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Distribution of CYP2C19 Polymorphisms among Cardiovascular Disease Patients in the Yunnan–Guizhou Highland Region of Southwest China

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ABSTRACT

The antiplatelet agent clopidogrel requires metabolic activation by the CYP2C19 enzyme to exert its effects. Individual responses to this medication are influenced by genetic variants in the CYP2C19 gene. In this study, we systematically examined the distribution of CYP2C19 alleles, genotype patterns, and predicted phenotype categories among cardiovascular disease patients originating from the Yunnan-Guizhou Plateau. These findings are intended to serve as a resource for guiding more personalized therapeutic strategies. Using RT qPCR, we genotyped the CYP2C19*2, *3, and *17 alleles in 1,934 individuals with cardiovascular disease recruited from ten distinct locations across the Yunnan Guizhou Plateau. Patient clinical information was evaluated with chi square tests. In the overall study population, the observed frequencies for CYP2C19 alleles were as follows: *1 at 64.94%, *2 at 29.81%, *3 at 4.42%, and *17 at 0.83%. Nine different genotype combinations were detected, with their respective prevalences being *1/*17 (1.03%), *1/*1 (42.09%), *2/*17 (0.57%), *3/*17 (0.05%), *1/*2 (38.73%), *1/*3 (5.95%), *2/*2 (8.89%), *2/*3 (2.53%), and *3/*3 (0.16%). Based on these genotypes, individuals were classified into four metabolic categories: rapid metabolizers (1.03%), normal metabolizers (42.09%), intermediate metabolizers (45.29%), and poor metabolizers (11.58%). Notable variations in both allele frequencies and phenotype distributions were found across different geographical areas within the region. This study provides the first detailed characterization of CYP2C19 genetic variants among cardiovascular disease patients residing in the Yunnan Guizhou Plateau, serving as an important pharmacogenetic resource for guiding the choice of appropriate therapeutic regimens.

Keywords: Phenotype, Clopidogrel, Genotype, CYP2C19, Allele, Plateau

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Introduction

Cardiovascular disease (CVD), particularly ischemic heart disease (IHD) and stroke, is a leading contributor to death and disability worldwide [1]. Clopidogrel is a frequently prescribed antiplatelet agent that irreversibly binds to the P2Y12 receptor on platelet surfaces, thereby blocking adenosine diphosphate-induced platelet aggregation. It is commonly used for managing acute coronary syndromes, post-percutaneous coronary intervention (PCI) care, and ischemic stroke [2–4]. Nevertheless, individual responses to this medication vary widely, with 4–30% of patients showing inadequate responsiveness, which diminishes treatment effectiveness and heightens the risk of adverse events [5]. Conversely, while clopidogrel prevents thrombus formation, excessive platelet inhibition can lead to major bleeding complications [6].

Genetic influences account for roughly 75% of this interindividual variation [7]. The cytochrome P450 (CYP) superfamily consists of approximately 57 polymorphic enzymes in humans and metabolizes more than 80% of clinically used drugs [8, 9]. Within this family, CYP2C19 serves as the main enzyme driving the two sequential reactions required to convert clopidogrel into its active form [10, 11]. Genetic variants in CYP2C19 therefore

create substantial differences in enzyme activity, which in turn affect how patients metabolize clopidogrel [12]. Based on enzyme function, individuals are categorized into five groups: ultrarapid metabolizers (UM), rapid metabolizers (RM), normal metabolizers (NM), intermediate metabolizers (IM), and poor metabolizers (PM) [13]. People homozygous for the 17 allele (17/17) fall into the UM category. Those carrying one normal and one gain-of-function allele (1/17) are classified as RM. NM status corresponds to two normal alleles (1/*1). IM includes one normal plus one non-functional allele or one non-functional plus one gain-of-function allele (i.e., *1/*2, *1/*3, *2/*17, *3/*17). PM status results from carrying two non-functional alleles (*2/*2, *2/*3, or *3/*3). The Pharmacogenetic Variation Consortium (PharmVar) recognizes 39 distinct CYP2C19 alleles, with *1, *2, *3, and *17 being the most clinically important [14]. The *2 and *3 variants are loss-of-function alleles that reduce the production of clopidogrel's active metabolite, thereby increasing cardiovascular risk [15]. In contrast, the *17 gain-of-function allele increases transcriptional activity of CYP2C19 substrates, leading to heightened clopidogrel responsiveness and greater bleeding risk. The US Food and Drug Administration (FDA) recommends genotyping patients for variants that influence clopidogrel metabolism to guide treatment modifications [16]. The distribution of CYP2C19 polymorphisms varies considerably across ethnic groups and geographic regions [17].

