ORIGINAL ARTICLE

THE ROLE OF INTEGRIN BETA 3 POLYMORPHISMS IN CORONARY ARTERY DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objectives: The literature on the role of integrin beta 3 (ITGB3) exonic variants in coronary artery disease (CAD) and lipid outcomes is scarce. However, the findings remained uncertain and still not clear. Therefore, the current study aims to determine the association of rs5918 polymorphism with coronary artery disease.

Methodology: All the eligible literature published in the English language from February 3, 2005, up to December 19, 2021, were searched by using different electronic databases and extracted all the required information from the available literature. The statistical analysis was performed through the MetaGenyo program, and pooled odds ratios (ORs) were calculated to determine the association between rs5918 and CAD.

Results: The final analysis includes four studies, and the overall rs5918 risk allele in all the tested genetic models as follow: allelic model: OR 0.80 CI 0.41-1.58; homozygote model: OR 1.66, 95% CI 0.20-2.16; recessive model: OR 0.71 CI 0.44-1.14; dominant model: OR 0.81 CI 0.22-3.03. In addition, the lipid outcomes, including lipoproteins, cholesterol, and triglycerides were associated with increased disease risk. The shapes of the funnel plots suggest no publication bias in our study.

Conclusion: In conclusion, our final pooled analysis revealed a non-significant role of this exonic polymorphism in coronary artery disease that may exert its effect by modulating various lipid parameters. However, more studies are required with a larger cohort size that may give us conclusive results in the future.

Keywords: Polymorphism, integrin beta 3, meta-analysis, coronary artery disease, ITGB3

Citation: Ashiq S, Ashiq K, Sabar MF. The Role of Integrin Beta 3 Polymorphisms in Coronary Artery Disease: A Systematic Review and Meta-analysis. Pak Heart J. 2023;56(01):66-71. DOI: https://doi.org/10.47144/phj.v56i1.2362

INTRODUCTION

Cardiovascular diseases (CVDs) are mainly responsible for patients' morbidity, mortality, and hospitalization.[1] Vascular disorders include a spectrum of disorders but coronary artery disease (CAD) is the most common. Coronary artery disease is responsible for hypoxia and cardiac tissue injury mainly caused by coronary vessel stenosis due to atherosclerosis.[2] Clinical manifestations of CAD include both acute and chronic conditions.[3] Based on the extent of coronary artery stenosis, clinical symptoms, and the level of myocardial injury it can be further classified into 3 categories first is the myocardial infarction, second is stable coronary artery disease and third is unstable angina.[4] A report from the World Health Organization (WHO) suggested that CVDs are responsible for 31% of mortality in the world while it is the most prevalent disease in developing countries. In Pakistan, every 1 individual out of 4 suffered from this fatal disease hence responsible for the huge burden to healthcare systems in South Asian countries.[5]

CAD is a complex and multifactorial disorder that involves the complex interaction between environmental and genetic factors.[6] Lifestyle, gender, ethnicity, or demographic processes contributed to genetic differences in the CAD risk among populations in the world. Other risk factors include smoking, hypertension, stress, diabetes, and hyperlipidemia.[7] The interplay between various factors such as hypercholesterolemia, smoking, obesity, hypertension, and inflammation plays a crucial role in the formation of atherosclerotic plaque, coronary vessels stenosis, and ischemic heart.[8] Genome-Wide Association Studies (GWAS) meta-analyses, further help in the better understanding of CAD genetics.[9] The *ITGB3* (integrin beta 3) gene that is alternatively also known as antigen CD61 or platelet glycoprotein IIIa is located on chromosome 17q21.32 and is comprised of 2367 nucleotides. This gene plays a vital function in the regulation of platelet adhesion and aggregation at the site of injury as it encodes glycoprotein IIIa receptors on the surface of platelets. To date, many single nucleotide polymorphisms (SNPs) have been reported in this gene.[10] We selected

one of the most common SNP i.e. rs5918 and its role in CAD is first reported by Marian et al.[11] This polymorphism results in the substitution of amino acid leucine (PlA1) for proline (PlA2) due to a single nucleotide change C→T in the exon number 2.[5] The mutant allele can alter the structure or thickness of atherosclerotic plaque in addition to high lipid total core volume.[12] Being a critical element of the coagulation mechanism this altered A2 allele of platelet specific alloantigen can play a crucial role in various diseases such as heart diseases, venous thromboembolism (VTE), resistance to aspirin treatment, and stroke.[13]

The purpose of the present study was to determine the role of rs5198 ITGB3 variant in coronary artery disease. The association of rs5918 in *ITGB3* with coronary artery disease susceptibility varied among different populations, including the Caucasians[14] and the Asian region.[5] Hence it is needed to analyze all the available reported literature that can provide us more definitive conclusions.

