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RESEARCH ARTICLE

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Associations of *PER3* polymorphisms with clopidogrel resistance among Chinese Han people treated with clopidogrel

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Abstract

Background: Changes in circadian rhythm are related to various diseases, such as immune system diseases and cardiovascular diseases. The *PERIOD3 (PER3)* clock gene is one of the most important genes in the rhythm regulation system. Our goal was to evaluate the possible association between the *PER3 rs228729* (*T/C*) polymorphism or *PER3 rs2797685*(*T/C*) polymorphism and clopidogrel resistance (CR) and to study the impact of clinical baseline data on clopidogrel resistance.

Methods: *PER3* polymorphisms *rs2797685* (*T/C*) and *rs228729* (*T/C*) were assessed in 156 patients with (72) and without (84) CR. Blood samples were collected and analyzed after the application of clopidogrel for interventional therapy.

Results: Age, albumin, PLT, and PCT levels influenced the risk of CR ($p < 0.05$). For *rs2797685*, when the PCT value was greater than 0.19, patients with the *TT + TC* genotype had an increased risk of clopidogrel resistance compared with those with the *CC* genotype (PCT ≥ 0.19, $p = 0.014$; PCT $p = 0.004$). In patients with albumin values greater than 40 or PCT greater than 0.19, those with the *rs228729 TT + TC* genotype had an increased risk of clopidogrel resistance compared with those with the *CC* genotype (albumin≥40, *TT+TC:CC*, $p = 0.01$, albumin $p = 0.005$; PCT ≥ 0.19, *TT+TC:CC*, $p < 0.001$, PCT $p = 0.004$). Logistic regression analysis of clinical baseline data and genotype showed that high albumin is a protective factor against clopidogrel resistance. The *PER3* gene polymorphism has no clear correlation with clopidogrel resistance.

Conclusion: In summary, our research shows that *PER3* SNPs may be helpful to assess the pathogenesis of CR.

KEYWORDS
acute coronary syndrome, clopidogrel resistance, percutaneous coronary interventions, *PERIOD3*, single-nucleotide polymorphisms

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BUN, blood urea nitrogen; CREA, creatinine; GLU, Glucose; HbA1C, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitive C reactive protein; LDL-C, low-density lipoprotein cholesterol; MPV, mean platelet volume; PCT, Platelet hematocrit; PDW, Platelet distribution width; PLT, platelet; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; UA, Uric acid.

Nan Zheng and Fengying Yin are the Equal contributors to this article, and they are the first co-authors.

1 | INTRODUCTION

Cardiovascular disease is the disease with the highest mortality, and acute coronary syndrome may be one of the most dangerous diseases. In Asian populations, the acute coronary syndrome is very harmful and causes great medical expenses and medical burden.[1] The most important process of the acute coronary syndrome (ACS) is the formation of arterial thrombosis involving platelets after the rupture of atherosclerotic plaques originally existing in the arterial wall. The use of aspirin and clopidogrel due to antiplatelet effects is very important in coronary artery disease.[2-4] Moreover, clopidogrel (P2Y12-receptor inhibitor) is the most widely used drug in dual antiplatelet therapy in coronary heart disease. It selectively inhibits the P2Y12-receptor, thereby suppressing the platelet aggregation pathway induced by ADP.[5-7] Clopidogrel has a good safety profile compared to ticlopidine, the first FDA-approved P2Y12-receptor inhibitor,[8] and it is the most widely studied P2Y12-receptor inhibitor.[9]

The active ingredient of clopidogrel after metabolism in the body further inhibits the P2Y12-receptor to prevent platelet aggregation.[8,10] The application of clopidogrel in cardiovascular disease has been proven to be effective [11]; in some patients, however, the effect is not obvious.[12] In most of the previous literature, Clopidogrel resistance is defined as the failure of platelet function inhibition or poor inhibition effect, with effects that are still not fully clear.[13]

At present, some clinical factors have been confirmed to be related to clopidogrel resistance, such as BMI.[14,15] However, the relationship between the *PER3* gene polymorphism and clopidogrel resistance remains unclear.

