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Original Article

Additive interaction between CYP2C19AA gene polymorphism and Lp(a) on the prognosis of stroke patients

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Abstract: Objective: To investigate the influence of cytochrome P450 2C19 (CYP2C19) gene polymorphism and lipoprotein (a) (Lp(a)) levels, and their interaction, on the prognosis of stroke patients. Methods: A total of 120 stroke patients admitted to Wuming Hospital of Guangxi Medical University from January 2022 to June 2024 were retrospectively selected as the observation group. Additionally, 118 healthy people with normal outpatient physical examination indices during the same period were selected as the control group, matched for age, gender, and body mass index (BMI). Patient prognosis was assessed three months post-stroke using the modified Rankin Scale (mRS). Patients with an mRS score > 2 were classified into the poor prognosis group, while those with an mRS score ≤ 2 were categorized into the good prognosis group. Polymerase chain reaction was utilized to detect CYP2C19 gene polymorphisms. General data were compared between patients with good and poor prognoses. Multivariate logistic regression analysis was performed to identify factors influencing poor prognosis in stroke patients and to examine the interaction between CYP2C19 gene polymorphism and Lp(a) on stroke outcomes. Results: Among 210 stroke patients, 82 (39.05%) had a poor prognosis, and 128 (60.95%) had a good prognosis. The NIHSS scores at admission of stroke patients with AA, AG, and GG genotypes increased sequentially ($P < 0.05$). Multivariate logistic regression analysis showed that CYP2C19 genotype and Lp(a) levels were independent factors influencing prognosis in stroke patients (both $P < 0.05$). The correlation between CYP2C19 gene polymorphism and stroke prognosis under additive, recessive, and dominant models showed that the CYP2C19 allele was a risk gene for poor prognosis, while the G allele was protective. Compared to the GG genotype, patients with AA or AG genotypes had a higher risk of poor prognosis ($P < 0.05$). Interaction analysis showed that the risk of poor prognosis in stroke patients with CYP2C19 AA genotype and Lp(a) levels in Q2-Q5 was 15.023 times higher than in those with good prognosis. Similarly, the risk for patients with CYP2C19 AG genotype and Lp(a) levels in Q2-Q5 was 6.435 times higher. After controlling for confounding factors, the relative excess risk (REPI) = 33.166 (-144.689-181.020), the attributable proportion (AP) = 0.901 (0.625-1.177), and the interaction index (S) = 13.526 (1.114-164.174), indicating an additive interaction between CYP2C19 gene polymorphism and Lp(a) on poor stroke prognosis. Conclusion: An additive interaction exists between CYP2C19 AA gene polymorphism and Lp(a) levels in influencing stroke prognosis. Clinically, timely interventions based on these factors can improve stroke patient outcomes.

Keywords: CYP2C19 gene polymorphism, lipoprotein (a), interaction, stroke, prognosis

Introduction

Stroke is a common cerebrovascular disease in clinical practice, predominantly affecting middle-aged and elderly individuals aged 45 years and older [1]. Current statistics indicate that there are approximately 11 million stroke patients in China, with approximately 2 million new cases and 1.5 million deaths reported annually [2]. With the increasing aging population in China, the incidence of stroke is rising each year [3]. The occurrence of stroke is influenced by various factors such as diet, environment, and genetics. Consequently, recent research focusing on genetic susceptibility genes associated with ischemic stroke has emerged as a prominent area of interest [4].

The activity of cytochrome P450 2C19 (CYP-2C19) exhibits significant variability among different races and individuals, primarily due to genetic polymorphism. TheG681A and G636A mutations are the most notable variants of the CYP2C19 gene. Some studies have found that CYP2C19 gene polymorphism can increase the incidence of cardiovascular events and is associated with poor cardiovascular prognosis [5, 6]. Antiplatelet aggregation represents the primary approach for stroke treatment. Aspirin and/or clopidogrel are recommended as first- and second-line preventive agents for ischemic stroke in both domestic and international guidelines on stroke prevention and treatment. However, significant individual variability exists regarding the inhibitory effects of aspirin and clopidogrel on platelet activity. Some studies have reported that 15%-48% and 17%-39% of ischemic stroke patients exhibit aspirin and clopidogrel resistance, respectively [7, 8]. The metabolism of antiplatelet drugs is affected by the activity of CYP2C19. Some studies have found that CYP2C19 gene polymorphism leads to different metabolic abilities of antiplatelet drugs in different populations and individuals, resulting in different treatment effects and prognosis [9, 10].

