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ORIGINAL ARTICLE

The Role of Paraoxonase 1 (*PON1*) Gene Polymorphisms in Coronary Artery Disease: A Systematic Review and Meta-Analysis

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Abstract

Although many studies have investigated the association of paraoxonase 1 (*PON1*) polymorphisms with coronary artery disease (CAD). However, the outcomes were not consistent and remain uncertain. Therefore, it is the need of the hour to analyze the available literature and evaluate the association of *PON1* polymorphisms with the CAD. All the relevant studies published in the English language from January 1, 2000, up to September 20, 2020, were identified by searching through various electronic databases. The two researchers independently extracted the information. The data were analyzed by using the MetaGenyo program. The pooled odds ratio was used to find the associations between CAD and *PON1* polymorphisms. In the final analysis, we include 10 studies regarding the association of *PON1* polymorphisms (rs662 and rs854560) with CAD. Overall, the Q192R polymorphism increased the risk of CAD in the tested genetic models including the homozygote model: OR 1.35, CI 1.02–1.79; allelic model: OR 1.16, CI 1.00–1.33; dominant model: OR 1.25, CI 1.03–1.52. The L55M polymorphism does not significantly associated with CAD in all the tested genetic models including the homozygote model: OR 1.00 CI, 0.64–1.56; allelic model: OR 1.02, 95% CI 0.84–1.23; dominant model: OR 1.08, CI 0.89–1.31. Further analysis showed no publication bias exists in meta-analysis. Our findings suggested that rs662 in the coding region was significantly associated with the CAD however, rs854560 has no significant association with the disease. Nevertheless, in future, there is a need for more studies with a larger sample size which may provide a more definite conclusion.

Study Registration: PROSPERO registration number CRD42020202278

Keywords Paraoxonase 1 · Polymorphisms · Coronary artery disease · *PON1* · Meta-analysis

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Introduction

Cardiovascular diseases (CVDs) are the group of disorders in the two systems, the circulatory system and the heart. Among the CVDs, the coronary artery disease (CAD) is the most prevalent. Due to the atherosclerosis the constriction of blood vessels leads to the poor blood supply to the heart that's why coronary artery disease is also known as ischemic heart disease (IHD) (Ashiq et al. 2020). Clinical manifestations of coronary artery disease consist a host of chronic and acute conditions such as heart failure, stable angina and acute coronary syndrome (Shabana et al. 2018). In developing countries, its prevalence rate ranked at the top. In the South Asian countries the increasing prevalence of coronary artery disease poses a major threat and burden to the healthcare system (Jamee Shahwan et al. 2019). Worldwide, CVDs are responsible for 31% of all global mortality. Approximately 7.4 million deaths were reported due to the coronary artery disease (Shahid et al. 2018). According to the recent World Health Organization (WHO) report among the CVDs group the CAD represent a non-communicable killer in Pakistan (Larifla et al. 2016).

The coronary artery disease is a multifactorial disorder involving the complex interaction between the genetic and environmental factors (Sekhri et al. 2014). There are two broad categories of the conventional risk factors modifiable and non-modifiable risk factors. Obesity, hypertension, diabetes mellitus and smoking are the modifiable risk factors while family history, age and sex are the non-modifiable risk factors (Matam et al. 2015).

The human paraoxonase 1 (*PON1*) is a calcium dependent glycoprotein which have a molecular weight of 44 kDa. Its initial identification was done by its ability to hydrolyze multiple organophosphates, including sarin, soman, paraoxon and diazoxon and arylesters (Hassan et al. 2013). It predominantly expressed in the liver, which is a high-density lipoprotein associated esterase that hydrolyses lipoperoxides. It prevents the low density lipoprotein cholesterol concentration by hydrolyzing lipid peroxides. The enzymatic activity of paraoxonase1 enzyme varies among the individuals. The *PON1* levels in serum are low if the high density lipoprotein levels are also low. There are several evidences of low *PON1* activity in serum in the patients with lipid disorders such as diabetes mellitus, myocardial infarction, atherosclerosis and familial hypercholesterolemia (Taşkıran et al. 2009).

To date, up to 184 single nucleotide polymorphisms (SNPs) have been reported five common SNPs, two within the coding sequence Q192R [rs662], L55M [rs854560] region, five within the promoter and one seventy six within gene sequence (Gupta et al. 2012).

We selected two single nucleotide polymorphisms in the *PON1* gene. The rs854560 caused by the substitution of the adenine at the place of thymine thus resulting M/L polymorphism at the position 55 (Shahsavari et al. 2020). In the rs662 caused by the substitution of the guanine at the place of the adenine which is located in exon six of the *PON1* gene thus resulting Q/R SNP at 192 in protein. The SNPs in the *PON1* gene affects the catalytic activity for various substrate hydrolysis and the oxidation of low density lipoprotein thus causing an increase in susceptibility to coronary artery disease (Ashiq et al. 2020).

