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***Helicobacter pylori* infection and susceptibility to cardiac syndrome X: A systematic review and meta-analysis**

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Abstract

BACKGROUND

Cardiac syndrome X (CSX) is characterized by persistent angina with normal coronary arteries. Several pathophysiologic mechanisms have been introduced, particularly *Helicobacter pylori* (*H. pylori*) infection.

AIM

To investigate the association between *H. pylori* infection and CSX.

METHODS

All studies related to *H. pylori* infection and CSX were evaluated by comprehensive searches of global databases such as ISI Web of Knowledge, PubMed, Scopus, EMBASE, and Google scholar. Statistical analyses of selected articles were evaluated based on the summary odds ratio (OR). Finally, heterogeneity and publication bias were estimated using the I^2 statistic and Cochrane Q-test as well as Begg's and Egger's tests.

RESULTS

A total of 11 studies met our inclusion criteria and 1435 patients (63% female, and 37% male) were reviewed. A significant association was observed between female patients and this syndrome ($P = 0.02$). Our results showed a positive association between infection with this pathogen and presence of CSX (OR: 5.65; 95% confidence interval [CI]: 4.17-7.64; I^2 : 82.20). However, no significant association

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was observed with *cagA*-positive *H. pylori* strains and this syndrome (OR: 0.97; 0.56-1.70 with 95%CI). Given the heterogeneity and publication bias, the results need to be confirmed by further prospective investigation.

CONCLUSION

Based on our results, *H. pylori* infection is associated with an increased risk of CSX. This bacterium appears to play a major role in the pathogenesis of CSX by inducing persistent inflammation.

Key Words: *Helicobacter pylori*; Cardiac syndrome X; Cardiovascular disease; Infection; Meta-analysis; Coronary diseases

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Core Tip: According to various studies, persistent colonization and chronic inflammation caused by *Helicobacter pylori* (*H. pylori*) infection can lead to systemic disorders outside the gastrointestinal tract. Recently, the role of *H. pylori* in cardiac syndrome X (CSX) has garnered attention. Nevertheless, the mechanism of this syndrome is not fully understood, and it remains controversial. Data from 11 studies were evaluated to assess the association between *H. pylori* infection and CSX. The results showed that there is a positive association between infection with this bacterium and the development of CSX. It seems that *H. pylori* increase the risk of CSX through dysregulation of the immune response and alternating epigenetic events. Statistical analyses showed that the presence of CSX was not dependent on *cagA* status. Several limitations such as small sample size, heterogeneity, and publication bias indicate that confirmation of the present results by further prospective investigation is necessary.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is one of the most important human pathogens in gastric conditions, causing infections in 4-4.5 billion people worldwide[1,2]. This bacterium successfully colonizes in the stomach in childhood and causes chronic infections[3]. After being diagnosed by two Australian physicians, Barry Marshall and Robin Warren in 1994, *H. pylori* was classified as a class I carcinogen[4] by the International Agency for Research on Cancer. Although 85%-90% of infected individuals remain asymptomatic, 10%-15% of cases progress to severe clinical outcomes such as peptic ulcer disease, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[5]. Most frequently, this bacterium is transmitted through gastro-oral, fecal-oral, or oral-oral pathways[6]. Today, there is ample evidence that the bacteria are isolated from out-of-stomach sites such as atherosclerotic plaques, synovial fluid and urine, suggesting that *H. pylori* plays an important role in extra-intestinal disorders by dysregulating immune response or direct attack[7-14]. According to the literature, *H. pylori* infection is significantly associated with hematological and cardiovascular disorders including iron deficiency anemia, primary immune thrombocytopenia, vitamin B12 deficiency, autoimmune neutropenia, anti-phospholipid syndrome, plasma cell dyscrasias, atherosclerosis, and ischemic stroke[15-22]. Surprisingly, many patients with various disorders such as chest pain, abnormal rest electrocardiogram and positive stress test have normal result of coronary angiogram; this disorder was first named cardiac syndrome X (CSX) by Harvey Kemp in 1973, and then was subsequently termed "angina with normal coronary arteries"[23]. CSX is characterized by a variety of features such as angina-like chest pain, positive exercise testing, positive thallium testing, and normal angiography, and accounts for about 20% of chest pain cases[24-26]. The prevalence of

