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Original Article

Risk of Coronary Artery Disease in Patients with Liver Cirrhosis: A Systematic Review and Meta-analysis

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Abstract

Background and Aims: Coronary artery disease (CAD) is increasingly observed in patients with liver cirrhosis. However, data on the incidence and prevalence of CAD in cirrhotic patients are heterogeneous, and the association remains uncertain. In this study, we aimed to conduct a systematic review and meta-analysis to address these issues. ***Methods:*** PubMed, EMBASE, and Cochrane Library databases were searched. Incidence, prevalence, and factors associated with CAD were pooled using a random-effects model. Risk ratio (RR) and odds ratio (OR), with their 95% confidence interval (CI), were calculated to evaluate differences in CAD incidence and prevalence between patients with and without liver cirrhosis. ***Results:*** Fifty-one studies were included. The pooled incidences of CAD, acute coronary syndromes, and myocardial infarction (MI) were 2.28%, 2.02%, and 1.80%, respectively. Liver cirrhosis was not significantly associated with CAD incidence (RR = 0.77; 95% CI = 0.46–1.28) or MI (RR = 0.87; 95% CI = 0.49–1.57). The pooled prevalence of CAD, acute coronary syndromes, and MI was 18.87%, 12.54%, and 6.12%, respectively. Liver cirrhosis was not significantly associated with CAD prevalence (OR = 1.29; 95% CI = 0.83–2.01) or MI (OR = 0.58; 95% CI = 0.28–1.22). Non-alcoholic steatohepatitis, hepatitis C virus, advanced age, male sex, diabetes mellitus, hypertension, hyperlipidemia, smoking history, and family history of CAD were significantly associated with CAD in cirrhotic patients. ***Conclusions:*** CAD is common in cirrhotic patients, but cirrhosis itself may not be associated with an increased CAD risk. In addition to traditional risk factors, non-alcoholic steatohepatitis and hepatitis C virus infection are also associated with CAD presence in cirrhotic patients.

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Introduction

Coronary artery disease (CAD) and liver cirrhosis are major causes of death worldwide and share common risk factors, such as obesity, diabetes, and metabolic syndrome.[1,2] CAD is classified into chronic coronary syndromes and acute coronary syndromes (ACS).[2] In 2020, an estimated 244.11 million people globally lived with CAD, and 8.95 million patients died from it, especially from ACS.[3] Liver cirrhosis is the end stage of chronic liver disease and leads to lethal complications, including bacterial infection, acute kidney injury, and acute gastrointestinal bleeding.[1] In 2017, it was reported that 122.60 million people worldwide lived with liver cirrhosis, with 1.32 million deaths attributed to the disease.[4]

Liver cirrhosis is often complicated by systemic inflammation, hyperactivity of the sympathetic nervous system, and increased cardiac output, all of which are potentially associated with the development of CAD.[5,6] Additionally, patients with liver cirrhosis have a high risk of bleeding due to the coexistence of portal hypertension and thrombocytopenia.[1] Consequently, CAD patients with liver cirrhosis are less likely to receive antithrombotic drugs and have a higher risk of adverse outcomes, including mortality, readmission, and gastrointestinal bleeding,[7] compared to those without liver cirrhosis. Conversely, the presence of CAD also increases post-transplant mortality in patients with advanced liver cirrhosis.[8]

Epidemiological data on CAD in patients with cirrhosis are heterogeneous among studies,[9,10] probably due to differences in target populations and the definitions and diagnostic approaches of CAD. To the best of our knowledge, only one meta-analysis has investigated the prevalence of CAD in liver cirrhosis, finding a pooled prevalence of 12.6%, though it included only five studies.[10] In recent years, the number of studies addressing the epidemiology of CAD in patients with cirrhosis has rapidly increased. However, there remains a lack of studies to estimate the incidence and prevalence of CAD in patients with cirrhosis, assess the association be-

Keywords: Coronary artery disease; Acute coronary syndromes; Myocardial infarction; Liver cirrhosis; Epidemiology; Association; Meta-analysis.
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tween the two diseases, and identify factors associated with CAD in cirrhosis. Therefore, we conducted this systematic review and meta-analysis to address these gaps.

Methods

This systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and Meta-analysis of Observational Studies in Epidemiology guidelines.[11,12]

Registration

This study was registered in the International Prospective Register of Systematic Reviews (hereinafter referred to as PROSPERO) with the registration number CRD42022315248. There was no significant deviation from the protocol registered in PROSPERO.

Search strategy

We searched the PubMed, EMBASE, and Cochrane Library databases from inception to May 17, 2023, without language restriction. Reference lists from relevant papers were manually screened to identify eligible studies. The search terms were as follows: ((liver cirrhosis [all fields]) OR (hepatic cirrhosis [all fields])) AND ((coronary disease [all fields]) OR (coronary heart disease [all fields]) OR (coronary artery disease [all fields]) OR (coronary arteriosclerosis [all fields]) OR (myocardial infarction [all fields]) OR (acute coronary syndrome [all fields]) OR (angina [all fields])).

Selection criteria

Selection criteria were established according to the PICO rule. Participants should be cirrhotic patients, regardless of stages and etiologies. Intervention was not restricted. Comparison should be conducted between patients with and without cirrhosis, if any. The outcome should be the incidence and/or prevalence of CAD.

Exclusion criteria were as follows: 1) duplicated articles; 2) comments, notes, or letters; 3) guidelines or consensus statements; 4) reviews and/or meta-analyses; 5) case reports; 6) experimental or animal studies; 7) patients not diagnosed with liver cirrhosis; 8) CAD not evaluated; 9) overlapping relevant data among studies; and 10) relevant data that could not be extracted.

