BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

Association of *CYP2C19* and *GP1BA* Genetic Variants With Antiplatelet Efficacy, and Prognosis in Patients With Acute Cerebral Infarction, and the Development of a Prognostic Risk Nomogram Model

Hui Sun[1], Yuyu Li[1,*]

[1]Department of Neurology, The First Affiliated Hospital of Bengbu Medical University, Bengbu, Anhui, China
*Correspondence: sev7nsuen@126.com (Yuyu Li)

Abstract

Aims/Background The efficacy of antiplatelet therapy exhibits interindividual variability, highlighting the need to identify underlying factors contributing to this heterogeneity in clinical settings. Increasing clinical attention has been directed toward genetic polymorphisms, aiming to optimise antiplatelet therapy based on patient genotype to enhance treatment efficacy and improve prognosis. This study aimed to analyse the relationship between cytochrome P450 2C19 (*CYP2C19*) and glycoprotein 1b alpha subunit gene (*GP1BA*) polymorphism and the efficacy of antiplatelet therapy and prognosis in patients with acute cerebral infarction (ACI).

Methods A total of 200 ACI patients treated at First Affiliated Hospital of Bengbu Medical University between January 2021 and May 2024 were enrolled. The distributions of *CYP2C19* and *GP1BA* gene polymorphisms were determined. Differences in platelet inhibition rates among patients with various *CYP2C19* and *GP1BA* genotypes were compared. Clinical characteristics and genotype distributions were analysed between patients with varying prognoses. A nomogram model was constructed to predict prognosis.

Results Among the *CYP2C19* genotypes, 84 patients were classified as fast metabolizers, 82 as intermediate metabolizers, and 34 as slow metabolizers. For *GP1BA*, 94 patients had the *CC* genotype, 78 had *CT*, and 28 had *TT*. The platelet inhibition rate in slow metabolizers was (50.12 $\pm$ 13.32) %, markedly lower than in fast and intermediate metabolizers ($p < 0.05$). Among *GP1BA* genotypes, the platelet inhibition rate in *CC* type patients was (55.30 $\pm$ 9.92) %, significantly lower than in *CT* and *TT* types ($p < 0.05$). Patients with poor prognosis had a mean age of (65.59 $\pm$ 9.92) years and a baseline National Institutes of Health Stroke Scale (NIHSS) score of (14.50 $\pm$ 2.02), both significantly higher than those in the good prognosis group ($p < 0.05$). The proportion of patients with diabetes in the poor prognosis group was 43.75%, significantly higher than in the good prognosis group ($p < 0.05$). Significant differences in *CYP2C19* and *GP1BA* genotype distributions were observed between patients with poor and good prognoses ($p < 0.05$). Logistic regression analysis identified age, NIHSS score at admission, diabetes, and both *CYP2C19* and *GP1BA* genotypes as independent factors influencing poor prognosis ($p < 0.05$). The nomogram model constructed for prognosis prediction showed good performance, with the area under the curve (AUC) of 0.815 (95% confidence interval [CI]: 0.737–0.894, $p < 0.05$). The model demonstrated a sensitivity of 87.5% and a specificity of 65.90%.

Conclusion *CYP2C19* and *GP1BA* polymorphisms are related to the efficacy of antiplatelet therapy and are influencing factors for prognosis in ACI patients. The constructed nomogram model demonstrates good predictive value for clinical outcomes.

Key words: *CYP2C19*; *GP1BA*; cerebral infarction; antiplatelet therapy; prognosis

Submitted: 17 October 2024 Revised: 22 May 2025 Accepted: 26 May 2025

How to cite this article:
Sun H, Li Y. Association of *CYP2C19* and *GP1BA* Genetic Variants With Antiplatelet Efficacy, and Prognosis in Patients With Acute Cerebral Infarction, and the Development of a Prognostic Risk Nomogram Model. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0776

Introduction

Acute cerebral infarction (ACI) refers to ischemia and hypoxia in brain tissue caused by cerebrovascular disease, leading to necrosis, and is associated with high mortality and disability rates in clinical practice (Li et al, 2023; Valgimigli et al, 2021). Thrombolytic therapy and subsequent antithrombotic treatment for ACI patients have been shown to effectively improve quality of life (Shah et al, 2022). However, the efficacy of antiplatelet therapy varies significantly among individuals, necessitating the identification of underlying factors contributing to this variability in clinical settings (Lee et al, 2023; Liu et al, 2021). In recent years, clinical attention has increasingly focused on genetic polymorphisms, with an emphasis on optimising antiplatelet therapy based on a patient's genotype to enhance treatment efficacy and improve prognosis (Russo et al, 2022). Among these, research on cytochrome P450 2C19 (*CYP2C19*) gene polymorphisms has gained prominence. The *CYP2C19* gene encodes the CYP2C19 enzyme, which plays a key role in converting the clopidogrel prodrug into its active metabolites, thereby influencing the metabolic efficacy of the drug. A Study has shown (Watanabe et al, 2024) that patients carrying loss-of-function alleles of *CYP2C19* often exhibit reduced responsiveness to clopidogrel, leading to reduced antiplatelet activity and increased risk of thrombotic events. Therefore, it is crucial to investigate the relationship between *CYP2C19* gene polymorphisms and the efficacy of antiplatelet therapy in ACI patients. Although *CYP2C19* polymorphisms are considered key contributors to clopidogrel response variability, their precise role in ACI occurrence, treatment response, and clinical prognosis remains to be fully elucidated.

In addition to *CYP2C19*, the gene polymorphism of the glycoprotein 1b alpha subunit gene (*GP1BA*) is also of clinical significance. *GP1BA* is closely related to platelet function and may similarly influence the efficacy of antiplatelet therapy (Suo et al, 2023). A previous study has suggested (Suo et al, 2023) that specific *GP1BA* genotypes may contribute to platelet dysfunction and an elevated risk of thrombotic events.