The circadian rhythm is a pivotal factor in the behavior of the individual or the physiological function of the body. The biological circadian rhythm in the human body is mainly a 24-hour cycle process that affects related cell rhythms. This rhythm can even affect immune cells, influencing the body's immune process.[16] *Clock genes can control the rhythmic expression of hundreds of downstream genes through the regulation of circadian rhythms and indirectly through macrophages and monocytes*.[16]

The mammalian circadian clock mechanism is driven by a set of genes: *PER1*, *PER2*, *PER3*, *Clock*, *Bmal1*, *Cry1*, and *Cry2*.[17] *Research on PER3 shows it to be indispensable to the sleep-wake cycle*.[18] Previous studies have addressed the effect of sleep on the normal function of the immune system and the role of *PER3* in sleep homeostasis, the role of *PER3* in human inflammatory diseases, and related cardiovascular diseases. Circadian rhythm disturbances can increase blood pressure and inflammatory markers.[19] The circadian rhythm of hypertension can also affect the incidence of cardiovascular system.[20] Recent research shows that the occurrence and development of acute myocardial infarction (AMI) are influenced by circadian rhythm changes.[21,22] At the molecular level, different cells (including cardiomyocytes) invoke related cycle regulation systems to regulate biological processes. When this mechanism is unbalanced or damaged, the metabolism and function of the heart may change, increasing susceptibility to cardiovascular disease. Not only that, some scholars have reported that even the daily ADP receptor-dependent platelet function and activation of ACS patients taking clopidogrel have periodic changes.[23]

Single-nucleotide polymorphisms (SNPs), which are considered to be the most common genetic variation, can predict the risk of genetic disease, the degree of related progress, and the related therapeutic effect.[24] *To date*, *there has been scant research on* clopidogrel resistance *and the polymorphic variants of PER3*. The main purpose of this study is to examine the relationship between SNP of the key circadian rhythm gene *PER3* and clopidogrel resistance and to assess the effect on subsequent clinical treatment.

2 | METHODS

2.1 | Population in this study

First of all, the population selected to enter this study are patients from the First Hospital of Ningbo City from 2015 to 2018, and these are patients with acute coronary syndromes, a total of 156 cases. All are of Han ethnicity who were from or lived in Ningbo City, Zhejiang Province for a long time. The inclusion criteria were as follows: (a) over 18 years old; (b) received a loading dose of clopidogrel and aspirin before PCI and was given daily after stent placement; (c) underwent PCI surgery with drug-eluting stent placement via the radial artery, with most patients having the disease in multiple coronary arteries or the left main artery. The exclusion criteria were as follows: (a) liver and kidney dysfunction; (b) combined treatment with warfarin and other anticoagulant drugs; (c) have a history of severe bleeding; and (d) total number of platelets <150 000 μl^{-1} or >500,000 μl^{-1}. In the interview before participating in the study, all patients provided written informed consent. The ethics committee of Ningbo First Hospital approved the research project. The research as a whole conformed to the guiding principles of the Declaration of Helsinki.[25]

2.2 | Clinical baseline data and blood test

Samples were collected on an empty stomach, in the morning after one night of fasting. After obtaining the serum sample, it will be stored in a cold storage facility until use. In the detection of serum marker levels, such as the concentration of HbA1c, BUN, and CREA, all steps are performed following standard operating procedures.[25]

2.3 | Platelet function measurements

According to previous related studies, blood samples were collected and analyzed 3–5 days after the application of clopidogrel for interventional therapy. At that time, the platelet reactivity had

stabilized.[26] During the analysis, the VerifyNow P2Y12 assay was used to assess the reactivity of P2Y12. The final test result is expressed in the form of a p2y12 reaction unit (PRU). The standard for clopidogrel resistance is PRU≥240.

2.4 | DNA extraction and genotype testing

In this experiment, we used QIAamp-DNA Serology Kit (Qiagen) to extract human genomic DNA from 3 ml of peripheral blood. (a) After sampling in an EDTA vacuum collection tube, store it in a refrigerator at 4°C for several days. Take the 3 ml blood sample and place it in a new EDTA vacuum collection tube. (b) Add 3 ml of red blood cell lysate and shake repeatedly for 20 seconds. After mixing thoroughly, place in a centrifuge, centrifuge at 3000 g at 4°C for 2 minutes and discard the supernatant. (c) Repeat the process of step (2) twice, until the content is white precipitate, and then stop. (d) Shake the test tube, and the cells are visible in suspension. Then add 300 μl of white blood cell lysate, shake the shaker for the 30 s, and see the cells suspended on it. (e) Then add 100 μl of protein precipitation solution and see red flocculent precipitate after shaking. 4°C 12,000 g Centrifuge for 10 min. (f) Take the supernatant and add it to a 1.5 ml EP tube, then add an equal volume (about 400μL) of isopropanol, invert and mix several times until a flocculent precipitate is seen. Centrifuge at 12,000 g at 4°C for 10 min. Discard Supernatant. (g) Add 500 μl of 70% ethanol to the EP tube and wash it. Repeatedly