Definitions

CAD, which refers to the development of thrombosis in the coronary vessels, is divided into chronic coronary syndrome and ACS. ACS primarily includes unstable angina, non-ST-segment elevation myocardial infarction (hereinafter referred to as NSTEMI), and ST-segment elevation myocardial infarction (hereinafter referred to as STEMI). NSTEMI and STEMI are collectively defined as myocardial infarction (MI). The incidence of CAD refers to the new onset of CAD events after a diagnosis of cirrhosis based on data from cohort studies. The prevalence of CAD refers to the presence of CAD in cirrhosis based on data from cross-sectional studies. Severity of CAD was categorized as non-obstructive, obstructive, and severe CAD, defined as luminal stenosis of <50%, ≥50%, and ≥70% in one of the three major coronary arteries, respectively.[13]

Data extraction

Two authors (CG and LD) independently extracted and evaluated the following data from the included studies: first author, publication year, region, enrollment period, study design, type of publication, number of patients with and without liver cirrhosis, number of patients who developed CAD, endpoint events (i.e., CAD, ACS, and MI), and etiology of cirrhosis. To evaluate the differences in baseline characteristics between cirrhotic patients with and without CAD, the following data were further extracted: diabetes mellitus, hypertension, hyperlipidemia, smoking history, family history of CAD, hepatocellular carcinoma, body mass index, and Child-Pugh and Model for End-Stage Liver Disease (MELD) scores. Disagreements between the two authors (CG and LD) were resolved through discussion with a third author (XQ) until a consensus was achieved.

Study quality assessment

Included studies were assessed using the Joanna Briggs Institute Critical Evaluation.[14] Assessment was mainly based on the risk of bias, adequate reporting, and statistical analysis. Responses included "yes", "no", "unclear", and "not applicable". Only "yes" was scored as one, while "no", "unclear", or "not applicable" were scored as zero. The maximum score was 10. Studies that scored ≥7, 5–6, and ≤4 were classified as high, moderate, and low quality, respectively.

Statistical analyses

All analyses were conducted using RStudio version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Version 20.0 (SPSS Software, Chicago, IL, USA). The incidence, prevalence, and risk factors of CAD were pooled using a random-effects model. The pooled incidence and prevalence of CAD were expressed as percentages with their 95% confidence intervals (CIs). The incidence rate of CAD in cirrhotic patients was calculated by dividing the number of individuals with new-onset CAD by the total number of individuals with liver cirrhosis. The incidence rate per 1,000 person-years was also calculated, when applicable. The prevalence rate of CAD in cirrhotic patients was calculated by dividing the total number of individuals with CAD by the total number of individuals with liver cirrhosis. Odds ratios (ORs), risk ratios (RRs), and mean differences (MD) with their 95% CIs were calculated for the combined estimates of raw data, when appropriate. A p-value of <0.05 was considered statistically significant. When the reported outcome was incomplete for meta-analysis, results were described in narrative form. Statistical heterogeneity was assessed via I^2 statistics and the Chi^2 test, where I^2 values of 25%, 50%, and 75% represented low, moderate, and high degrees of heterogeneity, respectively, and $p < 0.10$ by the Chi^2 test was considered significant for heterogeneity. The Egger test was used to assess publication bias, with $p < 0.1$ indicating significant publication bias. Meta-regression and subgroup analyses were performed to explore the sources of heterogeneity. The following covariates were used in the meta-regression and subgroup analyses: region (America vs. Asia vs. Europe vs. Africa), publication year (Before 2015 vs. After 2015), study design (Prospective vs. Retrospective), type of publication (Full-texts vs. Abstracts), study quality (High and Moderate vs. Low), sample size (≥4,545 vs. <4,545; ≥243 vs. <243), etiology of liver cirrhosis (Non-alcoholic steatohepatitis [NASH] cirrhosis vs. Hepatitis C virus [HCV] cirrhosis vs. Alcoholic cirrhosis vs. Primary biliary cirrhosis [PBC] vs. Hepatitis B virus [HBV] cirrhosis), sex (Male vs. Female), mean age (≥57 years vs. <57 years; ≥56 years vs. <56 years), diabetes mellitus (Yes vs. No), hypertension (Yes vs. No), smoking history (Yes vs. No), hyperlipidemia (Yes vs. No), family history of CAD (Yes vs. No), and severity of CAD (Non-obstructive vs. Obstructive vs. Severe). The interaction between subgroups was tested, with $p < 0.1$ considered indicative of a statistically significant interaction.

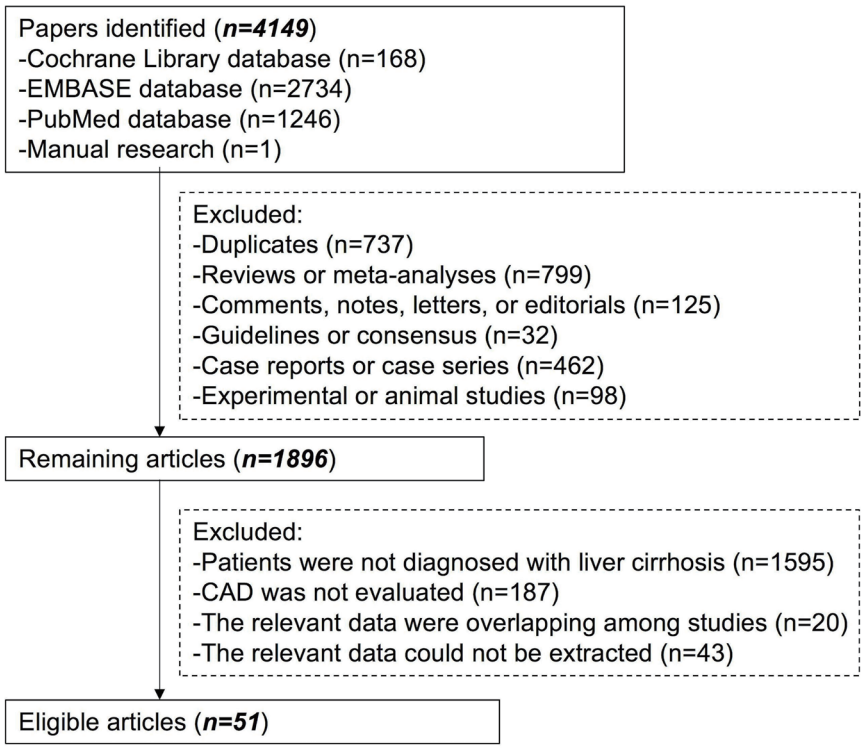

Fig. 1. Flow chart of study selection. CAD, coronary artery disease.

