https://doi.org/10.33472/AFJBS.6.1.2024. 204-216

African Journal of Biological Sciences

Frequency Of *CYP2C19*2* AND **17* Alleles In Patients With Cardiovascular Disease: A Cross Sectional Study From South India

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Article History
Volume 6, Issue 1, Jan 2024
Received: 20 Dec 2023
Accepted: 22 Jan 2024
Doi:10.33472/AFJBS.6.1.2024.204 216

Abstract

Introduction: *CYP2C19* is the principal enzyme involved in the hepatic metabolism of many therapeutically significant drugs. *CYP2C19*2* and *CYP2C19*17* are the most common alleles in the South Indian population.

Aim & objective: The purpose of the study is to determine the frequency of the **2* and **17* alleles in cardiovascular disease patients among the South Indian population.

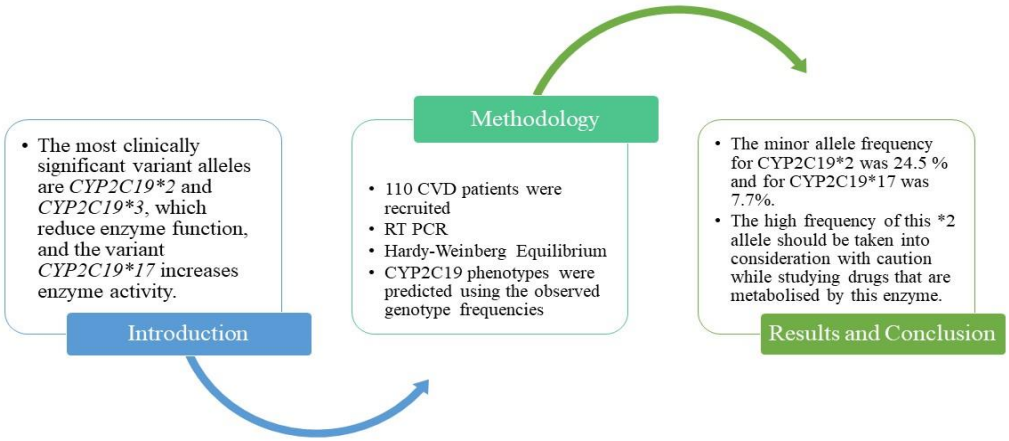
Methods: A cross-sectional study was conducted with 110 cardiovascular disease patients who were unrelated to each another. DNA was extracted from blood cells and subjected to Real Time-Polymerase Chain Reaction analysis. By comparing the observed and expected genotype frequencies in the study population, the Hardy-Weinberg equilibrium was computed and calculated Chi square and *P* value.

Results: It was found that the minor allele frequency for *CYP2C19*2* and *CYP2C19*17* were 0.24 and 0.07, respectively. In the South Indian population, the prevalence of the **1/*1* genotype was 0.59, **1/*2* was 0.33, and for **2/*2* was 0.08 for *CYP2C19*2*, whereas **1/*1* genotype was 0.85, **1/*17* was 0.13, and **17/*17* were 0.009 for *CYP2C19*17*. *CYP2C19* phenotypes were predicted using the observed genotype frequencies.

Conclusion: The results imply that genetically determined *CYP2C19* phenotypes should be taken into account to reduce individual risk and enhance the therapeutic benefits for the patients.

Keywords: *CYP2C19*, Polymorphism, Genotype, Phenotype, Kerala

Graphical Abstract



Introduction

Cytochrome P450 2C19 (*CYP2C19*) is reported to have the highest polymorphisms among the *CYP2C* gene [1]. *CYP2C19* is involved in the Phase I metabolism of several significant medication categories, namely proton pump inhibitors, antidepressants, cardiovascular medicines, majority of antiepileptics, and antimalarials [2]. The *CYP2C19* gene on chromosome 10 encodes the clinically significant drug-metabolizing enzyme CYP2C19, which is a key enzyme for the metabolism of around 5% of clinically utilised medicines [3]. The most clinically significant variant alleles are *CYP2C19*2* (*rs4244285, c.681G > A*) and *CYP2C19*3* (*rs4986893*), which reduce enzyme function, and the variant *CYP2C19*17* (*rs12248560, c.-806C > T*), increases gene activity [4]. Patients are classified as poor metabolizers (**2* and **3* alleles), normal metabolizers (**1*), and ultrarapid metabolizers (**17*) based on the genetic coding and metabolic status. Studies have shown that *CYP2C19*2* variations are more common in the Asian population (32.5%) and are particularly prevalent more in the South Indian population (40.2%) [5]. The most prevalent CYP2C19 deficiency in all populations is caused by the allele, *CYP2C19*2*, which results from a guanine (G) to adenine (A) replacement at position 681 in exon 5 (*rs4244285*) [6]. Similarly, a particular nuclear protein binds to the 5′-flanking regions as a result of the single nucleotide polymorphism *CYP2C19*17*, which has an *806 C>T* base pair. Increased gene transcription and elevated enzyme activity are the outcomes of this binding [7]. As a result, the activity of CYP2C19 changes according to the presence or absence of specific mutations in its gene, which also differs in its distribution among various ethnic groups [8].

