Hepatitis C virus infection and development of type 2 diabetes mellitus: systematic review and meta-analysis of the literature.

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Abstract

Type 2 diabetes mellitus (T2DM) is an endocrine disorder encompassing multifactorial mechanisms, and chronic hepatitis C virus infection (CHC) is a multifaceted disorder, associated with extrahepatic manifestations, including endocrinological disorders. CHC and T2DM are associated, but the subject remains controversial.

We performed a systematic review and meta-analysis evaluating such association, searching on PubMed until February 29, 2016.

Inclusion criteria were: 1) presence of at least one internal control group age- and gender-matched (non-hepatopathic controls; and/or hepatopathic, not HCV-positive, controls); 2) sufficient data to calculate odds ratio and relative risk. Exclusion criteria were: 1) literature reviews on the topic; 2) publications regarding special populations [human immunodeficiency virus and human T-lymphotropic virus-1 coinfections, hepatocellular carcinoma (HCC), post-transplantation DM, gender selection]; 3) no clear differentiation among HCV patients with CHC, cirrhosis or HCC.

Data from each study were independently extracted by two reviewers and cross-checked by AA.

Our systematic review returned 544 records, and 33 were included in our meta-analysis.

HCV infection is associated with an increased risk of T2DM independently from the severity of the associated liver disease, in CHC and cirrhotic HCV patients. As expected T2DM risk is higher in cirrhotic HCV patients, than CHC, and the prevalence of HCV infection in T2DM patients is higher than in non-diabetic controls. Regarding HBV infection prevalence, no difference exists in diabetic and non-diabetic subjects.

An unequivocal CHC and T2DM association was shown. A proactive, integrated approach to HCV and T2DM therapies should maximize benefits of both diseases treatment.

Keywords: Hepatitis C virus; hepatitis C extra-hepatic manifestations; hepatitis B virus; type 2 diabetes mellitus; meta-analysis.

Abbreviations

CH, chronic hepatitis - CHC, chronic hepatitis C virus infection - DAA, direct-acting antiviral treatment - DM, diabetes mellitus - EHM, extra-hepatic manifestations - HCC, hepatocellular carcinoma - HBV, hepatitis B virus - HCV, hepatitis C virus - HIV, human immunodeficiency virus - HTLV, human T-lymphotropic virus - IR, insulin resistance - NIDDM, non-insulin dependent diabetes - OR, odds ratio - PTDM, post transplantation diabetes mellitus - RR, relative risk - SVR, sustained virological response - T2DM, type 2 diabetes mellitus.

Introduction

Hepatitis C virus (HCV) infection and diabetes mellitus (DM) are two major public health problems worldwide that cause devastating health and financial burden [1,2].

There is an ever-increasing prevalence of type 2 DM (T2DM), that currently affects over 370 million people worldwide [3]. Normal regulation of glucose metabolism is determined by a feedback loop involving the islet β-cell and insulin-sensitive tissues in which tissue sensitivity to insulin determines the magnitude of the β-cell response [4]. When insulin resistance (IR) is present, the β-cell maintains normal glucose tolerance by increasing insulin output. It is only when the β-cell is incapable of releasing sufficient insulin in the presence of IR that glucose levels rise. While β-cell dysfunction has a clear genetic component, environmental changes play a vital role [5].

Moreover, there are several causes and associations known to be involved in the development of DM.

Seconday forms of DM are frequently disregarded [6]. Growth hormone (GH) deficiency, polycistic ovarian syndrome, testosterone deficiency, and others can lead to impaired glucose tolerance and DM [6].

Also "Non-Alcoholic Fatty Liver Disease" (NAFLD) is associated with insulin resistance, and/or diabetes [7]. NAFLD can present in a simple form characterized by lipid accumulation in the liver, however in about 20% of patients NAFLD progresses to "Non-Alcoholic Steatohepatitis" (NASH), characterized by hepatocellular injury, hepatic inflammatory infiltrates and fibrosis [7]. Both NAFLD, and NASH, are strongly associated with abnormal glucose tolerance, dyslipidemia, obesity, and diabetes [8].

Recently many studies have suggested that chronic hepatitis C virus infection (CHC) is associated with T2DM [9]. **CHC patients develop at least one extrahepatic manifestation, that consists of autoimmune disorders, as mixed cryoglobulinemia (MC), Sjogren's syndrome, and endocrinological diseases such as autoimmune thyroid disorders (AITD) or type 2 diabetes [10]. In genetically predisposed subjects in particular conditions, viruses and molecular mimicry between microbial and human antigens can turn a defensive immune response into autoimmunity [11]. Molecular mimicry has been studied much less in endocrinology, as the majority of papers concerns diabetes, and to a lesser extent, thyroid, pancreas and infertility [11].**

However the association between CHC and T2DM is not consistent across all studies, and the subject remains controversial [12-21]. Furthermore this association could be due to different pathogenetic mechanisms, related to the changes that HCV induces in the liver, or to systemic and extra-hepatic effects of the infection itself [22].

Here, we sistematically reviewed literature records, identified through PubMed database searching, on the increasing evidence of a link between HCV infection and the development of T2DM to understand whether epidemiological studies could confirm such a relationship, and then we performed a meta-analysis.

Methods

Systematic Review

The methods and findings of the present review have been reported based on the preferred reporting items for systematic reviews and meta-analysis checklist (PRISMA). Figure 1 provides a flow chart of the present review.

We searched the literature on PubMed library combining the terms "diabetes", "diabetes mellitus", "type 2 diabetes mellitus", "type 2 DM", "T2DM", "non-insulin dependent diabetes", or "NIDDM" and "hepatitis", "hepatitis C", "hepatitis C virus", " HCV", "HVC", or "chronic hepatitis" and "risk", "risk factor", "case-control", "cohort", "clinical trial", "crosssectional", "epidemiology", "observational", "meta-analysis", "systematic review", or "review".

We used no language or time restrictions. Search was concluded on February 29, 2016.

Two investigators independently reviewed the retrieved articles in two stages; first assessing relevance from the title and abstract and if relevance was still unclear, the full text was read. Any disagreement about inclusion was referred to a third reviewer and resolved by discussion.

Only epidemiological studies evaluating the possible association of HCV with T2DM (with respect to an internal control group), with a cross sectional, or longitudinal design, were selected.

We considered as inclusion criteria: 1) the presence of at least one internal control group matched by age and gender [non-hepatopathic controls; and/or hepatopathic, not HCV-positive, controls]; 2) provision of sufficient data to calculate odds ratio [OR] and relative risk [RR]. Exclusion criteria were: 1) literature reviews on the topic; 2) publications regarding special populations [see human immunodeficiency virus (HIV) and human T-lymphotropic virus (HTLV)-1 coinfections, hepatocellular carcinoma (HCC), post transplantation diabetes mellitus (PTDM), gender selection]; 3) no clear differentiation among HCV patients with chronic hepatitis (CH), cirrhosis or HCC.

Data collection

Data from each study were independently extracted by two reviewers and cross-checked by AA.