Results

Study selection

Initially, 4,149 papers were identified. Ultimately, 51 studies were included (Fig. 1). Of these, 12 studies reported the incidence of CAD in patients with liver cirrhosis,[15–26] and 39 studies reported the prevalence of CAD.[9,27–64] The quality assessment is provided in Supplementary Table 1.

Incidence of CAD in liver cirrhosis

Characteristics: Characteristics of the included studies that reported the incidence of CAD are shown in Table 1.[15-26] Among the 12 studies, two studies reported the incidence of ACS,[20,24] and seven reported MI[15–18,21,22,25]; four studies provided data to calculate the incidence rate per 1,000 person-years[17,18,20,25]; two studies were conducted in America,[15,22] three in Asia,[19,20,23] and seven in Europe[16–18,21,24–26]; four studies were published before 2015,[23–26] and eight after 2015[15–22]; seven studies were prospective cohort studies,[16–18,21,22,24,26] and five were retrospective cohort studies[15,19,20,23,25]; nine studies were published as full-texts,[15,17–21,23,25,26] and three as abstracts[16,22,24]; eight studies were of high or moderate quality,[15,17–21,25,26] and four were of low quality.[16,22–24]

CAD: Based on data from the 12 studies,[15–26] the pooled incidence of CAD in liver cirrhosis was 2.28% (95% CI = 1.55–3.01%) (Supplementary Fig. 1A). The pooled incidence of CAD was 3.01 (95% CI = 2.05–4.15) per 1,000 person-years. Significant heterogeneity was observed (I^2 = 97.9%, p < 0.01), with no evidence of publication bias (p = 0.42). Meta-regression analyses did not identify the source of heterogeneity (Supplementary Table 2). Subgroup analyses showed the pooled incidence of CAD in liver cirrhosis was 2.95% in America, 2.86% in Asia, and 1.75% in Europe; 1.91% in studies published before 2015 and 2.38% in studies published after 2015; 2.52% in prospective cohort studies and 2.11% in retrospective cohort studies; 2.00% in full-text publications and 3.21% in abstracts; 2.07% in high- and moderate-quality studies and 2.73% in low-quality studies; 2.15% in studies with sample sizes of ≥4,545 and 2.44% in studies with sample sizes of <4,545; 3.26% in male patients and 3.18% in female patients; 2.02% in patients with a mean age ≥57 years and 1.28% in those with a mean age <57 years; 5.30% in patients with diabetes mellitus and 2.34% in those without; 4.77% in patients with hypertension and 1.37% in those without; 7.96% in patients with hyperlipidemia and 2.67% in those without; 1.81% in PBC, 1.23% in alcoholic liver cirrhosis, and 1.14% in HCV cirrhosis (Table 2). Statistically significant interaction was observed among subgroups according to age and hyperlipidemia status.

Seven studies compared the incidence of CAD between patients with and without liver cirrhosis.[15–20,25] The available evidence showed no significant difference in CAD incidence between patients with and without cirrhosis (RR = 0.77; 95% CI = 0.46–1.28; p = 0.31) (Supplementary Fig. 2A). Significant heterogeneity was observed (I^2 = 99.2%; p < 0.01), with no evidence of publication bias (p = 0.41).

ACS: Based on data from two studies,[20,24] the pooled incidence of ACS in liver cirrhosis was 2.02% (95% CI = 1.91–2.14%) (Supplementary Fig. 1B). No significant heterogeneity was observed (I^2 = 0, p = 0.87).

Only one study compared the incidence of ACS between patients with and without liver cirrhosis.[20] A competing risk survival analysis using the Fine and Gray proportional subdistribution hazards model showed that ACS incidence was significantly higher in patients with cirrhosis than in those without [subhazard ratio = 1.14; 95% CI = 1.05–1.23; p < 0.01].

Table 1. Characteristics of studies regarding the incidence of CAD in liver cirrhosis

First author (Year)	Region	Study design	Published form	Enrollment period	Target population	Type of CAD	No. of cases (CAD/total)	No. of controls (CAD/total)
Huang (2023)[15]	USA	Retro-cohort	Full-text	2018–2019	Cirrhosis	MI	451/26,374	10,046/1,271,645
Abdul-Rahman (2022)[16]	German	Pro-cohort	Abstract	2010–2019	Cirrhosis	MI	182/6,517	33,371/1,283,483
Jepsen (2021)[17]	Denmark	Pro-cohort	Full-text	1996–2019	Cirrhosis	MI	56/5,854	416/23,870
Deleuran (2020)[18]	Denmark	Pro-cohort	Full-text	1996–2014	Alcoholic cirrhosis	MI	281/22,867	3,267/107,485
Cacoub (2018)[21]	France	Pro-cohort	Full-text	2006–2015	HCV cirrhosis	CAD	10/878	NA
						MI	8/878	
Lin (2018)[20]	China	Retro-cohort	Full-text	2000–2010	Cirrhosis	ACS	1,157/57,214	1,102/57,214
Tsai (2018)[19]	China	Retro-cohort	Full-text	2004–2011	Cirrhosis	CAD	165/3,236	2,814/16,180
Serper (2017)[22]	USA	Pro-cohort	Abstract	2008–2010	Cirrhosis	MI	923/21,984	NA
Wang (2014)[23]	China	Retro-cohort	Full-text	2007–2013	PBC	CAD	41/2,675	NA
Pavel (2012)[24]	Spain	Pro-cohort	Abstract	NA	Cirrhosis	ACS	6/277	NA/612
Solaymani-Dodaran (2008)[25]	UK	Retro-cohort	Full-text	NA	PBC	MI	22/930	222/9,202
Longo (2002)[26]	Italy	Pro-cohort	Full-text	1974–1997	PBC	CAD	8/350	NA

ACS, acute coronary syndromes; CAD, coronary artery disease; HCV, hepatitis C virus; MI, myocardial infarction; PBC, primary biliary cirrhosis; Pro, prospective; Retro, retrospective; UK, United Kingdom of Great Britain and Northern Ireland; USA, United States of America.