Kerala, a state in southern India, is at the forefront of the country's noncommunicable illness epidemic, especially cardiovascular disease (CVD) [8]. Acute coronary syndrome (ACS), a potentially fatal disease that comprises myocardial infarction (MI) with or without ST-segment elevation (STEMI/NSTEMI), is a common CVD consequence. The patients' pathophysiology is heavily influenced by increased platelet aggregation and subsequent thrombus development. The significant morbidity and mortality of this condition must therefore be decreased through safe and efficient antiplatelet treatment [9].

Clopidogrel, a P2Y12 adenosine diphosphate receptor antagonist and a prodrug which upon metabolism gets converted to its active form i.e., active thiol metabolite has been widely and successfully been utilised in patients with ACS, laying the groundwork for the use of dual antiplatelet treatment (DAPT) as the mainstay of current management of patients with ACS [10]. For the patients

receiving antiplatelet therapy, aspirin accounted for 46.03%, clopidogrel for 41.4%, aspirin and clopidogrel combined therapy for 6.01%, ticagrelor for 4.04%, and prasugrel for 1.02% [11]. The main enzyme responsible for converting clopidogrel prodrug into its active metabolite is CYP2C19. Age, gender, body weight, epigenetics, smoking, concomitant conditions, medications, genetic variation, and other factors all affect how the body reacts to clopidogrel. Genetic variations are the key contributor to all these factors that alter clopidogrel responsiveness. Numerous genetic variables, notably *CYP2C19*, have an impact on the pharmacokinetics and pharmacodynamics of clopidogrel [5]. With this regard, through this study we are attempting to determine the frequency of **2* and **17* alleles in cardiovascular disease patients among the South Indian Kerala population.

Materials and Methods

Study subjects

The study was conducted at Jubilee Mission Medical College & Research Institute, a tertiary care hospital situated at southern part of India. The research involved 110 adult patients with cardiovascular disease, both male and female, above 18 years of age, and who were enrolled in the inpatient cardiology department of the hospital. The inclusion criteria included the ancestry of the subjects, which was verified through interviews, and those who had lived in South India for at least three generations and spoke any of the south Indian language as their native language. Prior to the start of the study, Institutional Ethics Committee approval (IEC Study Ref.No.: 14/22/IEC/JMMC&RI) was obtained from the hospital, and all subjects were given the opportunity to ask any questions, before giving their consent for the study. The informed consent was provided by each participant in the study. The collection and analysis of blood samples, as well as the processing of the associated clinical and personal data, adhered to the guidelines and regulations outlined in the Helsinki Declaration of 1975 and the current national regulations in effect. The informed consent was provided by each participant in the study. Prior to the study, all patients were provided with a clear explanation of the study's objectives and the experimental procedures. Informed consent was obtained from all study subjects. All patients explicitly provided consent for genotyping and the collection of relevant clinical data.

Genotyping

5 ml of venous blood was drawn in EDTA tubes from all the subjects under sterile conditions. The *CYP2C19*2* (rs4244285) and *CYP2C19*17* (rs12248560) single nucleotide polymorphisms was targeted for genotyping by Real Time Polymerase chain reaction (RT-PCR). Genomic DNA was isolated using the phenol-chloroform extraction technique. RT-PCR using the Eurofins kit for human CYP2C19*1, *2 and *17 was used to determine *CYP2C19 *1, *2*, and **17* polymorphisms. Probes were designed, targeting the *CYP2C19*2* - rs4244285 and *CYP2C19*17* -rs12248560 region of the human genome sequence. The target-hybridising oligonucleotides (THOs) were synthesised with a FAM, HEX label at the 5′ end. The nucleotide sequence for mutation A (Allele-G>A) specific gene *(CYP2C19*2*-rs4244285) was labelled with probe FAM is 5'-*AATTTTCCCACTATCATTGATTATTTCCCA*-3'. The nucleotide sequence for another mutation T (Allele-C>T) specific gene (CYP2C19*17-rs12248560) was labelled with probe HEX is 5'-*TTTCAAATTTGTGTCTTCTGTTCTCAAAGT*-3'. Forward and reverse primers were designed to the upstream and downstream of the probe binding region. The nucleotide sequences for forward and reverse primer of different region of CYP gene as follows: *CYP2C19*2*-rs4244285 Forward primer: 5'-*CAACCAGAGCTTGGCATATTG*-3' and Reverse primer: 5'-*CCATCGATTCTTGGTGTTCTTT*-3'; CYP2C19*17 - rs12248560 Forward primer: 5'-*ATGAACAGGATGAATGTGGTAT*-3' and Reverse primer: 5'- *GGCGCATTATCTCTTACATCAG*-3' respectively. The PCR was performed according to the