METHODOLOGY

This study is conducted according to the 2009 guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009) and registered with the database (PROSPERO registration number CRD42021268545). The PRISMA checklist is also provided as a supplementary file.

The original published studies were retrieved from various databases including Web of Science (WOS), Cochrane Library, EMBASE, PubMed, MEDLINE, and the Ovid (from February 3, 2005, up to December 19, 2021) using the following keywords and MeSH terms: including '*ITGB3*', 'integrin beta-3', 'coronary artery disease', 'coronary heart disease', 'CAD', 'single nucleotide polymorphisms', 'SNPs', 'gene polymorphism', 'genotype', 'variant', 'worldwide' and 'atherosclerosis'. We have searched the relevant articles manually to exclude the duplicate studies and avoid missing any potential relevant original study.

The articles selection were based on the following inclusion and exclusion criteria 1) The research articles on the role of coronary artery disease and *ITGB3* rs5918 polymorphism published in the English language 2) Comparative studies using either a population-based (PB) or hospital-based (HB) design 3) Adequate data was given for the calculation of odds ratio (OR). The systematic reviews, meta-analyses, or studies not designed as case-control studies were excluded from the final analysis.

The authors used predesigned tables for the data extraction. All the authors independently extracted and reviewed all the eligible studies. The following information was abstracted from each original study: publication year, author names, country, ethnicity, baseline characteristics, genotyping procedure, population sample size, allele frequency, and genotype distribution and evidence of the Hardy-Weinberg equilibrium (HWE). The outcomes of lipid were also assessed from each included study. Table 1 and 2 describes the characteristics of each included article.

The Newcastle-Ottawa Scale (NOS) ranges from zero to nine was used for the quality evaluation of each included article. We independently evaluated the quality of studies, and to attain consensus disagreements were resolved through discussion.

The relationship between rs5918 in *ITGB3* and coronary artery disease was evaluated by calculating the pooled odds ratio and 95% confidence interval (CI). The I^2 statistic and chi-squared test were used to assess the heterogeneity among included original studies. A random-effect model was used to examine the variation. The homozygote, allelic, dominant, and recessive models were used for rs5918. A sensitivity test was conducted to ensure the stability of the final analysis. The Begg's and Egger's tests and funnel plots were used to evaluate the publication bias in this current study. The MetaGenyo tool was used for the statistical analysis.

RESULTS

Through comprehensive article searching, 210 studies were identified for initial analysis, and after removing the duplicate reports, 195 studies further proceeded for screening. In the final pooled analysis, a total of 04 eligible full-text published articles were selected according to the inclusion criteria. The detailed study screening flow diagram showed in Figure 1. Among these four studies, two studies were from the Asian population, whereas the other 2 studies involved Caucasians. Of all the 04 studies, the controls of one study were from the general population, while other studies' control subjects were hospital-based. The NOS score of included studies ranged from 7-8. Table 1 describes the baseline characteristics of included studies.5, 11, 14-15 The included studies were according to the HWE of genotype distributions. Table 2 explains the allele frequencies, genotype distributions, and outcome of lipid profiles.

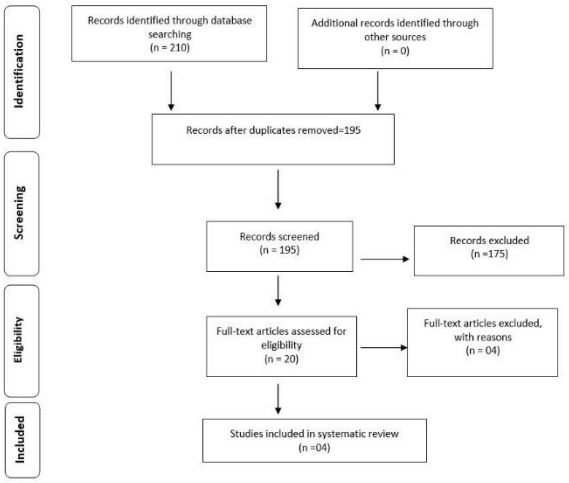

Figure 1: Study selection procedure

Role of rs5918 polymorphism in disease: The final pooled analysis suggests the non-significant role of rs5918 polymorphism in ITGB3 in coronary artery disease. The random-effects model was used to combine all genotypic data. Overall, the rs5918 risk allele distribution in all tested genetic models as shown in Figure 2.