MI: Based on data from seven studies,[15–18,21,22,25] the pooled incidence of MI in liver cirrhosis was 1.80% (95% CI = 1.18–2.75%) (Supplementary Fig. 1C). Significant heterogeneity was observed (I^2 = 98.9%, p < 0.01), with no evidence of publication bias (p = 0.25).

Five studies compared the incidence of MI between patients with and without liver cirrhosis.[15–18,25] The available evidence showed no significant difference in MI incidence between patients with and without cirrhosis (RR = 0.87; 95% CI = 0.49–1.57; p = 0.65) (Supplementary Fig. 2B). Significant heterogeneity was observed (I^2 = 99.2%; p < 0.01), with no evidence of publication bias (p = 0.57).

Prevalence of CAD in liver cirrhosis

Characteristics: Characteristics of the studies included that reported the prevalence of CAD are shown in Table 3.[9,22,27-64] Among the 39 studies, one reported the prevalence of ACS,[53] and nine reported MI.[28,40,46,51,58,60,62–64] By region, 23 studies were conducted in America,[27,29–31,33–35,37,38,40,41,44,47,49–52,54,55,59,62–64] eight in Asia,[9,28,39,43,45,53,56,57] six in Europe,[42,46,48,58,60,61] and two in Africa.[32,36] Regarding publication date, 20 studies were published before 2015,[9,46–64] and 19 after 2015.[27–45] Thirty-six studies were published as full-texts,[9,27–34,36–48,50,51,53–64] and three as abstracts.[35,49,52] In terms of quality, 30 studies were of high or moderate quality,[9,27–30,33,34,36–47,50,51,53–61] while nine were of low quality.[31,32,35,48,49,52,62–64]

CAD: Based on data from the 39 studies,[9,27–64] the pooled prevalence of CAD in liver cirrhosis was 18.87% (95% CI = 13.95–23.79%) (Supplementary Fig. 3A). Significant heterogeneity was observed (I^2 = 99.2%, p = 0.01), and there was evidence of publication bias (p < 0.01). Meta-regression analyses suggested that publication year and CAD severity may be sources of heterogeneity (Supplementary Table 3). Subgroup analyses showed that the pooled prevalence of CAD in liver cirrhosis was 17.35% in America, 19.39% in Asia, 19.64% in Europe, and 36.30% in Africa; 13.73% in studies published before 2015 and 24.49% in studies published after 2015; 18.81% in full-text publications and 19.74% in abstracts; 19.51% in high- and moderate-quality studies and 16.87% in low-quality studies; 14.96% in studies with a sample size of ≥243 and 22.90% in those with a sample size <243; 28.79% in male patients and 16.78% in female patients; 25.69% in patients with a mean age ≥56 years and 19.15% in those with a mean age <56 years; 36.89% in patients with diabetes mellitus and 21.70% in those without; 38.17% in patients with hypertension and 21.10% in those without; 44.25% in patients with hyperlipidemia and 27.13% in those without; 28.58% in patients with a history of smoking and 20.05% in those without; and 46.96% in patients with a family history of CAD and 25.08% in those without. The prevalence of CAD by liver disease type was 21.16% in NASH cirrhosis, 15.85% in HCV cirrhosis, 17.34% in alcoholic cirrhosis, 4.04% in PBC, and 5.05% in HBV (Table 4). The prevalence of non-obstructive, obstructive, and severe CAD in liver cirrhosis was 24.44%, 13.86%, and 7.05%, respectively. Statistically significant interactions were found among subgroups by publication year, liver cirrhosis etiology, and CAD severity.

Fifteen studies compared CAD prevalence between patients with and without liver cirrhosis.[9,28,31,35,36,40,42,45,53,55,57,58,60–62] The available evidence did not show a significant difference in CAD prevalence between patients with and without cirrhosis (OR = 1.29; 95% CI = 0.83–2.01; p = 0.26) (Supplementary Fig. 4A). Significant heterogeneity was present (I^2 = 99.6%; p = 0.01), and publication bias was observed (p = 0.03).