manufacturer's instructions. Each PCR was carried out in a volume of 20 µL consist of two equal amounts of mix: 10 µl of premix Ex Taq (2X) (Probe qPCR) (Takara Bio Inc) and 0.4 µl of primer, 0.8 µl of probe mix and 1 µl of genomic DNA template was added. Reaction amplification was performed using Gentier real-time PCR 48E system-IanlongR. The reaction condition was: pre incubation at 950C for 30 sec and two step amplification consists 40 cycles of 950C for 5 sec and 600C for 30 sec. Fluorescence emission measurements were recorded during the read steps at 600C.

The *CYP2C19* genotypes enzymatic activity was divided into four groups based on the combination of genotyping for *CYP2C19* polymorphisms in exons 5 and 4. Loss-of-function allele carriers are individuals with at least one *CYP2C19*2* allele variant. Poor metabolizers (PMs) were defined as those with at least two *CYP2C19*2* allele variations (**2/*2*). Patients were categorised as intermediate metabolizers (IMs) if they had one *CYP2C19* allele variant (**1/*2*) or one *CYP2C19* allele variation (**2/*17*) with one (**2*) allele variant. Normal metabolizers (NMs) are patients who do not carry the **2* or **17* allele variation. Ultra-rapid metabolizers (UMs) were defined as those who have at least one **17* allele variant (**1/*17* or **17/*17*) [12].

Statistical analysis

Quantitative variables were expressed as mean and standard deviation (SD). Categorical variables were expressed in frequency distribution. The Hardy-Weinberg equilibrium of the study population's genotype frequencies was calculated by comparing the observed and expected frequencies. Statistical analysis was performed using the Graphpad Instat statistical software (GraphPad Software Inc., San Diego, CA, USA).

Results

The percentage of male and female patients among the 110 total was 56.36% and 43.63%, respectively. The age of the patients in this study ranged from 35-91 years with a mean of 64.91 ± 11.19 years. The patients' body weight ranged from 43-86 kg with a mean of 65.01 ± 07.57 kg. By using the height and weight, Body Mass Index (BMI) was calculated which ranged from 17.8-31.6 with a mean value of 24.99±2.38. Out of 110 patients, 3.63% (n= 4) were under weight, 46.36% (n= 51) were in ideal weight range, 44.54% (n= 49) were overweight, and 11.11% (n=6) were in moderate health risk (obese). The allele frequencies of the CYP2C19*2 and *17 genotypes were found to be in Hardy-Weinberg equilibrium in this population. Fig. 1 and 2 show the calculated observed and expected frequencies. In the study population (n = 110) the frequency of the *CYP2C19*2* allele was found to be 0.24. Of the 110 participants, 9 (0.08) were homozygous for the CYP2C19*2 allele, 65 (0.59) were normal genotype, and 36 (0.32) were heterozygous for both alleles. Regarding allele **17*, out of 110 patients, 0.07 had this allele frequency. In the study population, there were two individuals with **2/*17* polymorphism, 15 (0.13) patients with heterozygous polymorphism (**1/*17*), and one patient with homozygous polymorphism (**17/*17*) and the table 1 summarizes the results for this alleles and genotype frequency. The allele and genotype distribution showed no deviation from Hardy-Weinberg's equilibrium: (*2: $\chi 2$ = 0.55, p= 0.76; *17: $\chi 2$ =1.04, p=0.59). Based on the *CYP2C19* genotype, the metabolic groups were classified into 4 groups: normal metabolizers (n= 51), intermediate metabolizers (n= 36), poor metabolizers (n= 9) and ultra rapid metabolizers (n= 14) which is presented in fig. 3. *CYP2C19* phenotypes were predicted using the observed genotype frequencies. The genotype and allele frequencies of CYP2C19 in a South Indian population were compared to other populations, and are shown in Tables 2, 3, and 4.