We recorded author and year of publication, samples size, hepatic definition status (healthy, CH, or cirrhosis) and diabetes definition status (presence or absence).

Statistical analysis

According to other similar studies [23,24] the results of the controlled studies were cumulated (see Tables), and analyzed performing the OR, and RR, by Java-Stat 2-way Contingency Table Analysis, STATA, and StatView.

Relative risks with 95% confidence intervals were calculated. The heterogeneity between studies was measured using I^2 values, the following ranges were considered for the analysis: no heterogeneity (I^2=0–25%); moderate heterogeneity (I^2=25%–50%); high heterogeneity (I^2=50%–75%); maximum heterogeneity (I^2=75%–100%). Egger's test was performed to value publication bias. Data were elaborated using Comprehensive Meta-Analysis software (Version 2) and summarized in the following forest plots (see Figure 2a, 2b, 2c, 3a, 3b, 3c, 4a, 4b).

Results

Our initial search yelded 544 articles, 145 of which had relevant titles and abstracts. Multiple publications using the same data were deleted. After accurate assessment 71 studies met our inclusion criteria (**Figure 1**), of which 33 were included in our meta-analysis [25-57], while 38 were excluded at the stage of data extraction (**Figure 1**) [12-21,58-85].

Since cirrhosis of whatever origin is associated with T2DM, we have analyzed separately data of HCV patients affected by CHC (**Tables 1a, b, c**), from those of HCV patients with cirrhosis (**Tables 2a, b, c**). Furthermore, we have presented data about HCV prevalence in diabetic patients in **Table 3a**, and for comparison data about HBV prevalence in diabetic patients in **Table 3b**.

The results of the studies that have evaluated patients with CHC (without cirrhosis) in comparison with "normal" non hepatopathic controls (matched by age and gender) are reported in **Table 1a**. A total of 1046 CHC patients and 1303 non hepatopathic controls were analyzed, showing an increased significant risk of T2DM in CHC (**Fig. 2a**).

To evaluate if the presence of hepatic disorders different from HCV infection might be related to T2DM (independently from the presence of HCV infection) we have evaluated patients with CHC (without cirrhosis) in comparison with hepatopathic (not HCV-positive) controls with HBV infection, alcohol, colestatic or cryptogenic related disorders

(without cirrhosis) (matched by age and gender) (**Table 1b**). A total of 2982 CHC patients and 1411 hepatopathic (not HCV-positive) controls were analyzed, showing an increased significant risk of T2DM in CHC (**Fig. 2b**).

To evaluate if the presence of hepatic disorders associated with another infection might be related to T2DM, independently from the presence of HCV infection, we have separately evaluated patients with CHC (without cirrhosis) in comparison with HBV-positive chronic hepatitis controls (HBV+CH controls) (without cirrhosis) (matched by age and gender) (**Table 1c**). A total of 2277 CHC patients and 1022 HBV+CH controls were analyzed, showing an increased significant risk of T2DM in HCV+CHC (**Fig. 2c**).

The results of the studies that have evaluated the presence of T2DM in HCV cirrhosis, in comparison with "normal" non hepatopathic controls (matched by age and gender) are reported in **Table 2a**. A total of 207 HCV cirrhotic patients and 694 "normal" non hepatopathic controls were analyzed, showing an increased significant risk of T2DM in HCV cirrhosis (**Fig. 3a**). It is evident that the risk of T2DM in HCV cirrhosis is higher than in CHC patients (**Fig. 3a**) (OR 6·8 versus 2·1; comparison with Table 1a).

To evaluate if the presence of HCV infection in cirrhosis might increase the risk of T2DM, we have compared patients with HCV cirrhosis with non HCV-cirrhotic controls (with HBV, alcohol, colestatic or cryptogenic disorders, or primary biliary cirrhosis or primary sclerosing cholangitis) (matched by age and gender) (**Table 2b**). A total of 2401 cirrhotic HCV patients and 1588 non HCV-cirrhotic controls were analyzed, showing an increased significant risk of T2DM in HCV cirrhosis (**Fig. 3b**).

To evaluate if the presence of cirrhosis associated with another infection might be related to T2DM, independently from the presence of HCV infection, we have separately evaluated patients with HCV cirrhosis in comparison with cirrhotic HBV controls (matched by age and gender) (**Table 2c**). A total of 1868 HCV patients and 518 HBV controls were analyzed, showing an increased significant risk of T2DM in HCV patients (**Fig. 3c**).

Data about HCV prevalence in diabetic patients versus non-diabetic controls are reported in **Table 3a**. A total of 7984 T2DM patients and 34488 not diabetic controls were analyzed, showing an increased prevalence of HCV infection in T2DM patients (**Fig. 4a**).

To evaluate if the presence of another hepatic viral infection might be related to T2DM, independently from the presence of HCV infection, data about the prevalence of HBV infection in diabetic patients, versus non-diabetic controls are reported in **Table 3b**, showing no significant difference (**Fig. 4b**).

Discussion

The results of our meta-analysis show that HCV infection is associated with an increased risk of T2DM independently from the severity of the associated liver disease, both in CHC patients, and in HCV cirrhotic ones. As expected, the risk of T2DM is higher in cirrhotic HCV patients, with respect to CHC patients. Furthermore, on the other side, the prevalence of HCV infection in T2DM patients is higher than in non diabetic controls; while the prevalence of HBV infection is not different in diabetic and non diabetic subjects. On the whole the results show an unequivocal association of HCV chronic infection and T2DM.

Concerning our study, next to this strength of association, some potential limitations exist: 1) lack of generalizability of results (e.g. exclusion of publications regarding special population; absence of distinct observation regarding gender, age and ethnicity); 2) small sample size which may be unable to reflect the actual prevalence of T2DM in HCV infected people; 3) selection of only studies reporting on presence or absence of overt diabetes with the possibility of underestimating the magnitude of the relationship between HCV infection and impaired glucose metabolism; 4)

insufficient available informations on patients' data for each study with consequent deficiency on further adjustments for important factors such as viral genotype, family history of diabetes, life style, visceral adiposity, and comorbidities.

Indeed, analyzing literature, viral factors and host immune response and characteristics, concerning genetic background, life style and comorbidities, can interact in determining the increased risk for T2DM in HCV patients [86]. Most of the studies that have evaluated the mechanisms underlying the association between HCV and T2DM suggest that IR has a very important role [18]. However, other studies have suggested a dysfunction of β-cells [87], or the importance of an immune mediated disorder [88], in HCV T2DM patients. The knowledge of the pathogenic mechanisms involved in diabetes associated with HCV infection will enable us not only to further identify those patients at high risk of developing diabetes but also to select the best therapeutic option.

