A Systematic Review and Meta-Analysis on the Relation Between Helicobacter Pylori Infection and Atherosclerosis in the Iranian Population

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Abstract

Background: Various evidences have recently been provided indicating the relationship between infection with *Helicobacter pylori* and the extra-gastric complication, especially atherosclerosis. Atherosclerosis is the most important predisposing factor for cardiovascular disorders due to the high prevalence of cardiovascular disorders in developing countries (areas where a high population of people are infected with *Helicobacter pylori*), in particular in Iran.

Methods: In a current systematic review and meta-analysis study, we collected all studies of the isolation of *Helicobacter pylori* from atherosclerotic plaques in Iranian cardiovascular patients to investigate the presence or absence of a relationship between *Helicobacter pylori* infection and susceptibility to atherosclerosis. The present meta-analysis was done by Comprehensive Meta-Analysis software (CMA-Ver. 2.0). This software has the ability to combine studies and impact sizes into the results and is highly acceptable.

Results: Overall, the frequency of *H. pylori* in atherosclerotic plaques in the coronary artery disease (CAD) patients was estimated to be 41.30%. However, the highest and lowest frequency of infection with *Helicobacter pylori* were 80% and 0%, respectively.

Conclusions: However generally, regarding the previous studies, we collected all the Iranian published articles and showed that the infection with *Helicobacter pylori* was significantly related with the atherosclerosis, but further complementary and more extensive studies are required to confirm this hypothesis.

1. Background

Cardiovascular disease (CVD) is the most common cause of mortality worldwide (50% of global mortality), with an unprecedented increase in the rate of coronary artery disease (CAD) mortality in the last two decades and it has become one of the most significant concerns of the global health system [1–3]. Atherosclerosis is undoubtedly the most important predisposing factor for cardiovascular disorders with a high prevalence in the developed as well as the developing countries [2–5]. Atherosclerosis is a chronic procedure with several factors being involved in its formation [6]. Based on the available evidence, traditional risk factors such as smoking, obesity, hypertension, hypercholesterolemia, and host genome polymorphisms have not had important impacts on the pathogenesis of atherosclerosis, and recent studies suggest that inflammatory diseases play a central role in this respect [7–8]. Infectious agents are considered as the most important inflammatory triggers in the body as well as a risk factor for atherosclerosis due to the stimulating the inflammatory procedure and damaging vascular endothelial cells [9–10]. According to the review of the literature, the most important infectious agents that are associated with atherosclerosis include: *Chlamydia pneumoniae, Hepatitis C virus, Human Immunodeficiency virus, Epstein-Barr virus, Hepatitis B virus, Human T lymphotropic virus type I, Cytomegalovirus, Mycobacterium tuberculosis* and *Helicobacter pylori* [11–17]. *Helicobacter pylori (H.*

pylori) is a gram-negative, of microaerophilic and spiral form that resides in the human gastric mucosa layer and is an etiologic agent of chronic gastritis, gastric ulcer, duodenal ulcer, and gastric cancer [18]. Recent studies have shown that H. pylori is also isolated from dental plaques, human saliva, duodenum, feces and atherosclerotic plaques and is strongly related with the extra-gastrointestinal disorders such as idiopathic thrombocytopenic purpurae, neurological disorders (stroke events), psychiatric, gynecological, pre- Eclampsia, infertility, glaucoma, dermatologic complications, lung cancer, iron deficiency anemia, and atherosclerosis [19–30]. Unfortunately, the rate of colonization with H. pylori is high worldwide, especially in Asia (from 25–50% in the developed countries to 90% in the developing countries), and despite the eradication of H. pylori infection due to the destruction of antibiotics in acidic stomach conditions, the influence of the bacterium under the gastric mucus and the antibiotic resistance has been reduced in the recent years [31–33]. According to the review of the literature, the rate of gastric cancer in Asia is higher than in the western countries, and many researchers attribute this to the high rate of colonization with H. pylori in this geographical region [34–35]. Moreover, the rate of atherosclerosis in the developing countries (where the rate of colonization with Helicobacter pylori is 90%) is higher than in the developed countries [4, 36–37]. The hypothesis of the correlation between H. pylori and atherosclerosis was first suggested by Mendall et al. in 1994 [38]. Despite extensive studies about the correlation of infection with H. pylori and atherosclerosis, it seems that one of the most important reasons for increasing the rate of atherosclerosis in the developing countries may be the high prevalence of colonization with H. pylori in these regions, especially since H. pylori has been isolated from atherosclerotic plaques of the patients [39–41]. However, some resources have rejected the relationship between H. pylori and atherosclerosis, and there is no precise response to the question. Thus, more extensive studies are required in this respect. [42–44]. The rate of atherosclerosis and cardiovascular disorders in Iran is high and based on the Iranian Society of Atherosclerosis, 300 deaths occur each day due to cardiovascular diseases in Iran. Moreover, considering that the high rate of colonization with H. pylori in Iran (estimated to be more than 85%), Iran is regarded as one of the most appropriate places to investigate the possible association between H. pylori infection and atherosclerosis, and the present study was conducted to investigate the relationship between the colonization with H. pylori and susceptibility to atherosclerosis in the Iranian patients.

