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Original article

Hepatitis C virus infection and risk of coronary artery disease: A meta-analysis

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ABSTRACT

Background: A few recent studies have demonstrated that hepatitis C virus (HCV) infection was associated with coronary artery diseases (CAD). However, there still existed studies did not confirm this correlation.
Objective: The objective of this study was to evaluate the association between HCV infection and CAD using a meta-analysis.
Methods: Pubmed, Embase, and Cochrane library databases were systemically searched. Data were extracted by two independent reviewers and pooled odds ratio (OR) and relative risk (RR) with 95% confidence interval (CI) were calculated using the fixed and random effects models.
Results: Eight cohort studies and six case-control and cross-sectional studies were enrolled in this meta-analysis. In the cohort studies, the overall RR and 95% CIs of HCV infection for CAD was 1.25, 1.12–1.40 in random effects model. For the case-control and cross-sectional studies, the overall OR and 95% CIs of HCV infection for CAD were 1.94, 1.58–2.38 in fixed effects model. No publication bias was found in this meta-analysis.
Conclusions: This meta-analysis showed that HCV infection was a risk factor for CAD.

1. Introduction

Chronic hepatitis C virus (HCV) infection is a global public health problem and could lead to cirrhosis and hepatocellular carcinoma. It is estimated that > 170 million people worldwide are associated with HCV infection, which is responsible for > 100,000 cases of liver cancer per year [1]. Furthermore, HCV infection has been suggested to cause several extrahepatic disorders including atherosclerosis, coronary artery diseases (CAD), cardiomyopathy, myocarditis, heart failure, stroke and cerebrovascular mortality [2–5].

HCV infection may cause liver inflammation by several molecular pathways, including pathogen recognition, increased oxidative and endoplasmic reticulum stress, antioxidants depletion, intrahepatic inflammatory cascade response, hepatic steatosis induction, which may lead to both chronic liver injury and extrahepatic disorders such as CAD [6–10].

At present, although HCV infection has been reported to be related to CAD risk, the evidence of the association between HCV infection and CAD remains conflicting. Therefore, we performed this meta-analysis to observe the potential relationships between HCV infection and the risk of CAD.

2. Methods

2.1. Search strategy

Two independent reviewers searched Pubmed, Embase, and Cochrane library databases systemically and extensively to obtain the studies about the association of HCV infection with CAD without any language restrictions. The Medical Subject Heading (MeSH) and keyword terms “HCV infection”, “coronary artery disease” and “cardiovascular disease” were used as search criteria.

2.2. Study selection and data abstraction

The studies enrolled in this meta-analysis were observational epidemiologic studies including cohort, case-control and cross-sectional studies. Articles were excluded from the analyses if the data were not available or multiple publications from the same population. Risk ratio (RR), odd ratio (OR) and 95% confidence interval (CI) were abstracted from the enrolled studies. Data abstraction was performed by two independent reviewers.

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2.3. Statistical analysis

Two techniques were used to calculate the pooled OR or RR: the Mantel-Haenszel method, assuming the fixed effects model, and the DerSimonian-Laird method, assuming the random effects model [11,12]. Heterogeneity between studies was tested with both Cochran's test and I^2 statistics. $P < .1$ or $I^2 > 50\%$ indicated significant heterogeneity in this study [13]. Publication bias was assessed by funnel plot and Egger's regression test [14]. Data of this meta-analysis were analyzed by Stata software (Version 12.0; Stata Corporation, College Station, TX). P-values $< .05$ were considered statistically significant.

3. Results

A total of sixteen relevant cohort, case-control and cross-sectional studies were identified by searching Pubmed, Embase, and Cochrane library databases systemically and extensively. Two studies were excluded due to duplicated studies from the same investigators with the same geographic area populations [15,16]. At last, fourteen articles with usable data met the inclusion criteria and were enrolled in this meta-analysis [4,17–29]. The characteristics of included studies in this present meta-analysis were demonstrated in Table 1.

As heterogeneity among the eight cohort studies was showed in fixed effects model, therefore, we used the random effects model to analyze. The overall RR and 95% CIs of HCV infection for CAD were 1.25 and 1.12–1.40 (Fig. 1). As far as the six case-control and cross-sectional studies were concerned, the overall OR and 95% CIs of HCV infection for CAD were 1.94 and 1.58–2.38 in fixed effects model (Fig. 3).