It has become increasingly apparent that IR with or without concomitant T2DM influences longterm outcomes in CHC, promoting more rapid progression of liver disease [89,90], to cirrhosis [91] or HCC [92,93]. Moreover, diabetic HCV positive patients have an increased risk for progression respect to non diabetic subjects, and DM itself seems to have a selective impact on HCC development [94,95]. The connection between HCV infection and the development of DM increases the need for implementation of prevention measures. Prevention has to be addressed to lifestyle changes that can reduce the risk of HCV infection and/or developing diabetes [90], regular diabetes screening for anti-HCV positive persons and analysis of other risk factors that can accelerate progression of both CHC and DM, such as obesity, dyslipidemia, and alcohol consumption. In these high-risk patients, a comprehensive treatment including lifestyle modifications has to be recommended.

Animal models also provide clues to the prevention and clinical management of diabetes in the setting of HCV infection [90]. Indeed, the identification of patients at risk of diabetes in CHC decelerates in liver disturbances progression [89], decreases incidence of HCC, and transplant-related morbidity and mortality, and improves the response to antiviral therapy, both increasing the likelihood of a sustained virological response (SVR), as demonstrated with interferon and ribavirin treatment [96] and as also conceivable, but still unclear, with new direct-acting antiviral treatment (DAA) [97,98], and reducing side effects of the treatment [96,99], by pretreating IR and DM [100].

Conversely, SVR has been demonstrated to ameliorate IR and improve β-cell function [101,102].

The availability of new interferon-free, well-tolerated anti-HCV treatment regimens is broadening the spectrum of patients available for therapy, including those in whom interferon was contraindicated, and will likely result in greater improvements in the extrahepatic manifestations of HCV, including diabetes.

Actually, the effect of DAA HCV treatments on IR and long-term risk of T2DM has yet to be clearly established [103].

Surely many factors may interfere with the reduction of the incidence of IR and T2DM in CHC patients who obtain SVR after therapy (among them, HCV genotype, genetic host factors and demographic, clinical, histological and lifestyle characteristics of the patients). For this reason, the eradication of HCV in patients with pre-disposing factors for T2DM should not preclude proper counseling on diet and physical activity [104].

Real-world evidence studies are needed to understand the total clinical and economic effects of HCV infection (with both hepatic and extrahepatic related manifestations) management and treatment on patients and society [105].

Compliance with Ethical Standards

Funding: The authors have nothing to declare.

Research involving Human Participants: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Table 1a T2DM prevalence among hepatopathic patients with HCV-related chronic hepatitis (without cirrhosis) versus non-hepatopathic controls

	HCV+ tot.	Diabetic pts among HCV + n (%)	HCV+ without T2DM n (%)	Non-hepatopathic controls tot.	Diabetic pts among non-hepatopathic controls n (%)	Non-hepatopathic controls without T2DM n (%)	Odds ratio	Relative risk
Ozyilkan et al (1996)[25]	106	22 (20·8)	84 (79·2)	200	3 (1·5)	197 (98·5)		
Mangia et al (1998)[26]	102	6 (5·9)	96 (94·1)	494	48 (9·7)	446 (90·3)		
Knobler et al (2000)[27]	45	15 (33·3)	30 (66·7)	90	5 (5·6)	85 (94·4)		
Antonelli et al (2004)[28]	229	33 (14.4)	196 (85·6)	217	15 (6·9)	202 (93·1)		
Antonelli et al (2005)[29]	564	71 (12·6)	493 (87·4)	302	22 (7·3)	280 (92·7)		
Total	1046	147	899	1303	93	1210		
							OR	RR
							2·12	1·969
95% confidence interval							1·60–2·82	1·52–2·54
							p=0·0000	p=0·000

HCV+ = HCV-positive; pts = patients

Table 1b T2DM prevalence among hepatopathic patients with HCV-related chronic hepatitis (without cirrhosis) versus hepatopathic (not HCV-positive) controls with HBV, alcohol, colestatic or cryptogenic disorders

	HCV+ tot.	Diabetic pts among HCV+ n (%)	HCV+ without T2DM n (%)	Non HCV-hepatopathic controls tot.	Diabetic pts among non HCV-hepatopathic controls n (%)	Non HCV-hepatopathic controls without T2DM n (%)	Odds ratio	Relative risk
Ozyilkan et al (1996)[25]	106	22 (25·8)	84 (79·2)	138	9 (6·5)	129 (93·5)		
Grimbert et al (1996)[30]	180	45 (25)	135 (75)	101	11 (11)	90 (89)		
Mangia et al (1998)[26]	102	6 (5·9)	96 (94·1)	36	0 (0)	36 (100)		
Caronia et al (1999)[31]	51	1 (2)	50 (98)	19	0 (0)	19 (100)		
Labropoulou-Karatza et al (1999)[32]	39	16 (41)	23 (59)	44	5 (11·4)	39 (88·6)		
Mason et al (1999)[33]	212	39 (18·4)	173 (81·6)	144	14 (9·7)	130 (90·3)		
Knobler et al (2000)[27]	45	15 (33)	30	88	11 (12)	77		
Ryu et al (2001)[34]	68	16 (23·5)	52 (76·5)	157	13 (8·3)	144 (91·7)		
Arao et al (2003)[35]	473	72 (15·2)	401 (84·8)	108	13 (12)	95 (88)		
Lecube et al (2004)[36]	380	65 (17·1)	315 (82·9)	92	6 (6·5)	86 (93·5)		
Antonelli et al (2005)[29]	564	71 (12·6)	493 (87·4)	82	4 (4·9)	78 (95·1)		
Imazeki et al (2008)[37]	544	74 (13·6)	470 (86·4)	286	18 (6·3)	268 (93·7)		
Rouabhia et al (2010)[39]	218	73 (33·5)	145 (66·5)	116	5 (4·3)	111 (95·7)		
Total	2982	515	2467	1411	109	1302		
							OR	RR
							2·49	2·23
95% confidence interval							1·99–2.74	1·83–2·74
							p=0·0000	p=0·000

HCV+ = HCV-positive; pts = patients

Table 1c T2DM prevalence among hepatopathic patients with HCV-related chronic hepatitis (without cirrhosis) versus hepatopathic HBV-positive controls

	HCV+ tot.	Diabetic pts among HCV + n (%)	HCV+ without T2DM n (%)	Hepatopathic HBV+ controls tot.	Diabetic pts among hepatopathic HBV+ controls n (%)	Hepatopathic HBV+ controls without T2DM n (%)	Odds ratio	Relative risk
Mangia et al (1998)[26]	102	6 (5·9)	96 (94·1)	22	0 (0)	22 (100)		
Caronia et al (1999)[31]	51	1 (2)	50 (98)	19	0 (0)	19 (100)		
Mason et al (1999)[33]	212	39 (18·4)	173 (81·6)	144	14 (9·7)	130 (90·3)		
Knobler et al (2000)[27]	45	15 (33·3)	30 (66·7)	88	11 (12·5)	77 (87·5)		
Ryu et al (2001)[34]	68	16 (23·5)	52 (76·5)	157	13 (8.2)	144 (88)		
Arao et al (2003)[35]	473	72 (15·2)	401 (84·8)	108	13 (12)	95 (88)		
Antonelli et al (2005)[29]	564	71 (12·6)	493 (87·4)	82	4 (4·9)	78 (95·1)		
Imazeki et al (2008)[37]	544	74 (13·6)	470 (86·4)	286	18 (6·3)	268 (93·7)		
Rouabhia et al (2010)[39]	218	73 (33·5)	145 (66·5)	116	5 (4·3)	111 (95·7)		
Total	2277	367	1910	1022	78	944		
95% confidence interval							OR 2·32 1·78–2·69 p=0·0000	RR 2·11 1·66–2·69 p=0·000