2. Methods

2.1. Search strategy

The present comprehensive meta-analysis was fulfilled based on the PRISMA guideline proposed by Liberati et al. [45]. t was intended in this study to evaluate the relation between colonization with Helicobacter pylori in cardiovascular patients with atherosclerotic plaques. For this purpose, the related articles the systematic literature searches in PubMed, Scopus, Google scholar databases and the domestic databases such as Iranmedex, SID, ISC and Magiran were collected considering the combination keywords including Helicobacter pylori, Iran, atherosclerosis, atherosclerotic plaques, cardiovascular diseases, DNA, Infection, Coronary artery disease and coronary arteries; in addition original articles and congress abstracts were studied independently by two the authors, without

considering the range of the required time. Finally, the duplicate articles were eliminated and the abstract and title of the studies were selected based on the eligible criteria (Fig. 1).

2.2. Selection criteria

The screening process of the studies was performed independently by two the authors. The titles and abstracts were initially evaluated; inclusion criteria included 1) studies on the isolation of *H. pylori* from atherosclerosis plaques, 2) the patients with cardiovascular disorders, 3) the studies limited to Iran, 4) cross-sectional, cohort and case-control studies, 5) method of *Helicobacter* infection diagnosis consisting of culture, PCR and serology (detection of IgG), and 6) studies in English and Farsi languages. However, the exclusion criteria were: 1) in vitro studies and lab animals, 2) studies containing inadequate or inadequate method or results, 3) case reports and review articles, 4) simultaneous co-infection with *Helicobacter pylori* and other infectious agents, 5) duplicate articles, and 6) not-free articles. It is to note that a study included in our study, despite being a letter to the editor, since it was subject to the eligible criteria.

2.3. Quality assessment and data extraction

The Joanna Briggs Institute (JBI) critical appraisal checklist (Data not shown) was used to evaluate the quality of the studies based on eligibility of criteria. Information such as the author, publishing year, province, diagnostic methods and frequency of *H. pylori* isolates were listed in Table 1 among CAD patients with atherosclerosis plaques.

Table 1
Characteristics of the Iranian studies about frequency of H. pylori in the CAD patients

Authors	Year	Provinces	Atherosclerosis plaque			Diagnostic method	Ref
			No. HP positive	Total	N (%)		
Abibiglou et al.	2018	East Azerbaijan	1	28	3.57	PCR	47
Izadi et al.	2012	Tehran	56	105	53.33	PCR/serology	48
Gharehdaghi et al.	2018	Tehran	10	90	11.11	PCR	49
Sadeghian et al.	2019	Khorasan Razavi	0	30	0	PCR	20
Nozari et al.	2009	Tehran	56	70	80	Serology	50
Yazdi et al.	2014	Tehran	1	90	1.11	Culture	51
Pouria et al.	2009	Kermanshah	8	30	26.66	Serology	52
Vafaeimanesh et al.	2014	Qom	47	62	75.80	Serology	53
Sayyah et al.	2012	Qazvin	32	40	68.08	Serology	54
Ansari et al.	2010	Urmia	49	100	49	Serology	55
Davoudi et al.	2010	Tehran	40	69	57.97	Serology	56
Ashtari et al.	2006	NR	29	42	69.04	Serology	57
(NR: Not reported)							

2.4. Data analysis

The possible relationship between *Helicobacter pylori* infection and atherosclerosis in atherosclerotic plaque samples of the Iranian CAD patients was evaluated and reported using the odds ratio (OR) at 95% confidence intervals (95% Cis) (random effects models when the heterogeneity was high; heterogeneity was assessed using I^2 statistic and Cochrane Q statistic; $I^2 > 25\%$ and P-value < 0.1). The statistical analysis for this study was done by Comprehensive Meta-Analysis (CMA) software-Ver. 2.0 (Biostat, Englewood, NJ) [46], and the publication bias were also measured by the asymmetry of the funnel plot.