this syndrome is higher in women than in men[27]. Several pathophysiologic mechanisms have been introduced for CSX including inflammation, endothelial dysfunction, genome polymorphism, dyslipidemia, hypertension, smoking, obesity, vasodilator stimuli, and insulin resistance[28-30]. This syndrome has a poor prognosis and may lead to myocardial infarction following repeated hospitalization[31,32]. The exact mechanism of CSX is not fully understood; however, factors such as chronic inflammation, endothelial dysfunction, and microvascular ischemia appear to be the most important risk factors for progression to CSX[33-35]. On the other hand, the role of infectious agents (both viral and bacterial) in susceptibility to cardiovascular diseases (CVDs) has been suggested[36]. According to extant evidence, *H. pylori* infection leads to CVDs through chronic inflammation and endothelial dysfunction (i.e. morphological and functional alterations in carotid artery or atrial stiffness)[37,38]. According to a case report, eliminating this infection could reduce the incidence of CSX[39]. Although several studies have confirmed the link between infection with *H. pylori* and this syndrome, there are some studies with controversial results[40,41]. Because no comprehensive study has been performed on the relationship between this infection and CSX, the present meta-analysis was undertaken to evaluate CSX susceptibility in patients with *H. pylori*.

MATERIALS AND METHODS

Search strategy and inclusion criteria

Initially, a systematic search was performed to evaluate the effects of *H. pylori* infection on susceptibility to CSX. For this purpose, we focused on global databases such as ISI Web of Knowledge, PubMed, Scopus, EMBASE, and Google Scholar, as well as MeSH-based keywords such as "*Helicobacter pylori*," "*H. pylori*," and "Cardiac Syndrome X." Relevant studies were retrieved regardless of publication date and language. The literature search process was conducted separately by two authors (Karbalaie M and Keikha M), and to avoid losing information, the references of each article were evaluated.

Study selection

The inclusion criteria were: cross-sectional, case-control, original, and cohort studies; studies associated with *H. pylori* infection and CSX; studies based on standard diagnostic methods for *H. pylori* infection; and studies on the human population. The exclusion criteria were: review articles, case-reports, and congress abstracts; duplicate studies; repetitive samples; *in vitro* or animal experiments; and unclear or insufficient data. Finally, 11 eligible studies were selected for analysis in this study[41-51].

Quality assessment and data extraction

At this stage, the Newcastle-Ottawa Scale was used to assess the quality of eligible articles. Required information such as first author, publication year, location of study, number of case-control samples, age, gender distribution, infection frequency, diagnostic methods, and reference number are listed in Table 1.

Statistical analyses

We pooled the data using statistical analysis software, Comprehensive Meta-Analysis version 2.2 (Biostat, Englewood, NJ, United States). The association between *H. pylori* infection and incidence of CSX was estimated based on the summary odds ratios (OR) and 95% confidence intervals (Cis). We used the I^2 index and the Cochrane Q -test to determine the heterogeneity between studies. Hence, $I^2 > 50$ and Cochrane Q -test P value < 0.05 were considered significant heterogeneity. Furthermore, in both high and low heterogeneity cases, the random-effects model and the fixed-effects model were used, respectively. Publication bias was also examined through funnel plots and Egger's and Begg's tests.

RESULTS

Literature search and data extraction

In this study, following an initial search in the global databases, we received 206 articles. After evaluating their titles and abstracts and removing duplicate full-text versions, 42 eligible articles were evaluated according to our inclusion criteria, and