Table 2. Incidence of CAD in liver cirrhosis: Results of subgroup analyses

Subgroup	No. studies	Pooled incidence (95%CI)	Heterogeneity		$P_{interaction}$
			I^2 (%)	*p*-value	
Region					0.43
America	2	2.95% (0.51–5.39%)	99.6	<0.01	
Asia	3	2.86% (0.70–5.02%)	97.0	<0.01	
Europe	7	1.75% (1.14–2.36%)	91.3	<0.01	
Publication year					0.45
After 2015	8	2.38% (1.34–3.42%)	98.7	<0.01	
Before 2015	4	1.91% (1.30–2.53%)	1.3	0.39	
Study design					0.61
Pro-cohort	7	2.52% (1.26–3.78%)	95.0	<0.01	
Retro-cohort	5	2.11% (1.17–3.04%)	98.7	<0.01	
Type of publication					0.10
Full-texts	9	2.00% (1.19–2.82%)	95.7	<0.01	
Abstracts	3	3.21% (2.04–4.39%)	94.5	<0.01	
Study quality					0.39
High and Moderate	8	2.07% (1.15–2.99%)	96.3	<0.01	
Low	4	2.73% (1.53–3.93%)	97.2	<0.01	
Sample size					0.71
≥4,545	6	2.15% (1.20–3.10%)	98.9	<0.01	
<4,545	6	2.44% (1.24–3.64%)	93.2	<0.01	
Sex					0.98
Male	2	3.26% (0.29–6.22%)	94.1	<0.01	
Female	2	3.18% (0.00–8.94%)	98.3	<0.01	
Age					0.02
≥57	4	2.02% (1.91–2.14%)	90.9	<0.01	
<57	1	1.28% (0.92–1.65%)	/	/	
Diabetes mellitus					0.33
Yes	2	5.30% (0.23–10.36%)	92.4	<0.01	
No	2	2.34% (0.00–5.53%)	97.3	<0.01	
Hypertension					0.22
Yes	2	4.77% (0.04–13.49%)	95.7	<0.01	
No	2	1.37% (0.49–2.68%)	76.2	<0.01	
Hyperlipidemia					0.01
Yes	2	7.96% (5.98–9.95%)	0	0.68	
No	2	2.67% (0.00–6.27%)	98.0	<0.01	
Etiology of cirrhosis					0.14
PBC	3	1.81% (1.28–2.43%)	18.7	0.29	
Alcohol	1	1.23% (1.09–1.37%)	/	/	
HCV	1	1.14% (0.44–1.84%)	/	/	

CAD, coronary artery disease; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; Pro, prospective; Retro, retrospective.

ACS: Based on data from one study,[53] the prevalence of ACS in liver cirrhosis was 12.54% (95% CI = 11.89–13.20%).

Only one study compared ACS prevalence between patients with and without liver cirrhosis,[53] reporting a significantly higher prevalence in those with cirrhosis [12.54% (1,218/9,711) vs. 10.39% (4,036/38,844), $p < 0.01$].

MI: Based on data from nine studies,[28,40,46,51,58,60,62–64] the pooled prevalence of MI in liver cirrhosis was 6.12%

Table 3. Characteristics of studies regarding the prevalence of CAD in liver cirrhosis

First author (year)	Region	Published form	Enrollment period	Target population	Type of CAD	No. of cases (CAD/total)	No. of controls (CAD/total)
Reznicek (2023)[27]	USA	Full-text	2013–2018	Cirrhosis	CAD	150/693	NA
Abureesh (2022)[31]	USA	Full-text	1999–2019	Cirrhosis	CAD	8,210/293,150	346,030/55,904,540
Berry (2022)[30]	USA	Full-text	2011–2020	Cirrhosis	CAD	99/1,623	NA
Pelayo (2022)[29]	USA	Full-text	2010–2020	Cirrhosis	CAD	30/127	NA
Wang (2022)[28]	China	Full-text	2000–2013	HCV cirrhosis	CAD	413/1,154	2,022/6,924
					MI	43/1,154	194/6,924
Aby (2021)[37]	USA	Full-text	2019–2019	Cirrhosis	CAD	12/94	NA
Afify (2021)[36]	Egypt	Full-text	2020–2020	HCV cirrhosis	CAD	7/64	5/61
Alshami (2021)[35]	USA	Abstract	2018–2021	Cirrhosis	CAD	783/10,170	360,010/20,000,530
Patel (2021)[33]	USA	Full-text	2010–2017	Cirrhosis	CAD	153/682	NA
Izzy (2021)[34]	USA	Full-text	2008–2017	Cirrhosis	CAD	32/141	NA
Srinivasamurthy (2021)[32]	India	Full-text	NA	Cirrhosis	CAD	25/40	NA
Hughes (2020)[38]	USA	Full-text	2012–2017	Cirrhosis	CAD	121/231	NA
Oud (2019)[40]	USA	Full-text	2009–2014	Cirrhosis	MI	306/2,511	14,114/51,969
Patil (2019)[39]	India	Full-text	2015–2017	Cirrhosis	CAD	11/177	NA
Patel (2018)[41]	USA	Full-text	2011–2014	Cirrhosis	CAD	84/228	NA
Bhadoria (2017)[43]	India	Full-text	2014–2016	NASH cirrhosis	CAD	268/1,133	NA
Kazankov (2017)[42]	Denmark	Full-text	2012–2014	Cirrhosis	CAD	40/52	34/52
Piazza (2016)[44]	USA	Full-text	2005–2010	Cirrhosis	CAD	20/143	NA
Ng (2015)[45]	China	Full-text	2005–2010	Cirrhosis	CAD	655/2,779	86,703/755,161
An (2014)[9]	Korea	Full-text	2007–2012	Cirrhosis	CAD	399/1,045	2,018/6,283
Josefsson (2014)[48]	Sweden	Full-text	1999–2007	Cirrhosis	CAD	13/202	NA
Kumar (2014)[47]	USA	Full-text	1988–2011	Cirrhosis	CAD	55/243	NA
Petit (2014)[46]	French	Full-text	2008–2013	Cirrhosis	MI	59/1,068	NA
Gologorsky (2013)[50]	USA	Full-text	2004–2006	Cirrhosis	CAD	321/11,280	NA
Simons (2013)[49]	USA	Abstract	2000–2011	Cirrhosis	CAD	80/324	NA
Hsu (2012)[53]	China	Full-text	1997–2006	Cirrhosis	ACS	1,218/9,711	4,036/38,844
Mouchli (2012)[52]	USA	Abstract	2000–2009	Cirrhosis	CAD	44/158	NA
Vanwagner (2012)[51]	USA	Full-text	1993–2010	Cirrhosis	CAD	34/242	NA
					MI	10/242	NA
Chen (2011)[57]	China	Full-text	2001–2003	Cirrhosis	CAD	138/2,336	556/11,680
Chen (2011)[56]	China	Full-text	2004–2008	Cirrhosis	CAD	280/2,945	NA
Doycheva (2011)[55]	USA	Full-text	1997–2005	PBC	CAD	14/180	8/151
Patel (2011)[54]	USA	Full-text	2000–2010	Cirrhosis	CAD	123/420	NA
Kalaitzakis (2010)[58]	Sweden	Full-text	2004–2005	Cirrhosis	CAD	26/127	21/203
					MI	9/127	10/203
Kadayifci (2008)[59]	USA	Full-text	1999–2006	Cirrhosis	CAD	15/120	NA
Berzigotti (2005)[60]	Italy	Full-text	NA	Cirrhosis	MI	2/118	15/236
Marchesini (1999)[61]	Italy	Full-text	1992–1995	Cirrhosis	CAD	11/122	6/40
Ruebner (1961)[62]	USA	Full-text	NA	Cirrhosis	MI	13/399	43/399
Howell (1960)[63]	USA	Full-text	1957	Cirrhosis	MI	32/639	NA
Grant (1959)[64]	USA	Full-text	1953–1957	Cirrhosis	MI	24/123	NA