Rationale

The results of rs662 and rs854560 in *PON1* gene inconsistent among different ethnic groups, including Asian (Ahmad et al. 2012), Turkish (Hazar et al. 2011) and Caucasian population (Szpakowicz et al. 2016) thus it is the need of hour to analyze the available literature that provides us the most conclusive results for the association of these two SNPs with CAD.

Objectives

The aim of the current study was to evaluate the association of genetic polymorphisms in *PON1* gene with coronary artery disease.

Materials and Methods

In the present study, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 statement. The current study is registered with PROSPERO (PROSPERO registration number CRD42020202278). A PRISMA checklist is shown in Table 1.

Search Strategy

We searched all published articles in, PubMed, MEDLINE, EMBASE, Web of Science, Ovid, and the Cochrane Library (from January 1, 2000, up to September 20, 2020) using the following MeSH terms and keywords:, including 'coronary artery disease', 'CAD', '*PON1*', 'Paraoxonase 1', 'gene polymorphism', 'variant', 'genotype', 'mutation', 'atherosclerosis', 'coronary heart disease' and 'worldwide'. To avoid missing any relevant study, we have also searched the related articles manually. Finally, all the duplicates studies were not included in the final analysis.

Inclusion and Exclusion Criteria

The articles consider eligible for the inclusion when the following conditions were met (1) retrospective case–control studies using either a hospital based design or population based design (2) The full length original articles on the association of *PON1* polymorphisms and CAD in human subjects (3) Adequate information was provided for estimating the statistical analysis, including odds ratio (OR). Those not written in English language or not provided the adequate data and not designed as case–control studies or designed as meta-analysis or systematic reviews, were excluded.

Table 1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	3, 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	3, 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	4

Table 1 (continued)

Section/topic	#	Checklist item	Reported on page #
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	4, 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	4, 5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	5, 6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	7, 8, 9, 10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	14, 15, 16
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	11, 12,13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	11, 12,13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	14, 15, 16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	14
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	16, 17, 18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	18

Table 1 (continued)

Section/topic	#	Checklist item	Reported on page #
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	18

Data Extraction

To reduce the selection bias, the authors used, predesigned data extraction table. Both the authors independently reviewed and extracted the data required from all the eligible studies. From each original article, the following data were abstracted: author names, year of publication, country, baseline characteristics, sample size (controls and cases), method, the distribution of genotypes and alleles in subjects, and evidence of conforming to the Hardy–Weinberg equilibrium (HWE). The detailed characteristics of each included study are given in Tables 2 and 3.

Quality Score Assessment

The quality of each included study was assessed by using the Newcastle–Ottawa Scale (NOS). The NOS ranges between 0 (worst) and 9 stars (best). Both the authors independently assessed the quality of articles and any disagreements were decided through discussion to achieve a consensus.

Statistical Analysis

The association of the *PON1* polymorphism and risk of CAD was estimated by calculating the pooled ORs and 95%CI. The heterogeneity among the included studies was calculated using the chi-squared test and I^2 statistic. A fixed effect model (Mantel–Haenszel) was used in the absence of heterogeneity and if heterogeneity is present then the random effect model (DerSimonian–Laird) was adopted to investigate the variation both from in-study and between-study. The genetic models used for both rs662 and rs854560 were: allelic model, homozygote model, recessive model and dominant model. The sensitivity test was performed to assess the stability of results. Publication bias was analyzed by using the funnel plot which was calculated by using the Begg's and Egger's tests. All statistical analysis was performed by using the MetaGenyo tool.

Results

Literature Search and Study Characteristics

Through a literature searching, initially 365 published articles were identified, of which 355 articles were excluded as they did not investigate the association of *PON1* polymorphisms with CAD. Thus, after a comprehensive literature search applying our inclusion criteria, 10 eligible full text published articles were included in the final analysis. The detailed screening process for all relevant literature is explained in a flow diagram shown in Fig. 1. Two studies involved Egyptian, Indian, 1 study involved Northern and Southern Han population and Iran whereas the other 4 studies were performed in European populations. Of all the 10 studies, controls of 5 studies

Table 2 Characteristics of studies included in systematic review and meta-analysis