3. Results

A total of 94 articles were considered from the databases of PubMed, Scopus, Google scholar, and Iranian databases. After omitting the duplicate studies, the rest of the articles were entered in Endnote software, and the title, abstract and full-text of the articles were reviewed and collected on the basis of

eligible criteria for the cross-sectional, case-control and cohort studies regarding the isolation of *Helicobacter pylori* from the atherosclerotic plaques in the Iranian CAD patients. Ultimately, 12 studies consisting of the original articles and congress abstracts included in the comprehensive meta-analysis (Fig. 1).

Population distribution, characteristics of studies and diagnostic methods of the studies were summarized in Table 1. Since the forms of the cardiovascular disease were not mentioned in a significant number of the studies, the patients were not categorized in the subgroups and the frequency of *Helicobacter pylori* infection was calculated simultaneously for all the CAD patients. Overall, the frequency of *H. pylori* in atherosclerotic plaques in the CAD patients was estimated to be 41.30%. However, the highest and lowest frequency of infection with *Helicobacter pylori* were 80% and 0%, respectively. In addition, the odds ratio was used to evaluate the relationship between infection with *Helicobacter pylori* and atherosclerosis. Based on the available evidence, the odds ratio appeared to be more reliable, in terms of the considered outcomes, than the relative risk method in the low populations and in the unavailability of incidences within the community to investigate the significant relations and therefore we used the odds ratio method for our purpose [58]. The present meta-analysis was done by Comprehensive Meta-Analysis software (CMA-Ver. 2.0). This software has the ability to combine studies and impact sizes into the results and is highly acceptable and commonly used [59]. Statistical analysis revealed that infection with *Helicobacter pylori* was significantly related with the atherosclerosis (The ORs 95% CI: 2.50 (1.83,3.42); P-value < 0.00) and the infection with *H. pylori* is predisposed to atherosclerosis and cardiovascular disorders in Iran (Fig. 2). Also, the asymmetry of the funnel plot demonstrated the potential publication bias in the present study (Fig. 3). However, the present study was also a comprehensive document confirming the relationship between the infection with *Helicobacter pylori* in atherosclerotic plaques formation and the susceptibility to CAD.

4. Discussion

Atherosclerosis is the most common cause of cardiovascular diseases, especially the ischemic heart disease and stroke, and is among the top four causes of death worldwide [60]. Atherosclerosis is a compound Greek word for athero meaning gruel or paste and sclerosis meaning hardness; it is a disorder of large and medium arteries that begins with damage to the vascular endothelial cells and changes in the blood circulation and subsequent to the formation of the atherosclerosis plaques including the necrotic cores, calcified region, lipid particles, smooth muscle cells (SMCs), endothelial cells (ECs), polymorphonuclear cells (PMNs) and foamy cells (alternative macrophages) [60−61]. According to the available evidence, the most prominent stimulants for the formation and development of the atherosclerotic plaques are processes of vascular endothelium damage (especially the intima) and the chronic inflammation [60−62]. Infectious agents, especially *Chlamydia pneumoniae*, *Mycobacterium tuberculosis* and *Helicobacter pylori*, are among the most important infections that can cause chronic inflammation to escape the immune system and appear to be involved in the formation of the atherosclerotic plaques [20]. The hypothesis of the role of *Helicobacter pylori* infection and atherosclerosis was first reported by Menall et al. and the track of *Helicobacter pylori* infection has been