Although the significance of *CYP2C19* and *GP1BA* polymorphisms in antiplatelet therapy is gradually being recognised, systematic studies investigating how different genotypes of these genes affect antiplatelet therapy and prognosis in ACI patients remain limited. Based on this research background, the present study aimed to analyse in detail the relationship between *CYP2C19* and *GP1BA* genetic polymorphisms and both the efficacy of antiplatelet therapy and patient prognosis in ACI. Furthermore, a prognostic nomogram model was constructed to identify and visualise key factors influencing clinical outcomes.

Methods

General Data

The sample size was calculated using the formula: $n = Za^2P\ (1 - P)/d^2$, where the significance level $\alpha = 0.05$, hence $Za = 1.96$, $P = 0.14$, and $d = 0.05$. The calculated sample size was 185. To account for potential exclusions, 200 ACI patients

treated at First Affiliated Hospital of Bengbu Medical University between January 2021 and May 2024 were enrolled in the study. Inclusion criteria were as follows: (1) diagnosis consistent with the 'Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke' (Chinese Society of Neurology and Stroke Group of Chinese Society of Neurology, 2018); (2) patients with high compliance and ability to cooperate with follow-up treatment; (3) patients aged between 30 and 80 years; (4) informed consent obtained from patients and their families; (5) complete clinical data available for each patient.

Exclusion criteria included: (1) patients coexisting cerebrovascular malformations, brain trauma, or other intracranial diseases; (2) patients with history of surgery or trauma within the past 6 months; (3) patients with malignant tumors, hepatic or renal dysfunction, peptic ulcer, acute or chronic infections, or other severe comorbidities; (4) patients who were allergic or intolerance to antiplatelet medications.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical University (Ethical Approval No. Lunkepi Zi [2022] No. 197). Written informed consent was obtained from all participants.

Patients were categorised into fast, intermediate, or slow metabolizer groups based on their *CYP2C19* gene polymorphisms. Similarly, based on *GP1BA* gene distribution, patients were categorised into *CC*, *CT*, or *TT* genotypes.

At 90 days post-treatment, the patient's prognosis was assessed using the modified Rankin Scale (mRS) (Isaksson et al, 2020). An mRS score ≥ 3 was defined as a poor prognosis, while a score <3 was considered a good prognosis. In total, 48 patients were assigned to the poor prognosis group and 152 patients to the good prognosis group.

Genetic Polymorphism Testing

CYP2C19 gene polymorphism testing: three milliliters of venous blood were collected from each patient and placed in sodium heparin anticoagulant tubes. Red blood cell lysis buffer was added, followed by centrifugation at 3000 r/min with a 10 cm radius for 5 minutes. The supernatant was collected for further analysis. Genomic DNA was extracted using the TIANamp Blood DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China, 20230056). The A260/A280 ratio of extracted DNA was confirmed to be no less than 1.80. Only samples meeting this criterion were used in subsequent experiments. Real-time fluorescence quantitative polymerase chain reaction (PCR) was performed using the LightCycler 480 II system (Roche, Basel, Switzerland). The reaction system had a total volume of 25 μL, comprising 2 μL of template DNA and 23 μL of PCR reaction mixture targeting two polymorphic loci. Based on *CYP2C19* gene sequence data (G681A and G636A genotypes) released by Sequenom Corporation (USA), primers were designed using Primer Premier 6.0 software (Premier Biosoft International Co., Ltd., Palo Alto, CA, USA). The forward primer sequence for the G681A site is 5′-ACGTGGATGGCAAATAATTCCACTATC-3′, and the reverse primer sequence is 5′-ACGTGGATGACTCCTAGATCC-3′; The forward primer sequence for the

G636A site is 5′-AGTTGGATGAACATCAGGATTGTAAGCAC-3′, and the reverse primer sequence is 5′-AGTTGGATGGACTGTAAGTGGTTTCTCAG-3′.

PCR conditions: initial denaturation at 95 °C for 10 minutes; followed by 40 cycles of 95 °C for 15 seconds (denaturation), 60 °C for 1 minute (annealing), and 72 °C for 45 seconds (extension). After amplification, 10 μL of the PCR product was subjected to genotyping using fluorescent probe-based PCR. DNA restriction endonucleases were then used to digest the amplified products, followed by electrophoresis to determine cleavage status and classify genotypes.

The genotypes were identified as *1/*1, *1/*2, *1/*3, *2/*3, or *2/*2. The metabolic phenotypes were categorised as follows: *1/*1, fast metabolizer; *1/*2 and *1/*3, intermediate metabolizer; *2/*2 and *2/*3, slow metabolizers (Liu et al, 2021).

GP1BA gene polymorphism detection: DNA sample collection followed the same procedure as above. Four pairs of primers (*GP1BA1–GP1BA4*) were designed for *GP1BA: GP1BA1* forward primer: 5′-TGCCTTCGGAGGTCTTTCTG-3′, reverse primer: 5′-GGCAGGGTCTTCAGCTCATT-3′; *GP1BA2* forward primer: 5′-TGGACGTCTCCTTCAACCG-3′, reverse primer: 5′-TGTGGTCTGCTCCTTAGTGG-3′; *GP1BA3* forward primer: 5′-CCTGGACGTCTCCTTCAACC-3′, reverse primer: 5′-GGGTCTTCAGCTCATTGCCT-3′; *GP1BA4* forward primer: 5′-AGGCAATGAGCTGAAGACCC-3′, reverse primer: 5′-AGGGGGTTGTATGGGCTTTG-3′.

PCR amplification was performed using a multi-channel instrument with the same reaction mixture ratio as *CYP2C19*. Reaction conditions: pre-denaturation at 95 °C for 3 minutes, followed by 40 cycles of 95 °C for 40 seconds (denaturation), annealing at appropriate temperatures for 30 seconds, extension for 1 minute, and a final extension step of 10 minutes. The products were stored at 4 °C.