Serial no.	Author	Year	Country	Clinical subtype	Gender wise distribution [M/F]	Mean age	Mean BMI	SOC	Sample Size		Genotyping	HWE	NOS score
									Cases [*N*]	Controls [*N*]			
1	Godbole	2020	Indian	CAD	Ca:77.3%/22.7% Co:59.4%/50.6%	0.017 [NS]	24.52	PB	241	247	PCR–RFLP	$p > 0.05$	9
2	Gonzalez et al.	2020	Mexico	CVDs	Ca:88/30 Co:87/32	67 = cases	27.56	PB	118	119	Real time PCR assays	$p > 0.05$	8
3	Shahsavari	2020	Iran	CAD	Ca:81/73 Co:62/83	63.39	31.25	HB	154	145	PCR–RFLP	$p > 0.05$	8
4	Fridman	2016	Argentina	CAD	Ca:83/43 Co:105/98	63.4	–	HB	126	203	PCR	$p > 0.05$	8
5	Munshi	2018	India	CAD	Ca:388/247 Co:369/266	54.24	26.21	PB	635	635	PCR–RFLP	$p > 0.05$	9
6	El-Lebedy	2014	Egypt	CVDs	Ca:50/16 Co:27/23	58.20	29.81	PB	66	50	Real time PCR		9
7	Brijmohun et al.	2009	UK	CAD	Ca:60%/40% Co:60%/40%	65	27.3	PB	1138	2237	KASPar technology	$p > 0.4$	9
8	Kaman	2009	Turkey	CAD	Ca:188/89 Co:54/38	58.06	26.47	HB	277	92	PCR–RFLP	$p > 0.05$	8
9	Liu et al.	2014	China	CAD	Northern: Ca:554/238 Co:581/283 Southern Ca:264/136 Co:264/136	*N*: 54.4 S: 54.5	*N*:27.2 S:26.4	HB	*N*:792 S:400	*N*:864 S:400	PCR–RFLP ABI PRISM 3130 XL (Applied Biosystems)	$p > 0.05$	8
10	Mohamed	2010	Egypt	CAD	Ca:119/31 Co:26/24	55.5	–	HB	150	50	PCR–RFLP	$p > 0.05$	7

Table 3 In each included study the distribution of genotypes and frequencies *PON1* polymorphism rs662 and rs854560

Serial no.	Author	Year	Genotypes distribution												Allele frequencies							
			Cases						Controls						Cases				Controls			
			QQ	QR	RR	LL	LM	MM	QQ	QR	RR	LL	LM	MM	Q	R	L	M	Q	R	L	M
1	Godbole	2020	101	103	37	195	45	1	126	90	31	194	52	1	0.63	0.37	0.90	0.10	0.69	0.31	0.89	0.11
2	Gonzalez et al.	2020	17.09	61.54	21.37	57.02	36.84	6.14	21.19	45.76	33.05	65.45	34.55	0	–	–	–	–	–	–	–	–
3	Shahsavari	2020	84	54	16	54	75	25	80	54	11	74	60	11	222	86	183	125	214	76	208	82
4	Fridman	2016	77	35	14	48	69	9	116	62	25	88	98	17	189	63	165	87	294	112	274	132
5	Munshi	2018	240	320	75	389	222	24	315	279	41	397	217	21	0.63	0.37	0.79	0.21	0.72	0.28	0.80	0.20
6	El-Lebedy	2014	60	59	15	23	66	45	33	12	5	7	14	29	179	89	112	156	78	22	28	72
7	Brijmohun et al.	2009	548	415	92	424	486	140	1092	847	177	869	932	263	–	–	–	–	–	–	–	–
8	Kaman	2009	42.2%	41.2%	16.6%	44.4%	44.4%	11.2%	46.7%	44.6%	8.7%	32.6%	46.7%	20.7%	62.8%	37.2%	66.4%	33.6%	69%	31%	56%	44%
9	Liu et al.	2014 Northern	110	405	277	709	79	4	164	452	248	759	98	7	625	959	1497	87	780	948	1616	112
		Southern	47	205	148	360	39	1	71	212	117	355	42	3	299	501	759	41	354	446	752	48
10	Mohamed	2010	18	56	76	–	–	–	23	17	10	–	–	–	208	–	–	–	37	–	–	–