TABLE 1 Statistics of clinical characteristics of the study population (Hypertension is defined as systolic blood pressure greater than or equal to 140 mmHg, or diastolic blood pressure greater than or equal to 90 mmHg; Diabetes is defined as being diagnosed as diabetes by a medical institution before or during this hospitalization; Hyperlipidemia is defined as plasma total cholesterol concentration >5.17 mmol/L (200 mg/dl) or plasma triacylglycerol concentration >2.3 mmol/L (200 mg/dl), or it has been clearly diagnosed before; Smoking is defined as continuous or cumulative smoking for 6 months or more in a lifetime; Alcohol abuse is defined as drinking 5 or more bottles of beer at a time.)

	Non-CR(84)	CR(72)	X^2/Z	*p* value
Gender (male), *n* (%)	66 (78.57)	53 (73.61)	0.527	0.468
Hypertension, *n* (%)	54 (64.29)	48 (66.67)	0.097	0.755
Diabetes mellitus, *n* (%)	17 (20.24)	12 (16.67)	0.327	0.568
Hyperlipidmia, *n* (%)	33 (39.29)	26 (36.11)	0.166	0.684
Smoke, *n* (%)	39 (46.43)	27 (37.5)	1.266	0.260
Alcohol abuse, *n* (%)	18 (21.43)	12 (16.67)	0.566	0.452
Age, y	61 (51–67)	66 (54–72.75)	−2.8	0.005
BMI, kg/m^2	23.77 (21.1–27.02)	24.09 (22.86–25.25)	−0.33	0.741
TC, mg/dl	4.52 (3.69–5.66)	4.13 (3.76–4.97)	−0.647	0.518
TG, mg/dl	1.35 (1.08–2.22)	1.36 (0.92–1.6)	−1.75	0.081
HDL, mg/dl	0.93 (0.79–1.11)	0.99 (0.77–1.24)	−1.29	0.195
GLU, mmol/l	5.13 (4.7–5.7)	5.33 (4.61–7.16)	0	0.138
LDL, mg/dl	2.54 (2–3.46)	2.51 (2.01–2.99)	−0.48	0.631
ALT, μmol/L	27.5 (18–45)	26 (15.25–61)	−0.05	0.959
AST, μmol/L	26 (18–118.75)	30.5 (19–118.25)	−0.48	0.628
TBIL, μmol/L	12.1 (9.45–16.11)	11.3 (7.4–25.6)	−0.09	0.926
HbA1c,%	5.9 (5.43–6.1)	5.8 (5.6–6.6)	−0.89	0.371
Albumin, g/L	40.5 (37.8–42.2)	38.25 (35.8–40.4)	−2.83	0.005
BUN, mmol/L	5.33 (4.42–6.92)	5.22 (4.85–6.66)	−0.46	0.648
CREA, mmol/L	67.85 (61.63–74.4)	71.7 (62.32–85.5)	−1.35	0.176
UA, μmol/L	323 (276–408)	327 (264–382)	−0.01	0.994
hsCRP, mg/L	2.16 (1.04–7.42)	3.21 (0.83–9.08)	−0.41	0.683
PLT,$*10^9$/L	187 (161–243.5)	186 (133.25–218.75)	−2.49	0.013
MPV, fL	8.2 (7.5–9.6)	8.1 (7.43–9.18)	−0.39	0.696
PCT, %	0.16 (0.14–0.21)	0.15 (0.13–0.18)	−2.92	0.004
PDW, %	16.2 (15.6–16.68)	16.3 (15.95–16.5)	−1.11	0.268

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; GLU, glucose; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; HbA1C, glycated hemoglobin; BUN, blood urea nitrogen; CREA, creatinine; UA, uric acid; hs-CRP, high sensitive C reactive protein; PLT, platelet; MPV, mean platelet volume; PCT, platelet hematocrit; PDW, platelet distribution width.