Overall, the calculated odds ratio did not vary significantly after excluding each study. Thus, it further confirmed that the results of this meta-analysis were statistically reliable.

The funnel plots shapes show symmetry in all the genetic models for rs5918 as shown in Figure 3. Moreover, no statistically significant effect of the literature bias was suggested by the Eggers test. The p-value were non-significant including homozygote model: 0.63 allelic model: 0.32 dominant model: 0.49 and recessive model: 0.12.

Table 1: Final parameters extracted from the literature

Serial no.	Author	Year	Genotype distribution						Allele Frequencies				Outcomes of Lipid [p-value]
			Cases			Controls			Cases		Controls		
			CC	CT	TT	CC	CT	TT	C	T	C	T	
1	Khatami et al	2016	14	30	88	3	18	101	58	206	24	220	Total cholesterol:0.001 Low density lipoprotein:0.145 High density lipoprotein:0.456 Triglycerides: 0.014
2	Shabana et al.	2018	190	171	43	129	64	26	----	----	----	----	Total cholesterol:9.5 × 10−14 Triglycerides: 3.9 × 10−5 Low density lipoprotein:1.14 × 10−21 High density lipoprotein:1.56 × 10−65
3	Grinshtein et al.	2018	2	31	58	5	54	115	35	147	58	284	----
4	Conkbayir et al	2021	----	----	----	----	----	----	High p:0.001	----	----	----	Total cholesterol:0.0006 High density lipoprotein:0.016

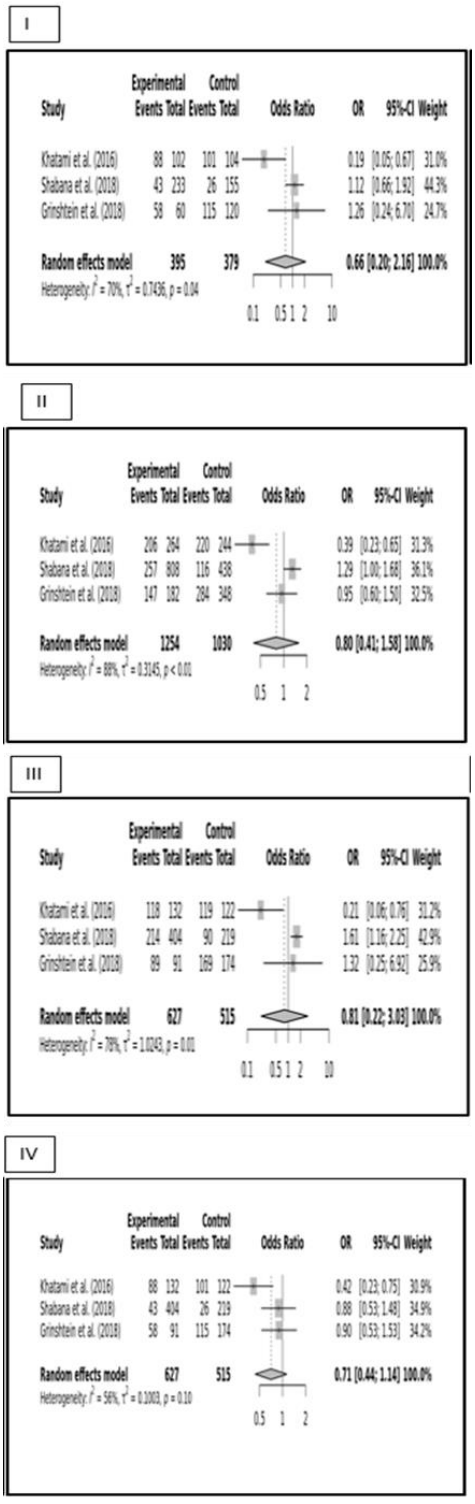

Figure 2: Analysis for rs5918 as shown by I, II, III, and IV for the homozygote, allelic, dominant, and recessive models respectively