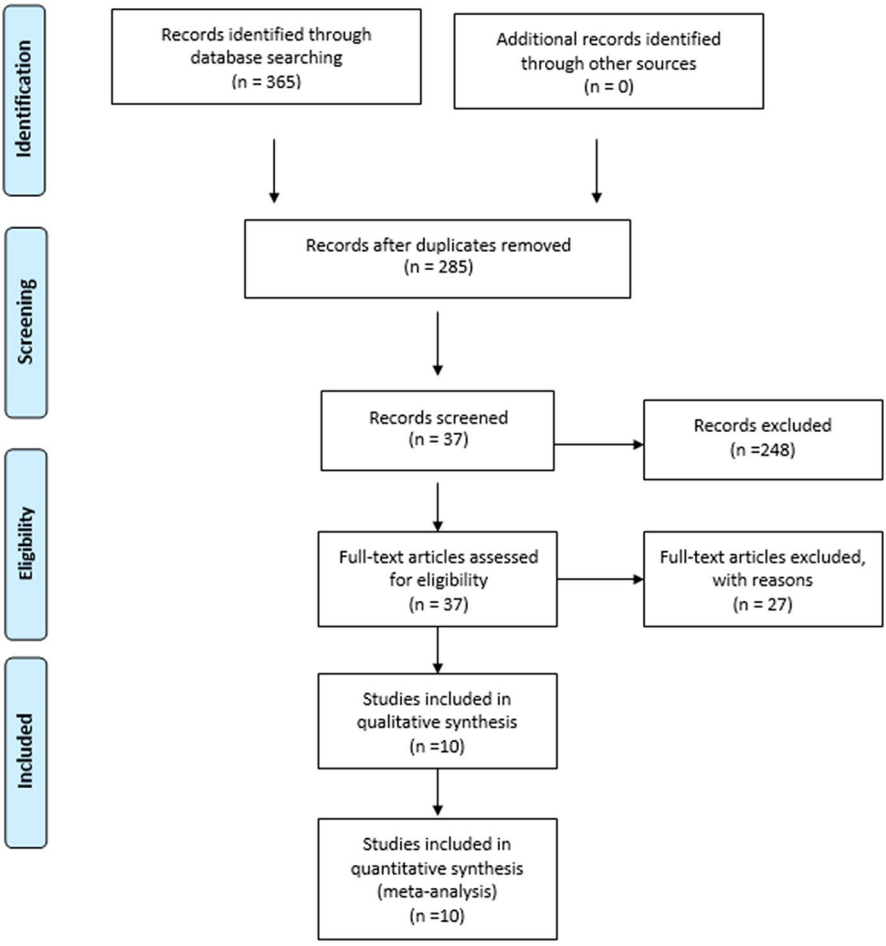

Fig. 1 Flow diagram of study selection

were based on hospital population and the other five were from the general population (Table 2) (Godbole et al. 2020; Murillo-González et al. 2020; Fridman et al. 2016; Munshi et al. 2018; El-Lebedy et al. 2014; Birjmohun et al. 2009; Kaman et al. 2009; Liu et al. 2014; Mohamed et al. 2010; Shahsavari et al. 2020). The controls of 10 studies met Hardy–Weinberg equilibrium of genotype distributions. The detailed genotype distribution and allele frequencies were described in Table 3. All the included studies investigate the effect of rs662 and rs854560 genotypes on paraoxonase enzymatic activity (Table 4).

Association of rs662 with Coronary Artery Disease

The result of the pooled analysis of rs662 polymorphism in *PON1* shows the significant association with coronary artery disease. We chose random effects models to

Table 4 Effect of PON1 polymorphisms on paraoxonase enzymatic activity

Serial no.	Author	Year	Genotype	*PON1* activity (U/L)		*p*-value
				Cases	Controls	
1	Godbole	2020	QQ	28.47	39.6	0.04
			QR	46.87	65.3	0.07
			RR	93.06	136.8	0.02
			LL	43.06	57.6	0.01
			LM	38.89	39.6	0.94
			MM	12.5	89.6	ND
2	Gonzalez et al.	2020	NA [By study group]	OR 95% CI 0.99 (0.99–0.99)	Reference OR 95% CI	0.028
3	Shahsavari	2020	QQ	139.07	119.87	<0.001
			QR	137.46	110.69	<0.001
			RR	148.67	126.69	0.018
			LL	149.07	123.72	<0.001
			LM	134.93	112.85	<0.001
			MM	100.85	117.16	0.012
4	Fridman	2016	QQ	36.3×10^{-3}	44.5×10^{-3}	<0.05
			QR	84.6×10^{-3}	81.3×10^{-3}	<0.05
			RR	113.1×10^{-3}	106.0×10^{-3}	<0.05
			LL	83.0×10^{-3}	83.8×10^{-3}	<0.05
			LM	47.5×10^{-3}	52.7×10^{-3}	<0.05
			MM	21.1×10^{-3}	22.1×10^{-3}	<0.05

Table 4 (continued)

2	Gonzalez et al.	2020	NA [By study group]	OR 95% CI 0.99 (0.99–0.99)	Reference OR 95% CI	0.028
5	Munshi	2018	QQ	47.55	67.01	$p<0.05$
			QR	71.96	89.65	$p<0.05$
			RR	89.7	101.9	$p<0.0001$
			LL	54.44	68.64	$p<0.05$
			LM	63.71	70.18	$p>0.05$
			MM	65.42	69.33	$p>0.05$
6	El-Lebedy	2014	QQ	12.97×10^{-3}	15.75×10^{-3}	>0.05
			QR, RR	8.95×10^{-3}	10.2×10^{-3}	0.04
			LL	9.07×10^{-3}	6.22×10^{-3}	0.18
			LM,MM	11.80×10^{-3}	15.77×10^{-3}	>0.05
7	Brijmohun et al.	2009	QQ [$N=1640$]	27		<0.0001
			QR [$N=1262$]	87		<0.0001
			RR [$N=269$]	152		<0.0001
			LL [$N=1293$]	84		<0.0001
			LM [$N=1418$]	54		<0.0001
			MM [$N=403$]	23		<0.0001
8	Kaman	2009	QQ	335.4	369.7	<0.01
			QR	339.3	395.6	<0.01
			RR	381.3	531.0	<0.001
			LL	369.1	423.7	<0.01
			LM	326.0	386.5	<0.01
			MM	321.4	370.1	<0.001