After gel electrophoresis detection, qualified PCR amplification products were selected for sequencing. Sequencing chromatograms were compared, and a universal sequencing reaction kit (item number: 20220303, Huaxia Times Gene Technology Development Co., Ltd., Beijing, China) was used to analyse *GP1BA* subtypes. Sequencing peak characteristics were observed and accurately aligned with known standard sequences. Based on specific single nucleotide polymorphism (SNP) site information, including peak type, peak position, and base identity, subtypes were determined as follows: *CC* subtype (a single clear peak corresponding to the C base at the target SNP site and matching the standard sequence), *TT* subtype (a single clear peak corresponding to the T base), and *CT* subtype (two peaks of similar intensity corresponding to the positions of C and T bases, respectively).

Laboratory Testing

After 7 days of treatment, venous blood was collected, anticoagulated, and analysed within 2 hours using a BD FACSCanto II flow cytometer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The following parameters were measured: clot strength induced by thrombin (MA_{th}), fibrin network strength in

the absence of thrombin (MA_{fib}), and clot strength after ADP-induced platelet activation (MA_{ADP}). The platelet inhibition rate was calculated using the formula:

Platelet inhibition rate = $(MA_{ADP} - MA_{fib}) / (MA_{th} - MA_{fib}) \times 100\%$.

Patient general data were collected, including gender, age, body mass index (BMI), and presence of comorbidities such as diabetes and hypertension. Additional clinical parameters included infarction location (subcortical, cortical, brainstem or cerebellum, or other), National Institutes of Health Stroke Scale (NIHSS) score at admission (a scale evaluating consciousness, gaze, visual fields, facial paralysis, among others; the total score is 42 points, with higher scores indicating more severe the patient's condition) (Kwah and Diong, 2014), time from symptom onset to thrombolysis, *CYP2C19* genotype (fast, intermediate, or slow metabolizer), and *GP1BA* genotype (*CC*, *CT*, or *TT* type).

Treatment

Treatment was administered in accordance with Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke (Chinese Society of Neurology and Stroke Group of Chinese Society of Neurology, 2018). Patients who met the eligibility criteria for thrombolysis and had no contraindications received intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) (lot number: 20230901, Boehringer Ingelheim Pharma GmbH & Co. KG, German; Specification: 50 mg/vial) within 4.5 hours of symptom onset. For patients with severe presentations, large vessel occlusion, and within the recommended time window for endovascular therapy, mechanical thrombectomy was considered as either the primary or a rescue treatment option. For patients who did not meet the criteria for thrombolysis or endovascular intervention, 300 mg of aspirin (lot number: 20231101, Jinling Pharmaceutical Co., Ltd., Nanjing, China; Specification: 100 mg/vial) was administered for intensified antiplatelet therapy. If the patient's condition stabilised, the aspirin dosage was adjusted to 100 mg daily and maintained for at least one year. Across all treatment strategies, patients received comprehensive supportive therapies, including oxygen supplementation, vasodilation, neuroprotection, and brain-protective measures.

Statistical Processing

Data analysis was performed using SPSS 22.0 software (IBM, Armonk, NY, USA). Bartlett's test for homogeneity of variances and the Kolmogorov-Smirnov test for normality were used to verify assumptions. Data with approximately normal distribution and equal variances were expressed as mean ± standard deviation ($\bar{x} \pm s$). Differences between the two groups were assessed using *t*-tests, while analysis of variance (ANOVA) was employed for comparisons among multiple groups, with pairwise comparisons performed using the Least Significant Difference (LSD)-*t* test. Categorical variables, such as gender, were expressed as frequencies and percentages [n (%)], and differences between groups were evaluated using the chi-square (χ^2) test. Prognostic factors and their interactions were analysed using logistic regression. A nomogram prediction model was constructed using R software (Ross Ihaka and Robert Gentleman, University of Auckland, Auckland,

Table 1. Distribution of *CYP2C19* gene polymorphisms among study participants.

Metabolizer classification	Genotype polymorphism	Number of cases (n)
Fast metabolizer	*CYP2C19*1/*1*	84
Intermediate metabolizer	*CYP2C19*1/*2*	65
	*CYP2C19*1/*3*	17
Slow metabolizer	*CYP2C19*2/*2*	22
	*CYP2C19*2/*3*	12
Total		200

Note: The asterisks are the genotypes of CYP2C19. *CYP2C19*, cytochrome P450 2C19.

Table 2. Distribution of *GP1BA* gene polymorphisms among study participants.

Genotype polymorphism	Number of cases (n)
CC	94
CT	78
TT	28

Note: *GP1BA*, glycoprotein 1b alpha subunit gene.

New Zealand). The goodness-of-fit for the model was assessed using the Hosmer-Lemeshow test. A p-value < 0.05 was considered statistically significant for all analyses.

Results

Determination of *CYP2C19* and *GP1BA* Genotype Distributions

Among the *CYP2C19* genotypes, 84 patients were classified as fast metabolizers, 82 as intermediate metabolizers, and 34 as slow metabolizers, as shown in Table 1. For the distribution of *GP1BA* genotypes, 94 patients had the *CC* type, 78 had the *CT* type, and 28 had the *TT* type, as shown in Table 2.

Comparison of Platelet Inhibition Rates Among Different *CYP2C19* and *GP1BA* Genotypes

The platelet inhibition rate in patients classified as slow metabolizers of the *CYP2C19* gene was significantly lower than that in fast and intermediate metabolizers ($p < 0.05$). Similarly, patients with the *CC* type of the *GP1BA* gene exhibited a significantly lower platelet inhibition rate compared to those with the *CT* and *TT* types ($p < 0.05$) (Table 3).

Comparison of Clinical Data and Gene Distribution in Patients With Different Prognoses

Patients with a poor prognosis had significantly higher ages and NIHSS scores at admission compared to those with a good prognosis ($p < 0.05$). Additionally, the proportion of patients with diabetes was markedly higher in the poor prognosis group ($p < 0.05$). Statistically significant differences were also observed in

Table 3. Comparison of platelet inhibition rates by *CYP2C19* and *GP1BA* genotypes [$\bar{x} \pm s$].