HCV+ = HCV-positive; pts = patients

Table 2a T2DM prevalence among hepatopathic patients with HCV-related cirrhosis versus non-hepatopathic controls

	HCV+ tot.	Diabetic pts among HCV + n (%)	HCV+ without T2DM n (%)	Non-hepatopathic controls tot.	Diabetic pts among non-hepatopathic controls	Non-hepatopathic controls without T2DM n (%)	Odds ratio	Relative risk
Ozyilkan et al (1996)[25]	50	19 (38)	31 (62)	200	3 (1·5)	197 (98·5)		
Mangia et al (1998)[26]	157	54 (34·4)	103 (65·6)	494	48 (9·7)	446 (90·3)		
Total	207	73	134	694	51	643		
							OR	RR
							6·82	4·79
95% confidence interval							4·50–10·49	3·44–6·70
							p=0·000	p=0·000

HCV+ = HCV-positive; pts = patients

Table 2b T2DM prevalence among hepatopathic patients with HCV-related cirrhosis versus non HCV-cirrhotic controls (with HBV, alcohol, colestatic or cryptogenic disorders, or primary biliary cirrhosis or primary sclerosing cholangitis)

	HCV+ tot.	Diabetic pts among HCV+ n (%)	HCV+ without T2DM n (%)	Non HCV-cirrhotic controls tot.	Diabetic pts among non HCV-cirrhotic controls n (%)	Non HCV-cirrhotic controls without T2DM n (%)	Odds ratio	Relative risk
Allison et al (1994)[40]	34	17 (50)	17 (50)	66	6 (9)	60 (91)		
Ozyilkan et al (1996)[25]	50	19 (38)	31 (62)	133	16 (12)	117 (88)		
Mangia et al (1998)[26]	157	54 (34·4)	103 (65·6)	90	26 (28·9)	64 (71·1)		
Guerrero et al (1998)[41]	28	8 (28·6)	20 (71·4)	47	5 (10·6)	42 (89·4)		
Caronia et al (1999)[31]	1151	272 (23·6)	879 (76·4)	181	17 (9·4)	164 (90·6)		
Mason et al (1999)[33]	145	48 (33·1)	97 (66·9)	88	18 (20·5)	70 (79·5)		
Bigam et al (2000)[42]	110	32 (29)	78 (71)	168	8 (4·8)	160 (95·2)		
Zein et al (2000)[43]	73	17 (23·3)	56 (76·7)	131	11 (8·4)	120 (91·6)		
Baid et al (2001)[44]	47	8 (17)	39 (83)	111	14 (12·6)	97 (87·4)		
Garrido Serrano et al (2001)[45]	50	18 (36)	32 (64)	50	9 (18)	41 (82)		
Ryu et al (2001)[34]	28	2 (7·1)	26 (92·9)	151	27 (17·9)	124 (82·2)		
Arao et al (2003)[35]	234	72 (30·8)	162 (69·2)	51	6 (11·8)	45 (88·2)		
Thuluvath et al (2003)[46]	97	19 (19·6)	78 (80·4)	194	22 (11·3)	172 (88·7)		
Lecube et al (2004)[36]	118	47 (39·8)	71 (60·2)	52	19 (36·5)	33 (63·5)		

Parolin et al (2004)[47]	36	13 (36·1)	23 (63·9)	70	18 (25·7)	52 (74·3)		
Rouabhia et al (2010)[39]	43	29 (67·4)	14 (32·6)	5	1 (20)	4 (80)		
Total	2401	675	1726	1588	223	1365		
							OR	RR
							2·39	2·00
95% confidence interval							2·02–2·84	1·74–2·30
							p=0·000	p=0·000

HCV+ = HCV-positive; pts = patients

Table 2c T2DM prevalence among hepatopathic patients with HCV-related cirrhosis versus HBV-related cirrhosis controls

	HCV+ tot.	Diabetic pts among HCV + n (%)	HCV+ without T2DM n (%)	HBV-related cirrhosis controls tot.	Diabetic pts among HBV-related cirrhosis controls n (%)	HBV-related cirrhosis controls without T2DM n (%)	Odds ratio	Relative risk
Mangia et al (1998)[26]	157	54 (34·4)	103 (65·6)	38	12 (31·6)	26 (68·4)		
Caronia et al (1999)[31]	1151	272 (23·6)	879 (76·4)	181	17 (9·4)	164 (90·6)		
Mason et al (1999)[33]	145	48 (33·1)	97 (66·9)	88	18 (20·5)	70 (79·5)		
Bigam et al (2000)[42]	110	32 (29)	78 (71)	53	3 (5·7)	50 (94·3)		
Ryu et al (2001)[34]	28	2 (7·1)	26 (92·9)	102	14 (13·7)	88 (86·3)		
Arao et al (2003)[35]	234	72 (30·8)	162 (69·2)	51	6 (11·8)	45 (88·2)		
Rouabhia et al (2010)[39]	43	29 (67·4)	14 (32·6)	5	1 (20)	4 (80)		
Total	1868	509	1359	518	71	447		
							OR	RR
							2·35	1·98
95% confidence interval							1·75–3·11	1·57–2·52
							p=0·0000	p=0·000

HCV+ = HCV-positive; pts = patients

Table 3a HCV positive rate among diabetic patients, matched with non diabetic subjects

	Diabetics			Non diabetics			Odds ratio	Relative risk
	tot	HCV + n (%)	HCV – n (%)	Tot	HCV+ n (%)	HCV – n (%)		
Simò et al (1996)[48]	176	18 (10·2)	158 (89·8)	6172	156 (2·5)	6016 (97·5)		
Labropoulou-Karatza et al (1999)[32]	36	30 (83·3)	6 (16·7)	72	34 (47·2)	38 (52·8)		
Rudoni et al (1999)[49]	259	8 (3·1)	251 (96·9)	14100	6 (0·1)	14094 (99·9)		
Chen et al (2006)[50]	820	56 (6·8)	764 (93·2)	905	23 (2·5)	882 (97·5)		
Ocak et al (2006)[51]	67	14 (20·9)	53 (79·1)	200	20 (10)	180 (90)		
Gulcan et al (2008)[52]	617	19 (3·1)	598 (96·9)	314	4 (1·3)	310 (98·7)		
Nwokediuk et al (2008)[38]	191	27 (14·1)	164 (85·9)	134	5 (3·7)	129 (96·3)		
Sjöberg et al (2008)[53]	375	2 (0·5)	373 (99·5)	331	2 (0·6)	329 (99·4)		
Kaabia et al (2009)[54]	1269	17 (1·3)	1252 (98·7)	1315	8 (0·6)	1307 (99·4)		
Jadoon et al (2010)[55]	3000	410 (13·7)	2590 (86·3)	10000	496 (5)	9504 (95)		
Chehadeh et al (2011)[56]	438	31 (7)	407 (93)	440	4 (1)	436 (99)		
Korkmaz et al (2015)[57]	736	24 (3·3)	712 (96·7)	505	9 (1·8)	496 (98·2)		
Total	7984	656	7328	34488	767	33721		
							OR	RR
							3·94	2·58
95% confidence interval							3·53–4·39	2·43–2·74
							p=0·0000	p=0·000