The Yunnan Guizhou Plateau in southwestern China sits at an average altitude exceeding 2,000 meters and is inhabited by several ethnic minorities (including Yi, Miao, and Hui populations). Its high-altitude environment—characterized by hypoxia and intense ultraviolet radiation—along with the diverse genetic ancestry of its multi-ethnic communities, may give rise to unique pharmacogenetic patterns. Although many studies have reported on CYP2C19 polymorphisms elsewhere in China, no data have been available for the Yunnan Guizhou Plateau until now. In this study, we assessed the frequencies of the CYP2C19*2, *3, and *17 variants in this regional population to predict metabolizer phenotypes and provide a pharmacogenetic reference for drug therapy.

Materials and Methods

Subjects

A total of 2,065 unrelated patients underwent CYP2C19 genetic screening at Kunming Medical University Affiliated Qujing Hospital from April 2017 to April 2023. After removing individuals whose birthplace was not within the Yunnan-Guizhou Plateau or was not recorded, 1,934 participants remained (741 women, 1,193 men). The average age of the study population was 64 years, ranging from 19 to 95 years. These subjects were residents of ten different administrative areas on the plateau: Qilin, Zhanyi, Malong, Xuanwei, Fuyuan, Luliang, Huize, Luoping, Shizong, and Guizhou. The study was designed in accordance with the ethical standards of the Declaration of Helsinki. The ethics committee at the First People's Hospital of Qujing approved the research protocol (approval number 20170223.01). Written informed consent was obtained from all enrolled individuals.

DNA extraction

From each patient, 3 mL of blood was drawn into EDTA-containing tubes. Genomic DNA was purified using a commercial kit (TIANamAp Blood DNA Kit, Tiangen Biotech, Beijing, China) according to the supplier's instructions.

CYP2C19 allele testing

The detection of CYP2C192, CYP2C193, and CYP2C1917 alleles was performed using a Human CYP2C19 Gene Detection Kit (Youzhiyou Co., Ltd., Wuhan, China) employing a real-time PCR assay with fluorescence probes. The kit comprised three separate PCR reactions targeting CYP2C192, *3, and *17, respectively, each containing probes labeled with FAM for the wild-type allele, VIC for the mutant allele, and ROX as an internal control.

For each assay, 2 μL of extracted DNA, along with positive and negative controls, was added to a 20 μL reaction mixture. Amplification and fluorescence detection were carried out using a Bio-Rad CFX96 Real-Time PCR System. The thermal cycling protocol consisted of UNG treatment at 37 °C for 10 minutes, followed by 40 cycles of denaturation at 95 °C for 15 seconds and extension at 62 °C for 60 seconds, with fluorescence signals recorded during the extension step.

Genotype interpretation was based on fluorescence patterns: amplification in the FAM channel alone indicated a wild-type homozygous genotype, signals in both FAM and VIC channels indicated heterozygosity, and amplification only in the VIC channel was interpreted as a mutant homozygous genotype.

Statistical analysis

Data analysis was performed using Microsoft Excel and IBM SPSS Statistics (version 23.0). Comparisons of allele and genotype distributions across different regions and population groups were conducted using chi-square tests, with statistical significance defined as $P < 0.05$. Conformity of allele frequencies to the Hardy–Weinberg equilibrium was also evaluated using chi-square analysis.