Table 1 Characteristics of included studies

Ref.	Publication year	Location	Number of cases		Age		Gender (F/M)		<i>Helicobacter pylori</i> infection		Diagnostic method	NOS score
			Case	Control	Case	Control	Case	Control	Case	Control		
Lanza <i>et al</i> [41]	2004	Italy	55	60	57 ± 8	57 ± 1	27/28	24/36	53%	64%	ELISA	9
Eskandarian <i>et al</i> [42]	2005	Iran	23	23	42 ± 4	41 ± 4	17/6	16/7	91%	48%	UBT	7
Eskandarian <i>et al</i> [43]	2006	Iran	40	40	45 ± 5	44 ± 4	29/11	28/12	95%	47.5%	UBT	7
Song <i>et al</i> [44]	2008	China	50	50	NA	NA	NA	NA	85.2%	46.7%	UBT	4
Said MohammadZade <i>et al</i> [45]	2009	Iran	54	168	54.5	55.2	42/12	125/43	81.48%	56.54%	ELISA	7
Assadi <i>et al</i> [46]	2009	Iran	30	30	53.2	52.6	18/12	18/12	50%	0%	UBT	6
Rasmi <i>et al</i> [47]	2012	Iran	88	97	53.8	45.7	56/32	61/36	98.86%	57.73%	ELISA	9
Rasmi <i>et al</i> [48]	2012	Iran	100	100	51.8	48.9	61/39	61/39	92%	56%	ELISA	9
Rasmi <i>et al</i> [49]	2013	Iran	60	60	51.8	48.9	38/22	39/21	95%	40%	ELISA	7
Rasmi <i>et al</i> [50]	2016	Iran	88	97	53.8	45.7	56/32	61/36	93.18%	57.73%	ELISA	6
Yu <i>et al</i> [51]	2018	China	61	61	NA	NA	NA	NA	92.8%	57.6%	ELISA	5

NA: Not available.

finally 11 articles were selected (Figure 1).

All selected studies were conducted during 2004-2018, and the geographical distribution of the articles was limited to some countries such as Iran, China, and Italy. In eligible studies, the enzyme-linked immunoassay and urea breath test were used to diagnose *H. pylori*. In this meta-analysis, data from 1,435 participants including 649 CSX patients and 786 controls were evaluated. All cases of CSX were diagnosed by typical history of angina with normal or near normal coronary angiography plus a positive none-invasive test or abnormal ECG diagram. Of all patients, 36.61% were male and the rest were female. There was a significant relationship between female sex and getting CSX ($P = 0.02$); the mean ages of patients and the controls were 51.48 and 48.81, respectively. Despite the positive correlation in most studies, in three studies, this relationship was inconsistent, even the relationship between the *cagA* gene and CSX[47-49]. In general, all eligible studies evaluated factors including hypertension, diabetes, hyperlipidemia, smoking, systolic/diastolic blood pressure values, serum homocysteine levels, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride.

Association between *H. pylori* and CSX

Statistical analyses showed that the frequency of infection with *H. pylori* in CSX patients was 77.3% (95%CI: 71.7-82, $P = 0.01$, $I^2 = 89.47$, $Q = 66.51$, $P = 0.01$; Begg's $P = 0.86$; Egger's $P = 0.01$), while that of infection in healthy individuals was 54.2% (95%CI: 50-58.3, $P = 0.05$; $I^2 = 60.7$, $Q = 17.82$, $P = 0.01$; Begg's $P = 0.13$; Egger's $P = 0.03$). Based on the summary OR, we found a strong positive association between this infection and CSX (OR: 5.65, 95%CI: 4.17-7.64, $P = 0.01$, $I^2 = 82.20$, $Q = 56.19$, $P = 0.01$; Begg's $P = 0.40$; Egger's $P = 0.21$), suggesting that patients infected with *H. pylori* might be more susceptible to progression to CSX (Figure 2).

CagA is regarded as one of the main bacterial factors causing alterations in normal signaling pathways and dysregulation of actin-rearrangement, as well as induction of chronic and severe immune responses[52,53]. Based on statistical analyses, no significant relationship was observed between *cagA*-positive strains and susceptibility to CSX (OR: 0.97; 95%CI: 0.56-1.70; $P = 0.93$, $I^2 = 0.00$, $Q = 0.006$, $P = 0.96$). According to the literature, hypertension and hyperlipidemia are the most important CSX-related factors caused by chronic inflammation[31,54,55]. *H. pylori* infection via dysregulating the immune system (MALT lymphogenesis) may lead to disruption of normal homeostasis and basal metabolism, and eventually cardiovascular risk[56-60]. Our