observed in atherosclerotic plaques of coronary, carotid and aortic arteries [38, 63]. In particular, the eradication of *H. pylori* infection decreased the CRP and proinflammatory response and improved the endothelial dysfunction and protective effect on early stages of the atherosclerosis formation [64–66]. In the present study, we collected and analyzed all the published articles about *Helicobacter pylori* infection in the Iranian cardiovascular patients, since the prevalence of atherosclerosis is high in Iran and a significant population in Iran is infected with *H. pylori*. Thus, the studies about the Iranian patients can provide very valuable results regarding the impact of *H. pylori* infection and the susceptibility to cardiovascular disorders. According to the present comprehensive meta-analysis, the rate of colonization with *Helicobacter pylori* and the formation of atherosclerotic plaques in the Iranian CAD patients are significantly related and may make the individuals susceptible to the cardiovascular disorders. According to the literature review, *Helicobacter pylori* contributes to the formation of the atherosclerotic plaques and CAD through the chronic inflammation, injuries and endothelial dysfunction, as well as the impaired body metabolism (Fig. 4). Studies have shown that chronic inflammation during atherosclerosis stimulates Th1 activity and causes the production of pro-inflammatory responses that result in calling and recruiting the inflammatory cells especially PMNs subsequent to the IL-1, IL-6, IFN-Y and TNF-α production, and macrophages also enter into the location in response to MCP1 / 2, inducing the inflammatory reactions that result in the destruction and dysfunction of the endothelial cells [61–63, 67–68]. Since *H. pylori* is capable of inducing the chronic inflammatory and Th1 response, it seems that it may be involved in the pathogenesis of atherosclerosis [67–68]. Furthermore, *H. pylori* can in some cases of chronic gastritis lead to atrophy and malabsorption of vitamin B12 and folic acid by stopping the gastric acid production, resulting in high levels of homocysteine, which increases the damage to the vessel wall through the stimulation of nitric oxide (NO) production and inflammation, and its serum level is elevated in a large number of patients affected by atherosclerosis and CAD [69–72]. According to existing studies, the people infected with *H. pylori* develop dyslipidemia [73]. Hoffmeister et al. demonstrated that the CAD patients infected with *Helicobacter pylori* had higher levels of cholesterol, LDL, triglyceride, and apolipoprotein-B as compared to the CAD patients infected with chlamydia pneumonia or cytomegalovirus, and the HDL levels of these patients were also lower [74]. However, similar studies have shown that after eradication of the infection with *H. pylori*, the serum levels of HDL and apolipoprotein-AI / AII increase and cholesterol, triglyceride, while that of the LDL levels decrease. It seems that *helicobacter pylori* increase the fatty acid by disrupting the fatty acid metabolism and causes it to be deposited on the vessel wall [73–75]. Metabolic disorders can also provide the of incidence of atherosclerosis [76]. Gillum et al. showed that there was a significant relationship between *H. pylori* seropositivity and CAD in the diabetic patients [77]. Moreover, de Luis showed that the rate of CAD and cerebrovascular disorders between the diabetic patients infected with *H. pylori* is high [78]. In his studies, Polyzos et al. proved that infection with *H. pylori* is associated with resistance to insulin, and perhaps the infection with *H. pylori* via the impact on the metabolism (particularly glucose) of the body might lead to atherosclerosis, especially since the glucose resistance is improved subsequent to the eradication of infection with *H. pylori* and the level of the adiponectin (a factor for preventing metabolic disorders) is increased [79–80]. Processes such as hypertension and arterial stiffness have been implicated in the process of atherosclerosis, and studies have shown that there is a significant relationship between infection with *helicobacter pylori* and

these factors [81–82]. Recently, the effect of *Helicobacter pylori* virulence factors has also been studied on atherosclerosis, and a previous report has shown a significant relationship between the infection with cytotoxin-associated gene A (CagA) positive strains and carotid plaque [83]. Also, Bastiani et al. showed that *H. pylori* CagA seropositivity was very high in the patients who encountered stroke [84]. It has been found in this respect that CagA strains induce atherosclerosis by the destruction of the vascular endothelial cells, modification of the oxidized LDL and stimulating the inflammation, and eradicating *H. pylori* CagA infection has stopped the above processes having a protective effect in the patients [85–87]. In addition, it has nowadays been suggested that CagA and *HSPs* stimulate the production of autoantibodies and endothelial dysfunction that ultimately lead to atherosclerosis [88–89]. There have been numerous reports about the relationship between *Helicobacter pylori* infection and the cardiovascular disease (CAD) [63, 89]. According to the literature review, Longo-Mbenza et al. evaluated the cardiovascular risk factors, in a longitudinal (provident) study, in 205 patients for a ten-year follow-up and showed that *H. pylori IgG* titers were high in a substantial population of CAD patients [90]. In their studies on a population of 2029 in South Korea, Park et al. demonstrated that there was a significant relationship between *H. pylori* seropositivity and the CAD patients (ORs: 1.23; p = 0.049) [91]. Other case-control studies conducted in India, Turkey, and Japan confirmed the results of previous studies [91–94]. Our study also confirmed the relationship between *Helicobacter pylori* infection and atherosclerosis in the CAD patients. Isolation of *H. pylori* from the atherosclerotic plaques is one of the most important evidence for approval of the role of this microorganism in the atherosclerosis and CAD [63, 89]. Extensive studies are so far fulfilled in this regard. For instance, the rate of isolation of H. pylori from atherosclerosis was 27.2–33.5% in the study by Jha et al. [92]. In another study in Argentina, the carotid plaque isolation was about 83% [95]. In a cross-sectional study in Turkey, Kilic et al. found that the rates of *H. pylori* isolation from the atherosclerotic plaques and non-atherosclerotic vascular wall specimens were 48.2% and 19.2%, respectively [96]. However, H. pylori was not isolated from any atherosclerotic plaques in the studies in Italy and Poland [97–98]. Rahmani et al. demonstrated in their meta-analysis study that there was a significant relationship between the infection with *H. pylori* and Myocardial infraction in the Iranian patients (ORs = 2.53) [99]. In a meta-analysis of 18 epidemiological studies Danesh et al. found no significant relationship between *H. pylori* infection and the coronary heart disease (CHD) [100]. In a meta-analysis that Zhong et al. did on a 4041 population of stroke patients, it was shown that there was a significant relationship between H. pylori infection and ischemic stroke [21]. In another study by Zhong et al., it was found that there was a significant relationship between *H. pylori* infection and the coronary artery disease in the European (ORs: 2.11) and US (ORs: 1.43) patient populations [101]. However, in another meta-analysis, 13 studies were reviewed and no significant relationship was found between *H. pylori* and the stroke [102]. Recent studies have suggested that infection with strains lacking CagA and vacuolating cytotoxin A (VacA) may lead to controversial results. Thus, the role of virulence *helicobacter pylori* factors and the cardiovascular disorders have been considered in the recent studies [63, 89]. In a study on 684 CAD patients, Mayr et al. showed that infection with CagA strains has a significant relationship with the atherosclerosis (P = 0.08) [103]. In a cross-sectional study on seven case-control studies, Cremonini et al. found a significant relationship between the stroke and CagA seropositivity (ORs: 1.65) [104]. In their studies, Sun et al. showed that there was no