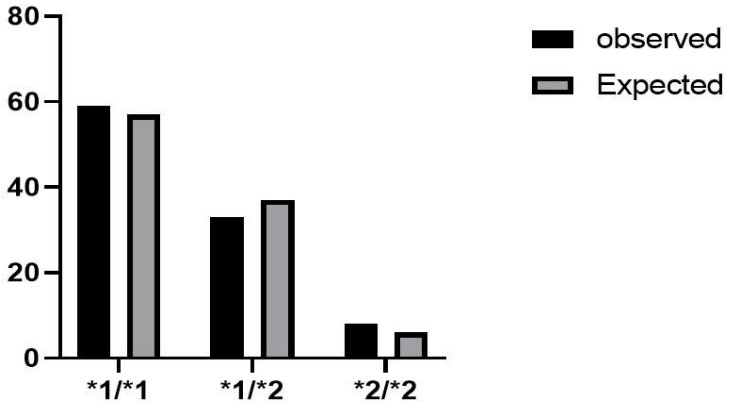


Fig 1. The observed and expected frequencies of *CYP2C19*2* genotype

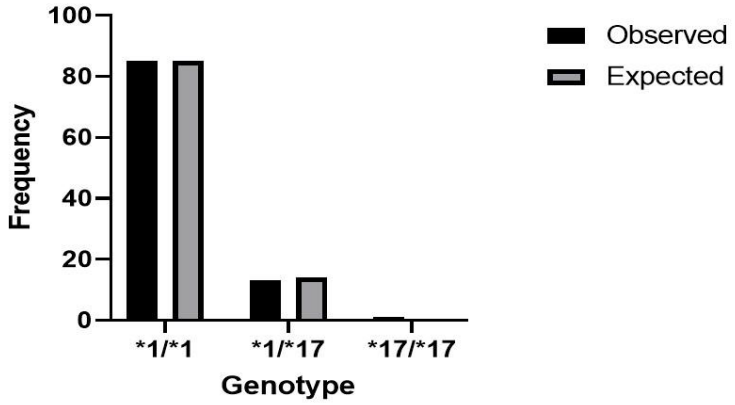


Fig 2. The observed and expected frequencies of *CYP2C19*17* genotype

Table 1. *CYP2C19*2* and **17* allele and genotype frequency

CYP2C19	N	Frequency
	*CYP2C19*2*	
Allele		
**1*	220	0.75
**2*	220	0.24
Genotype		
**1/*1*	110	0.59
**1/*2*	110	0.33
**2/*2*	110	0.08
	*CYP2C19*17*	

Fig 1. The observed and expected frequencies of *CYP2C19*2* genotype

Allele		
**1*	220	0.92
**17*	220	0.07
Genotype		
**1/*1*	110	0.85
**1/*17*	110	0.13
**17/*17*	110	0.009
**2/*17*	110	0.018

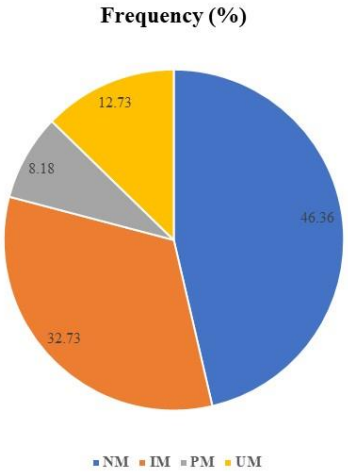


Fig 3. Predicted Phenotype frequency

Table 2. The genotype and allele frequencies of *CYP2C19*2* in a Kerala population compared with other populations

Population and Year	No. of subjects	Genotype Frequency			Allele frequency		Reference
		*1/*1	*1/*2	*2/*2	*1	*2	
Kerala 2022	110	59	33	8.8	0.75	0.245	Present study
Thai 2021	1205	54.11	40.58	5.31	74.39	25.6	[13]
Pakistan 2021	405	75.80	18.27	5.92	84.93	15.06	[14]
Colombia 2021	239	61.5	8.8	0.8	NR	NR	[15]
Indonesia 2021	166	46.4	39.2	14.5	65.96	34.03	[16]
Han patients, China 2020	602	46.5	42.2	11.3	67.6	32.4	[17]
Uygur, China, 2020	527	64.1	30.4	5.5	79.3	20.7	[17]
Iranian 2018	1229	63.6	30.1	6.3	49.8	21.4	[18]