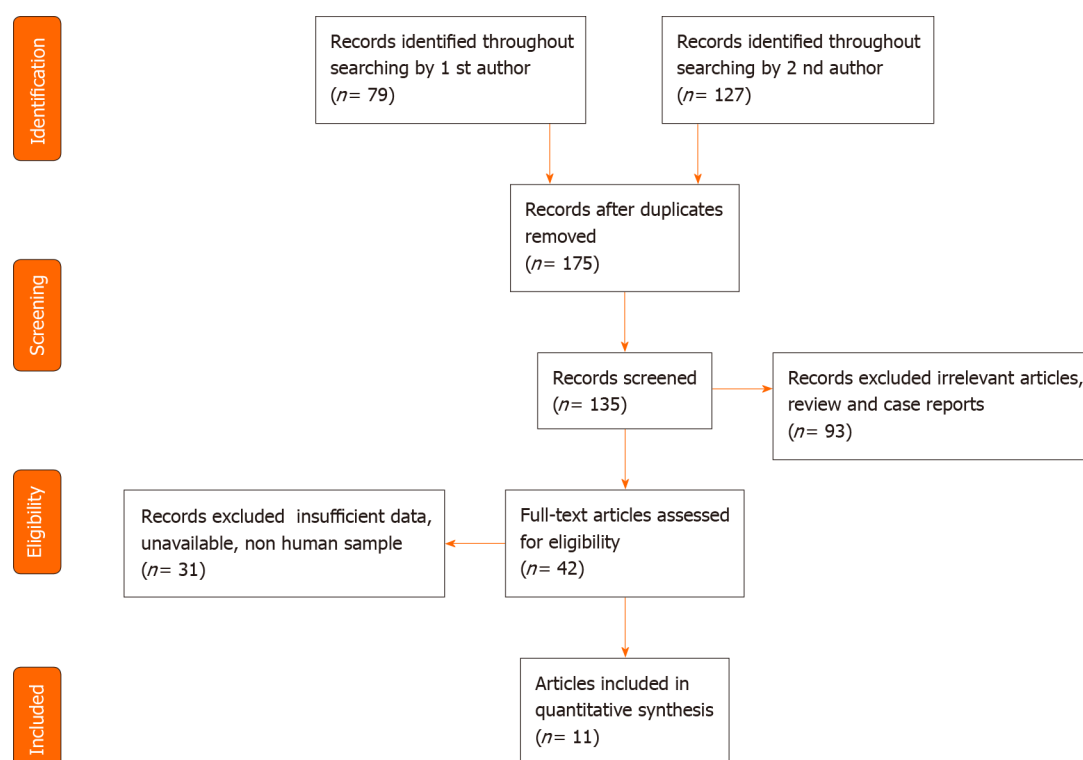
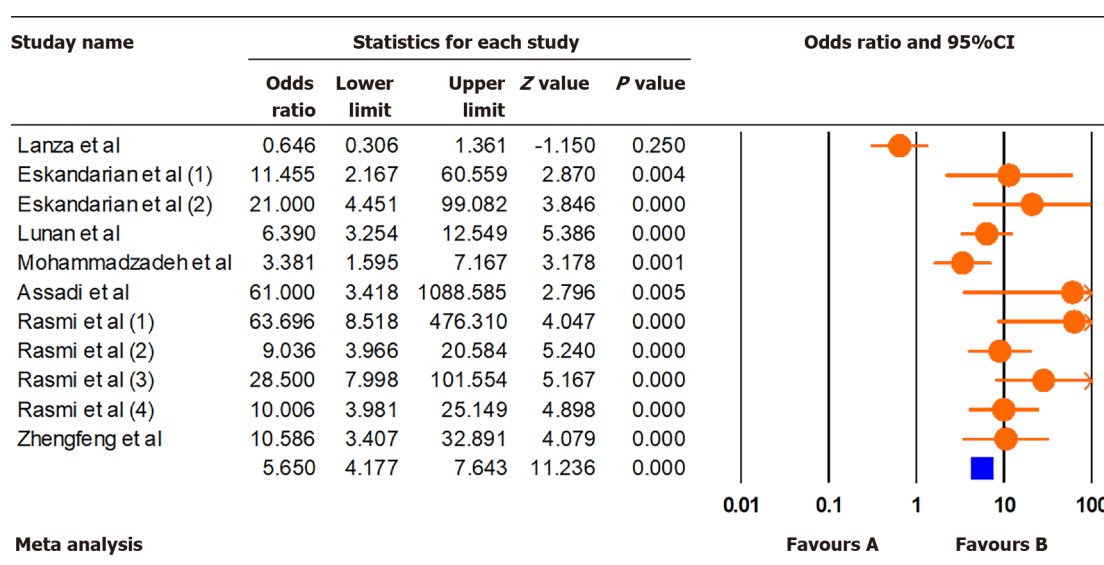