relationship between *H. pylori* CagA + strains infection and the coronary heart disease (CHD) (ORs: 0.8) [105].

5. Conclusions

We had limitations in this study, the first of which was the limited number of studies that required more extensive studies. Moreover, in some studies, the diagnosis of *H. pylori* was based on the evaluation of *H. pylori* IgG seropositivity, but this test also yielded false positive results after the treatments. Thirdly, studies were restricted to geographic regions and this led to the selection bias. Fourthly, the type of CAD was not considered in several studies (e.g. coronary disease, ischemia, stroke, etc.). Fifthly, the studies were of case-control and cross-sectional basis, while the provident (longitudinal) studies were more appropriate for investigations of this study. Sixth, the virulence factors such as CagA and VacA were not suggested, and the seventh point was about the publication bias of the studies. However generally, regarding the previous studies, we collected all the Iranian published articles and showed that the infection with *Helicobacter pylori* was significantly related with the atherosclerosis, but further complementary and more extensive studies are required to confirm this hypothesis.

6. List Of Abbreviations

Helicobacter pylori (*H. pylori*)

Cardiovascular disease (CVD)

Coronary artery disease (CAD)

Coronary heart disease (CHD)

Nitric oxide (NO)

Cytotoxin-associated gene A (CagA)

Vacuolating cytotoxin A (VacA)

Joanna Briggs Institute (JBI)

Smooth muscle cells (SMCs)

Endothelial cells (ECs)

Polymorphonuclear cells (PMNs)

7. Declarations

- Ethics approval and consent to participate

The manuscript methods was based on researching on global databases.

- Consent for publication

All authors have consent for publication of data

- Availability of data and materials

All data generated or analyzed during this study are included in this published article