invert several times. After the precipitate is floating, centrifuge at 12,000 g at 4°C for 10 min. Discard the supernatant and repeat. (h) Dry in an incubator at 40°C for about half an hour. After taking it out, add about 50 μl of DNA dissolving solution to the EP tube, mix well and dissolve it thoroughly. We used the PyroMark Assay Design software to design primers. Then, the polymerase chain reaction was used for amplification. The amplified product was purified and sequenced.[25]

2.5 | Statistical analysis

All data were statistically analyzed using SPSS version 26.0 (SPSS, Somers, New York, USA). A chi-square test was used to calculate the Hardy-Weinberg equilibrium of the genotypes. For continuous variables, results that conformed to a normal distribution are described as the mean ± standard deviation; those not conforming to a normal distribution are presented as the interquartile range (IQR). Categorical variables were mainly analyzed using Pearson's chi-square test. The Wilcoxon rank-sum test was applied to evaluate nonparametric continuous variance. Logistic regression analysis was employed to examine the interaction between PER3 single-nucleotide polymorphisms and clinical baseline data previously confirmed as possible influencing factors. A $p < 0.05$ was considered a statistically significant difference.

TABLE 2 The frequency of alleles and genotypes of *rs2797685* and *rs228729*

rs228729	Non-CR	CR	X^2	*p* value
CC	42	28	6.631	0.036
TC	28	38		
TT	14	6		
rs2797685				
CC	20	10	3.635	0.162
TC	31	36		
TT	33	26		

3 | RESULTS

3.1 | Analysis of baseline data or clinical characteristics

The comparison of baseline data and clinical characteristics of clopidogrel-resistant and non-resistant groups is shown in Table 1.

Seventy-two patients were defined as having clopidogrel resistance, with PRU ≥240. In 84 patients, PRU was lower than 240. A tendency toward clopidogrel resistance was observed for the following: older age (case and control group: 66 (54–72.75) versus 61 (51–67), $p = 0.005$); lower albumin levels (case and control group: 38.25 (35.8–40.4) versus 40.5 (37.8–42.2), $p = 0.005$); lower PLT (platelet) levels (case and control group: 186 (133.25–218.75) versus 187 (161–243.5), $p = 0.013$); and lower PCT levels (case and control: 0.15 (0.13–0.18) versus 0.16 (0.14–0.21), $p = 0.004$). The above data suggest that older age, lower plasma albumin level, lower platelet count, and lower plateletcrit may increase the risk of clopidogrel resistance.

TABLE 3 Comparison of the *rs2797685* genotype between the two groups

rs2797685	CC	vs	TC+TT	*p* value	CC+TC	vs	TT	*p* value	CC	vs	TT	*p* value	C	vs	T	*p* value
CR	10		62	0.117	46		26	0.6836	10		26	0.3294	56		88	0.5455
Non-CR	20		64		51		33		20		33		71		97	

TABLE 4 Comparison of the *rs228729* genotype between the two groups

rs228729	CC	vs	TC+TT	*p* value	CC+TC	vs	TT	*p* value	CC	vs	TT	*p* value	C	vs	T	*p* value
CR	28		44	0.1642	66		6	0.1207	28		6	0.4159	94		50	0.7962
Non-CR	42		42		70		14		42		14		112		56	

TABLE 5 Platelet function in the two genotypes

		PRU			Inhibition	*p* value
RS2797685	CC	178 (141–242.75)	0.197	CC	0.29 (0.155–0.4925)	0.087
	TC	228 (169–292)		TC	0.22 (0.07–0.42)	
	TT	212 (152–253)		TT	0.25 (0.19–0.57)	
rs228729	CC	171.5 (135–248)	0.022	CC	0.33 (0.15–0.58)	<0.001
	TC	231 (173–285.75)		TC	0.2 (0.04–0.29)	
	TT	196 (176–228.5)		TT	0.34 (0.22–0.555)	

3.2 | The relationship between clopidogrel resistance and polymorphisms *rs228729* and *rs2797685*

The *rs2797685* (*C*/*T*) and *rs228729* (*C*/*T*) polymorphisms of *PER3* showed Hardy-Weinberg equilibrium ($p > 0.05$). Table 2 shows the frequency of alleles and genotypes of SNPs in the two groups.

The genotype of *rs228729* was statistically significant in the comparison between the two groups (Table 2). As indicated in Tables 3 and 4, the *C* or *T* genotype of *rs2797685* and *rs228729* had no obvious effect on clopidogrel resistance ($p > 0.05$).