Funnel plot and Egger's regression test showed no publication bias in either cohort studies ($P = .935$) or case-control and cross-sectional studies ($P = .832$) in this meta-analysis (Figs. 2,4).

4. Discussion

Our results in this present study indicated that HCV infection was a risk factor for CAD.

HCV has been reported to be a cause of systemic inflammation and extrahepatic immunological response. HCV chronic infection may be related to vascular injury, endothelial dysfunction, oxidative stress, lipid disturbances, metabolic disturbances, autoimmunity response, and subsequent development of atherosclerosis, which is the underlying cause of CAD [30]. HCV was strongly associated with ischemic electrocardiogram (ECG) findings and early atherosclerosis independent of classical risk factors, insulin resistance and metabolic syndrome components, and it could be a nonconventional risk factor for CAD [31,32].

Multiple studies have indicated elevated inflammatory biomarkers levels in HCV-infected individuals. Chronic HCV infection has been considered as a metabolic disorder, which is strongly related to Type 2 diabetic mellitus and insulin resistance by interfering with insulin signaling pathway in hepatocytes. It could increase inflammatory response with production of cytokines and oxidative stress [33]. Increased inflammation and endothelial dysfunction biomarkers, which correlated with the risk of atherosclerosis, the development of coronary heart disease and cardiovascular mortality, were demonstrated in chronic HCV-infected individuals [21,34,35].

Several findings suggested that HCV infection may be correlated with increased prevalence of CAD risk factors compared with non-HCV-infected subjects. HCV ribonucleic acid was observed localized in carotid plaque tissues by HCV RNA sequences suggesting local pro-atherogenetic action of the virus inside the plaque, which may facilitate the occurrence of carotid atherosclerotic lesions [36,37]. HCV elimination was helpful for cardiac functional recovery in heart failure [38]. Antiviral treatment for HCV infection was associated with improved renal and cardiovascular outcomes in diabetic patients [39]. Interferon-based therapy may reduce the long-term risk of stroke in patients with chronic HCV infection [40]. In organ transplantation, HCV could be transmitted to heart transplant recipients by donor organs. Donor HCV seropositivity has been considered as an independent risk factor for the development of accelerated allograft vasculopathy after cardiac transplantation and for increased all causes of mortality [41].

Recently, although several studies have suggested the possible relationships between HCV infection and the risk of CAD, no general consensus about the association was reached. In a prospective cohort study of patients with coronary heart disease, HCV seropositive individuals had high rates of death, cardiovascular events, and heart failure hospitalizations during follow-up. HCV seropositivity was independently associated with risk for heart failure events, after adjustment for cardiovascular risk factors [24]. Satapathy et al. also observed that the prevalence and severity of CAD were high in HCV individuals compared with non-HCV subjects, and HCV-positive status was potentially a risk factor for CAD [19]. Furthermore, HCV infection was showed an independent predictor for increased coronary atherosclerosis, as measured by higher Reardon severity score [25]. Patients with HCV seropositivity undergoing coronary angiography for chest pain showed significantly increased prevalence of obstructive CAD, of obstructive 3-vessel CAD, and of obstructive 2-vessel or 3-vessel CAD compared with non-HCV individuals [20].

Moreover, HCV seropositivity was considered as one of the risk factors associated with the onset and development of CAD, such as unstable angina [4,28]. HCV infection would lead to a 1.759-fold risk to ischemic ECG when compared with non-HCV subjects. HCV was

Table 1
Characteristics of included studies in the meta-analysis.