Results and Discussion

In the studied Yunnan–Guizhou Plateau population, the frequency distribution of CYP2C19*1, *2, *3, and *17 alleles was consistent with Hardy–Weinberg equilibrium expectations, as no significant differences were observed between the observed and expected genotype proportions ($P > 0.05$). Analysis by sex also showed comparable distributions, with no statistically meaningful differences between males and females ($P > 0.05$).

Allele frequencies

The overall allele frequencies in the study population were 64.94% for CYP2C19*1, 29.81% for CYP2C19*2*, 4.42% for CYP2C19*3, and 0.83% for CYP2C19*17. **Table 1** presents the distribution of these alleles across the regions of Xuanwei, Qilin, Malong, Zhanyi, Luliang, Huize, Luoping, Shizong, Fuyuan, and Guizhou.

Regional comparisons revealed significant variability in CYP2C19*1 frequencies, with Luliang showing higher levels than Malong ($P = 0.00$, $\chi^2 = 14.865$). Similarly, Zhanyi exhibited a greater proportion of CYP2C19*1 compared with Malong ($P = 0.026$, $\chi^2 = 4.935$) and Huize ($P = 0.022$, $\chi^2 = 5.245$), while CYP2C19*2 was less frequent in Zhanyi than in Malong ($P = 0.035$, $\chi^2 = 4.428$) and Huize ($P = 0.006$, $\chi^2 = 7.423$).

In contrast, CYP2C19*3 showed no significant differences among the ten regions ($P > 0.05$, χ^2 test). The CYP2C19*17 allele was absent in Luoping and displayed its highest frequency in Malong, significantly exceeding that observed in Qilin ($P = 0.032$, $\chi^2 = 4.640$), Zhanyi ($P = 0.009$, $\chi^2 = 6.821$), Xuanwei ($P = 0.039$, $\chi^2 = 4.244$), and Fuyuan ($P = 0.012$, $\chi^2 = 6.328$).

Overall, these results demonstrate marked regional heterogeneity in the distribution of CYP2C19 alleles across the Yunnan–Guizhou Plateau. This fills an important gap in pharmacogenetic data for high-altitude populations in Southwest China. Notably, the CYP2C19*17 frequency (0.83%) was the lowest reported among East Asian populations, indicating a distinctive genetic profile in this cohort.

Table 1. Distribution of CYP2C19 alleles in the Yunnan–Guizhou plateau population.

Alleles	Total	Shizong	Luoping	Huize	Xuanwei	Malong	Fuyuan	Guizhou	Luliang	Zhanyi	Qilin
	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)	N F(%) (95% CI)
***3**	171 4.42 (3.77–5.07)	5 5.68 (0.75–10.61)	8 5.13 (1.63–8.63)	6 4.41 (0.92–7.91)	22 3.96 (2.33–5.58)	9 4.50 (1.60–7.40)	22 4.44 (2.62–6.25)	4 3.51 (0.08–6.94)	7 2.85 (0.75–4.94)	26 6.28 (3.93–8.63)	62 4.24 (3.21–5.27)
***2**	1153 29.81 (28.37–31.25)	27 30.68 (20.85–40.51)	48 30.77 (23.45–38.09)	51 37.50 (29.26–45.74)	172 30.94 (27.08–34.79)	67 33.50 (26.90–40.10)	144 29.03 (25.02–33.04)	31 27.19 (18.90–35.49)	74 30.08 (24.31–35.85)	105 25.36 (21.15–29.57)	434 29.69 (27.34–32.03)
***1**	2512 64.94 (63.44–66.45)	54 61.36 (50.99–71.74)	100 64.10 (56.49–71.71)	78 57.35 (48.93–65.77)	358 64.39 (60.40–68.38)	118 59.00 (52.12–65.88)	328 66.13 (61.95–70.31)	78 68.42 (59.76–77.08)	164 66.67 (60.73–72.60)	282 68.12 (63.61–72.62)	952 65.12 (62.67–67.56)

	32	2		1	4	6	2	1	1	1	14
***1**	0.83	2.27	ND	0.74	0.72	3.00	0.40	0.88	0.41	0.24	0.96
7	(0.54–1.11)	(−0.90 –5.45)		(−0.74 –2.19)	(0.01–1.42)	(0.62–5.38)	(−0.16 –0.96)	(−0.86 –2.62)	(−0.39 –1.21)	(−0.23 –0.72)	(0.46–1.46)

Abbreviations: N = total number; F = allele frequency; CI = confidence interval; ND = not detected.