Lipoprotein (a) (Lp(a)) is a complex lipid particle that has been implicated in the pathogenesis of cardiovascular and cerebrovascular diseases. However, its association with the prognosis of stroke patients remains unclear [11]. Furthermore, it is not well established whether there exists an interaction between CYP2C19 gene polymorphism and Lp(a) levels concerning prognosis of stroke patients. Based on this, this study mainly evaluated the interaction between CYP2C19 gene polymorphism and Lp(a) levels and explored the influence of CYP2C19 gene polymorphism and Lp(a) levels on the prognosis of stroke patients, to reasonably classify stroke patients and provide more basis for the long-term survival management of patients.

Materials and methods

Research subjects

A total of 210 stroke patients admitted to Wuming Hospital of Guangxi Medical University from January 2021 to June 2024 were retrospectively selected as the observation group. Inclusion criteria: 1) Meeting the clinical diagnostic criteria for stroke [12], confirmed by imaging examination; 2) Patients admitted to the hospital within 48 hours after the first onset of the disease; 3) Age > 50 years; 4) Complete clinical data. Exclusion criteria: 1) Complicated with severe malignant tumors; 2) Suffering from severe cardiopulmonary diseases, infections, or chronic diseases; 3) Combined with severe liver and kidney dysfunction; 4) History of brain tumors, brain trauma, ischemic stroke, subarachnoid hemorrhage, or other brain diseases; 5) Condition aggravated, died, or transfer to another hospital; 6) Patients with mental illness and impaired consciousness. Additionally, 180 healthy individuals with no obvious abnormalities in outpatient physical examination indices during the same period were collected as healthy control group, matched for age, gender, and body mass index (BMI). The healthy control group had no history of stroke, and their clinical data were complete. The exclusion criteria for the healthy control group were the same as those for the observation group. This research protocol was approved by the Medical Ethics Committee of Wuming Hospital of Guangxi Medical University.

Methods

Data collection: The information of all subjects was collected, including demographic data (gender, age, BMI, etc.), history-related data (hypertension, diabetes, coronary heart disease, etc.), lifestyle data (smoking, drinking, etc.), NIHSS score at admission, laboratory test results (White blood cell count, neutrophil count, triglyceride, serum creatinine, uric acid, total serum protein, Lp(a)). After collecting the general data, all patients received routine internal medicine treatment and rehabilitation function training. Three months after the onset of the disease, their prognosis was evaluated using the modified Rankin Scale (mRS). According to the mRS score, patients were divided into a good prognosis group (mRS score > 2) and a poor prognosis group (mRS score ≤ 2).

CYP2C19 gene polymorphism detection: The polymerase chain reaction-restriction fragment length polymorphism (PCR - RFLP) method was employed to detect the CYP2C19 genotype. A total of 2 ml of venous blood was collected from the median cubital vein of each subject

and placed in an ethylene diamine tetraacetic acid (EDTA) vacuum anticoagulant tube, subsequently stored at -20°C for testing. DNA was extracted according to the instructions provided with the kit. The CYP2C19 gene primers (forward: ACGTTGGATGGCAATAATTTTCCCACTATC, reverse: ACGTTGGATGACTTTCTCCAAAATATCC) were synthesized according to the sequence reported by Sequenom in the United States and were synthesized by BGI. The PCR amplification reaction system (25 μl) consisted of: 2× premix 10 μl, forward and reverse primers (0.5 μl each), DNA template (3 μl), distilled water (8 μl), and Taq enzyme (0.25 μl). The PCR amplification conditions were as follows: pre-denaturation at 95°C for 5 min, denaturation at 94°C for 30 s, annealing at 60°C for 30 s, extension at 72°C for 30 s, for a total of 30 cycles, and final extension at 72°C for 10 min. A 5 μl aliquot of the PCR amplification product was subjected to restriction enzyme digestion with Sma I and BamHI, and then 1.2% agarose gel electrophoresis was performed, and the results were observed under a gel imaging analyzer. The primary genotypes detected included wild-type (GG), mutant heterozygous type (AG), and mutant homozygous type (AA). Those carrying the wild-type (GG) gene were fast metabolizers, those with the mutant heterozygous type (AG) were intermediate metabolizers, and those with the mutant homozygous type (AA) were slow metabolizers. The PCR product was sent to BGI for bidirectional sequencing, and the sequencing results were compared and analyzed with the sequence reported by Sequenom in the United States.