Figure 1 Flow-diagram of literature search and study selection.

Figure 2 The forest plot represents a probable association between *Helicobacter pylori* infection and susceptibility to cardiac syndrome X.

results also indicate a positive significant relationship between infection caused by this bacterium and the presence of hyperlipidemia/ hypertension in CSX patients (OR: 3.33; 95%CI: 1.92-5.76; and OR: 2.30; 95%CI: 1.37-3.87, respectively). About 14.1% of CSX patients were smokers; however, there was no significant association between smoking and the risk of CSX (OR: 0.95, 95%CI: 0.62-1.45, $P = 0.83$).

Publication bias

In the present meta-analysis, we evaluated publication bias using several tests such as Begg's, Egger's, and funnel plot evaluation (Figure 3). According to the results, there was significant publication bias that seems to be due to the low number of available articles.

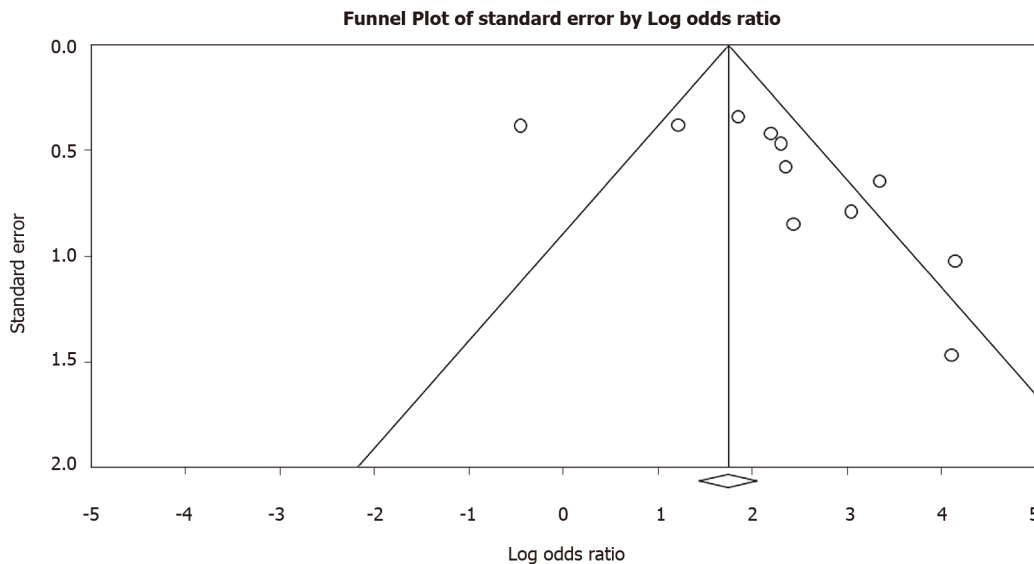


Figure 3 Funnel plot of the meta-analysis on the association between *Helicobacter pylori* infection and cardiac syndrome X.