Gene distribution	Case (n)	Platelet inhibition rate (%)	*F*-value	*p*-value
CYP2C19 genotype				
Fast metabolizer	84	62.28 ± 10.18^a		
Moderate metabolizer	82	60.92 ± 11.83^a	14.517	<0.001
Slow metabolizer	34	50.12 ± 13.32		
GP1BA genotype				
CC	94	55.30 ± 9.92		
CT	78	63.25 ± 10.11^b	16.269	<0.001
TT	28	64.45 ± 11.82^b		

Note: ^{a} compared with slow metabolic type, $p < 0.05$; ^{b} compared with *CC* type, $p < 0.05$.

the distributions of *CYP2C19* and *GP1BA* genotypes between the poor and good prognosis groups ($p < 0.05$) (Table 4).

Analysis of Prognostic Influencing Factors

A Logistic regression analysis was performed using age, NIHSS score at admission, diabetes status, *CYP2C19* genotype, and *GP1BA* genotype as independent variables, with poor prognosis as the dependent variable. The results indicated that all five factors, age, NIHSS score at admission, diabetes status, *CYP2C19* genotype, and *GP1BA* genotype, were significantly associated with poor prognosis ($p < 0.05$). No significant interactions were found between the *CYP2C19* genotype and age or diabetes ($p > 0.05$), nor between the *GP1BA* genotypes and either age or diabetes ($p > 0.05$) (Table 5).

Construction of Nomogram Model for Predicting Poor Prognosis

A nomogram model was constructed based on the identified prognostic factors to predict poor outcomes, as illustrated in Fig. 1. As shown in Fig. 2 and Table 6, the area under the curve (AUC) for this model was the largest among all predictors, at 0.815 (95% confidence interval [CI]: 0.737–0.894), with $p < 0.05$. The model demonstrated a sensitivity of 87.50% and a specificity of 65.90%. The Hosmer-Lemeshow goodness-of-fit test indicated that the model predictions were well-calibrated, with no significant difference between predicted and observed outcomes ($\chi^2 = 5.596$, $p = 0.821$), as shown in Fig. 3.

Discussion

Antiplatelet therapy plays a crucial role in the treatment of ACI patients, although its efficacy varies significantly between individuals (Yokoi et al, 2022). Previous study (Meschia et al, 2020) has shown that genetic characteristics of *CYP2C19* and *GP1BA* significantly influence the metabolism of antiplatelet drugs and the regulation of platelet function.

CYP2C19, a member of the second subfamily of the CYP450 enzyme family, is an essential enzyme in human drug metabolism. The gene is located at the

Table 4. Comparison of clinical characteristics and genotype distributions between patients with poor and good prognoses [$\bar{x} \pm s$, n (%)].

Variable	Poor prognosis (n = 48)	Good prognosis (n = 152)	t/χ^2	*p*-value
Gender				
Male	30 (62.50)	103 (67.76)	0.454	0.501
Female	18 (37.50)	49 (32.24)		
Age (years)	65.59 ± 9.92	60.20 ± 10.11	3.234	0.001
Body mass index (kg/m^2)	22.24 ± 2.92	22.12 ± 2.13	0.310	0.757
Diabetes	21 (43.75)	20 (13.16)	20.948	<0.001
Hypertension	31 (64.58)	92 (60.53)	0.254	0.615
Infarct location				
Subcortical area	21 (43.75)	61 (40.13)	0.980	0.806
Cortex	14 (29.17)	39 (25.66)		
Brainstem or cerebellum	8 (16.67)	29 (19.08)		
Other	5 (10.42)	23 (15.13)		
NIHSS score at admission (points)	14.50 ± 2.02	9.60 ± 1.82	15.831	<0.001
Time from onset to thrombolysis (hours)	3.10 ± 0.88	3.02 ± 0.97	0.509	0.611
CYP2C19 genotype				
Fast metabolizer	11 (22.92)	73 (48.03)	37.827	<0.001
Intermediate metabolizer	15 (31.25)	67 (44.08)		
Slow metabolizer	22 (45.83)	12 (7.89)		
GP1BA genotype				
CC	32 (66.67)	62 (40.79)	12.576	0.002
CT	15 (31.25)	63 (41.45)		
TT	1 (2.08)	27 (17.76)		

Note: NIHSS, National Institutes of Health Stroke Scale.

10q24.2 chromosomal region and is encoded by nine exons (Sykora et al, 2023). This gene exhibits significant polymorphism, which profoundly influences the absorption, distribution, metabolism, and excretion of various drugs (Tarantini et al, 2023; van de Graaf et al, 2021). In this study, an in-depth analysis of *CYP2C19* genotype distribution identified 84 fast metabolizers, 82 intermediate metabolizers, and 34 slow metabolizers. The platelet inhibition rate was significantly lower in slow metabolizers compared to fast and intermediate metabolizers, highlighting the crucial influence of *CYP2C19* polymorphism on the efficacy of antiplatelet therapy. The CYP2C19 enzyme plays a key role in the hepatic conversion of the antiplatelet drug clopidogrel into its active metabolites (Meng et al, 2024). Genotypic variation directly determines the efficiency and speed of this conversion, thereby influencing the efficacy of platelet inhibition and the risk of cardiovascular events. In patients with slow metabolizer variants, enzyme activity is reduced or lost, resulting in impaired clopidogrel activation and weakened platelet inhibition (Mo et al, 2023; Wang et al, 2023). Conversely, fast and intermediate metabolizers retain near-normal enzyme function, enabling efficient clopidogrel metabolism and effective platelet aggregation inhibition.

Table 5. Multivariate logistic regression analysis of prognostic factors.