Statistical methods

SPSS version 29.0 was utilized for statistical analysis. Non-normally distributed measurement data were represented by M(Q1, Q3), and the rank sum test was employed for intergroup comparisons. Normally distributed data were represented by (Mean ± SD), with one-way ANOVA applied for comparison among multiple groups. While the independent sample t-test was used for pairwise comparison, count data were represented by n (%), and the χ^2 test was used for comparison between groups. The Hardy - Weinberg equilibrium was verified for each genotype frequency. Logistic regression analysis was used to identify risk factors for poor prognosis, and the multiplicative model was used to evaluate the interaction between CYP2C19 gene polymorphism and Lp(a) levels. The "EpiR package" of R 4.1.2 software was used to analyze the additive interaction between CYP2C19 gene polymorphism and Lp(a) levels. The evaluation indices included: relative excess risk (RERI), attributable proportion of interaction (AP), and interaction index (S). A two-sided test level $\alpha = 0.05$ was used for all statistical analyses.

Results

Comparison of clinical characteristics and laboratory test values of stroke patients with different prognoses and the healthy control group

Among the 210 stroke patients in this study, 82 (39.05%) had a poor prognosis, and 128 (60.95%) had a good prognosis. There were no significant differences in gender, age, BMI, hypertension, diabetes, coronary heart disease, smoking, drinking, white blood cell count, neutrophil count, triglyceride, serum creatinine, uric acid, and total serum protein among the good prognosis group, poor prognosis group, and healthy control group ($P > 0.05$). However, significant differences were observed in the NIHSS score at admission, the distribution of CYP2C19 genotypes (AA/AG/GG), and Lp(a) levels between the good prognosis group and the poor prognosis group ($P < 0.05$, **Table 1**).

Comparison of NIHSS scores of stroke patients with different CYP2C19 genotypes at admission

The NIHSS scores at admission of stroke patients with AA, AG, and GG genotypes increased sequentially ($P < 0.05$, **Table 2**).

Multivariate analysis of influencing factors for poor prognosis in stroke patients

Taking the prognosis situation (1 = poor prognosis group, 0 = good prognosis group) as the dependent variable, and including the indicators that showed significant differences in the univariate analysis [NIHSS score at admission, CYP2C19 genotype AA/AG/GG, Lp(a)] as independent variables, with specific assignments as shown in **Table 3**, multivariate logistic regression analysis was performed. The results showed that CYP2C19 genotype and Lp(a) lev-

Table 1. Comparison of clinical features and laboratory parameters among stroke patients with different prognosis and healthy controls

Groups	Poor prognosis group (n = 82)	Good prognosis group (n = 128)	Control group (n = 180)	$t/\chi^2/F$	P
Sex				3.515	0.172
Male	61 (74.39)	96 (75.00)	119 (66.11)		
Female	21 (25.61)	32 (25.00)	61 (33.89)		
Age (years)	63.52±10.54	62.10±11.32	63.05±10.65	0.493	0.611
BMI (kg/m^2)	24.12±3.11	24.01±3.11	23.34±2.85	2.753	0.065
Hypertension				0.379	0.827
Yes	51 (62.20)	83 (64.84)	119 (66.11)		
No	31 (37.80)	45 (35.16)	61 (33.89)		
Diabetes				0.060	0.971
Yes	60 (73.17)	93 (72.66)	133 (73.89)		
No	22 (26.83)	35 (27.34)	47 (26.11)		
Coronary heart disease				0.008	0.996
Yes	19 (23.17)	29 (22.66)	41 (22.78)		
No	63 (76.83)	99 (77.34)	139 (77.22)		
Smoking				0.205	0.902
Yes	29 (35.37)	42 (32.81)	63 (35.00)		
No	53 (64.63)	86 (67.19)	117 (65.00)		
Drinking				0.783	0.676
Yes	31 (37.80)	41 (32.03)	60 (33.33)		
No	51 (62.20)	87 (67.97)	120 (66.67)		
NIHSS score on admission					
White blood cell count	11.40±3.76	11.15±3.24	11.19±3.54	0.146	0.864
Neutrophil count	6.92±1.36	6.75±1.40	6.62±1.41	1.346	0.261
Triglyceride	1.75±0.35	1.71±0.36	1.67±0.37	1.450	0.236
Serum creatinine	85.33±10.23	83.55±9.67	82.22±9.49	2.928	0.055
Serum total protein	37.20±5.65	38.73±5.89	38.55±5.46	2.102	0.124
Lp(a)				12.724	0.002
Q_1	16 (19.51)	70 (54.69)	66 (36.67)		
Q_2-Q_5	66 (80.49)	58 (45.31)	114 (63.33)		
CYP2C19 gene					
Genotype (AA/AG/GG)	29/38/15	22/69/37	56/77/47	10.280	0.006