Table 4 (continued)

2	Gonzalez et al.	2020	NA [By study group]	OR 95% CI 0.99 (0.99–0.99)	Reference OR 95% CI	0.028
9	Liu et al.	2014 PONase activity	QQ	98.7×10^{-3}	121.6×10^{-3}	<0.01
			QR	120.5×10^{-3}	146.7×10^{-3}	<0.01
			RR	136.4×10^{-3}	171.6×10^{-3}	<0.01
		PON1 concentrations	QQ	84.3×10^{-3}	57.3×10^{-3}	<0.05
			QR	96.1×10^{-3}	73.8×10^{-3}	<0.05
			RR	108.8×10^{-3}	88.2×10^{-3}	<0.05
10	Mohamed	2010	QQ [$N=41$]	164.9×10^{-3}		>0.05
			QR [$N=73$]	185.2×10^{-3}		<0.05
			RR $N=63$]	227.6×10^{-3}		<0.05

merge all data based. Overall, the Q192R polymorphism increased the risk of CAD in all the tested genetic models (allelic model: OR 1.16, 95% CI 1.00–1.33; homozygote model: OR 1.35, CI 1.02–1.79; recessive model: OR 1.18, CI 0.94–1.49; dominant model: OR 1.25, CI 1.03–1.52). The main results of meta-analysis are shown in Fig. 2.

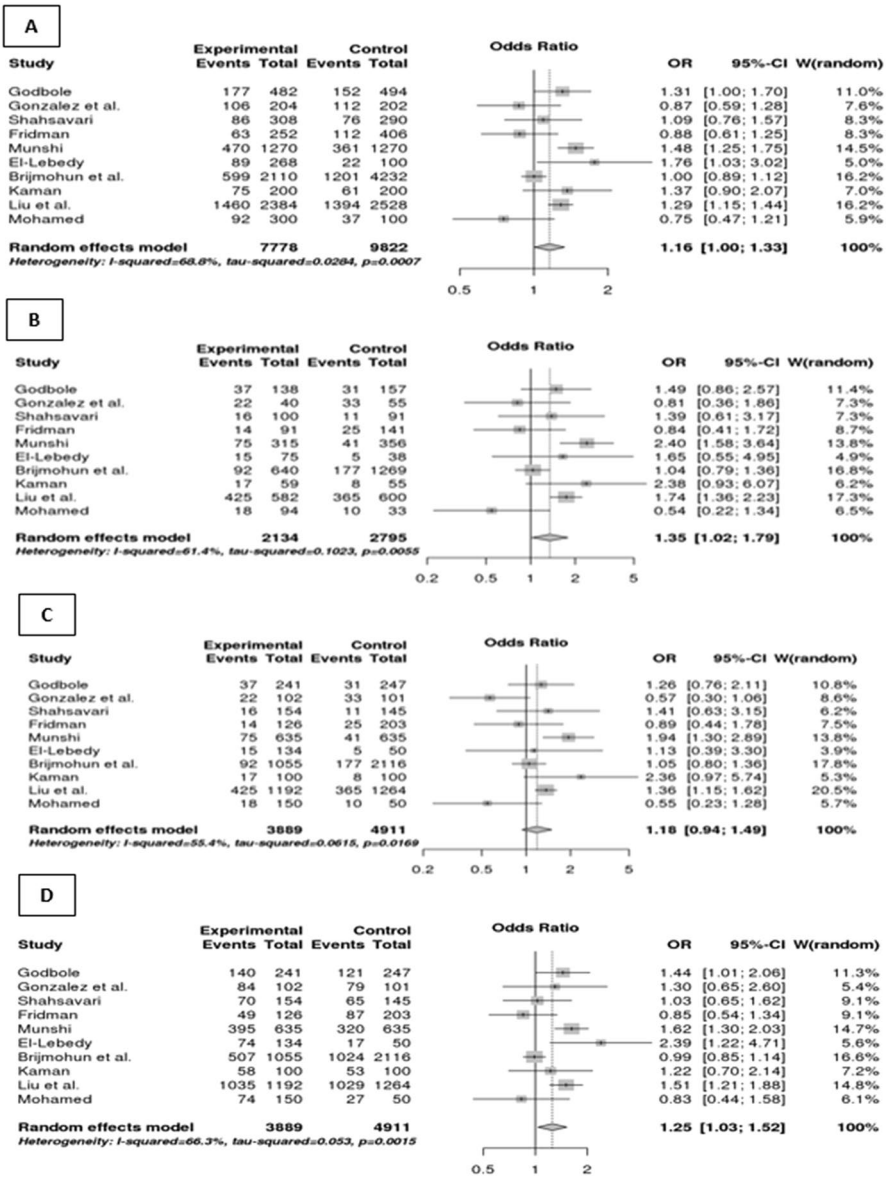

Fig. 2 Result analysis for rs662 association with CAD **a**, **b**, **c** and **d** showing the forest plot for genetic models: allelic, homozygote, recessive and dominant respectively

