)	19 (45.2%)	0.21
Smoking history	26 (33.8%)	20 (30.0%)	14 (33.3%)	0.09
Hyperlipidemia	18 (23.4%)	12 (17.4%)	9 (21.4%)	0.34
Diabetes history	14 (18.1%)	17 (24.6%)	5 (11.9%)	016

A_2: Carotid artery stenting rapid-metabolism group; B_2: Medium-metabolism group of carotid artery stenting; C_2: Carotid artery stenting slow-metabolism group. Age is represented as mean±SD. All others are as *n* (%)

Table 2: Thromboelastogram platelet inhibition rate (ADP%) of patients before and after treatment, *n* (%)

Group	*N*	Platelet inhibition rate (ADP%)		*P*
		Before treatment	6 months after discharge	
A_1	105	34 (32.4%)	89 (84.8%)	0.022*
B_1	111	38 (34.2%)	56 (50.5%)	0.136
C_1	76	22 (29.0%)	31 (40.8%)	0.321
P_1		0.288	0.029	
A_2	77	20 (26.0%)	62 (80.5%)	0.018*
B_2	69	19 (27.5%)	27 (39.1%)	0.221
C_2	42	11 (26.2%)	14 (33.3%)	0.614
P_2		0.429	0.012*	

ADP=Adenosine diphosphate. *P<0.05

the slow-metabolism group [Table 2], irrespective of whether they were undergoing endovascular therapy or selective carotid artery stenting.

Incidence of adverse events during hospitalization and 6 months after discharge

As shown in Tables 3 and 4, patients in the rapid-metabolism groups of both patients with acute endovascular recanalization and patients with carotid artery stenting showed a lower incidence of acute ischemic stroke during hospitalization (P_1=0.021 and P_2=0.013, respectively). The study recorded the mortality rates of patients during their hospital stay. Specifically, one patient in group A_1 (105), two patients in group B_1 (111), and one patient in group C_1 (76) have expired. It is worth noting that no patients who received selective carotid artery treatment died. At the 6-month follow-up after discharge, it was noted that the likelihood of a repeat occurrence of acute ischemic stroke was significantly lower in the *CYP2C19* rapid-metabolism groups compared to the other *CYP2C19* groups. This finding was observed in both patient groups, specifically those who underwent acute endovascular recanalization and those who received carotid artery stenting (P_1 = 0.024 and P_2 = 0.019, respectively). We detected mortality in two patients from the A_1 group (105), one patient from the B_1 group (111), and two patients from the C_1 group (76). However, no mortality was reported in the patients who received carotid artery more frequently.

Ninety-day good prognosis in patients with acute endovascular recanalization and 6-month restenosis rate in patients receiving carotid artery stenting

Subsequent examinations of patients who underwent endovascular therapy revealed that the rate of favorable prognosis was notably higher in patients belonging to the *CYP2C19* rapid-metabolism group with mRS scores ≤2 compared to other groups (P = 0.035) [Table 5]. The 6-month examination of patients who underwent carotid artery stenting revealed that the possibility of restenosis in the internal carotid artery was significantly reduced in the *CYP2C19* rapid-metabolism group compared to other groups (P = 0.047) [Table 6].

Discussion

Clopidogrel is an antiplatelet drug that is widely used in patients with cerebral infarction and can also effectively prevent ischemic events in patients with atherosclerosis. However, the antiplatelet action of clopidogrel is closely associated with the function of *CYP2C19* and is, thus, affected by polymorphism in the gene.[20,21] Previous research has shown that variations in the *CYP2C19* gene impact the outlook of patients with coronary heart disease who undergo percutaneous coronary intervention.[22,23] Consequently, it is probable that *CYP2C19* polymorphism also influences the prognosis of patients who undergo endovascular therapy and selective carotid artery stenting. The present study evaluated the prognosis of 292 patients who received endovascular therapy and 188 patients who received internal carotid artery implantation and explored the impact of *CYP2C19* polymorphism on their prognosis. According to the results, patients' *CYP2C19* polymorphism status should be ascertained before starting clopidogrel, to lower the risk of unfavorable ischemic events.