Note: BMI, body mass index; NIHSS, National Institute of Health stroke scale; Lp(a), Lipoprotein (a); CYP2C19, cytochrome P450 2C19.

els were independent influencing factors for poor prognosis in stroke patients (both P < 0.05, **Table 4**).

Correlation between CYP2C19 gene polymorphism and the prognosis of stroke patients

Among the 210 stroke patients, there were 47 cases (22.38%) of CYP2C19 gene GG type (wild homozygous), 112 cases (53.33%) of GA type (mutant heterozygous), and 51 cases (24.29%) of AA type (mutant homozygous). The frequency of the A allele was 66.88%, and the frequency of the G allele was 33.12%. The Hardy - Weinberg equilibrium test results showed that the genotype distribution frequency of stroke patients conformed to the Hardy - Weinberg equilibrium law (P > 0.05). The correlation between CYP2C19 gene polymorphism and the prognosis of stroke patients was analyzed under additive, recessive, and dominant models. The results showed that for stroke patients, the CYP2C19 A allele was a risk gene for poor prognosis, while the G allele was a pro-

Table 2. Comparison of NIHSS scores of stroke patients with different CYP2C19 genotypes

CYP2C19 genotype	Number of cases	NIHSS Score (points)
AA	51	14.00±3.29
AG	112	12.29±2.35[a]
GG	47	10.72±2.85[a]
F	19.027	
P	< 0.001	

Note: NIHSS, National Institute of Health stroke scale; [a]P < 0.05, compared with AA genotype; CYP2C19, cytochrome P450 2C19.

Table 3. Assignment table

Variables	Assignment
Sex	1 = Male, 0 = Female
Age	Original value entry
BMI	Original value entry
Hypertension	1 = Yes, 0 = No
Diabetes	1 = Yes, 0 = No
Coronary heart disease	1 = Yes, 0 = No
Smoking	1 = Yes, 0 = No
Drinking	1 = Yes, 0 = No
NIHSS score on admission	Original value entry
White blood cell count	Original value entry
Neutrophil count	Original value entry
Triglyceride	Original value entry
Serum creatinine	Original value entry
Serum total protein	Original value entry
Lp(a)	Original value entry
CYP2C19 gene polymorphism	1 = AA, 2 = AG, 3 = GG

Note: BMI, body mass index; NIHSS, National Institute of Health stroke scale; Lp(a), Lipoprotein (a); CYP2C19, cytochrome P450 2C19.

tective gene. Compared with the GG genotype, patients with AA or AG genotypes had a significantly higher risk of poor prognosis (P < 0.05, **Table 5**).

Influence of the interaction between CYP2C19 gene polymorphism and Lp(a) on the prognosis of stroke patients

Multiplicative interaction: Taking the prognosis of stroke patients (1 = poor prognosis group, 0 = good prognosis group) as the dependent variable, and CYP2C19 gene, Lp(a) level, and their product as independent variables, a multivariate logistic regression analysis was performed while controlling for confounding factors such as gender, age, BMI, hypertension, diabetes, coronary heart disease, smoking, drinking, NIHSS score at admission, white blood cell count, neutrophil count, triglyceride, serum creatinine, total serum protein (assignments as shown in **Table 2**). The results showed that CYP2C19 gene × Lp(a) did not have a multiplicative interaction on the poor prognosis of stroke patients (P > 0.05, **Table 6**).