Association of rs854560 with Coronary Artery Disease

The result of the pooled analysis of rs854560 polymorphism in *PON1* reveals the non- significant association with CAD. The main results of meta-analysis are shown in Fig. 3. We chose random-effects models to merge all data based. Overall, the L55M polymorphism does not increase the risk of CAD in all the tested genetic models (allelic model: OR 1.02, 95% CI 0.84–1.23; homozygote model: OR 1.00, CI 0.64–1.56; recessive model: OR 0.89 CI, 0.58–1.37; dominant model: OR 1.08, CI 0.89–1.31).

Sensitivity Analysis

Sensitivity analyses revealed that after excluding each literature the overall calculated odd ratio did not change significantly, which confirmed the stability and reliability of our analysis.

Publication Bias

The shapes of funnel plots do not show any apparent asymmetry in all the genetic models for both rs662 and rs854560 as shown in Figs. 4 and 5. The Eggers test also showed no statistical significant effect of the publication bias in both the tested SNPs. For the rs662 the *p*-value in all genetic models were non-significant for all genetic models (allelic: 0.77 homozygote: 0.57 recessive: 0.45 and dominant: 0.18). For the rs854560 the *p*-value in all genetic models were non-significant for all genetic models (allelic: 0.86 homozygote: 0.98 recessive: 0.88 and dominant: 0.75).

Discussion

Although several recent systematic review and meta-analysis, investigate the potential role of *PON1* gene polymorphisms in coronary artery disease (Hernández-Díaz et al. 2016), but current analysis was the comprehensive assessment of its association with coronary artery disease. Moreover, our systematic review also provides insight about the effect of *PON1* polymorphism on paraoxonase enzyme levels. The key characteristic of paraoxonase enzyme is that it exhibits hydrolytic activity and plays a vital role in inhibiting the oxidation of low density lipoprotein and high density lipoproteins. Thus, a single nucleotide polymorphism in the *PON1* gene can affect the catalytic activity of enzyme and hence can be associated with CAD (Moreno-Godínez et al. 2018).

In the present study, we selected two major SNPs (rs662 and rs854560) in the *PON1* gene and the pooled analysis results indicated a significant association between rs662 and coronary artery disease. While in the present study the rs854560 showed the non-significant association with CAD. The current study results for the SNP rs662 suggested that the minor allele G is significantly associated with