Hakka Population,China 2017	6686	41.73	39.65	9.57	64.33	31.06	[19]
Northern Siberia 2017	87	72.4	25.3	2.3	NR	14.9	[20]
Central Siberia 2017	222	77.9	22.1	0	NR	11.5	[20]
Eastern Siberia 2017	122	79.5	19.7	1	NR	10.6	[20]
Moscow region 2017	81	84	16	0	NR	8	[20]
Malaysia 2016	62	66.1	9.7	NR	80.7	5.7	[21]
Tibetan 2015	96	56.25	30.21	NR	50	15.10	[22]
Palestinian 2014	100	81	19	0	NR	9.5	[23]
Turkish 2014	100	73	27	0	NR	13.5	[23]
Thai 2013	1051	40.72	35.10	7.32	63	27	[24]
Roma 2012	500	63.6	31.8	4.6	79.5	20.5	[2]
Hungaria 2012	370	75.9	23.0	1.1	87.4	12.6	[2]
Mestizos 2012	145	87.6	11	1.4	93.1	6.9	[25]
Tarahumaras 2012	84	48.8	40.5	10.7	69	31	[25]
Pure´pechas 2012	101	89.1	10.9	NR	94.6	5.4	[25]
Tojolabales 2012	68	93.3	6.6	NR	96.3	3.6	[25]
Tzotziles 2012	88	88.6	11.3	NR	94.3	5.6	[25]
Chinese Han 2012	214	43.5	30.4	11.2	70.3	29.7	[26]
Chinese Hui 2012	108	39.8	26.9	13.9	67.6	32.4	[26]
Chinese Mongolian 2012	129	51.9	21.7	6.2	81.8	18.2	[26]
Egypt 2012	120	93	6	0.8	96.3	3.80	[27]
Belgian 2003	121	83.5	14.9	1.6	90.9	9.1	[28]
Beninese 2003	111	73.9	26.1	NR	87	13	[28]
Egypt 2001	247	78.56	20.24	0.80	88.8	11	[29]

NA: Not available, NR; Not reported

Table 3. The genotype and allele frequencies of *CYP2C19* 17* in a Kerala population compared with other populations.

Population and Year	Number of subjects	Genotype frequency				Allele frequency		Reference
		*1/*1	*1/*17	*17/*17	*2/*17	*1	*17	
Kerala 2023	110	85.4	13.6	0.90	1.81	92.2	7.7	Present study
Thai 2021	1205	96.43	2.16	NA	1.41	NR	1.8	[13]
Colombia 2021	239	NR	9.2	12.9	6.7	NR	NR	[15]
Han patients, China 2020	602	96.2	3.8	NA	NR	98.1	1.9	[17]
Uygur, China, 2020	527	77.2	20.3	2.5	NR	87.4	12.6	[17]
Iranian 2018	1229	54.24	37.64	8.12	NR	NR	27.1	[18]
Northern Siberia 2017	87	50.6	32.2	17.2	NR	NR	33.3	[20]
Central Siberia 2017	222	68.9	27.9	3.2	NR	NR	17.1	[20]
Eastern Siberia 2017	122	59.8	35.2	4.9	NR	NR	22.2	[20]
Moscow region 2017	81	70.4	28.4	1.2	NR	NR	15.4	[20]
Malaysia, 2016	62	66.1	9.7	NR	NR	80.7	4.8	[21]
Tibetan 2015	96	NR	3.13	NR	NR	NR	1.56	[22]
Thai 2013	1051	NR	4.30	NA	NA	63	4	[24]

NA: Not available, NR; Not reported

Table 4. The allele frequencies of *CYP2C19*2* and **17* in a Kerala population compared with other Indian population

Indian Ethnicity	No. of subjects	Allele frequency			Reference
		**1*	**2*	**17*	
Kerala population	110	0.69	0.24	0.07	Present study
India	20	0.63	0.31		[30]
Indians (Pan India)	2000	NR	32.0	13.95	[31]
Tamil Nadu	206	NR	NA	19.2	[32]
North India	110	23.64	47.23	35.45	[33]
Maharashtra	139	57.1	41.7	NA	[34]
Shimoga, Karnataka	48	80	NA	20	[35]
Tamil Nadu	112	0.598	0.379	NA	[36]