HCV+ = HCV-positive

Table 3b HBV positive rate among diabetic patients, matched with non diabetic subjects

	Diabetics			Non diabetics			Odds ratio	Relative risk
	tot	HBsAg+ n (%)	HBsAg– n (%)	tot	HBsAg+ n (%)	HBsAg – n (%)		
Chen et al (2006)[50]	820	111 (13·5)	709 (86·5)	905	112 (12·4)	793 (87·6)		
Gulcan et al (2008)[52]	617	31 (5)	586 (95)	314	12 (3·8)	302 (96·2)		
Korkmaz et al (2015)[57]	736	28 (3·8)	708 (96·2)	505	15 (3)	490 (97)		
Total	2173	170	2003	1724	139	1585		
							OR	RR
							0·97	0·98
95% confidence interval							0·76–1·23	0·87–1·09
							p=ns	p=ns

Figure Legend

Fig. 1 PRISMA flow chart: data collection and selection of studies

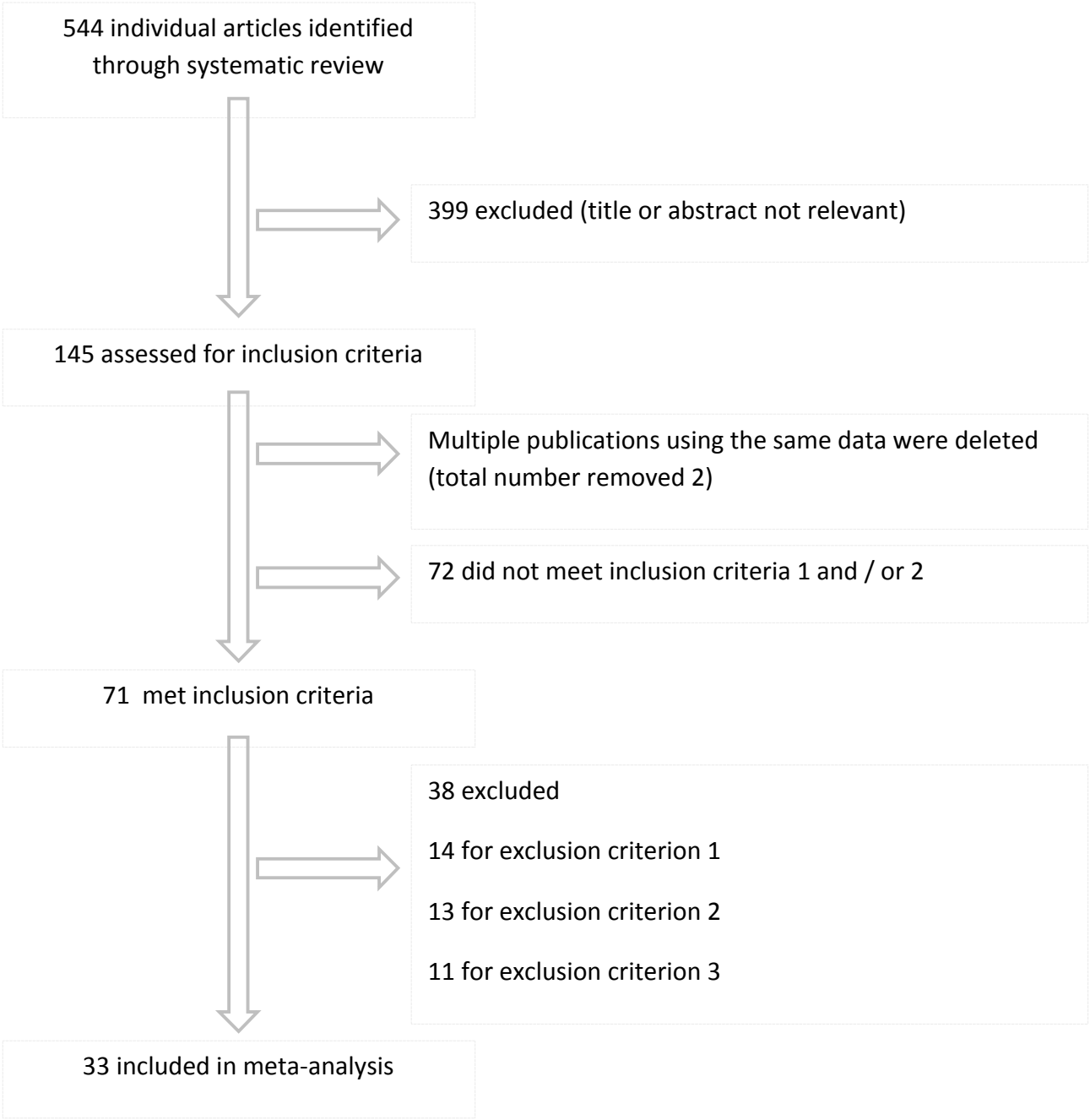

Figure Legend

Fig. 2a Forest plot related to the studies reported in Table 1a, showing T2DM risk in hepatopathic patients with HCV-related chronic hepatitis (without cirrhosis) versus non-hepatopathic controls