ACS, acute coronary syndromes; CAD, coronary artery disease; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; MI, myocardial infarction; NA, not available; USA, United States of America.

Table 4. Prevalence of CAD in liver cirrhosis: Results of meta-analyses

Subgroup	No. studies	Pooled prevalence (95%CI)	Heterogeneity		$P_{interaction}$
			I^2 (%)	*p*-value	
Region					0.88
America	23	17.35% (12.42–22.27%)	98.7	<0.01	
Asia	8	19.39% (10.51–28.28%)	99.3	<0.01	
Europe	6	19.64% (0.00–42.01%)	97.2	<0.01	
Africa	2	36.30% (0.00–86.82%)	97.2	<0.01	
Publication year					0.03
After 2015	20	24.49% (15.81–33.16%)	99.4	<0.01	
Before 2015	19	13.73% (9.18–18.28%)	98.8	<0.01	
Type of publication					0.89
Full-texts	36	18.81% (13.52–24.09%)	99.2	<0.01	
Abstracts	3	19.74% (7.24–32.23%)	97.5	<0.01	
Study quality					0.69
High and Moderate	30	19.51% (14.01–25.01%)	99.1	<0.01	
Low	9	16.87% (5.31–28.43%)	98.6	<0.01	
Sample size					0.11
≥243	19	14.96% (9.93–19.98%)	99.6	<0.01	
<243	20	22.90% (14.49–31.31%)	96.7	<0.01	
Sex					0.33
Male	4	28.79% (7.57–50.02%)	98.5	<0.01	
Female	4	16.78% (5.04–28.52%)	93.9	<0.01	
Age					0.39
≥56	12	25.69% (13.86–37.52%)	98.8	<0.01	
<56	8	19.15% (10.20–28.11%)	98.9	<0.01	
Diabetes mellitus					0.39
Yes	3	36.89% (11.48–62.30%)	97.3	<0.01	
No	3	21.70% (0.00–45.38%)	97.3	<0.01	
Hypertension					0.37
Yes	3	38.17% (9.01–67.32%)	98.2	<0.01	
No	3	21.10% (0.00–43.99%)	96.8	<0.01	
Smoking history					0.50
Yes	4	28.58% (8.61–48.55%)	98.1	<0.01	
No	4	20.05% (5.35–34.76%)	95.0	<0.01	
Family history of CAD					0.36
Yes	3	46.96% (7.53–86.39%)	94.9	<0.01	
No	3	25.08% (0.28–49.88%)	98.1	<0.01	
Hyperlipidemia					0.59
Yes	2	44.25% (0.00–93.36%)	93.2	<0.01	
No	2	27.13% (0.00–65.30%)	99.0	<0.01	
Etiology of cirrhosis					<0.01
HCV	7	15.85% (7.93–25.74%)	99.4	<0.01	
NASH	9	21.16% (15.71–27.15%)	92.3	<0.01	
Alcohol	9	17.34% (7.73–29.66%)	96.8	<0.01	
PBC	2	4.04% (0.17–12.08%)	93.4	<0.01	
HBV	2	5.05% (0.67–13.06%)	97.0	<0.01	
Severity of CAD					<0.01
Non-obstructive	7	24.44% (14.42–36.07%)	96.4	<0.01	
Obstructive	7	13.86% (8.96–19.60%)	90.0	<0.01	
Severe	4	7.05% (3.03–12.46%)	87.8	<0.01	

CAD, coronary artery disease; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis.

Table 5. Factors associated with CAD in cirrhosis

Variables	Effect size (95% CI)	Heterogeneity		*p*-value
		I^2 (%)	*p*-value	
Incidence				
Sex (male)	RR:0.90 (0.79–1.03)	0	0.862	0.12
Diabetes mellitus	RR:1.52 (1.30–1.78)	0	0.755	<0.01
Hypertension	RR:2.14 (1.13–4.04)	78.5	0.031	0.02
Prevalence				
Age	MD:5.68 (2.46–8.90)	73.6	0.023	<0.01
MELD score	MD:1.23 (−0.42–2.88)	75.7	0.016	0.14
Child-Pugh score	MD:0.23 (−0.24–0.71)	0	0.698	0.34
BMI	MD:−0.12 (−0.74–0.50)	0	0.532	0.70
Sex (male)	OR:2.35 (1.26–4.36)	61.8	0.049	0.01
Diabetes mellitus	OR:2.67 (1.70–4.18)	27.6	0.251	<0.01
Hypertension	OR:2.39 (1.23–4.61)	61	0.077	0.01
History of smoking	OR:1.56 (1.03–2.38)	0	0.931	0.04
Family history of CAD	OR:2.18 (1.22–3.92)	49.7	0.137	0.01
Hyperlipidemia	OR:4.12 (2.09–8.13)	0	0.522	<0.01
HCC	OR:0.89 (0.64–1.23)	0	0.959	0.46
NASH cirrhosis	OR:1.59 (1.09–2.33)	0	0.933	0.02
HCV cirrhosis	OR:1.35 (1.19–1.54)	0	0.977	<0.01
Alcoholic cirrhosis	OR:1.74 (0.95–3.21)	76.7	0.050	0.07

BMI, body mass index; CAD, coronary artery disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; NASH, non-alcoholic steatohepatitis.