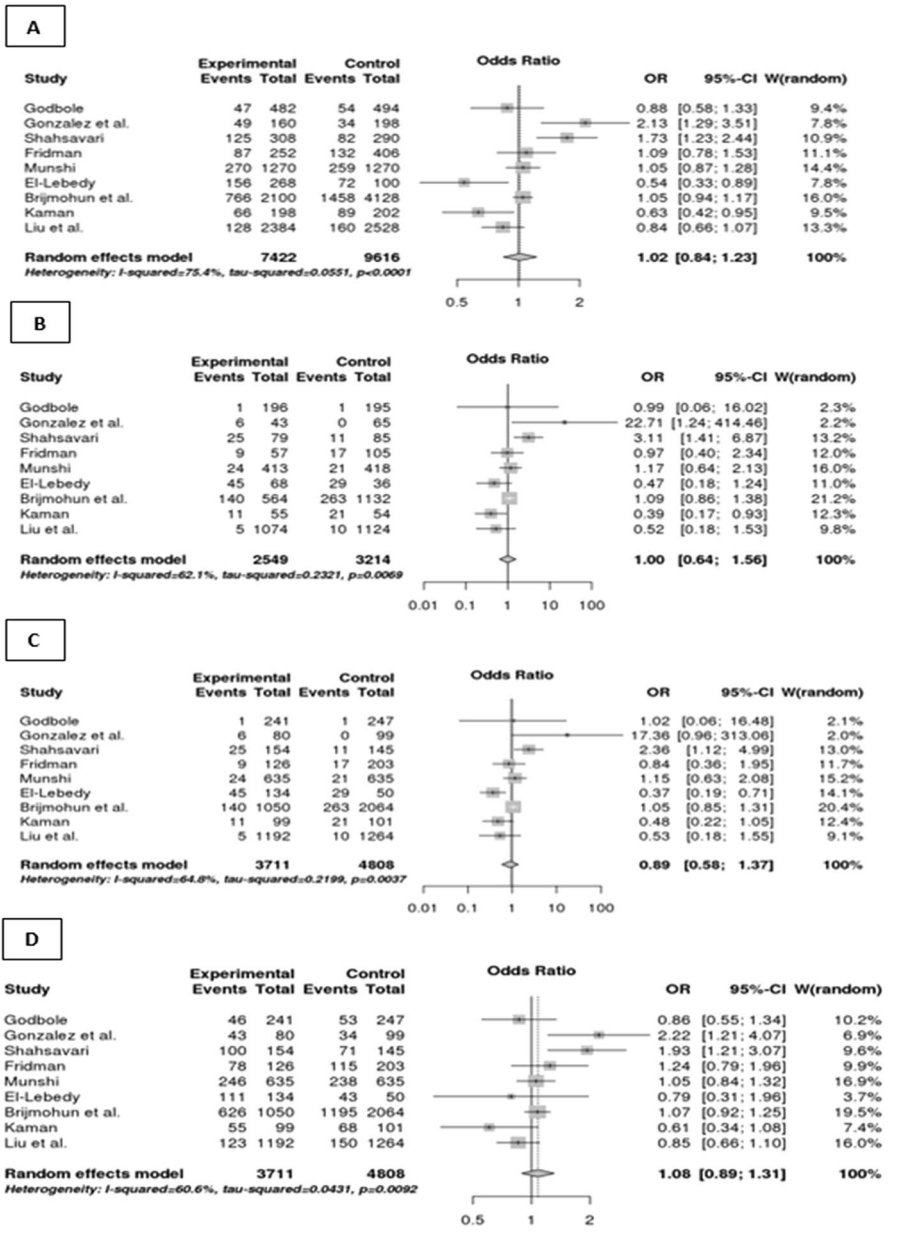

Fig. 3 Result analysis for rs854560 association with CAD **a**, **b**, **c** and **d** showing the forest plot for genetic models: allelic, homozygote, recessive and dominant, respectively

coronary artery disease and the genotypes also have the significant effect on paraoxonase enzyme activity. We found the association between the CAD and all the genetic models tested for the rs662 in the analysis.

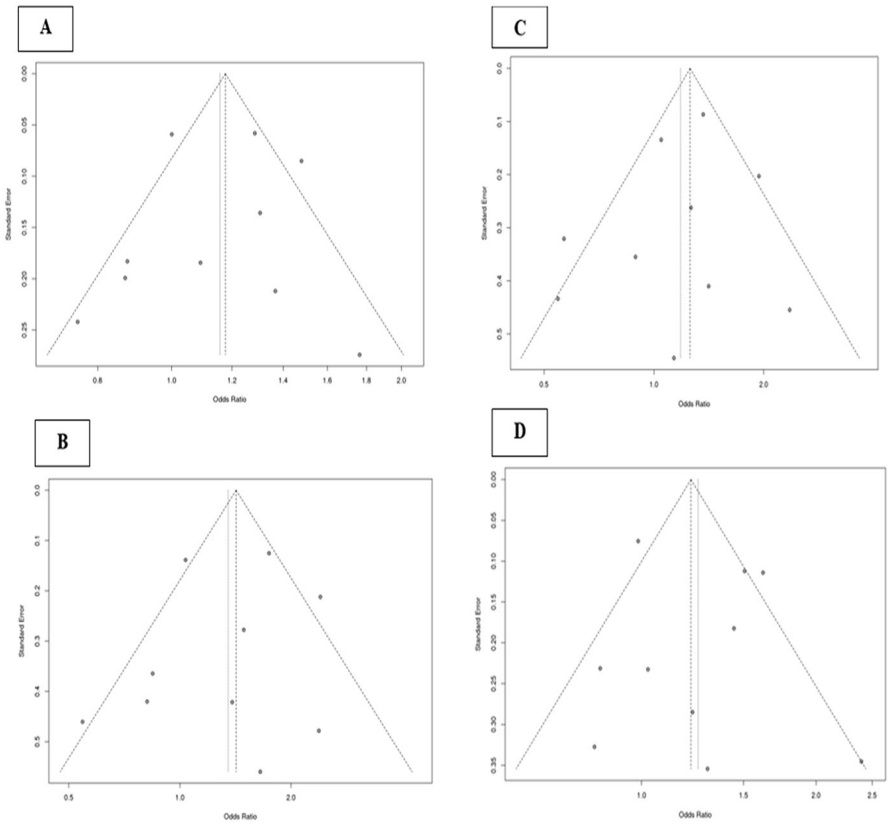

Fig. 4 Result analysis for rs662 association with CAD **a**, **b**, **c** and **d** showing the funnel plot for genetic models: allelic, homozygote, recessive and dominant respectively

Our findings consistent with previous results reported by Shabana et al. (2018) and Liu et al. (2014) but contrast to those performed by the Birjmohun et al. (2009). Similarly a meta-analysis conducted by the Zhang et al. in Chinese population showed the weak association of Q192R polymorphism in *PON1* with coronary artery disease (Zhang et al. 2018). Our study results also in general agreement those performed by the Kaur et al. in Asian Indians (Kaur et al. 2018). Lawlor et al. performed a meta-analysis in Caucasian populations, but they reported non-significant association of rs662 polymorphism in coronary artery disease (Lawlor et al. 2004). The results of the current study also in accordance to the meta-analysis study performed by the Wang et al. (Wang et al. 2018). Zeng et al. also performed a meta-analysis and reported the significant association of rs662 with CAD in Caucasians, South Asians and East Asians populations (Zeng and Zeng 2019).