Factor	β	SE	Wald	*p*-value	Odds ratio (95% CI)
Age	0.891	0.218	16.705	<0.001	2.438 (1.590–3.737)
NIHSS score at admission	1.432	0.308	21.616	<0.001	4.187 (2.289–7.657)
Diabetes	0.776	0.217	12.788	<0.001	2.173 (1.420–3.325)
No	-	-	-	-	1.000 (reference)
Yes	0.776	0.217	12.788	<0.001	2.173 (1.420–3.325)
CYP2C19 genotype	0.889	0.244	13.275	<0.001	2.433 (1.508–3.925)
Fast metabolizer	-	-	-	-	1.000 (reference)
Intermediate metabolizer	0.665	0.182	13.351	<0.001	1.944 (1.361–2.778)
Slow metabolizer	0.902	0.223	16.361	<0.001	2.465 (1.592–3.816)
GP1BA genotype	0.912	0.251	13.202	<0.001	2.489 (1.522–4.071)
TT	-	-	-	-	1.000 (reference)
CT	0.782	0.223	12.297	<0.001	2.186 (1.412–3.384)
CC	1.102	0.301	13.404	<0.001	3.010 (1.669–5.430)
CYP2C19 genotype × Age	0.334	0.573	0.340	0.562	1.397 (0.454–4.293)
GP1BA genotype × Age	0.283	0.771	0.135	0.718	1.327 (0.293–6.014)
CYP2C19 genotype × Diabetes	0.471	0.801	0.346	0.555	1.602 (0.333–7.698)
GP1BA genotype × Diabetes	0.302	0.665	0.206	0.653	1.353 (0.367–4.980)

Note: CI, confidence interval.

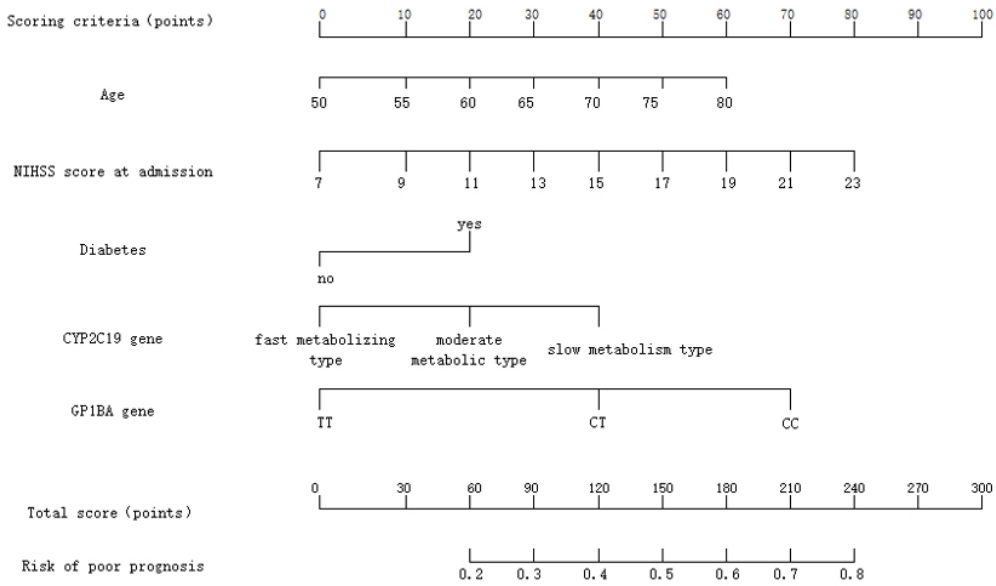

Fig. 1. Nomogram model for predicting poor prognosis in acute cerebral infarction (ACI) patients.

Previous studies have revealed that loss-of-function *CYP2C19* alleles independently increase the risk of adverse cardiovascular events in patients with acute coronary syndrome (ACS) and stable angina (Lee et al, 2022; Li et al, 2024). Our study also revealed significant differences in *CYP2C19* gene distribution among patients with poor prognoses, with slow metabolizers more likely to experience

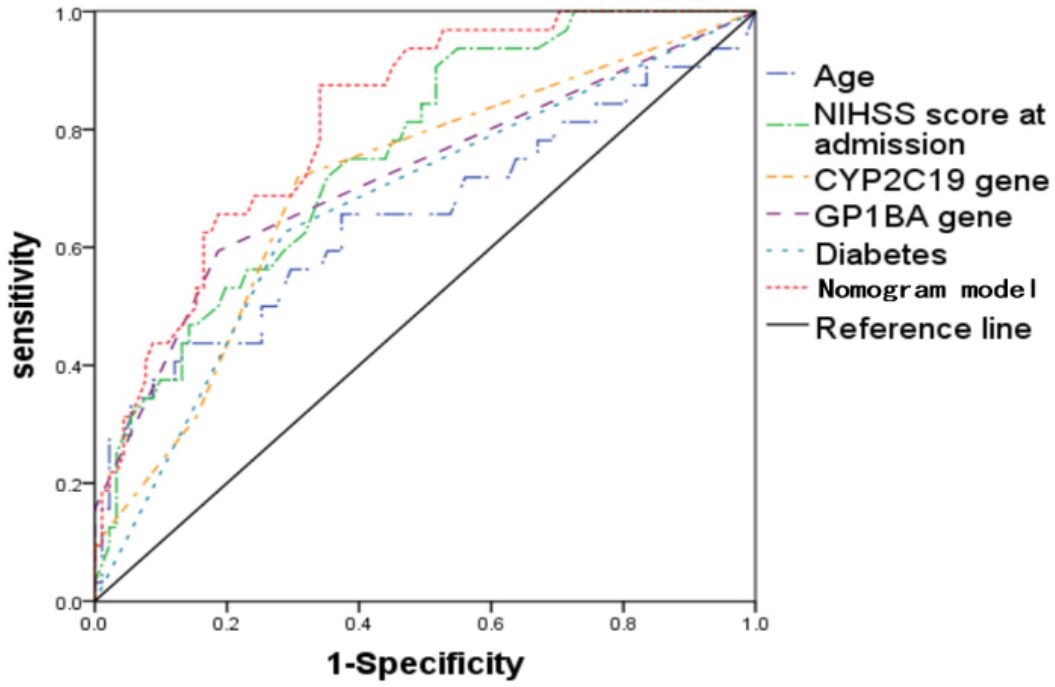

Fig. 2. Receiver operating characteristic (ROC) curve of the nomogram model.