Additive interaction: Taking the prognosis of stroke patients (1 = poor prognosis group, 0 = good prognosis group) as the dependent variable, and CYP2C19 gene, Lp(a) level, and their product as independent variables, multivariate Logistic regression analysis was performed while controlling for confounding factors such as gender, age, BMI, hypertension, diabetes, coronary heart disease, smoking, drinking, NIHSS score at admission, white blood cell count, neutrophil count, triglyceride, serum creatinine, total serum protein (assignments as shown in **Table 2**). The results revealed the following: the poor prognosis of stroke patients with CYP2C19 AA genotype and Lp(a) levels in Q_2-Q_5 was 15.023 times higher than that of stroke patients with good prognosis; the risk of poor prognosis in stroke patients with CYP2C19 AG genotype and Lp(a) levels in Q_2-Q_5 was 6.435 times higher than that of stroke patients with good prognosis; the risk of poor prognosis in stroke patients with CYP2C19 GG genotype and Lp(a) levels in Q_2-Q_5 was 22.042 times higher than that of stroke patients with good prognosis (**Table 7**). The additive interaction analysis yielded the following indices: REPI[a] = 33.166 (-144.689-181.020), AP[a] = 0.901 (0.625-1.177), S[a] = 13.526 (1.114-164.174), indicating that there was an additive interaction between CYP2C19 gene polymorphism and Lp(a) on the poor prognosis of stroke (As shown in **Figure 1**).

Discussion

CYP2C19 is an important drug-metabolizing enzyme in the CYP450 family, participating in about 2% of drug metabolism in clinical practice [13]. Recent studies have shown that the CYP2C19 GG genotype is associated with the incidence of coronary heart disease and coronary syndrome [14, 15]. Bykov et al. [16] reported that individuals with the AG genotype at the G636A site of CYP2C19 exhibited a 3.8-

Table 4. Multivariate analysis of adverse prognostic factors in stroke patients

Factor	β	SE	Wald χ^2	*P*	OR (95% CI)
NIHSS score on admission	0.054	0.063	0.736	0.391	1.055 (0.933-1.193)
CYP2C19					
AG genotype compared to AA genotype	1.293	0.486	7.068	0.008	3.645 (1.405-9.456)
GG genotype compared to AA genotype	1.099	0.427	6.029	0.010	3.001 (1.298-6.935)
Lp(a)	1.908	0.863	26.515	< 0.001	6.742 (3.261-13.940)

Note: BMI, body mass index; NIHSS, National Institute of Health stroke scale; Lp(a), Lipoprotein (a); CYP2C19, cytochrome P450 2C19.

Table 5. Correlation between CYP2C19 gene polymorphism and prognosis of stroke patients with different genotypes

CYP2C19 gene	Poor prognosis group (n)	Good prognosis group (n)	OR (95% CI)	P	OR (95% CI)[a]	P
Additive model A allele compared to G allele	96/68	113/143	0.493 (0.251-0.966)	0.039	0.483 (0.234-0.995)	0.048
Dominant model AA genotype compared to GG or AG genotype	29/53	22/106	2.636 (1.383-5.024)	0.003	2.718 (1.373-5.381)	0.004
Recessive model AA or AG genotype compared to GG genotype	68/15	96/32	0.493 (0.251-0.966)	0.039	0.483 (0.234-0.995)	0.048

Note: [a]adjusted for gender, age, BMI, hypertension, diabetes, coronary heart disease, smoking, alcohol consumption, NIHSS score at admission, white blood cell count, neutrophil count, triglyceride, blood creatinine, and serum total protein; BMI, body mass index; CYP2C19, Cytochrome P450 2C19; Lp(a), Lipoprotein (a).

Table 6. Interaction of CYP2C19 gene polymorphism and Lp(a) on poor prognosis in stroke patients based on multivariate Logistic regression analysis

Variables	Model 1		Model 2[a]	
	OR (95% CI)	P	OR (95% CI)	P
CYP2C19gene	1.349 (0.441-4.129)	0.600	1.230 (0.411-3.684)	0.712
Lp(a)	58.289 (4.652-730.332)	0.002	70.598 (5.640-883.647)	< 0.001
Multiplicative model	0.300 (0.089-1.014)	0.053	0.310 (0.092-1.048)	0.059

Note: [a]adjusted for gender, age, BMI, hypertension, diabetes, coronary heart disease, smoking, alcohol consumption, NIHSS score at admission, white blood cell count, neutrophil count, triglyceride, blood creatinine, and serum total protein; BMI, body mass index; CYP2C19, Cytochrome P450 2C19; Lp(a), Lipoprotein (a).