In the comparison of the two groups of PRU and inhibition at the two sites, there is a relationship between the platelet function index of *rs228729* and clopidogrel resistance. This is consistent with the previous conclusion that *rs228729* is related to resistance (Table 5). However, the specific relationship is still unclear.

3.3 | Subgroup analysis

Based on differences in clinical baseline data between the two groups, we retained several different indicators, including age, albumin, PLT, and PCT, for further subgroup analysis (Table 6). For *rs2797685*, the comparison of the various genotypes revealed statistical significance when PCT > 0.19 ($p = 0.047$) (Table 7). For *rs2797685*, patients with the *TT* + *TC* genotype had an increased risk of clopidogrel resistance compared with the *CC* genotypewhen the PCT≥0.19 ($p = 0.014$). However, the genotype of *CC*+*TC* and the genotype of *TT* had no obvious relationship with clopidogrel resistance when PCT ≥ 0.19 ($p = 0.406$).

Regarding subgroup analysis of *rs228729*, comparison of the various genotypes showed statistical significance when albumin ≥ 40, PCT < 0.19, and PCT ≥ 0.19 ($p = 0.021$, $p = 0.016$, $p = 0.001$) (Table 8). Among patients with albumin ≥40 or PCT ≥0.19, those with the *TT* + *TC* genotype of *rs228729* were more likely to develop resistance than those with the *CC* genotype ($p = 0.01$; albumin $p = 0.005$; PCT

TABLE 7 Comparison of *rs2797685* genotypes when PCT >0.19.

RS2797685		non-CR	CR	*p* value
PCT ≥0.19	TT+TC	22	14	0.014
	CC	11	0	
PCT ≥0.19	CC+TC	23	8	0.406
	TT	10	6	

TABLE 6 Subgroup analysis of *rs2797685* between cases and controls

Rs2797685		Non-CR	CR	X^2	*p* value
Age <60	CC	9	2	1.504	0.471
	TC	16	10		
	TT	16	9		
≥60	CC	11	8	2.764	0.251
	TC	15	26		
	TT	17	17		
Albumin <40	CC	9	8	3.761	0.153
	TC	15	29		
	TT	17	14		
≥40	CC	11	2	3.131	0.209
	TC	16	7		
	TT	16	12		
PLT <125	CC	0	3	3.111	0.211
	TC	2	4		
	TT	0	5		
≥125	CC	20	7	5.804	0.055
	TC	29	32		
	TT	33	21		
PCT<0.19	CC	9	10	1.542	0.463
	TC	19	28		
	TT	23	20		
≥0.19	CC	11	0	6.119	0.047
	TC	12	8		
	TT	10	6		

TABLE 8 Subgroup analysis of *rs228729* between cases and controls

RS228729		non-CR	CR	X^2	*p* value
Age <60	CC	22	8	2.296	0.317
	TC	10	9		
	TT	9	4		
≥60	CC	20	20	3.203	0.202
	TC	18	29		
	TT	5	2		
Albumin <40	CC	15	22	4.459	0.108
	TC	19	27		
	TT	7	2		
≥40	CC	27	6	7.733	0.021
	TC	9	11		
	TT	7	4		
PLT <125	CC	0	2	0.636	0.727
	TC	2	9		
	TT	0	1		
≥125	CC	42	26	4.901	0.086
	TC	26	29		
	TT	14	5		
PCT <0.19	CC	23	28	8.289	0.016
	TC	16	27		
	TT	12	3		
≥0.19	CC	19	0	13.821	0.001
	TC	12	11		
	TT	2	3		

≥0.19, $p < 0.001$, PCT $p = 0.004$) (Table 9). The *CC+TC* genotype was associated with a greater risk of clopidogrel resistance than the *TT* genotype when PCT <0.19($p = 0.006$). This is consistent with the result of the comparison between *CC+TC* and *TT* at the *rs228729* site in Table 4 above.

3.4 | Multivariate logistic regression analysis

Taking into account the confounding effects of multiple factors suggested above, we performed a regression analysis on several related clinical data and genotypes (Table 10). The results suggest that albumin is a protective factor for clopidogrel resistance ($p = 0.037$).