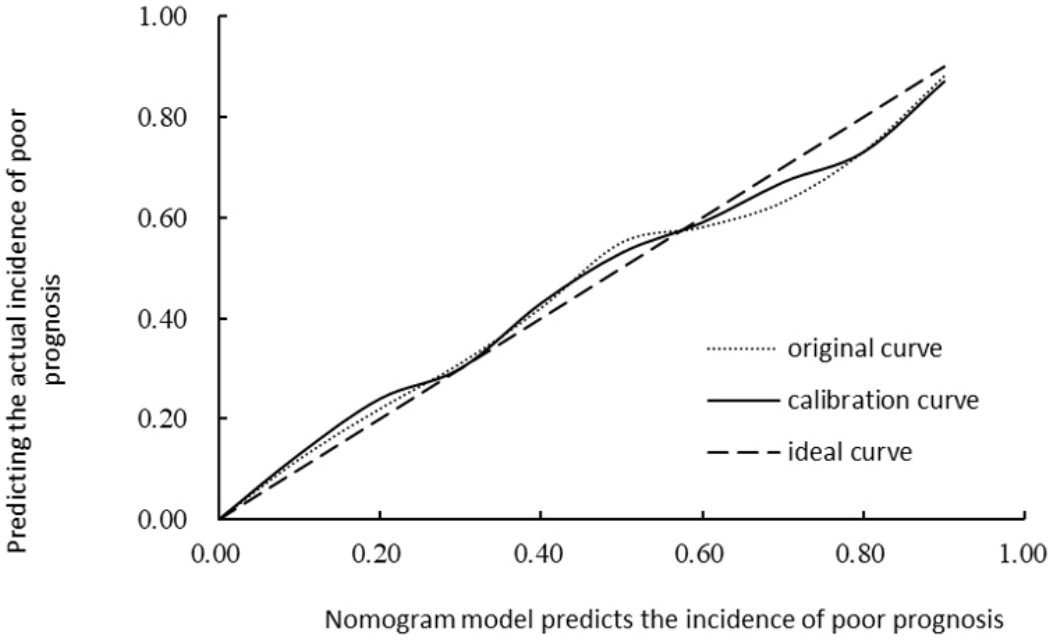

Fig. 3. Hosmer-Lemeshow goodness-of-fit test for the nomogram model.

unfavourable outcomes. Due to limited clopidogrel activation, the antiplatelet effect in these individuals is reduced, increasing the risk of poor clinical prognosis. Therefore, genetic testing before administering *CYP2C19*-dependent antiplatelet drugs like clopidogrel is crucial (Lee et al, 2023). All patients in our study received aspirin. Although aspirin is not metabolised via the *CYP2C19* pathway, *CYP2C19* polymorphisms may still influence treatment outcomes by affecting the absorption, distribution, metabolism, or excretion of the drug. Additionally, *CYP2C19* may

Table 6. ROC curve analysis of prognostic indicators.

Factor	AUC (95% CI)	*p*-value	Cutoff value	Sensitivity (%)	Specificity (%)
Age	0.651 (0.528–0.775)	0.011	65	43.80	86.80
NIHSS score at admission	0.758 (0.667–0.848)	<0.001	13	90.60	48.40
CYP2C19 genotype	0.706 (0.600–0.812)	0.050	Slow metabolism type	71.90	69.20
GP1BA genotype	0.759 (0.648–0.869)	<0.001	*CC*	59.40	90.10
Diabetes	0.670 (0.558–0.781)	0.004	Yes	62.50	71.40
Nomogram model	0.815 (0.737–0.894)	<0.001	-	87.50	65.90

Note: AUC, area under the curve.

indirectly affect patient prognosis by regulating physiological processes such as inflammation and oxidative stress. However, this study did not directly evaluate the specific interaction between aspirin and *CYP2C19*, which will be a focus of our future investigations.

Studies have indicated that the arachidonic acid metabolic pathway can aggravate the tendency for platelet aggregation, thereby increasing the frequency of platelet aggregation events (Dib et al, 2022; Monteiro et al, 2023). As a critical target of aspirin, polymorphism in the *GP1BA* gene plays a key role in antiplatelet therapy. The results of this study showed a diverse *GP1BA* gene distribution among patients, with the majority being of the *CC* genotype, followed by *CT* and *TT* genotypes. The study further revealed that the platelet inhibition rate in *CC* genotype patients was significantly lower than that in *CT* and *TT* genotype patients, suggesting a strong association between *GP1BA* gene polymorphism and the efficacy of antiplatelet therapy. The *GP1BA* gene is central to aspirin's mechanism of action. It encodes the GPIb glycoprotein, an essential component of the platelet membrane, composed of α and β subunits linked by disulfide bonds. This structure plays a crucial role in mediating platelet interaction with the von Willebrand factor. Previous studies have confirmed that the T allele of the *GP1BA* (5792 C > T) polymorphism is closely associated with enhanced aspirin responsiveness (Zhang et al, 2023). Therefore, patients carrying the T allele (*CT* and *TT* genotypes) tend to exhibit higher platelet inhibition rates following aspirin administration. The findings of this study are consistent with previous reports (Liu et al, 2024).

In ACI patients, differences in *GP1BA* genotypes are directly related to individual variability in the efficacy of aspirin. Patients with the *CC* genotype, due to alterations in GPIb receptor function or expression, exhibit reduced sensitivity to aspirin, which compromises platelet inhibition. In contrast, patients with *CT* and *TT* genotypes experience enhanced antiplatelet effects due to greater responsiveness to aspirin. Additional analysis revealed significant differences in *GP1BA* gene distribution among patients with poor prognosis. This observation, together with the earlier findings on platelet inhibition, underscores the critical impact of the *GP1BA* genotype on ACI prognosis. In *CC* genotype individuals, lower platelet sensitivity to aspirin leads to suboptimal antiplatelet efficacy, resulting in insufficient platelet inhibition, increased thrombotic risk, and poorer prognosis. Conversely, *CT* and *TT* genotype carriers benefit from higher platelet inhibition, reduced thrombosis

risk, and favourable prognoses. Thus, variations in *GP1BA* genotypes, by modulating aspirin sensitivity, emerge as key factors influencing clinical outcomes in ACI patients.