Study	Year	Country	Study design	Cases/controls	Endpoint event	HCV infection definition
Butt [17]	2009	America	Retrospective cohort	82,083/89582	CAD	anti-HCV antibody (+) HCV RNA(+)
Pothineni [18]	2014	America	Retrospective cohort	9685/14799	CAD, chronic stable angina, unstable angina, AMI	anti-HCV antibody (+) HCV RNA (+)
Ramdeen [20]	2008	America	Prospective cohort	36/36	Obstructive CAD	anti-HCV antibody (+)
Arcari [27]	2006	America	Case-control	292/290	AMI	anti-HCV antibody (+)
Tsui [24]	2009	America	Prospective cohort	84/897	AMI, CV death	anti-HCV antibody (+)
Freiberg [22]	2011	America	Retrospective cohort	97/835	CHD	anti-HCV antibody (+)
Forde [26]	2012	America	Retrospective cohort	4809/71668	AMI	anti-HCV antibody (+) HCV RNA (+)
Satapathy [19]	2013	America	Case-control	63/63	CAD	anti-HCV antibody (+)
Alyan [25]	2008	Italy	Case-control	139/225	CAA	anti-HCV antibody (+)
Vassalle [4]	2004	Italy	Case-control	35/651	CAD	anti-HCV antibody (+)
Roed [21]	2014	Denmark	cross-sectional	60/60	CAD	anti-HCV antibody (+)
Enger [28]	2014	America	Retrospective cohort	22,733/ 68,198	MI, UA	–
Younossi [23]	2013	America	Retrospective cohort	173/19568	IHD	HCV RNA (+)
Shoeib [29]	2018	Egypt	Case-control	50/50	CAD	anti-HCV antibody (+)

HCV, hepatitis C virus; CAD, coronary artery disease; CV, cardiovascular; CAA, Coronary artery atherosclerosis; AMI, acute myocardial infarction; UA, unstable angina; CHD, coronary heart disease; IHD, ischemic heart disease.

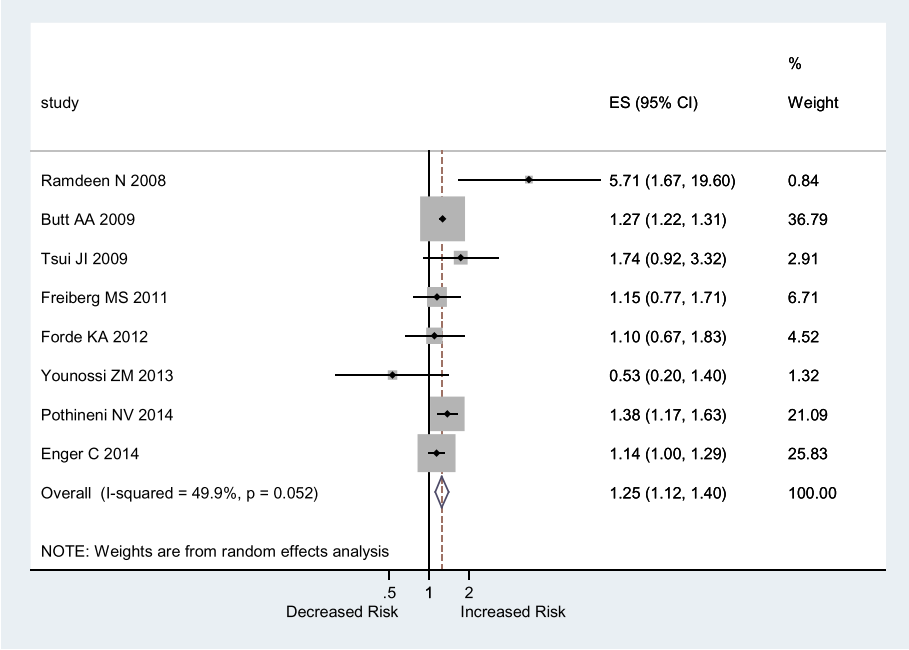

Fig. 1. The association between HCV infection and CAD in cohort studies.

strongly associated with ischemic ECG findings in the individuals who were older than 40 years, and it could be considered as a nonconventional risk factor for CAD [32]. A prospective cohort study reported that HCV+ HIV+ veterans showed an increased risk of coronary heart disease compared with HIV + HCV- and HIV-HCV- veterans [22].

In addition, Pothineni et al. reported an increased incidence of coronary heart disease events in patients with HCV seropositivity, and demonstrated that the incidence was significantly high in patients with detectable HCV RNA compared with those who were only antibody positive [18]. Furthermore, individuals with active HCV infection were reported to have similar angiographic CAD burden compared with HCV-negative ones. Viral load did not seem to correlate with atherosclerosis burden [15].