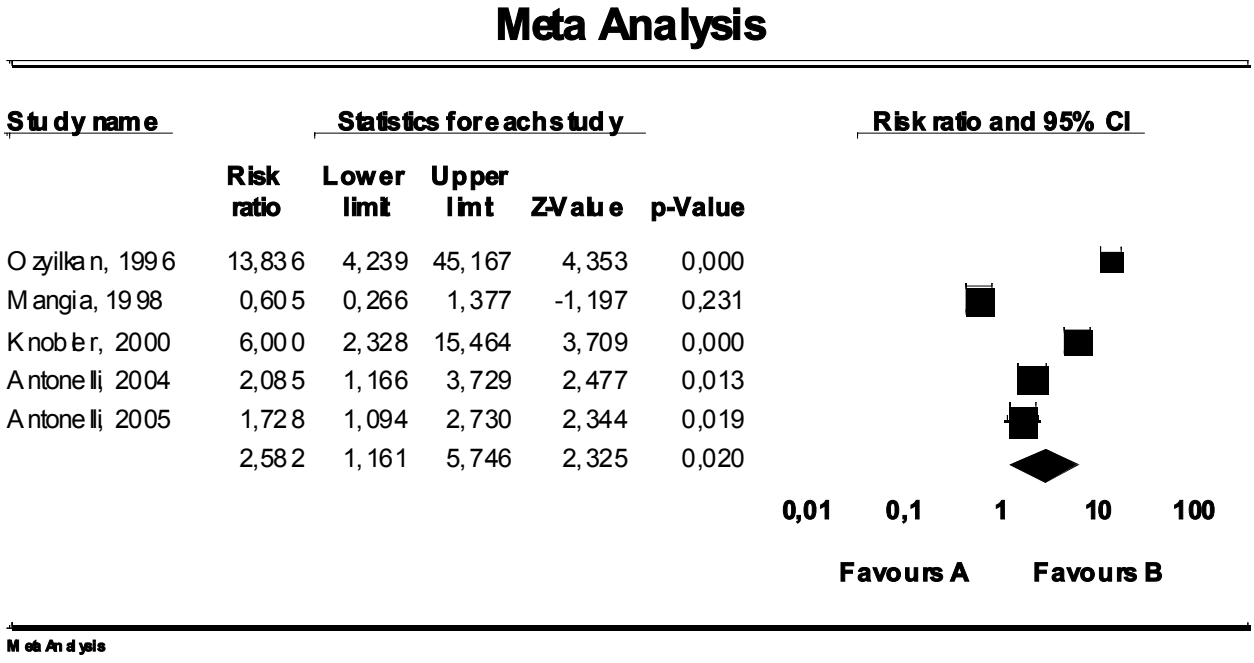

Figure Legend

Fig. 2b Forest plot related to the studies reported in Table 1b, showing T2DM risk among hepatopathic patients with HCV-related cirrhosis versus non HCV-cirrhotic controls (with HBV, alcohol, colestatic or cryptogenic disorders, or primary biliary cirrhosis or primary sclerosing cholangitis)

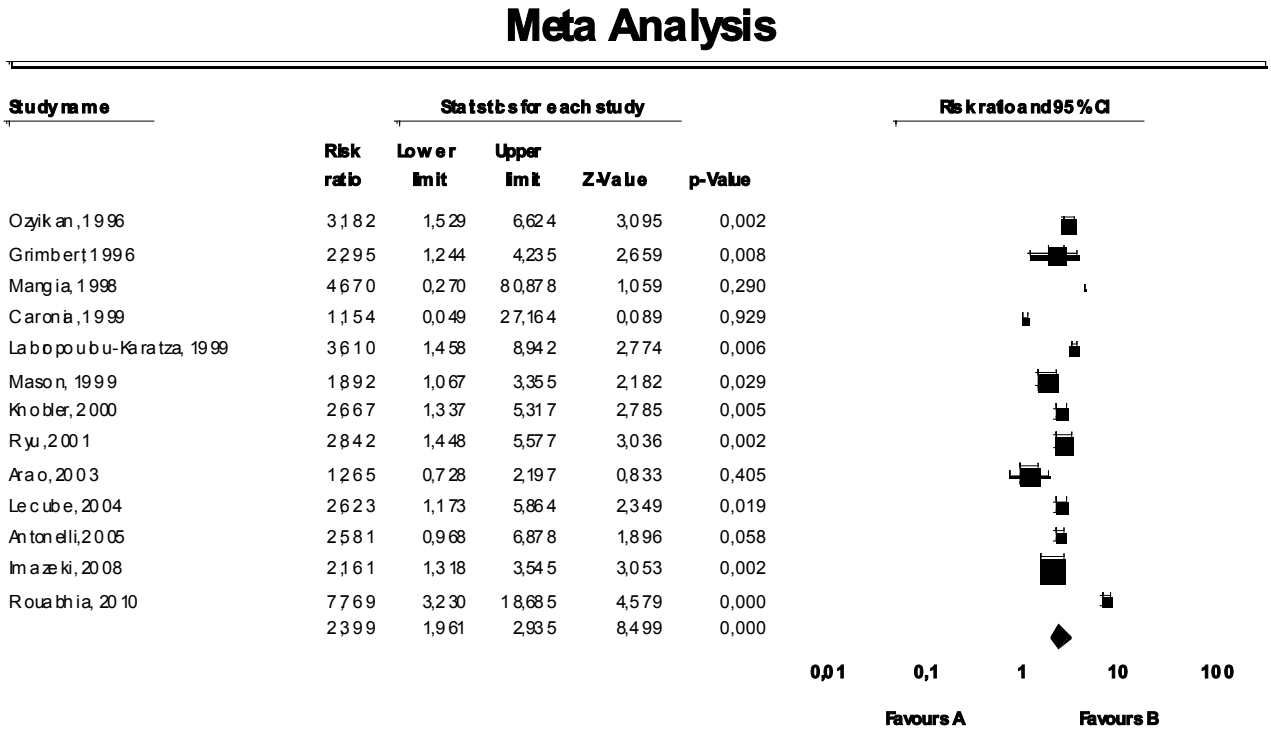

Figure Legend

Fig. 2c Forest plot related to the studies reported in Table 1c, showing T2DM risk among hepatopathic patients with HCV-related chronic hepatitis (without cirrhosis) versus hepatopathic HBV-positive controls