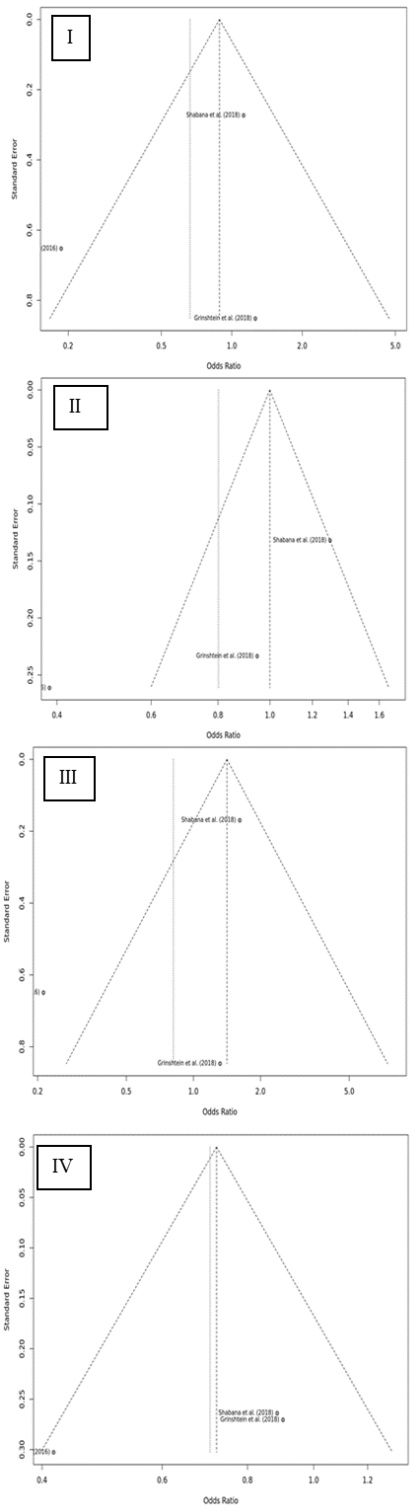

Figure 3: Analysis for rs5918 association with disease I, II, III and IV showing the funnel plots for homozygote, allelic, dominant and recessive models respectively

DISCUSSION

To the best of our knowledge, this was the first comprehensive meta-analysis on the role of rs5918 polymorphism in coronary artery disease. Furthermore, we also studied lipid outcomes as this SNP may exert its effect through modulating lipid parameters such as triglycerides, cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). One of the most studied single nucleotide polymorphisms in the *ITGB3* gene is PIA1/A2. This nucleotide change may result in conformational changes in the fibrinogen binding domain and may affect the coagulation mechanism.[5] Moreover, this SNP may be associated with abnormal lipid outcomes in coronary artery disease patients.[15]

In this study, we selected one of the most studied exonic polymorphisms of the *ITGB3* gene. Our pooled analysis showed a non-significant association between rs5918 in coronary artery disease that may be associated with poor lipid outcomes. The findings of our study indicated a potential association of coronary artery disease with lipid profile including HDL, low-density lipoprotein, triglycerides, and total cholesterol. We found no publication bias in this meta-analysis.

The findings of this meta-analysis were in contrast to the previous study results as reported by Mikkelsson et al.[16] while a weak association of this polymorphism was found in Caucasians.[17] The Framingham heart study results also suggested the significant role of this polymorphism in altered platelet aggregation and high fibrinogen levels.[18] Similarly, results from the Chinese population reported the significant association.[19] While a study report from the Asian population suggests no significant association of this polymorphism with coronary artery diseases.[20] Papp et al. study results suggest that the PIA2 allele is significantly associated with disease risk and aspirin resistance.[21] Conkbayir et al. also suggested the significant association of risk allele with CAD and different lipid outcomes, including high-density lipoprotein cholesterol and total cholesterol.[15] However, information for the relationship between genotypes of rs5918 and various lipid parameters is scarce. Hence, in the future, it is required to conduct studies to determine the effect of genotypes on lipid outcomes in coronary artery disease patients.

We also performed analysis to determine the false-positive results due to publication biases[22] we did the Begg and Egger test, and analysis suggested no publication bias in our meta-analysis. From this study findings, we confirmed that altered lipid outcomes have a potential role in high susceptibility to coronary artery disease.

To the best of our knowledge, the current report is the first comprehensive meta-analysis, however, some limitations exist in this study are:

- First, there is insufficient literature available for this exonic SNP, and we did not include other polymorphisms.
- Second, lack of information about other extrinsic factors, including lipid parameters.
- Third, our study is limited to the English language literature search that may influence results due to publication biasness, although our final analysis suggests no biases.

CONCLUSION

The pooled analysis in this study suggested that PIA1/A2 SNP in the exonic region of ITGB3 was non-significantly associated with the increased risk of coronary artery disease. In addition, this polymorphism may exert its effect by modulating certain lipid parameters. However, in the future, there is a need to conduct studies with a large cohort size in different subgroups that may give us more conclusive results and provide more insight into disease pathogenesis.

AUTHORS' CONTRIBUTION

SA and KA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. SA, KA, and MFS: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

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