Genotype frequencies and metabolic phenotypes

A total of nine distinct genotype combinations were observed in the study population: *1/*17 (20 cases, 1.03%), *1/*1 (814, 42.09%), *2/*17 (11, 0.57%), *3/*17 (1, 0.05%), *1/*2 (749, 38.73%), *1/*3 (115, 5.95%), *2/*2 (172, 8.89%), *2/*3 (49, 2.53%), and *3/*3 (3, 0.16%). **Figure 1** shows the distribution of these genotypes across the various regions of the Yunnan-Guizhou Plateau. The *1/*17 genotype was absent in both Zhanyi and Luoping. The frequency of *1/*1 was significantly higher in Qilin (P = 0.043, $\chi^2 = 4.076$), Zhanyi (P = 0.029, $\chi^2 = 4.792$), Xuanwei (P = 0.038, $\chi^2 = 4.290$), Fuyuan (P = 0.047, $\chi^2 = 3.955$), and Luliang (P = 0.022, $\chi^2 = 5.216$) when compared to Huize. Zhanyi had a higher proportion of *1/*3 than Qilin (P = 0.016, $\chi^2 = 5.794$), Xuanwei (P = 0.048, $\chi^2 = 3.895$), and Luliang (P = 0.047, $\chi^2 = 3.929$). The *3/*17 genotype appeared exclusively in Qilin. The *2/*2 genotype occurred more frequently in Xuanwei (P = 0.024, $\chi^2 = 5.111$) and Luliang (P = 0.044, $\chi^2 = 4.057$) relative to Zhanyi, while *3/*3 was detected only in Qilin and Fuyuan.

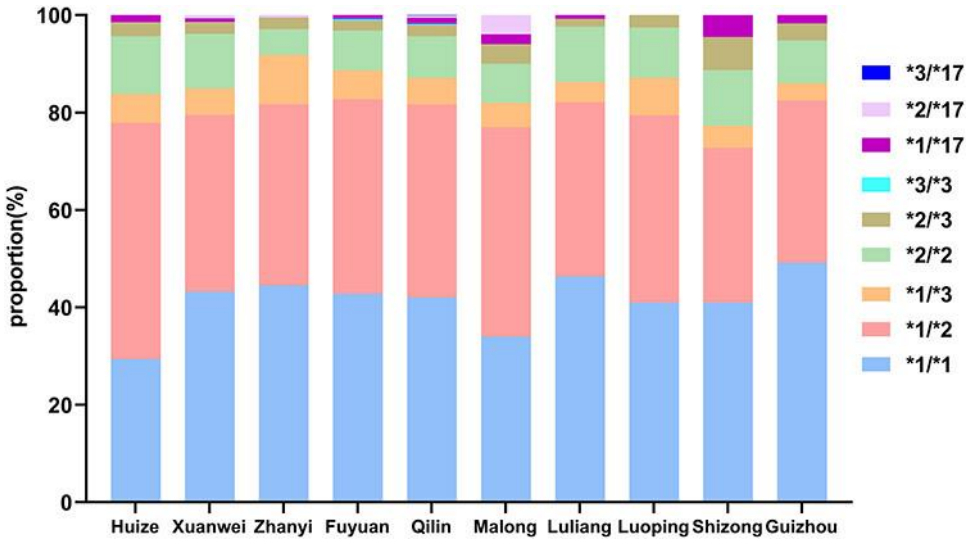

Figure 1. Geographic distribution of CYP2C19 genotype frequencies across different locations within the Yunnan-Guizhou Plateau.