We also found no association between our second SNP, i.e. rs854560 and coronary artery disease. The current analysis results consistent with the meta-analysis performed by the Hazar et al. in Turkish population (Hazar et al. 2011). While the

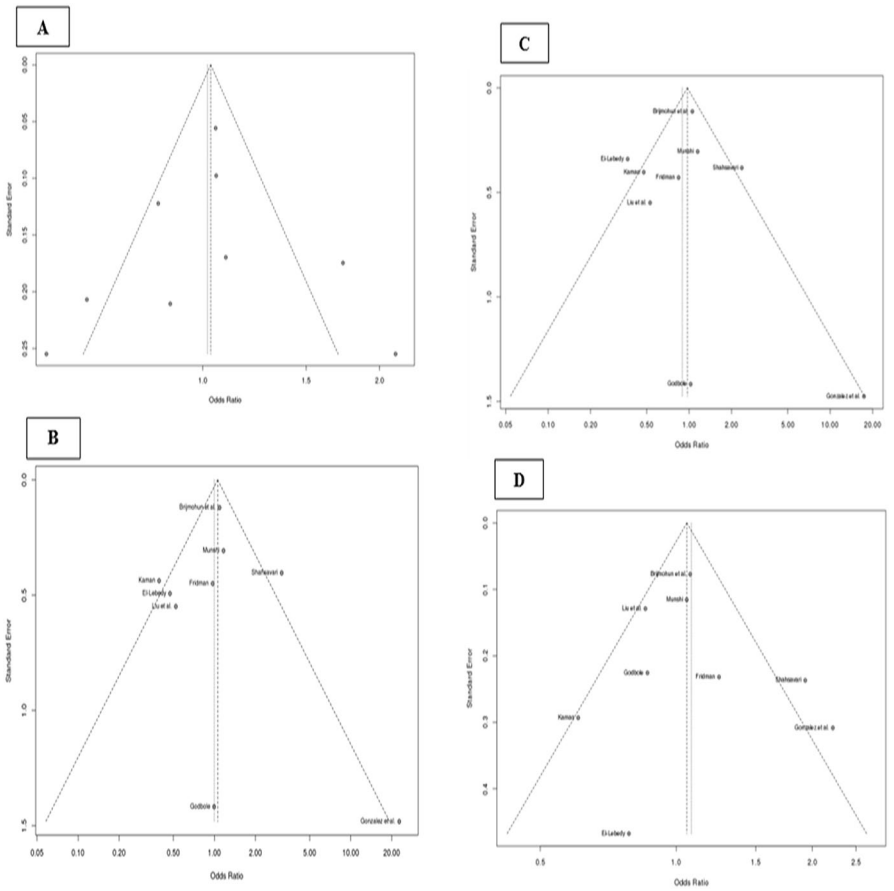

Fig. 5 Result analysis for rs854560 association with CAD **a**, **b**, **c** and **d** showing the funnel plot for genetic models: allelic, homozygote, recessive and dominant respectively

significant association of L55M polymorphism reported by the Zeng and Zeng (2019). Similarly the meta-analysis results reported by the Hernández-Díaz et al. showed the significant association of the rs854560 polymorphism with CAD in European and Asian populations (Hernández-Díaz et al. 2016). Bounafaa et al. also reported that the M allele and R allele are significantly associated with coronary artery disease. Furthermore, these polymorphisms also affect the paraoxonase enzyme catalytic activity which may prove an important marker for monitoring the atherosclerosis (Bounafaa et al. 2015). In addition to all the analysis, it is also important to assess the publication bias that may introduce false positive in a meta-analysis study (Egger et al. 1997). So, in order to avoid this publication bias, we performed Begg and Egger test on the enrolled studies and we found no significant bias in our study. From the current analysis results, we confirmed that subjects with the R allele in *PON1* gene are at high risk of CAD and need to be detected early in

addition to receive the appropriate counseling in case contracting coronary artery disease.

Limitations

Though, the results of the present meta-analysis are quite comprehensive, however, there are a few study limitations also exist. First, we only select the articles that were published in English language and possibly this can influence the publication biasness. Second, in this study, we mainly focused on the two coding region SNPs in the *PON1* gene and were not able to evaluate the other genes association with coronary artery disease.

Conclusions

It is concluded that the Q192R single nucleotide polymorphism in the coding region was significantly associated with CAD. However, in the current study L55M showed non-significant role in CAD. It is suggested that there is a need for more studies with a larger sample size in different subgroups, which could be beneficial to get a more definite conclusion.

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Compliance with Ethical Standards

Conflicts of interests The authors declare that they have no conflict of interest.

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