On the contrary, some studies have not confirmed this correlation. Mostafa et al. observed that atherosclerosis, as measured by intima media thickness on carotid ultrasound, was not elevated in individuals with chronic infection, even though chronic HCV infection was associated with central fat deposition on ultrasound, and increased risk of diabetes and insulin resistance [42]. Younossi et al. reported that chronic HCV infection was independently associated with presence of metabolic conditions including insulin resistance, type 2 diabetes mellitus and hypertension, and congestive heart failure, but not with ischemic heart disease and stroke [23]. Forde et al. also reported that HCV infection was not associated with an increased risk of incident

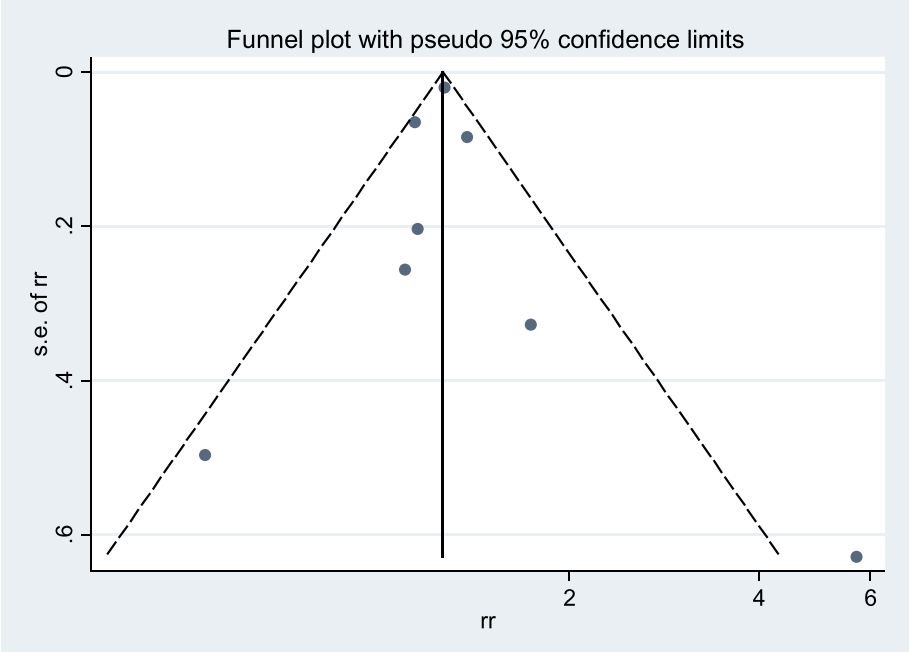

Fig. 2. Egger's funnel plot in assessing publication bias about HCV infection and CAD in cohort studies.

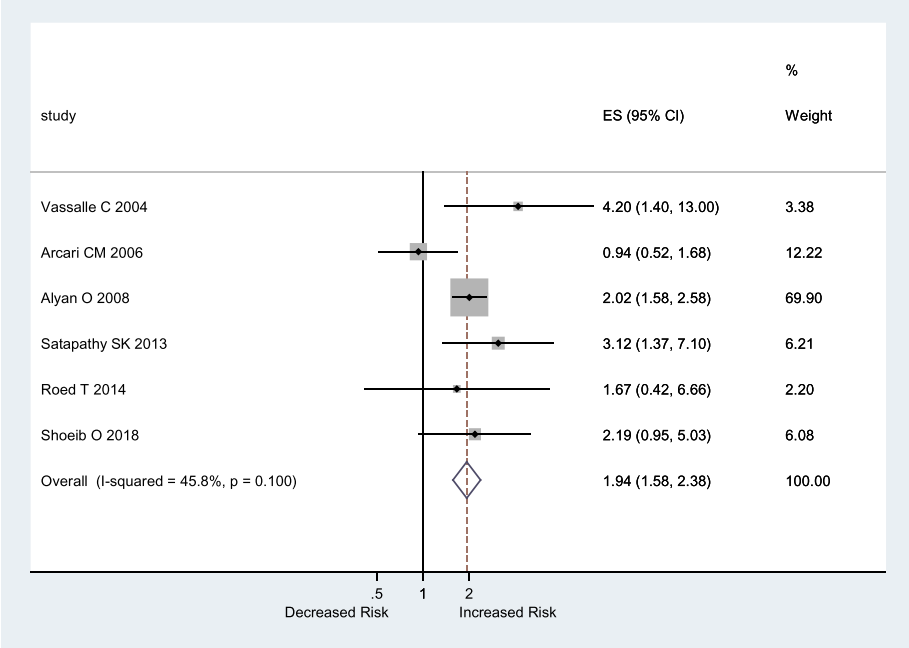

Fig. 3. The association between HCV infection and CAD in case-control and cross-sectional studies.