In the entire study population, the observed proportions of metabolic phenotypes were as follows: rapid metabolizers (RM) at 1.03%, normal metabolizers (NM) at 42.09%, intermediate metabolizers (IM) at 45.29%, and poor metabolizers (PM) at 11.58%. No ultrarapid metabolizers (UM) were detected. **Figure 2** presents the phenotype breakdown for each area. RM was absent from both Zhanyi and Luoping. Shizong had a significantly higher PM rate compared to Zhanyi (P = 0.046, Fisher's exact test). When combined, PM and IM accounted for 56.87% of the total cohort, with Huize showing a notably higher combined prevalence of 69.12%. These findings highlight the value of region-specific pharmacogenetic testing to guide antiplatelet therapy, especially for ethnically diverse populations living on the Yunnan-Guizhou Plateau.

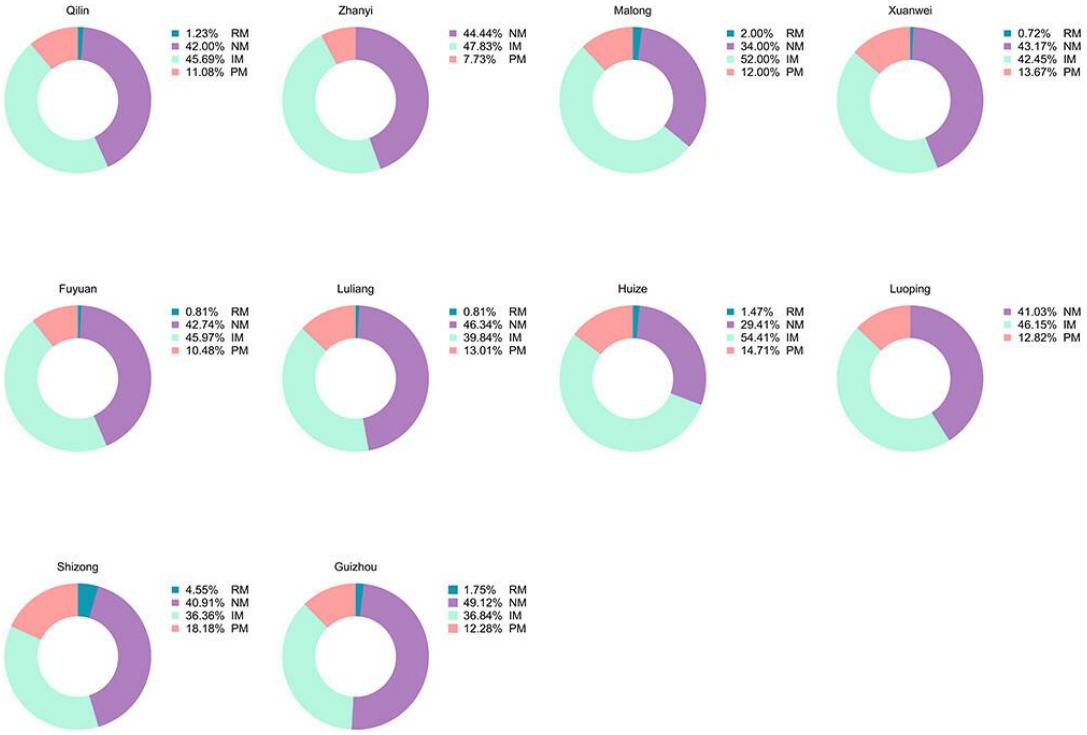

Figure 2. Comparison of metabolic phenotype patterns observed across various locations within the Yunnan-Guizhou Plateau.