(95% CI = 3.51–9.36%) (Supplementary Fig. 3B). Significant heterogeneity was observed (I^2 = 94.7%, p < 0.01), with no evidence of publication bias (p = 0.06).

Five studies compared MI prevalence between patients with and without liver cirrhosis.[28,40,58,60,62] Available evidence showed no significant difference in MI prevalence between these groups (OR = 0.58; 95% CI = 0.28–1.22; p = 0.15) (Supplementary Fig. 4B). Significant heterogeneity was observed (I^2 = 93.2%; p < 0.01), but there was no evidence of publication bias (p = 0.50).

Risk factors associated with CAD in cirrhosis

Risk factors for CAD occurrence: Two studies evaluated factors associated with CAD occurrence in liver cirrhosis.[19,23] Meta-analyses found that diabetes mellitus (RR = 1.52; 95% CI = 1.30–1.78; p < 0.01) and hypertension (RR = 2.14; 95% CI = 1.13–4.04; p = 0.02), but not male sex, were significantly associated with CAD occurrence in liver cirrhosis (Table 5).

Risk factors for CAD presence: Six studies evaluated factors associated with CAD presence in liver cirrhosis.[9,27,28,36,38,58] Meta-analyses found that advanced age (MD = 5.68; 95% CI = 2.46–8.90; p < 0.01), male sex (OR = 2.35; 95% CI = 1.26–4.36; p = 0.01), diabetes mellitus (OR = 2.67; 95% CI = 1.70–4.18; p < 0.01), hypertension (OR = 2.39; 95% CI = 1.23–4.61; p = 0.01), hyperlipidemia (OR = 4.12; 95% CI = 2.09–8.13; p < 0.01), smoking history (OR = 1.56; 95% CI = 1.03–2.38; p = 0.04), family history of CAD (OR = 2.18; 95% CI = 1.22–3.92; p = 0.01), and NASH (OR = 1.59; 95% CI = 1.09–2.33; p = 0.02) and HCV (OR = 1.35; 95% CI = 1.19–1.54; p < 0.01) as etiologies of liver cirrhosis, but not alcohol abuse, hepatocellular carcinoma, BMI, or Child-Pugh or MELD scores, were significantly associated with CAD presence in liver cirrhosis (Table 5).

Discussion

Our study aimed to assess the epidemiology of CAD in patients with liver cirrhosis and evaluate the association between cirrhosis and CAD. We found that CAD is not uncommon in patients with liver cirrhosis, but current evidence does not support a definitive association between liver cirrhosis and CAD. Additionally, traditional cardiovascular risk factors, including advanced age, male sex, diabetes mellitus, hypertension, dyslipidemia, smoking, family history of CAD, and certain etiologies of chronic liver disease—namely NASH and HCV—are associated with the presence of CAD in these patients.

Our study confirms that traditional risk factors for CAD may also predict or promote the development of cardiovascular disease in patients with cirrhosis. Furthermore, liver cirrhosis is characterized by decreased nitric oxide levels, increased oxidative stress, and elevated levels of vasoconstrictor agents (such as thromboxane A2, COX-1-derived prostanoids, and endothelin-1), as well as inflammatory markers (such as tumor necrosis factor-alpha, nuclear factor kappa B, Toll-like receptor, and angiotensin II). These factors play a significant role in endothelial dysfunction, which can contribute to the development of CAD.[6,65–67] In cases of infection, encephalopathy, or bleeding, a fragile hemostatic balance may be disrupted, leading to a heightened risk of thrombosis. Jepsen et al. demonstrated an 8.7-fold increased risk

of MI in patients with decompensated cirrhosis who had recently undergone variceal ligation/sclerotherapy or ascites puncture/drainage within 90 days of treatment, compared to those with compensated cirrhosis.[17] Additionally, decreased peripheral resistance, compensatory hyperdynamic circulation, and increased cardiac output and heart rate may reduce coronary blood flow, thereby increasing the risk of ACS.[1]

Patients with cirrhosis should be referred for transplantation when they develop severe hepatic dysfunction (i.e., MELD score ≥15) or experience decompensation events (i.e., ascites, variceal bleeding, hepatic encephalopathy, or hepatorenal syndrome).[68] However, CAD is a significant predictor of adverse prognosis in liver transplantation candidates.[13] The American Heart Association and the American College of Cardiology Foundation have recommended noninvasive stress testing for liver transplantation candidates with multiple risk factors (e.g., diabetes, prior cardiovascular disease, left ventricular hypertrophy, age over 60 years, smoking, hypertension, or dyslipidemia).[69] Patients with known cardiac disease and those with abnormal screening tests should undergo further evaluation with coronary computed tomography angiography. The European Association for the Study of the Liver guidelines recommend that all liver transplant candidates undergo electrocardiography and echocardiography and that patients with multiple risk factors or those older than 50 years undergo cardiopulmonary exercise testing to identify asymptomatic CAD.[70] Most guidelines focus on evaluating CAD in liver transplant candidates, with less emphasis on patients with advanced cirrhosis. High-risk cirrhotic patients should undergo a careful cardiac evaluation to promptly identify the type of CAD and stratify risk, enabling the formulation of appropriate management strategies that could reduce overall and cardiac-related mortality.