myocardial infarction [26], which was similar to the study findings about the young men in the US military by Arcari et al. [27]. Similarly, Butt et al. reported that the prevalence and odds of having CAD and stroke were lower in the HCV-infected subjects than that in HCV-uninfected ones demonstrating the protective effect of HCV on CAD [16]. However, in a later study also by Butt et al., despite a favorable lipid profile, HCV infection demonstrated higher risk for CAD after adjustment for traditional risk factors including age, hypertension, chronic obstructive pulmonary disease, diabetes, and hyperlipidemia [17].

At present, three systematic reviews about the relationships between HCV infection and CAD were performed. One review failed to get a consistent conclusion about the association between HCV infection and CAD risk [43], while the other two reviews confirmed the increased risk of CAD in HCV-infected individuals [44,45]. Our findings suggested that HCV infection was associated with increased risk of CAD by analyze both cohort studies (RR = 1.25; 95% CIs, 1.12–1.40) and case-control and cross-sectional studies (OR = 1.94; 95% CIs, 1.58–2.38) about the correlation between HCV infection and risk of CAD. No publication bias was found in this meta-analysis.

However, potential limitations might exist. Firstly, different HCV infection positive criterion was used in the enrolled studies. Some studies used HCV antibody measurement rather than HCV RNA testing, which could identify individuals who had chronic HCV infection more accurately. Secondly, different study design and ethnic groups and

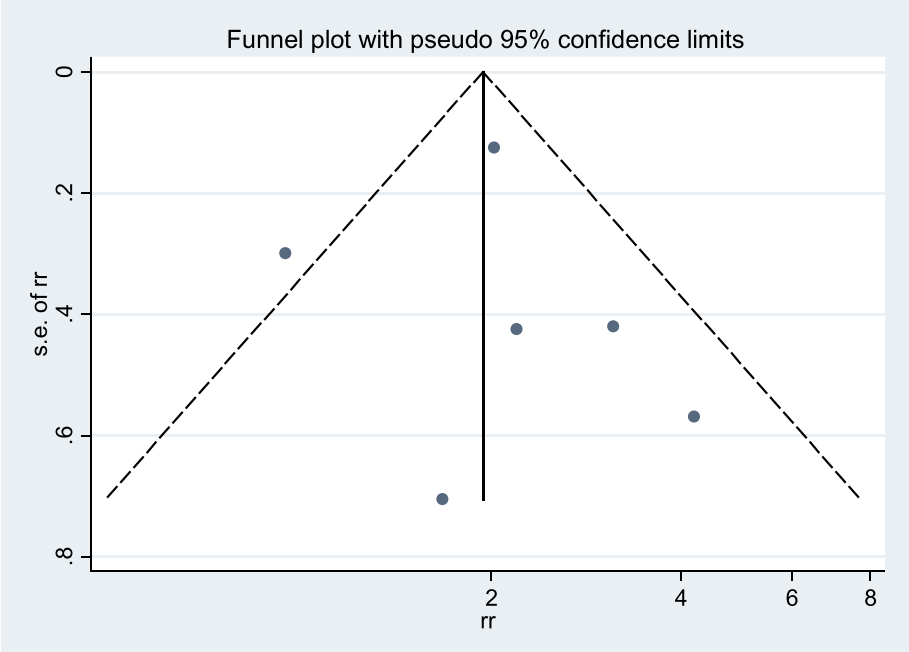

Fig. 4. Egger's funnel plot in assessing publication bias about HCV infection and CAD in case-control and cross-sectional studies.

relatively small sample size exist among studies. Data obtained from the studies may not be representative of the general population. Thirdly, most studies do not provide the information of anti-HCV treatment and follow-up of successful viral clearance. Fourthly, data of the cause of death were not available. Therefore, prospective cohort research with large sample size and appropriate stratifications is warrant to diminish the discrepancies among studies.

5. Conclusions

In conclusion, we concluded that HCV infection was a risk factor for CAD.

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