Table 7. Additive interaction of CYP2C19 gene polymorphism and Lp(a) on poor prognosis in stroke patients based on multivariate Logistic regression analysis

Lp(a) (mg/L)	CYP2C19gene	Poor prognosis group (n = 82)	Good prognosis group (n = 128)	Model 1		Model 2	
				OR (95% CI)	P	OR (95% CI)	P
Q_1	AA	6	7	1		1	
	AG	4	6	3.333 (0.896-12.399)	0.72	2.725 (0.564-13.176)	0.213
	GG	6	2	0.255 (0.073-0.889)	0.032	0.214 (0.055-0.833)	0.026
Q_2-Q_5	AA	23	15	11.667 (2.007-67.811)	0.006	15.023 (2.057-109.730)	0.008
	AG	34	8	5.963 (2.239-15.882)	< 0.001	6.435 (1.979-20.921)	0.002
	GG	9	35	16.528 (5.710-47.844	< 0.001	22.042 (6.428-75.580)	< 0.001
Additive model	REPI[a] = 33.166 (-144.689-181.020), AP[a] = 0.901 (0.625-1.177), S[a] = 13.526 (1.114-164.174)						

Note: [a]adjusted for gender, age, BMI, hypertension, diabetes, coronary heart disease, smoking, alcohol consumption, NIHSS score at admission, white blood cell count, neutrophil count, triglyceride, blood creatinine, and serum total protein; BMI, body mass index; CYP2C19, Cytochrome P450 2C19; Lp(a), Lipoprotein (a).

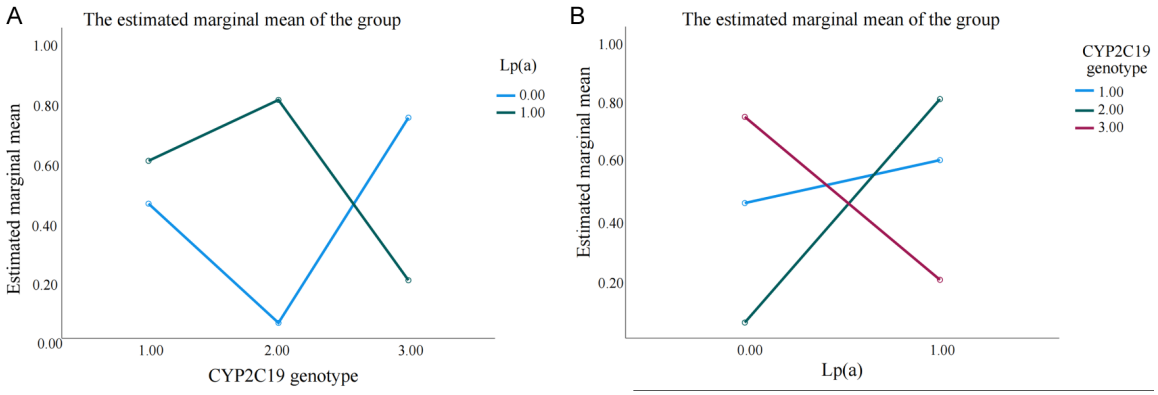

Figure 1. Additive interaction. A. CYP2C19 genotype + Lp(a); B. Lp(a) + CYP2C19 genotype. CYP2C19, Cytochrome P450 2C19; Lp(a), Lipoprotein (a).

fold increased risk of developing atherosclerosis. Additionally, Daniel et al. [17] found in a study of patients with acute coronary syndrome that the risk of stroke in patients carrying CYP2C19 AA and AG genotypes was significantly increased compared with those without these genotypes. CYP2C19 plays a vital role in the metabolism of antiplatelet drugs. Both aspirin and clopidogrel, as prodrugs, require conversion by the CYP2C19 enzyme into their active forms to exert antiplatelet aggregation effects [18]. In recent years, it has been observed that there are large individual differences in the drug resistance among patients with cardiovascular and cerebrovascular diseases after taking aspirin and clopidogrel, which may be related to CYP2C19 gene polymorphism [19, 20].