Clopidogrel's therapeutic action is strongly influenced by genetic variants in CYP2C19, which modify its activation and affect bleeding risk. Such genetic variations are known to differ between ethnicities and geographic regions. Although a wealth of information exists regarding CYP2C19 alleles, genotypes, and predicted phenotypes across numerous populations worldwide, no such data are available for people living on the Yunnan-Guizhou Plateau. Consequently, the current results fill a pharmacogenomic knowledge gap in this high-altitude, ethnically diverse region and underscore the need for customized antiplatelet regimens in this distinctive environment.

We analyzed four CYP2C19 variants and uncovered nine distinct genotype combinations. **Table 2** presents the allele frequencies for each ethnic subgroup. Earlier investigations have shown that the *1 allele occurs less frequently in Asian groups than in Caucasian or African populations, with India reporting only 42%. The *2 variant is most common in Asians (11.2%–40.2%) [18–31] and least common in Caucasians (8.7%–20.5%) [32–37]. Our observed *2 frequency was significantly elevated ($P < 0.05$) relative to figures documented for African, Caucasian, and certain Asian populations (e.g., Iranian, Saudi Arabian) [38, 39]. Yet, it closely matched values from other Asian studies [18–20, 23, 24, 26–28]. The *3 allele is infrequent in Caucasians (0.04%) and Africans (0.037%), but is more common in Asians (2%–9%) [40–42]. Interestingly, our *3 rate (4.42%) was significantly lower than that reported for the low-altitude Foshan population ($P < 0.05$), suggesting that altitude influences CYP2C19 distribution patterns. Both *2 and *3 are loss-of-function variants, together representing over 90% of all deficient CYP2C19 alleles.

The *2 mutation (rs4244285, c.681G > A) is located in exon 5. It generates a cryptic splice site, leading to a reading frame shift and producing a truncated, catalytically dead protein lacking the heme-binding domain [43]. The *3 mutation (rs4986893, c.636G > A) in exon 4 introduces a stop codon at amino acid 212, also resulting in a shortened inactive protein [44]. Loss-of-function variants are strongly associated with significantly diminished clopidogrel effectiveness [45]. Our allele frequencies did not differ significantly from those observed in Chinese Han populations ($P > 0.05$).

Table 2. Comparison of CYP2C19 allele frequencies across different populations (tabular format).

Populations	Sample size	Allele frequency (%)				References
		***17**	***3**	***2**	***1**	
Chinese Foshan	1231	_	5.65*	30.46	63.89	[19]

Chinese Ningxia	1050	2.1**	4.5	31.7	63.2	[18]
Vietnamese	100	1.0	2.5	20.5*	76.0*	[25]
Chinese Hakka	2982	_	5.0	30.8	64.2	[20]
Chinese Han	831	1.0	5.0	30.0	64.0	[21]
Chinese Hui	85	2.9*	5.9	30.6	60.6	[21]
Chinese Uygur	352	13.6**	3.1	22.0**	61.2	[21]
Chinese Kazakh	69	10.9**	6.5	18.8*	63.8	[21]
Chinese Mongolian	280	_	4.0	24.0**	72.0*	[22]
Korean	271	1.5	10.1**	28.4	60.0*	[23]
Indian	87	17.9**	0	40.2*	42.0**	[29]
Japanese	265	1.3	12.8*	27.9	57.9*	[24]
Thai	1051	4.0**	6.0*	27.0	63.0	[26]
Malaysian	142	_	6.0	28.0	66.0	[27]
Burmese	127	_	4.0	30.0	66.0	[28]
Saudi Arabian	201	25.7**	_	11.2**	62.9	[31]
Iranian	180	21.6**	0	13.1**	65.3	[30]
Yunnan-Guizhou Plateau	1934	0.83	4.42	29.81	64.94	Present study
Caucasians						
Mexican Americans	346	_	0.1**	9.7**	90.2**	[32]
Italian	360	_	0	11.1**	88.9**	[33]
Colombian	189	_	0	8.7**	91.3**	[34]
Roma	500	_	0	20.5**	79.5**	[35]
Hungarian	370	_	0	12.6**	87.4**	[35]
Faroese	311	_	0	18.8**	81.8**	[36]
Belgian	121	_	0	9.1**	90.9**	[37]
Africans						
Bantu Tanzanians	251	_	0.6**	17.9**	81.5**	[38]
Venda	76	_	0	21.7	78.3*	[39]
Zimbabwean	84	_	0	13.1**	86.9**	[39]

Notes: *P < 0.05; **P < 0.01; - indicates not reported.