The prognosis of 188 patients who underwent selective internal carotid artery implantation and 292 patients who underwent endovascular therapy was examined in this study. First, the thromboelastogram platelet inhibition rates (ADP%) of all patients before and 6 months after treatment were determined, which showed a significantly better rate in the *CYP2C19* rapid-metabolism group compared to the other *CYP2C19* groups, regardless of whether the patients received endovascular therapy or carotid artery stenting, demonstrating that the *CYP2C19* rapid-metabolism genetic variant is relatively sensitive to clopidogrel. The antiplatelet effect of the group with slow metabolism was inferior to that of the other group, which is consistent with previous studies. Subsequently, we assessed the occurrence of negative events 6 months after discharge and the 90-day favorable prognosis mRS of the 292 patients who underwent endovascular therapy. Our findings revealed that patients in the *CYP2C19* rapid-metabolism category

Table 3: Incidence of adverse events in the different groups during hospitalization, *n* (%)

	Group A_1	Group B_1	Group C_1	P_1	Group A_2	Group B_2	Group C_2	P_2
n	105	111	76		77	69	42	
Recurrence of cerebral apoplexy	0	8 (7.2%)	9 (11.8%)	0.021*	1 (1.2%)	10 (14.5%)	9 (21.4%)	0.013*
Cerebral hemorrhage	1 (1.0%)	2 (1.8%)	1 (1.3%)	0.429	0	1 (1.4%)	0	0.716
Other adverse events	13 (12.4%)	25 (22.5%)	12 (15.8%)	0.551	14 (18.0%)	11 (16.0%)	8 (19.0%)	0.342
Died	1 (1.0%)	2 (1.8%)	1 (1.3%)	0.671	0	0	0	-

*P<0.05

Table 4: Incidence of adverse events in the different groups 6 months after discharge, *n* (%)

	Group A_1	Group B_1	Group C_1	P_1	Group A_2	Group B_2	Group C_2	P_2
n	105	111	76		77	69	42	
Recurrence of cerebral apoplexy	0	13 (11.7%)	16 (21.1%)	0.024*	1 (1.2%)	9 (13.1%)	14 (33.3%)	0.019*
Cerebral hemorrhage	0	1 (0.9%)	1 (1.31%)	0.524	0	1 (1.4%)	0	0.271
Other adverse events	21 (20.0%)	33 (29.7%)	23 (30.3%)	0.426	31 (40.3%)	26 (37.7%)	19 (45.2%)	0.526
Died	2 (1.9%)	1 (0.9%)	2 (2.6%)	0.559	0	0	0	-

*P<0.05

Table 5: mRS scores of patients with endovascular therapy 3 months after discharge, *n* (%)

	Group A_1	Group B_1	Group C_1	*P*
n	105	111	76	
mRS ≤2	57 (54.3%)	30 (27.0%)	17 (22.5%)	0.035*

mRS=Modified Rankin scale. *P<0.05

Table 6: Blood vessel restenosis 6 months after discharge in patients who received selective carotid artery stenting, *n* (%)

	Group A_2	Group B_2	Group C_2	*P*
n	77	69	42	
Blood vessel restenosis	5 (6.5%)	20 (28.9%)	18 (42.5%)	0.047*

*P<0.05

exhibited superior values for all measures. This included a lower likelihood of brain hemorrhage recurrence during hospitalization ($P_1 = 0.021$), a reduced probability of brain hemorrhage recurrence after 6 months ($P_1 = 0.024$), and a more favorable 90-day mRS score ($P = 0.035$). These results were significantly better compared to the other groups. Patients who underwent a selective cardiac artery stenting also showed similar differences, with $P_2 = 0.013$ for the probability of acute ischemic stroke recurrence during hospitalization, $P_2 = 0.019$ for the probability of recurrence after 6 months, and $P = 0.047$ for the probability of 90-day vascular restenosis, all significantly lower than in the other groups. Thus, regarding prognosis, it is evident that patients in the *CYP2C19* rapid-metabolism group had a superior prognosis compared to the other groups. This suggests that the effectiveness of clopidogrel's antiplatelet activity is greatly influenced by *CYP2C19* polymorphism.