Analysis of the clinical data from patients with different prognoses showed that those with poor prognoses had significantly higher age and NIHSS scores at admission compared to patients with good prognoses. Additionally, the proportion of diabetic patients was significantly higher in the poor prognosis group. These findings are consistent with previous reports (Jia et al, 2024). Elderly individuals, due to multiple comorbidities and reduced physiological capacity, often exhibit slower drug metabolism, potentially affecting the efficacy of antiplatelet therapy. A high NIHSS score indicates more severe neurological impairment and is widely recognised as a strong predictor of poor prognosis (Khalid et al, 2024; Pan et al, 2023). In diabetic patients, persistent hyperglycemia may impair prognosis by disrupting vascular function and enhancing coagulation and inflammatory pathways.

Logistic regression analysis confirmed that age, NIHSS score, diabetes, and *CYP2C19* and *GP1BA* gene polymorphisms are independent predictors of poor prognosis. Notably, there were no significant interactions between *CYP2C19* or *GP1BA* polymorphisms and age or diabetes. Based on these findings, a prognostic nomogram model was constructed, demonstrating an AUC of 0.815 and high sensitivity. Compared with individual predictors such as NIHSS score at admission, the model significantly improved the predictive accuracy and exhibited strong clinical utility. By integrating multiple genetic and clinical indicators, the model offers a more comprehensive tool for early identification and management of high-risk patients, potentially improving patient prognosis.

However, this study has several limitations. It did not fully evaluate potential interactions among genetic factors or between genetic and clinical variables. Future research should focus on these interactions to clarify the complex mechanisms underlying antiplatelet drug resistance. In addition, *CYP2C19* and *GP1BA* genotyping involves considerable cost and requires specialised equipment and technical expertise, which may increase the financial burden on patients and limit its feasibility as a routine diagnostic measure for all ACI patients. Nonetheless, for ACI patients with poor response to antiplatelet therapy, genetic testing may serve as a valuable tool to guide treatment adjustments.

Conclusion

CYP2C19 and *GP1BA* genetic characteristics are related to the efficacy of antiplatelet therapy in ACI patients, and both serve as important factors that influence patient prognosis. The nomogram model constructed for predicting prognosis demonstrates strong predictive performance and clinical applicability.

Key Points

- *CYP2C19* and *GP1BA* genetic characteristics are related to the efficacy of antiplatelet therapy in ACI patients.
- *CYP2C19* and *GP1BA* genetic variations are related to the prognosis of ACI patients.
- ACI patients' prognosis is also associated with age, NIHSS score at admission, and the presence of diabetes.
- The nomogram model constructed for prognosis prediction demonstrates strong predictive value.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

Study concepts: HS; Study design: HS, YL; Definition of intellectual content: HS; Data analysis: HS; Statistical analysis: HS; Manuscript drafting: HS; Manuscript review and Guarantor of the integrity of the entire study: YL. Both authors contributed to important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical University (Ethical Approval No. Lunkepi Zi [2022] No. 197). Written informed consent was obtained from all participants.

Acknowledgement

The authors sincerely thank all the study participants.

Funding

This study is supported by the Key Natural Science Project of Bengbu Medical College (2021byzd152).

Conflict of Interest

The authors declare no conflict of interest.

References

Chinese Society of Neurology and Stroke Group of Chinese Society of Neurology. Chinese guidelines for the diagnosis and treatment of acute ischemic stroke 2018. Chinese Journal of Neurology. 2018; 51: 666–682. http://doi.org/10.3760/cma.j.issn.1006-7876.2018.09.004.

Dib F, Quéméner A, Bayart S, Boisseau P, Babuty A, Trossaërt M, et al. Biological, clinical features and modelling of heterozygous variants of glycoprotein Ib platelet subunit alpha (GP1BA) and glycoprotein Ib platelet subunit beta (GP1BB) genes responsible for constitutional thrombocytopenia. British Journal of Haematology. 2022; 199: 744–753. https://doi.org/10.1111/bjh.18462

Isaksson E, Wester P, Laska AC, Näsman P, Lundström E. Validation of the Simplified Modified Rankin Scale Questionnaire. European Neurology. 2020; 83: 493–499. https://doi.org/10.1159/000510721

Jia S, Liu X, Qu H, Jia X. Observation of the Therapeutic Effect of Dual Antiplatelet Therapy with Aspirin and Clopidogrel on the Incidence, Characteristics, and Outcome in Acute Ischemic Stroke Patients with Cerebral Microbleeds at a Teaching Hospital, China. International Journal of General Medicine. 2024; 17: 2327–2336. https://doi.org/10.2147/IJGM.S459323

Khalid AR, Ahmad F, Naeem MAB, Ahmed S, Umar M, Mehmood H, et al. Safety of Clopidogrel vs. Ticagrelor in Dual Antiplatelet Therapy Regimens for High-Bleeding Risk Acute Coronary Syndrome Patients: A Comprehensive Meta-analysis of Adverse Outcomes. High Blood Pressure & Cardiovascular Prevention. 2024; 31: 141–155. https://doi.org/10.1007/s40292-024-00635-3

Kwah LK, Diong J. National Institutes of Health Stroke Scale (NIHSS). Journal of Physiotherapy. 2014; 60: 61. https://doi.org/10.1016/j.jphys.2013.12.012

Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clinical Pharmacology and Therapeutics. 2022; 112: 959–967. https://doi.org/10.1002/cpt.2526

Lee TL, Chang YM, Sung PS. Clinical Updates on Antiplatelet Therapy for Secondary Prevention in Acute Ischemic Stroke. Acta Neurologica Taiwanica. 2023; 32: 138–144.