DISCUSSION

CSX is one of the heterogeneous syndromes in which cardiac (malfunction of Na-H⁺ pump, smooth muscle cell migration, endothelial dysfunction, *etc.*) and non-cardiac (sympathetic reactions, inflammation) mechanisms are involved[61]. Although CSX is a multifactorial disease, the most important pathological factors associated with this syndrome are endothelial dysfunction, coronary artery disease, and myocardial ischemia[62,63]. Recently, the role of inflammation in pathogenesis of CSX, has been defined[64,65]. Pro-inflammatory cytokines, especially interleukin (IL)-1 β , IL-6, and tumor necrosis factor alpha (TNF- α), cause several pathological changes, such as endothelial dysfunction, motility vessels, and microvascular stenosis, which in turn predispose to CSX[66]. In general, infectious agents are considered risk factors for CVDs due to long-term stimulation of the immune response[67]. Today, the role of *H. pylori* infection in CVDs immunopathogenesis has received increasing attention[68]. Immune responses (*e.g.*, cytokines and reactive oxygen species) against this pathogen lead to extracellular disorders[69,70]. Innocenti *et al*[71] showed that this bacterium can activate endothelial cells. In another study, Oshima *et al*[72] found that complications such as systemic inflammation and endothelial dysfunction were more common in patients infected with *H. pylori* than in healthy individuals. In this study, we performed a comprehensive analysis of this association, and finally the results showed that there is a meaningful positive relationship between infection with this bacterium and CSX (OR: 5.65; 4.17-7.64 with 95% CIs). In their study, Rasmi *et al*[47] also showed a significant correlation between these two events in the Iranian population. Moreover, according to a study by Nocente *et al*[39], eliminating infection can significantly contribute to CSX regression. Our results also showed that the rate of *H. pylori* infection is higher in CSX patients than in nested-healthy controls (77.3% *vs* 54.2%). The bacterium contains various virulence factors that act as bacterial super-antigens, and stimulate lamina propria macrophages and local T cells[73]. During the infection, inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF- α increase the infiltration of leucocytes, and aggregation of platelets and PMNs into the site of infection. Bacteria cause some events such as platelet activation and endothelial dysfunction by increasing von Willebrand factor[74,75]. Chemokine receptors such as E-selectin, P-selectin, and intercellular adhesion molecule 1 damage endothelial vessels by increasing the influx of leukocytes[76]. Cannon *et al*[77] showed that the number of chemokine receptors in CSX patients was higher than that in the control group. Other parameters such as serum fibrinogen level, and white blood cell or platelet count in patients with long-term infection are significantly higher than those in the control group[78,79]. Lanza *et al*[41] found that IL-1/C-reactive protein levels were higher in CSX patients than in the healthy group, so they identified these as CSX biomarkers. Chronic infection may cause several disorders, such as motility vessel, contraction of small vessels, and eventually endothelial dysfunction, by inducing inflammation and increasing immune responses[80-82]. The phenomenon of cross-reaction between *H. pylori* antigens and autoantigens increases endothelial damage[83]. Although CagA