There is a mutual interaction between liver cirrhosis and CAD. Evidence suggests that CAD may be more severe in cirrhotic individuals compared to non-cirrhotic individuals.[9,42] Patients with cirrhosis often exhibit significantly more non-obstructive lesions, more extensive involvement of coronary vessels,[9] longer atherosclerotic plaques, and higher total volumes of calcified or non-calcified plaques.[42] Additionally, increasing levels of liver fibrosis and cirrhosis biomarkers are associated with more severe plaque and CAD. Liver fibrosis (LF) scores, including the Fibrosis-4 score and the non-alcoholic fatty liver disease fibrosis score, have been shown to predict the presence of coronary calcification.[71] The non-alcoholic fatty liver disease fibrosis score is positively associated with the degree of coronary stenosis, while the Fibrosis-4 score correlates with the number of diseased coronary vessels.[72] LF also negatively impacts the long-term prognosis of CAD patients. A prospective cohort study indicated that higher LF scores are associated with increased risks of all-cause and cardiovascular mortality among CAD patients.[73] Taken together, advanced liver fibrosis appears to correlate with the severity of CAD, suggesting that these patients may require closer monitoring and screening for cardiovascular risk factors.

Notably, the association between liver cirrhosis and CAD may depend on the underlying etiology of the cirrhosis. Our study found a positive association between HCV cirrhosis and the presence of CAD. Similarly, previous studies have shown that HCV increases the risk of CAD.[74] HCV directly and indirectly influences glucose and lipid metabolism, leading to a high prevalence of insulin resistance, steatosis, and diabetes mellitus.[75] Additionally, the virus may have direct effects on the vessel wall.[76] Our study also found that NASH was positively associated with CAD presence in liver cirrhosis. NASH is commonly associated with dyslipidemia, insulin resistance, and increased pro-inflammatory cytokines, all of which play important roles in the pathophysiology of atherosclerosis.[77] Conversely, we did not find a significant association between alcoholic cirrhosis and CAD presence; however, other studies suggest that alcoholic cirrhosis is associated with both the occurrence and severity of CAD.[18,20] Furthermore, coronary arteriosclerosis is particularly extensive in alcoholic cirrhosis. Patients with alcoholic cirrhosis had significantly higher median coronary artery calcium scores, which quantify coronary artery calcification, compared to those with non-alcoholic cirrhosis.[78] Alcohol-related liver disease was also significantly associated with a coronary artery calcium score >300, indicating a high risk of cardiovascular events.[79] This is likely due to excessive alcohol consumption, which is associated with increased levels of low-density lipoprotein and the expression of adhesion molecules.[80]

A meta-analysis conducted by Zhao et al. included five studies but only pooled the prevalence of CAD in cirrhosis.[10] Another meta-analysis by Ungprasert et al. included four studies and reported an increased risk of CAD in PBC patients,[81] a finding not confirmed by our study. In comparison, our study has several strengths. First, to our knowledge, we are the first to systematically report the incidence of CAD, the association between CAD and liver cirrhosis, and the factors related to the occurrence and presence of CAD in cirrhosis. Second, we included all types of cirrhosis rather than focusing solely on a single type, such as PBC. Third, we performed a comprehensive literature search using three major databases without language limitations to maximize the inclusion of epidemiological studies on CAD in liver cirrhosis. Fourth, we categorized CAD into ACS and MI to explore the effects of cirrhosis on different types of CAD.

Our study also has some limitations. First, significant heterogeneity remains in our meta-analyses, which necessitates cautious interpretation of our findings. Most of the included studies were retrospective, some had small sample sizes, and they utilized various definitions and diagnostic approaches for cirrhosis and CAD, potentially introducing bias into the results. Due to substantial differences and publication bias among the included studies, the pooled results may not accurately reflect the true effect size, impacting the reliability of the results. Second, the number of relevant studies was limited, and some were of low quality, which compromised the reliability of our findings. Only five studies reported associations between specific etiologies and CAD, making our conclusions implausible. Large-scale, well-designed prospective cohort studies are necessary to support our findings in the future. Additionally, we were unable to obtain information on the use of antithrombotic drugs and antiviral drugs for HCV, which could affect CAD development. Meanwhile, we could not perform subgroup analyses according to the different stages of cirrhosis and were unable to explore the association of HBV and PBC—with significant effects on lipid metabolism—with CAD in cirrhotic patients. Third, two previous meta-analyses found significant associations between NASH and HCV with cardiovascular diseases,[74,77] which appear to contradict our findings. This discrepancy may be attributed to the differences in the etiologies of cirrhosis evaluated. Our included studies featured patients with mixed etiologies of liver cirrhosis, suggesting that liver cirrhosis is related not only to NASH but also to other causes, such as HBV. Indeed, two other previous meta-analyses indicated that HBV infection does not increase the risk of CAD.[82,83] Our subgroup analyses based on different etiologies of cirrhosis demonstrated that the prevalence of CAD in NASH-related cirrhosis was higher than in other etiologies. Additionally, we found that the presence of NASH in cirrhosis increased the risk of

CAD by 1.59 times. Fourth, the term "primary biliary cirrhosis" has been replaced by "primary biliary cholangitis" in recent years.[84] However, earlier studies specifically referred to primary biliary cirrhosis, and some patients without a definitive diagnosis of liver cirrhosis were also attributed to the primary biliary cirrhosis group, which raises the possibility of misclassification. Finally, potential competing events, such as liver-related deaths, may compromise the development of CAD during follow-up, thereby influencing the true estimates of CAD.

Conclusions

CAD is common in cirrhotic patients, but its risk may not be increased solely by the presence of liver cirrhosis. NASH and HCV do increase the risk of CAD in these patients, along with traditional cardiovascular risk factors. Large-scale prospective studies are needed to clarify how to screen for and prevent CAD in the high-risk population with liver cirrhosis.

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Conflict of interest

XQ has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2023. The other authors have no conflict of interests related to this publication.

Author contributions

Reviewed and searched the literature, collected and analyzed the data, discussed the findings, drafted the manuscript (CG), searched the literature, collected the data (LD), discussed the findings, gave critical comments (LC, ZT, FG, WA, FGR), conceived the work, reviewed the literature, interpreted the findings, and revised the manuscript (XQ). All authors contributed intellectually to the manuscript and approved the final version and publication of the manuscript.

Data sharing statement

Data synthesized in this meta-analysis were extracted from published studies.

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