- Competing interests

The authors declare that they have no competing interests

- Funding

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- Authors' contributions

All authors are medical bacteriologist

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Figures

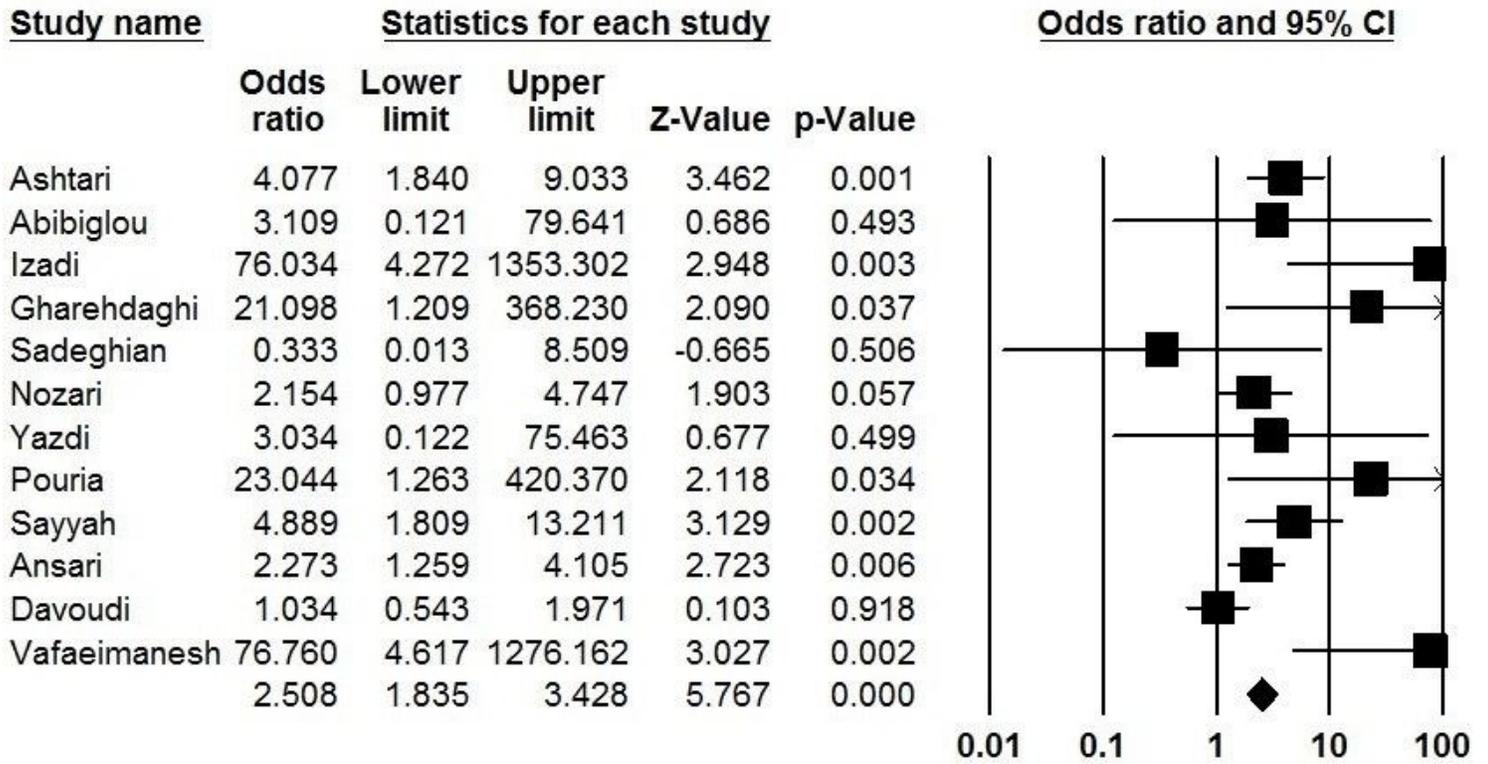| Study name	Statistics for each study					Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Ashtari	4.077	1.840	9.033	3.462	0.001	
Abibiglou	3.109	0.121	79.641	0.686	0.493	
Izadi	76.034	4.272	1353.302	2.948	0.003	
Gharehdaghi	21.098	1.209	368.230	2.090	0.037	
Sadeghian	0.333	0.013	8.509	-0.665	0.506	
Nozari	2.154	0.977	4.747	1.903	0.057	
Yazdi	3.034	0.122	75.463	0.677	0.499	
Pouria	23.044	1.263	420.370	2.118	0.034	
Sayyah	4.889	1.809	13.211	3.129	0.002	
Ansari	2.273	1.259	4.105	2.723	0.006	
Davoudi	1.034	0.543	1.971	0.103	0.918	
Vafaeimanesh	76.760	4.617	1276.162	3.027	0.002	
	2.508	1.835	3.428	5.767	0.000	