4 | DISCUSSION

The circadian rhythm is essential for regulating all aspects of physiology, such as blood sugar in the endocrine system and inflammatory cells in the immune system.[27-30] Studies show that changes in biological rhythms can affect the body's physiological activities. The *PER3* gene has been proven to be one of the very important clock genes in the human body, and it can affect downstream physiological activity changes by regulating sleep rhythm.[31,32] *PER3* not only plays a key role in the circadian rhythm but also plays a regulatory role in many tissues of the human body.[33] *Furthermore, the PER3 clock gene is part of the circadian clock transcription/translation feedback loop and encodes a protein involved in sleep regulation.*[17]

PER3 has been studied concerning heart tissue and heart diseases,[21,34-36] and SNPs of the *PER3* gene have been confirmed to play an important role in the endocrine system and psychological disease progression. For example, effects on depression and anxiety symptoms[37] and melaton in treatment,[38] analysis of Graves' disease susceptibility,[39] and even effects on tumors such as breast cancer[40] have been proven in previous studies. Furthermore, polymorphisms may affect physiology through unknown mechanisms. Thus far, evidence shows that *PER3* polymorphisms are related to these diseases, though the specific mechanisms are unclear.

Nonetheless, there is no study to date on the relationship between *PER3* and the cornerstone drug of cardiovascular disease-clopidogrel. Indeed, our study is the first to examine the effect of the clock gene *PER3* on clopidogrel resistance. In this study, our purpose was to detect whether the SNPs *rs2797685* and *rs228729* in *PER3* are related to clopidogrel resistance.

Logistic regression showed that albumin is a protective factor for clopidogrel resistance. Albumin has been proven in previous in vitro studies to reverse the effects of clopidogrel and other P2Y12 receptor inhibitors to a certain extent.[41] Our research shows that albumin is a protective factor for clopidogrel resistance, and it can reduce the occurrence of clopidogrel resistance. We believe that this may be related to the effect of albumin on the receptor function of P2Y12 in the body, resulting in a decrease in the receptor baseline, which can reduce the corresponding occurrence of clopidogrel resistance compared with normal conditions. And this does not prove that albumin can reduce the occurrence of resistance in an individual's situation. This requires further comparative analysis and research. This is a shortcoming in our research, and there is no relevant comparison for the influencing factor of albumin.

In previous studies, patients with *TT + TC* genotype had a higher risk of CR in the high albumin subgroup than patients with *CC* genotype. Although we speculate whether it is related to the chain reaction of the protein involved, the specific connection remains unclear. The comparison between CC+TC and TT genotypes was different in the preceding and following tables, because the prerequisite of PCT <0.19 was added. And why PCT <0.19 affects the relationship between clopidogrel resistance is still unclear. And we also admit that this is the limitation of the study.

TABLE 9 Comparison of *rs228729* genotypes when albumin ≥40, PCT ≥0.19, and PCT <0.19

Rs228729		non-CR	CR	*p* value
Albumin≥40	TT+TC	16	15	0.01
	CC	27	6	
Albumin≥40	CC+TC	36	17	0.783
	TT	7	4	
PCT<0.19	TT+TC	28	30	0.74
	CC	23	28	
PCT≥0.19	TT+TC	14	14	<0.001
	CC	19	0	
PCT<0.19	CC+TC	39	55	0.006
	TT	12	3	
PCT≥0.19	CC+TC	31	11	0.118
	TT	2	3	

TABLE 10 Multiple logistic regression analysis of *rs228729*

	B	Std. Error	Wald	*p* value	Exp(B)	Exp(B) 95% CI
Age	0.008	0.018	0.190	0.663	1.008	0.973–1.045
Albumin	−0.092	0.044	4.343	0.037	.912	0.836–0.995
PLT	0.001	0.004	0.021	0.886	1.001	0.992–1.009
PCT	−12.434	6.506	3.652	0.056	0.000	0.000–1.375
RS228729 TT+TC/CC	0.423	0.346	1.497	0.221	1.527	0.775–3.009

Our conclusions may provide certain research ideas for future research. Due to the small sample size, we cannot analyze more loci and more genotypes of the *PER3* gene. We also did not evaluate the specific mechanism between SNPs and clopidogrel resistance because this would require more data and complicated pathway analysis. This is another flaw in our research. Perhaps increasing the sample size in the future can help us address these issues.

5 | CONCLUSIONS

In summary, our study found that *rs228729* is associated with CR in patients with elevated albumin and elevated PCT; *rs2797685* is related to CR in patients with elevated PCT. When the clinical baseline data and genotype were subjected to logistic regression, albumin was found to be a protective factor against clopidogrel resistance. These findings provide ideas for future research.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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