Andhra Pradesh	230	0.67	0.33	NA	[37]
Karnataka	216	0.60	0.39	NA	[37]

NA: Not available, NR; Not reported

Discussion

This study describes the *CYP2C19* genotype and phenotype of Cardiovascular patients in the Kerala population. To ascertain the distribution of *CYP2C19* polymorphisms in this study population, 110 individuals were genotyped for clinically significant allele variants of *CYP2C19*2*, splicing defect *G681A*, and *CYP2C19*17*, *C806T*. To the best of our knowledge, this is the first study to show the prevalence of the *CYP2C19*17* allelic variant in cardiovascular patients in Kerala. According to the current study, up to 25% **2* allele is present in this population, which is almost similar with findings from a prior study of this community conducted by Jose et al., and according to their study previously conducted among Kerala population showed 31% **2* allele was present [37]. Similar to the previously reported study, this population has an 8% frequency of the **2/*2* genotype [37]. The south east Asian country Thailand populations almost exactly match the current study's **2* allele frequency [13]. Romani people (20.8%) were found to have a high prevalence of *CYP2C19*2*, which contrasted sharply with the host Hungarian community (13.3%) and the allele frequency of the Romani people *2 was nearly identical to that of this study population [2]. The Roma minority is a North-West Indian ethnic group that is relatively homogeneous due to a number of population bottlenecks, several founder events, and infrequent interethnic marriages. Due to this complicated population history, *CYP2C19*2* frequencies in Roma people were comparable to those found in North Indian populations [38]. China (32.4%) and Indonesia (34.3%) are Southeast Asian nations with greater **2* allele frequencies than Malaysia, whose population has only 5.7% of this allele frequency [16,17,21]. It has been discovered that the frequency of the **17* allele is almost 13%, which is almost identical to the population in China [19]. Coming to the Indian population, two thousand healthy individuals participated in a pan-Indian study that found the frequency of the **17* allele to be around 14%, which is almost identical to the findings of this study [31]. North Indian subjects have significantly higher frequencies of the **17* allele than the south Indian population [33]. The prevalence of the *CYP2C19*17* enhanced activity allele was lowest in Mediterranean-South Europeans (11-24%) and highest in Central Europe (25-33%) populations [38]. According to our study, 8.18% (poor metabolizers) of participants are not properly metabolising their clopidogrel treatment, and about 33% (intermediate metabolizers) of them were partially responding to the medication. The principal drug metabolising enzyme for several substances, including the antiplatelet medication clopidogrel, is *CYP2C19*. As a result, the drug may not be adequately metabolised by the dysfunctional enzyme [5]. According to clinical research, the pharmacodynamic response to clopidogrel varies, with 20% to 30% of patients being categorised as poor responders, non-responders, or clopidogrel resistant [39]. As a result of the Indian population's prevalence of this **2* allele, which ranges from 29.7-41.7%, and it indicates that dosage optimisation is required for medications that are metabolizing by this enzyme. According to the study's findings, about 25% of Keralite people carry the **2* allele. The relationship between this gene's polymorphism and clopidogrel activity in this population has to be determined through additional research. This study did not examine the influence of the *CYP2C19* genetic polymorphism on the effects of drugs like clopidogrel; it just measured the frequency of this polymorphism. The clopidogrel impact and gene polymorphism in this population must thus be discovered through additional research.

Conclusion

The main drug metabolising enzyme for many medications is *CYP2C19*. Therefore, genetic variation will have an impact on both enzyme activity and drug metabolism. This study indicated that the prevalence of the *CYP2C19*2* and **17* polymorphisms among Kerala cardio vascular patients is approximately 25% and 7.7%, respectively. For drugs that are metabolised by this enzyme, the high frequency of this **2* allele should be taken into consideration with caution.

Acknowledgment

The Indian Council of Medical Research (ICMR), Department of Pharmacy Practice, JSS College of Pharmacy, Ooty and Department of Cardiology, Jubilee Mission Medical College and Research Institute are acknowledged by the authors for providing a variety of materials for the current research work.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest

All authors have none to declare.

Funding source

This research study was not financially supported directly by any funding agency. However, the first author is the recipient of 'Senior Research Fellowship (2019-5791/CMB-BMS)' from Indian Council for Medical Research (ICMR), New Delhi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Contribution of Authors

Aswathy and KP Arun proposed and designed the study, developed a study title and conducted the study. Govindan Unni and Maria Jose monitored the patient recruitment and sample collection. All the authors contributed to the manuscript drafting, review of the article and the final approval of the manuscript.

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