Furthermore, patients who underwent artery stenting and were classified as part of the *CYP2C19* rapid-metabolism group exhibited a more favorable prognosis.[24,25] The study revealed that *CYP2C19* polymorphism significantly affects the prognosis of patients undergoing carotid artery stenting and endovascular therapy. Therefore, it is recommended to assess *CYP2C19* genetic polymorphism in patients receiving either treatment and adjust drug therapy accordingly based on different genotypes. This approach aims to minimize the occurrence of recurrent acute ischemic stroke and enhance the patient's prognosis.

In summary, *CYP2C19* gene polymorphism is strongly associated with the prognosis of patients undergoing selective internal carotid artery implantation and endovascular therapy. For both types of patients, the *CYP2C19* rapid-metabolism group had a considerably higher rate of excellent prognosis than the other *CYP2C19* groups. In addition, the risk of adverse prognostic outcomes, including recurrent cerebral infarction, was lower in this group than in the medium- and slow-metabolism groups. Consequently, it can be concluded that patients with *CYP2C19* rapid metabolism benefit more from antiplatelet therapy than patients with medium and slow metabolism. This implies that in the future, endovascular therapy patients' antiplatelet regimens should be modified based on their *CYP2C19* gene polymorphism. To discover *CYP2C19* gene polymorphism, patients with atheromatous cerebral infarction may be admitted to the hospital. For patients with medium or slow *CYP2C19* metabolism, different antiplatelet drugs, such as ticagrelor, could be used. This study aims to investigate a novel approach to antiplatelet therapy: (1) Patients with clopidogrel resistance who switched to ticagrelor showed decreased platelet aggregation and enhanced brain function, according to reports.[26-28] Therefore, to improve the prognosis of patients with *CYP2C19*-associated medium and slow metabolism, it is suggested that the antiplatelet regimen be changed from aspirin plus clopidogrel to aspirin along with ticagrelor. (2) In the case of an antiplatelet regimen of aspirin plus ticagrelor for patients with cerebral infarction associated

with atherosclerosis, the corresponding antiplatelet drug should be replaced following evaluation of the patient's *CYP2C19* genotype. Clopidogrel may be used as a temporary measure before receiving genotyping results. However, its efficacy may be reduced in patients with medium and slow metabolism linked with *CYP2C19*, perhaps resulting in repeated cerebral apoplexy. This study primarily focuses on the drug adjustment strategy described.

Limitations

The very limited sample size of this study is one of the limitations of this study. Hence, future research should address this issue for additional verification and to keep improving the prognosis of cerebral infarction patients.

Conclusion

In conclusion, *CYP2C19* gene polymorphism allows for the modification of the antiplatelet regimen for patients undergoing endovascular therapy. Our findings should stimulate additional investigation into the significance of the relationship between the genetic variant of *CYP2C19* and prognosis in patients undergoing endovascular therapy.

Acknowledgements

The authors would like to extend their sincere thanks and acknowledge the financial support provided by the Chongqing Key Discipline of Traditional Chinese Medicine (Traditional Chinese Medicine encephalopathy) Project and the First batch of key Disciplines On Public Health in Chongqing.

Ethical approval/Informed consent

The study was conducted in accordance with ethical protocols. The Chongqing Hospital of Traditional Chinese Medicine granted ethical approval for this study.

Financial support and sponsorship

This work was supported by the Chongqing Key Discipline of Traditional Chinese Medicine (Traditional Chinese Medicine encephalopathy) Project and the First batch of key Disciplines On Public Health in Chongqing.

Conflicts of interest

There are no conflicts of interest.

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