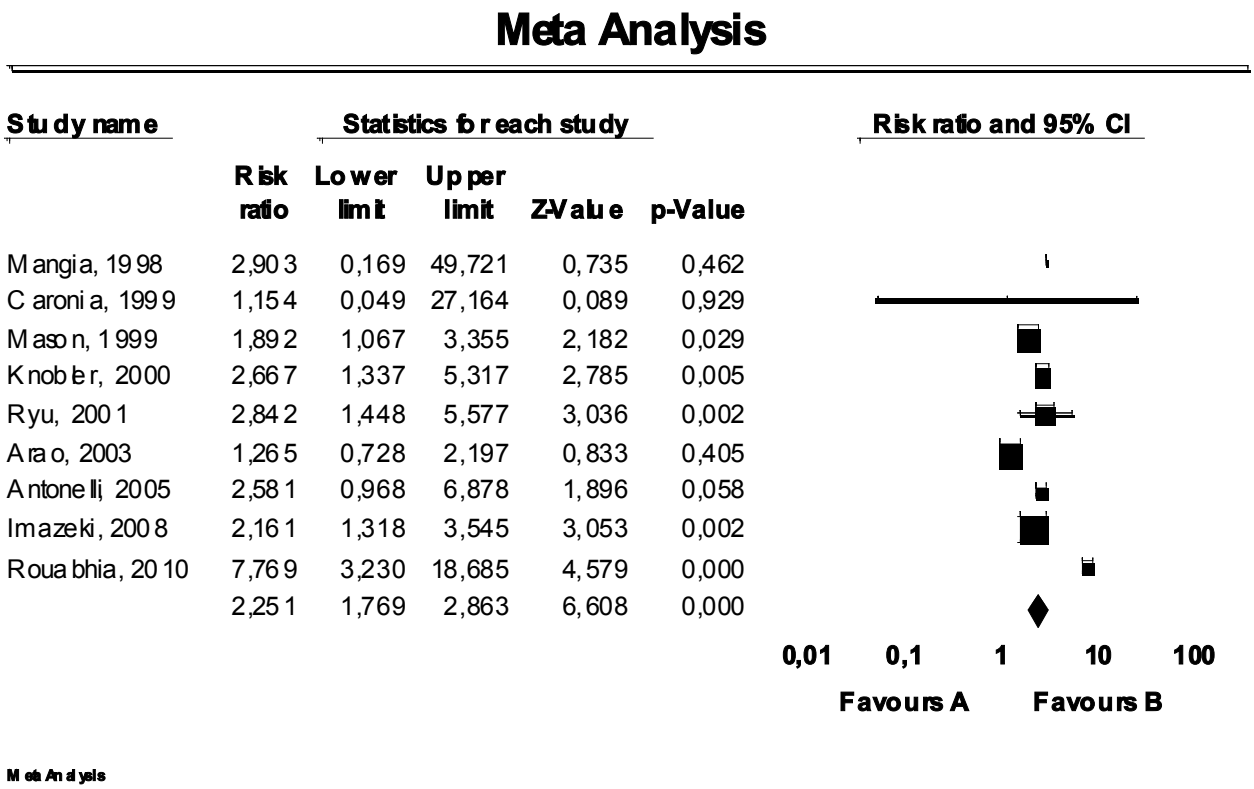

Figure Legend

Fig. 3a Forest plot related to the studies reported in Table 2a, showing the risk of T2DM in HCV cirrhosis, in comparison with "normal" non hepatopathic controls (matched by age and gender)

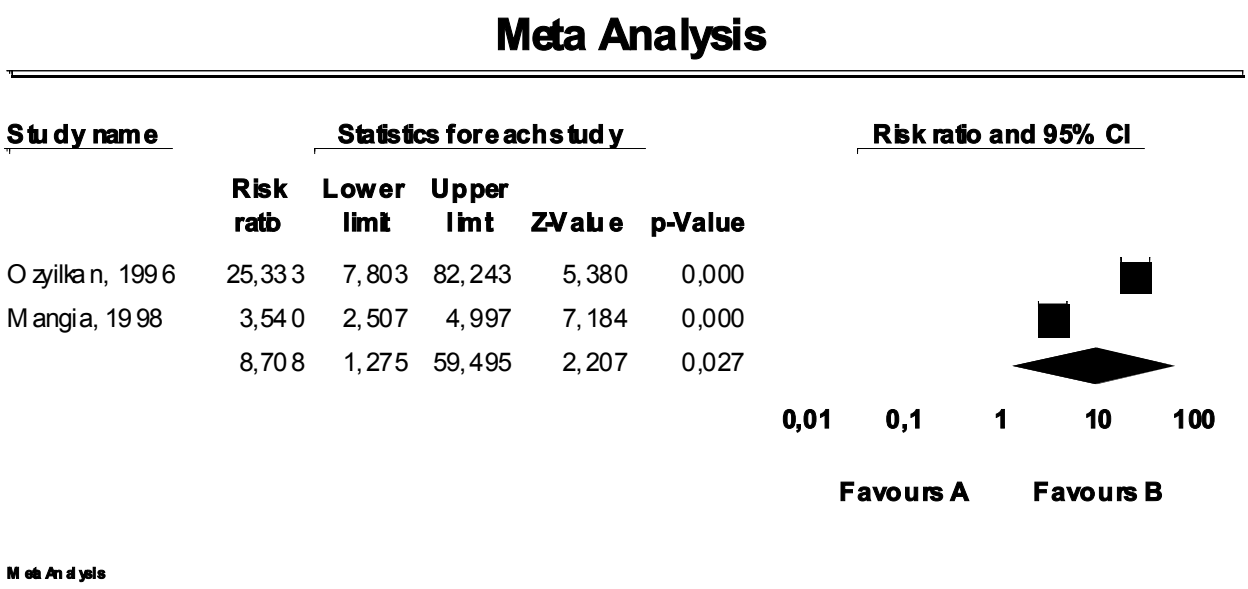

Figure Legend

Fig. 3b Forest plot related to the studies reported in Table 2b, showing the risk of T2DM in HCV patients with cirrhosis in comparison with non HCV-cirrhotic controls (with HBV, alcohol, colestatic or cryptogenic disorders, or primary biliary cirrhosis or primary sclerosing cholangitis)

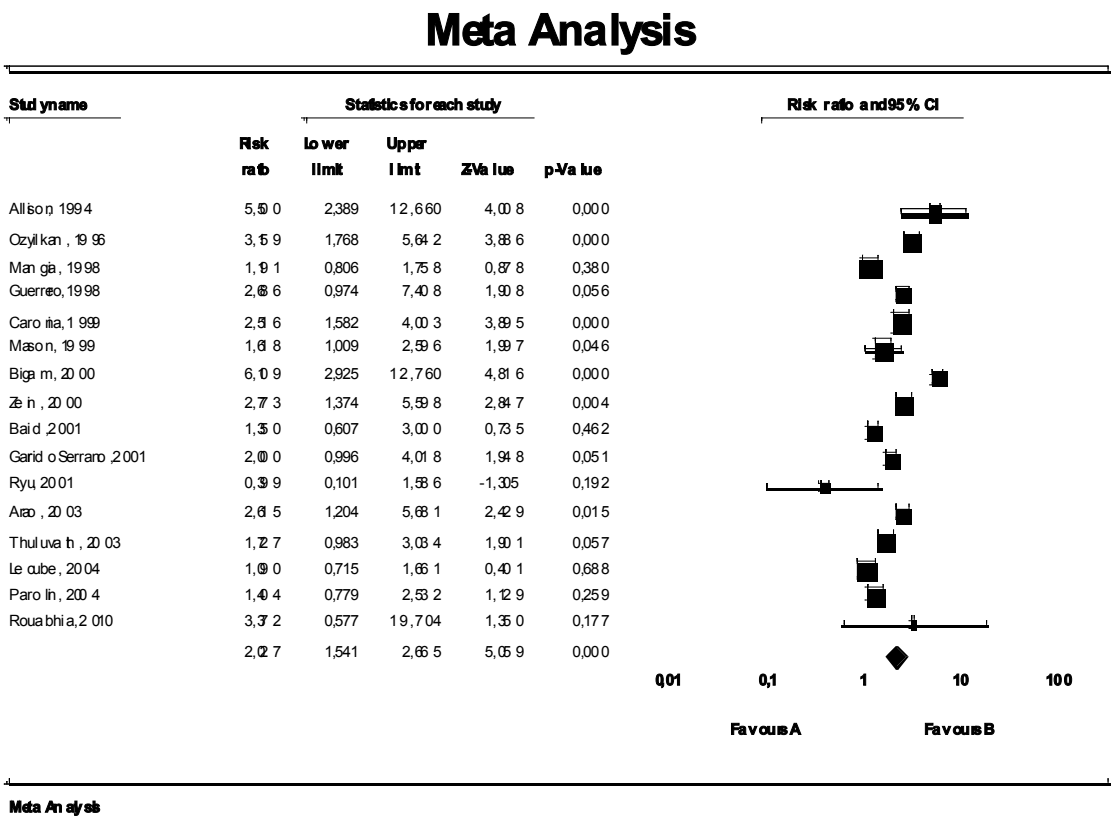

Figure Legend

Fig. 3c Forest plot related to the studies reported in Table 2c, showing risk of T2DM in HCV cirrhosis in comparison with cirrhotic HBV controls