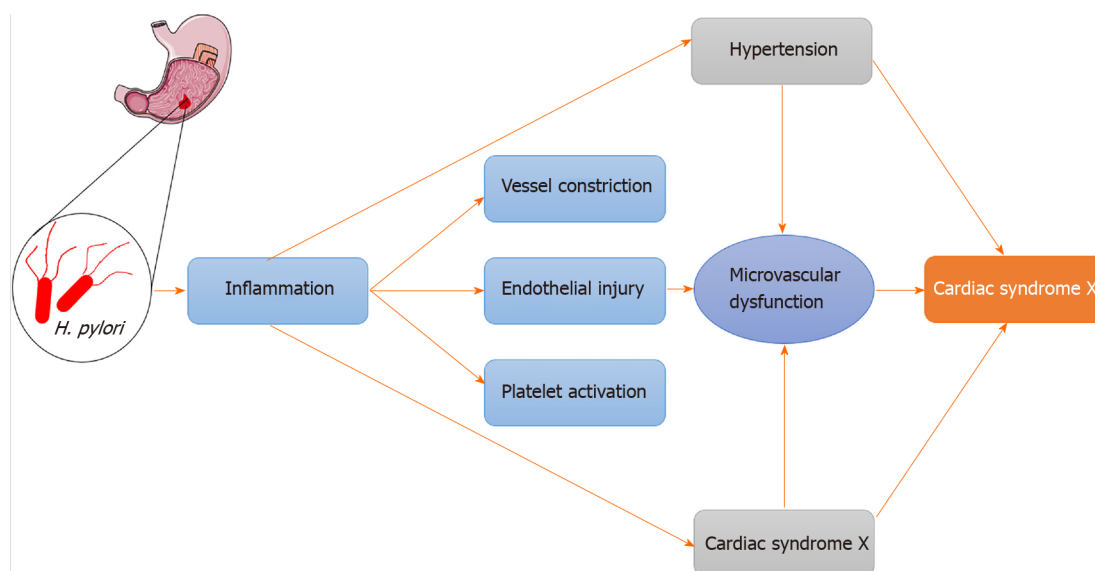


Figure 4 Main involved mechanisms of *Helicobacter pylori* infection in susceptibility and progression to cardiac syndrome X.

antigen is a known virulence factor that is associated with complications such as peptic ulcer disease and gastric cancer, no significant relationship was found between the *cagA* status and CSX disease (OR: 0.97; 0.56-1.70 with 95% CIs). Risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, and alcoholism are among major risk factors for CSX[84,85]. In general, inflammatory responses to chronic infections dysregulate the basal metabolism; for example, IL-6 affects the liver and increases gluconeogenesis and synthesis of fatty acids[86-90]. Another inflammatory cytokine, TNF- α , reduces the clearance of blood fat particles by blocking liver lipoprotein lipase, thus, it is associated with hyperlipidemia[91-93]. Nowadays, there is ample evidence of a positive correlation between chronic *H. pylori* infection and hypertension. In the study conducted by Migneco *et al*[94], it was shown that complete eradication of infection with these bacteria significantly reduced hypertension in infected patients[93]. Based on previous studies, this bacterium affects the immune system, leading to defects in lipid metabolism and eventually hyperlipidemia[95-98]. In general, prolonged *H. pylori* infection leads to extra-gastrointestinal complications such as motility vessel, microvascular constriction, endothelial dysfunction, hypertension, and hyperlipidemia, and at the end CSX (Figure 4).

Limitation

Our meta-analysis had several limitations such as: small number of participants, limited geographical distribution, high heterogeneity, significant publication bias, and lack of adjustment for covariates such as age and CV risk factors, nature of studies (case-control and no cohort), and lack of access to raw data such as socio-economic status, alcohol consumption, and environmental hygiene. However, due to heterogeneity, we need further research to confirm the present findings.

CONCLUSION

The present study was the first comprehensive study to evaluate the relationship between *H. pylori* infection and CSX. Overall, our results suggested an association between *H. pylori* infection and the risk of CSX; however, we need further research with larger sample sizes to confirm the present findings. In this study, using a systematic review, we showed that *H. pylori* infection increases the risk of developing the CSX disease through inflammation, endothelial damage, and the effect on related risk factors.

ARTICLE HIGHLIGHTS

Research background

Cardiac syndrome X (CSX) is multilateral condition that not well characterized.

Research motivation

For the first time, we investigated the probable association between *Helicobacter pylori* (*H. pylori*) infection and risk of develop to cardiac syndrome.

Research objectives

In the present study, the association between *H. pylori* infection and CSX was investigated.

Research methods

We searched several databases to collecting all available documents relevant to impact of *H. pylori* infection and susceptibility to CSX. odds ratio (OR) is used for estimation of probable link between *H. pylori* infection and CSX.

Research results

There is a positive association between *H. pylori* infection and risk of develop to CSX (OR: 5.65, 95%CI: 4.17-7.64, *P*: 82.20).

Research conclusions

In this study, we found that *H. pylori* infection increases the risk of CSX. We showed that there is no significant relationship between *cagA* status and progression to CSX. The frequency of vascular endothelial destructive risk factors such as hyperlipidemia and hypertension in patients infected with *H. pylori* was significantly higher than the control group.

Research perspectives

Infectious agents such as *H. pylori* infection can provide a condition to susceptibility of CSX.

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