The results of this study showed that the NIHSS scores of stroke patients with CYP2C19 gene GG, AG, and AA genotypes gradually increased

at admission. Furthermore, the proportion of patients with the AA genotype among those experiencing poor prognosis following acute cerebral infarction (ACI) was notably higher. This suggests that mutations in the CYP2C19 gene may exacerbate neurological function impairment in stroke patients; specifically, a greater number of A alleles correlates with more severe nerve function damage and poorer prognostic outcomes. The underlying mechanisms for these observations may be linked to the impact of CYP2C19 gene mutations on arachidonic acid metabolism. As individuals carry an increasing number of A alleles, there is a corresponding escalation in cerebrovascular and neurological dysfunction. In addition, CYP2C19 gene mutation can also reduce the ability of stroke patients to metabolize antiplatelet drugs, leading to decreased production of active drug metabolites, insufficient antiplatelet effect, reduced efficacy, and an increased likelihood of poor prognosis.

Currently, the research on the influence of CYP2C19 gene polymorphism on the prognosis of stroke mainly focuses on the influence of CYP2C19 gene on clopidogrel resistance. Yi et al. [21] reported that clopidogrel-resistant patients carried significantly more slow metabolizing loss-of-function alleles (AA, AG) compared to clopidogrel-sensitive patients, and the prognosis of clopidogrel-resistant patients was worse. Yi et al. [22] reported that the CYP2C19*2 AG/AA genotype and ischemic stroke patients carrying two loss-of-function variant alleles were independent risk factors for poor prognosis. The results of this study align with these findings, demonstrating that the CYP2C19 genotype is a risk factor for poor prognosis in stroke patients. In addition, the results of this study showed that Lp(a) was also a risk factor for poor prognosis in stroke patients. Lp(a) is a risk factor closely associated with cardiovascular and cerebrovascular diseases, and its expression level is strongly correlated with disease severity [23, 24]. Studies [25, 26] have pointed out that the Lp(a) level is positively correlated with the severity of acute ischemic stroke. Elevated Lp(a) levels typically indicate lipid metabolism disorder and impaired vascular endothelial function, which exacerbate damage to the cerebrovascular system [27]. Therefore, monitoring Lp(a) level in acute ischemic stroke patients holds important clinical value and serves as an important indicator for predicting short-term prognosis in these patients [28, 29].

The interaction analysis results of this study revealed an additive interaction between CYP2C19 gene polymorphism and Lp(a) level on the prognosis of stroke patients. Among them, 28.05% of stroke patients with poor prognosis were attributed to the synergistic effect of CYP2C19 AA genotype and Lp(a) levels in Q_2-Q_5; and 41.46% of stroke patients with poor prognosis were attributed to the synergistic effect of CYP2C19 AG genotype and Lp(a) levels in Q_2-Q_5. To the best of the author's knowledge, no previous studies have reported such findings. This study systematically expounded the relationship between CYP2C19 gene polymorphism and Lp(a) level from a statistical perspective, demonstrating that the risk of poor prognosis in stroke patients with both CYP2C19 AA/AG genotypes and high Lp(a) levels was much higher than the individual effects of either factor alone. This highlights the importance of clinical attention to CYP2C19 gene polymorphism detection in stroke patients. For patients carrying A allele and high Lp(a) levels, early drug intervention or adjustments to antiplatelet drug treatment regimens should be considered to improve prognosis.

There are still some limitations to this study: (1) The subjects were recruited from a single hospital, and the sample size was relatively small, which may introduce sample size and selection bias. (2) In this study, polymerase chain reaction was used to detect CYP2C19 gene polymorphism. Although this is a common detection method, there may be some technical errors. Additionally, the accuracy of gene polymorphism detection can be influenced by factors such as sample processing and storage conditions. (3) While this study identified an additive interaction between CYP2C19 gene polymorphism and Lp(a) levels on poor prognosis of stroke, the mechanism of interaction remain unclear. In summary, future research can increase sample size, conduct multi-center data collection to enhance the generalizability of the findings, and high-quality prospective research is warranted to further validate the results. At the same time, the biological basis of this interaction and whether other genes or factors are involved should be further explored.

Conclusion

In conclusion, there is an additive interaction between CYP2C19 AA gene polymorphism and Lp(a) levels on the prognosis of stroke patients. Clinically, timely interventions based on the analysis of these two factors can help improve the prognosis of stroke patients.

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Disclosure of conflict of interest

None.

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