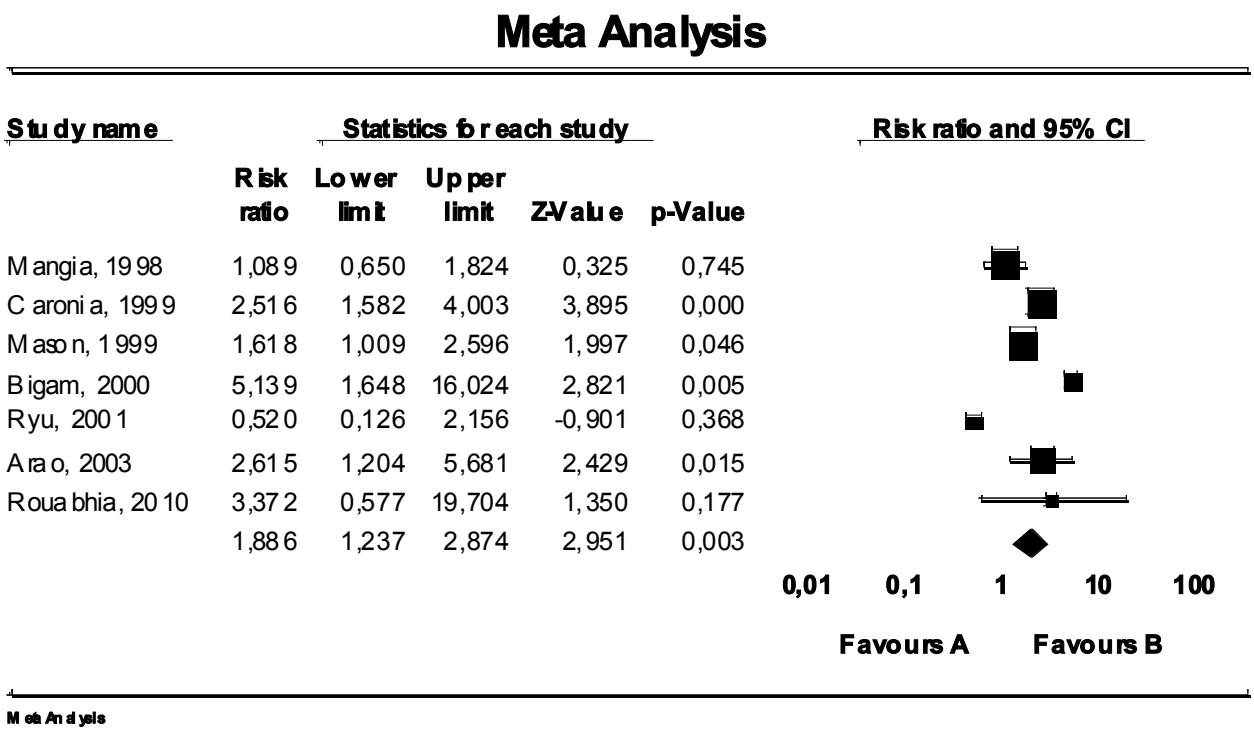

Figure Legend

Fig. 4a Forest plot related to the studies reported in Table 3a, showing risk of HCV infection in diabetic patients versus non-diabetic controls

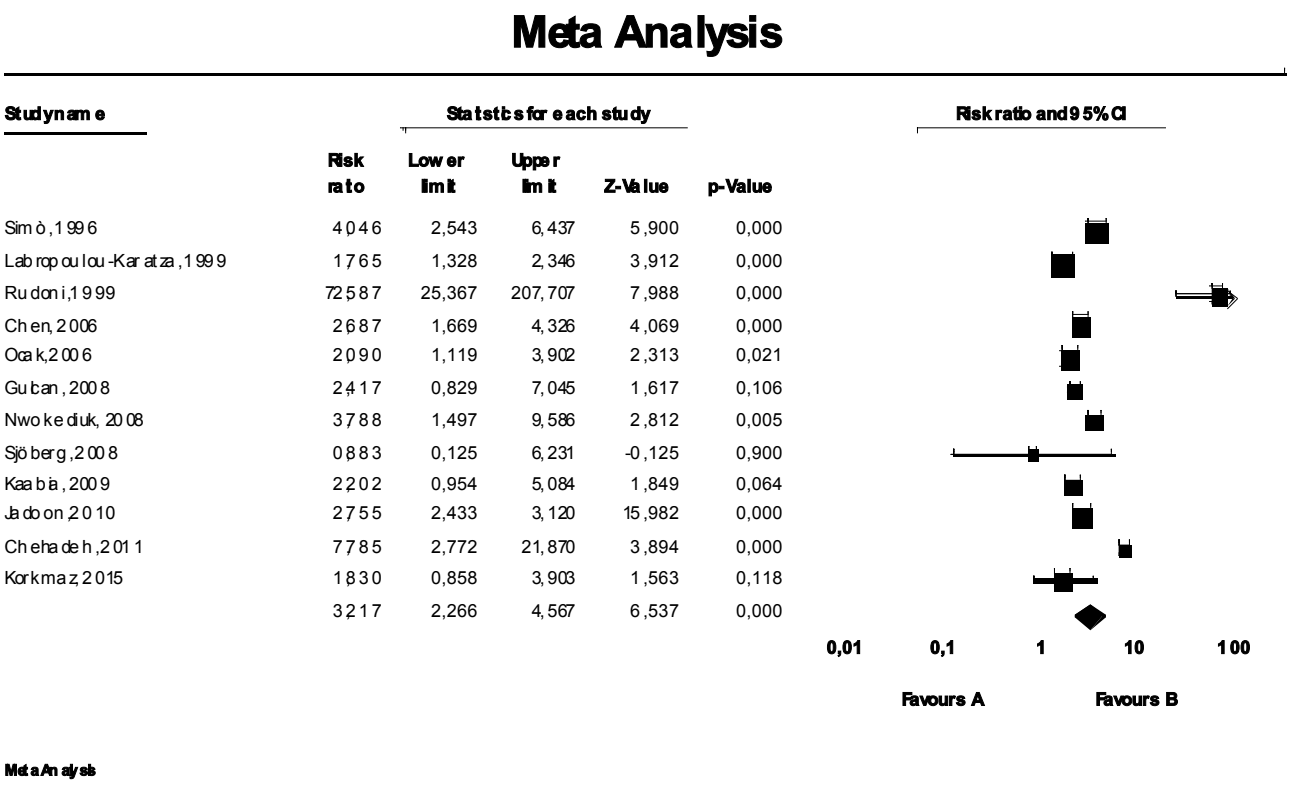

Figure Legend

Fig. 4b Forest plot related to the studies reported in Table 3b, showing the risk of HBV infection in diabetic patients, versus non-diabetic controls are reported