Li W, Wang A, Ma C, Wang Y, Zhao Y, Zhang Y, et al. Antiplatelet therapy adjustment improved the radiomic characteristics of acute silent cerebral infarction after stent-assisted coiling in patients with high on-treatment platelet reactivity: A prospective study. Frontiers in Neuroscience. 2023; 17: 1068047. https://doi.org/10.3389/fnins.2023.1068047

Li W, Yang X, Chen J, Zhu JW, Zeng LH, Long HH, et al. The Association between *CYP2C19* Genetic Polymorphism and Prognosis in Patients Receiving Endovascular Therapy. Annals of Indian Academy of Neurology. 2024; 27: 27–33. https://doi.org/10.4103/aian.aian_564_23

Liu Q, Guo S, Wang N, Wang K, Mo S, Li X, et al. Model based on single-nucleotide polymorphism to discriminate aspirin resistance patients. Stroke and Vascular Neurology. 2024; 9: 212–220. https://doi.org/10.1136/svn-2022-002228

Liu Y, Yang J, Jiang P, Wang S, Wang M, Wang M, et al. DAPT score: predictive model of dual-antiplatelet therapy for acute cerebral infarction. Neurological Sciences. 2021; 42: 681–688. https://doi.org/10.1007/s10072-020-04552-w

Meng X, Wang A, Tian X, Johnston C, Li H, Bath PM, et al. One-Year Outcomes of Early Therapy With Ticagrelor vs Clopidogrel in *CYP2C19* Loss-of-Function Carriers With Stroke or TIA Trial. Neurology. 2024; 102: e207809. https://doi.org/10.1212/WNL.0000000000207809

Meschia JF, Walton RL, Farrugia LP, Ross OA, Elm JJ, Farrant M, et al. Efficacy of Clopidogrel for Prevention of Stroke Based on *CYP2C19* Allele Status in the POINT Trial. Stroke. 2020; 51: 2058–2065. https://doi.org/10.1161/STROKEAHA.119.028713

Mo Y, Lu Y, Guo F, Wu A, Weng Y. Analysis of *CYP2C19* gene polymorphism and influencing factors of pharmacological response of clopidogrel in patients with cerebral infarction in Zhejiang, China. Frontiers in Cardiovascular Medicine. 2023; 10: 1020593. https://doi.org/10.3389/fcvm.2023.1020593

Monteiro C, Gonçalves A, Pereira M, Lau C, Morais S, Santos R. A new case of platelet-type von Willebrand disease supports the recent findings of gain-of-function GP1BA variants outside the C-terminal disulphide loop enhances affinity for von Willebrand factor. British Journal of Haematology. 2023; 203: 673–677. https://doi.org/10.1111/bjh.19025

Pan SC, Wang H, Zhang TT, Wang YJ. Expression significance of YKL-40, Lp-PLA2, and miR-151a-3p in ACI patients and their relationship with prognosis based on the NIHSS score. Asian Journal of Surgery. 2023; 46: 2031–2032. https://doi.org/10.1016/j.asjsur.2022.11.009

Russo JJ, Yan AT, Pocock SJ, Brieger D, Owen R, Sundell KA, et al. Determinants of long-term dual antiplatelet therapy use in post myocardial infarction patients: Insights from the TIGRIS registry. Journal of Cardiology. 2022; 79: 522–529. https://doi.org/10.1016/j.jjcc.2021.10.024

Shah J, Liu S, Yu W. Contemporary antiplatelet therapy for secondary stroke prevention: a narrative review of current literature and guidelines. Stroke and Vascular Neurology. 2022; 7: 406–414. https://doi.org/10.1136/svn-2021-001166

Suo Y, Pan Y, Chen W, Jing J, Yan H, Li H, et al. Aminotransferase Level and the Effects of Dual Antiplatelet in Minor Stroke or Transient Ischemic Attack: A post hoc Analysis of a Randomized Control Trial. Cerebrovascular Diseases. 2023; 52: 442–450. https://doi.org/10.1159/000527611

Sykora M, Krebs S, Miksova D, Badic I, Gattringer T, Fandler-Höfler S, et al. IV Thrombolysis vs Early Dual Antiplatelet Therapy in Patients With Mild Noncardioembolic Ischemic Stroke. Neurology. 2023; 101: e933–e939. https://doi.org/10.1212/WNL.0000000000207538

Tarantini G, Smits PC, Lhermusier T, Honton B, Rangé G, Piot C, et al. A prospective study comparing short versus standard dual antiplatelet therapy in patients with acute myocardial infarction: design and rationale of the TARGET-FIRST trial. EuroIntervention. 2023; 19: 240–247. https://doi.org/10.4244/EIJ-D-22-01006

Valgimigli M, Frigoli E, Heg D, Tijssen J, Jüni P, Vranckx P, et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. The New England Journal of Medicine. 2021; 385: 1643–1655. https://doi.org/10.1056/NEJMoa2108749

van de Graaf RA, Zinkstok SM, Chalos V, Goldhoorn RJB, Majoie CB, van Oostenbrugge RJ, et al. Prior antiplatelet therapy in patients undergoing endovascular treatment for acute ischemic stroke: Results from the MR CLEAN Registry. International Journal of Stroke. 2021; 16: 476–485. https://doi.org/10.1177/1747493020946975

Wang A, Meng X, Tian X, Zuo Y, Bath PM, Li H, et al. Ticagrelor Aspirin vs Clopidogrel Aspirin in *CYP2C19* Loss-of-Function Carriers With Minor Stroke or TIA Stratified by Risk Profile. Neurology. 2023; 100: e497–e504. https://doi.org/10.1212/WNL.0000000000201454

Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Nishikawa R, et al. Clopidogrel vs Aspirin Monotherapy Beyond 1 Year After Percutaneous Coronary Intervention. Journal of the American College of Cardiology. 2024; 83: 17–31. https://doi.org/10.1016/j.jacc.2023.10.013

Yokoi H, Oda E, Kaneko K, Matsubayashi K. Duration and clinical outcome of dual antiplatelet therapy after percutaneous coronary intervention: a retrospective cohort study using a medical information database from Japanese hospitals. Cardiovascular Intervention and Therapeutics. 2022; 37: 465–474. https://doi.org/10.1007/s12928-021-00833-z

Zhang T, Huang X, Gao X, Liu L, Chen D, Huan X, et al. Effect of pathological high shear exposure time on platelet activation and aggregation. Clinical Hemorheology and Microcirculation. 2023; 84: 125–139. https://doi.org/10.3233/CH-221567