Figure 1

Flowchart of included articles according to PRISMA strategy.
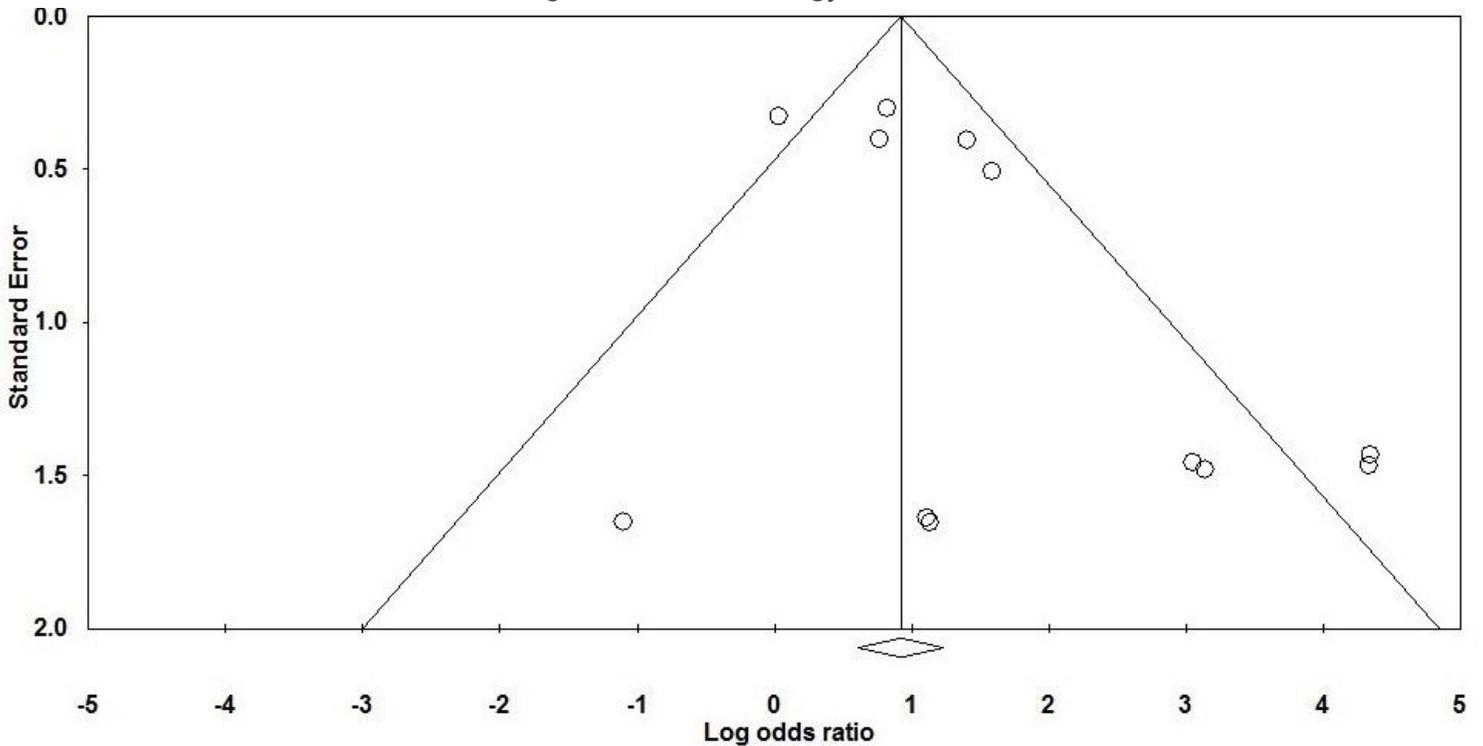

Figure 2

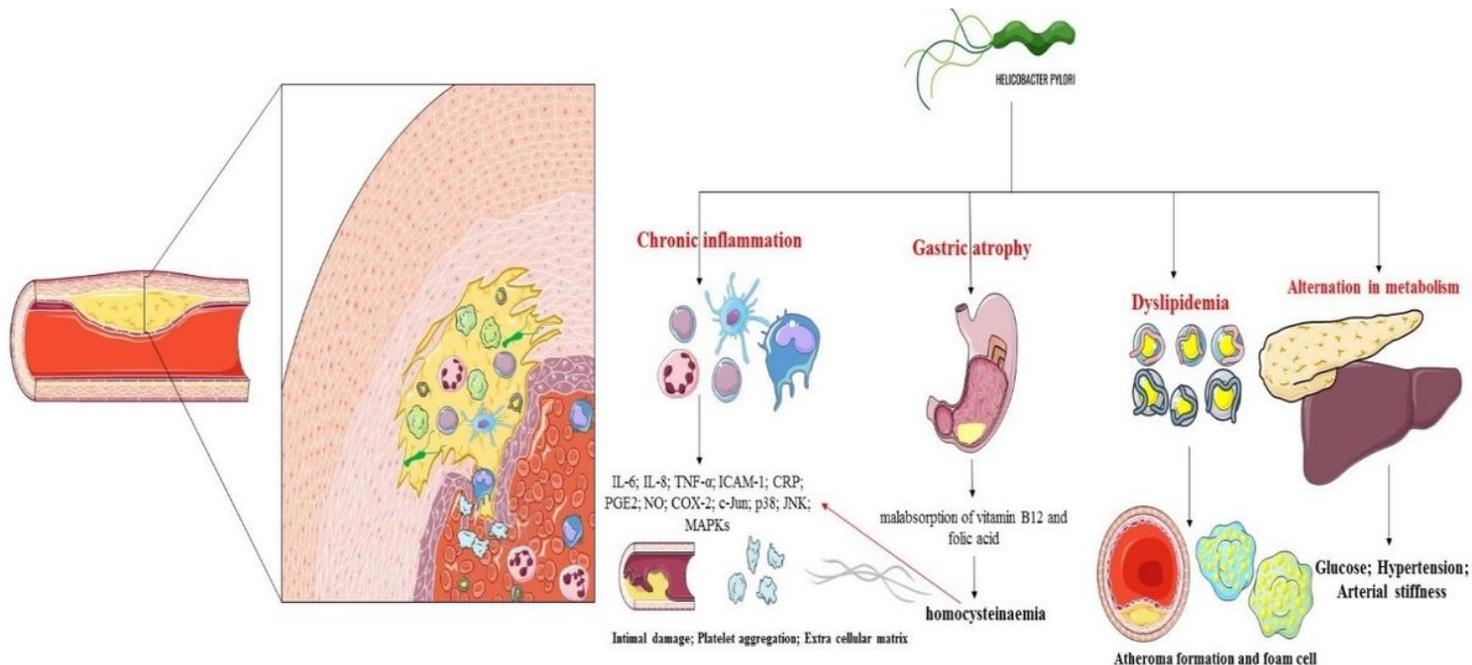Forrest plot of the probable link between H. pylori infection and atherosclerosis in Iranian CAD patients.