In contrast to the *2 and *3 variants, the *17 allele is extremely uncommon in East Asia (around 2%). In contrast, its highest frequency occurs in Central Europe [9] (33%), followed by Saudi Arabia [31] (25.7%), Africa (18.2%), and Caucasian populations (15.8%) [46]. Our cohort exhibited a *17 frequency of only 0.83%, which is even lower than that seen in other East Asian groups. The *17 variant (rs12248560, c. 806C > T), first described by Sim and colleagues in 2006, is located in the 5’ flanking promoter region and enhances transcriptional activity [47]. This mutation accelerates the metabolism of CYP2C19 substrates, leading to stronger platelet inhibition and a heightened bleeding tendency [48]. The exceptionally low *17 frequency observed here (0.83%) may reflect evolutionary adaptation to the hypoxic conditions of high altitude environments. These findings further emphasize the importance of conducting pharmacogenomic studies tailored to specific geographic regions.

CYP2C19 genetic variants substantially impact clopidogrel’s clinical effectiveness, and predicting metabolic phenotypes through genotyping is clinically useful. Our phenotype distribution was dominated by intermediate metabolizers, with rates of RM, NM, IM, and PM at 1.03%, 42.09%, 45.29%, and 11.58%, respectively—figures comparable to those reported for Chinese Han populations [21]. The proportion of RMs in our study was lower than that documented for African Americans (23.74%), Americans (13.64%), Central/South Asians (18.57%), and Europeans [11] (27.12%) according to PharmGKB data (11). Conversely, our PM rate exceeded those reported for African Americans (4.05%), Americans (1.48%), and Europeans (2.38%). The distribution of metabolic phenotypes also varied across different localities. The southern region of Shizong showed a substantially higher PM frequency than the northern region of Zhanyi, and Shizong also had the highest overall RM proportion, yet no RMs were found in Zhanyi. These differences may stem from interethnic genetic diversity and geographic

separation. Residents of Zhanyi include Han, Yi, and Hui populations with a few small ethnic settlements, whereas Shizong is home to 35 distinct ethnic minorities living together. Additional studies are required to confirm this hypothesis. Research has shown that poor metabolizers have lower levels of active clopidogrel, while ultrarapid metabolizers face increased bleeding risk. Both treatment failure and bleeding complications are serious concerns with clopidogrel. The high combined prevalence of IM and PM in this region (56.87%) strongly supports the use of genotype-guided antiplatelet strategies. In settings where CYP2C19 genotyping is not feasible, alternative therapies that do not rely on CYP2C19 metabolism should be prioritized to reduce thrombotic events.

Several limitations of this study should be acknowledged. First, due to research constraints, sample sizes from some remote areas were relatively small. Second, this investigation primarily characterized CYP2C19 polymorphisms on the Yunnan-Guizhou Plateau and did not assess clinical outcomes in relation to phenotype. Finally, larger-scale studies are needed to further explore CYP2C19 variation across different ethnic groups.

Conclusion

In conclusion, this study examined the allele frequency patterns of CYP2C19 among cardiovascular disease patients from the Yunnan-Guizhou Plateau using a large sample of 1,934 individuals, providing the first detailed pharmacogenomic characterization of this high-altitude, multi-ethnic population. Considerable geographic variation in CYP2C19 allele, genotype, and phenotype distributions was observed across different areas of the plateau. The overall allele and phenotype frequencies were similar to those found in Chinese Han populations. These findings provide a scientific foundation for selecting appropriate therapeutic approaches to reduce the risk of adverse cardiovascular events.

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Conflict of Interest: None

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Ethics Statement: None

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