Figure 3

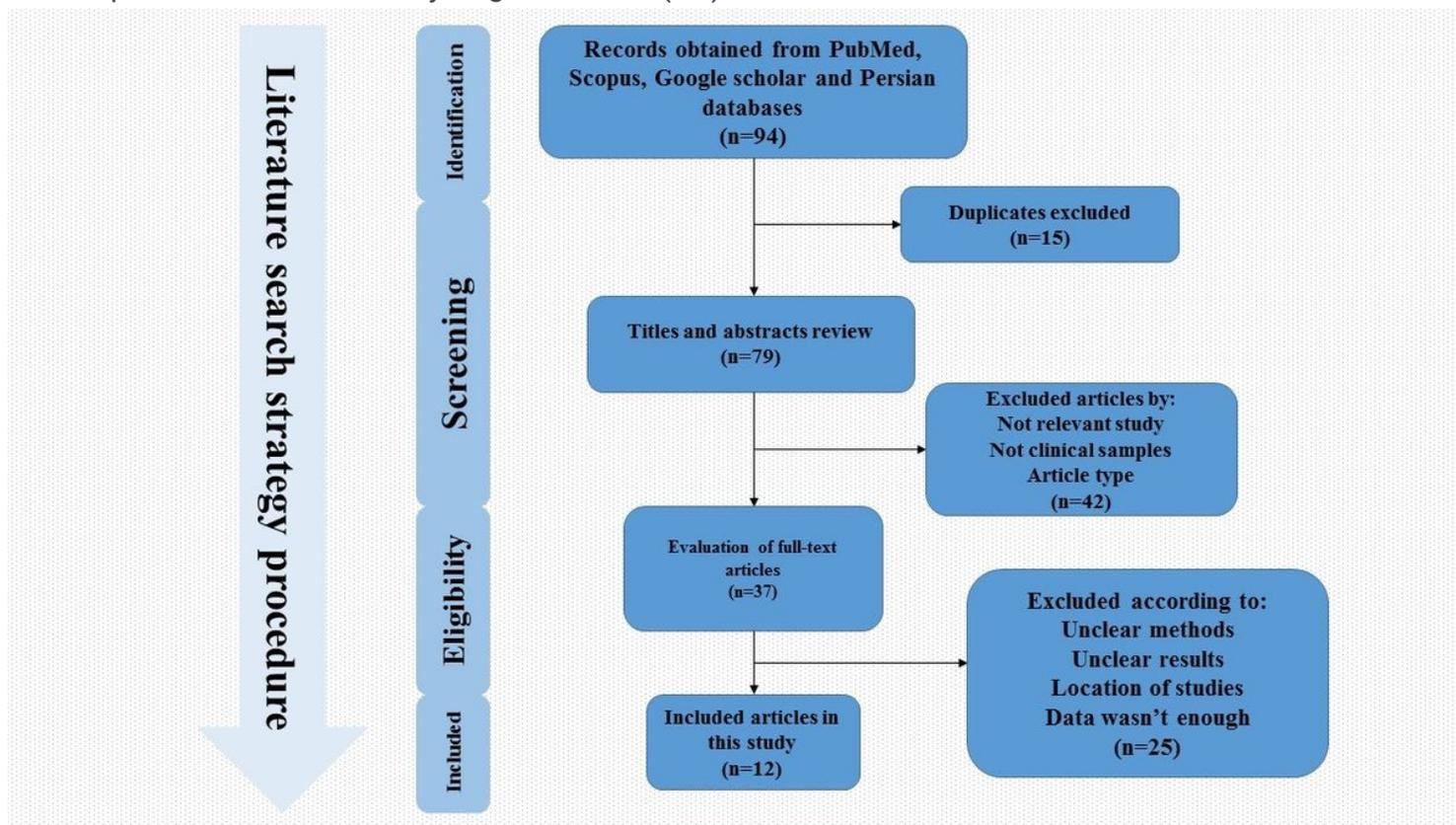Funnel plot of standard error by Log odds ratio (OR).

Figure 4

Hypothetic scheme of H. pylori infection and atherosclerosis.