

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.

Secondary forms of DM are frequently disregarded [6]. Growth hormone (GH) deficiency, polycystic 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 systematically 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 yielded 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.

References

1. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med*. 2001;345:41–52.
2. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001;414:782–7.
3. International Diabetes Federation Sixth Edition (2014). Available: <http://www.idf.org/diabetesatlas>.
4. Ferrannini E, Mari A. β -Cell function in type 2 diabetes. *Metabolism*. 2014;63:1217–27.
5. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspective on the past, present and future. *Lancet*. 2014;383:1068–83.
6. **East HE, Subauste JS, Gandhi A, Koch CA. About secondary causes of diabetes mellitus. *J Miss State Med Assoc*. 2012;53:380-3.**
7. **Nati M, Haddad D, Birkenfeld AL, Koch CA, Chavakis T, Chatzigeorgiou A. The role of immune cells in metabolism-related liver inflammation and development of non-alcoholic steatohepatitis (NASH). *Rev Endocr Metab Disord*. 2016;17:29-39.**
8. **Koch CA, Bornstein SR, Birkenfeld AL. Introduction to Hanefeld Symposium: 40+ years of metabolic syndrome. *Rev Endocr Metab Disord*. 2016;17:1-4.**
9. Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. *Gastroenterology*. 2015;149:1345–60.
10. **Fallahi P, Ferrari SM, Vita R, Benvenga S, Antonelli A. The role of human parvovirus B19 and hepatitis C virus in the development of thyroid disorders. *Rev Endocr Metab Disord*. 2016;17:529-35.**
11. **Benvenga S, Guarneri F. Molecular mimicry and autoimmune thyroid disease. *Rev Endocr Metab Disord*. 2016;17:485-98.**
12. Alexander GJ. An association between hepatitis C virus infection and type 2 diabetes mellitus: what is the connection?. *Ann Intern Med*. 2000;133:650–2.
13. Mehta SH, Strathdee SA, Thomas DL. Association between hepatitis C virus infection and diabetes mellitus. *Epidemiol Rev*. 2001;23:302–12.
14. Mayo MJ. Extrahepatic manifestations of hepatitis C infection. *Am J Med Sci*. 2003;325:135–48.
15. Lecube A, Hernández C, Genescà J, Simó R. Glucose abnormalities in patients with hepatitis C virus infection: Epidemiology and pathogenesis. *Diabetes Care*. 2006;29:1140–9.
16. Noto H, Raskin P. Hepatitis C infection and diabetes. *J Diabetes Complications*. 2006;20:113–20.
17. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. *J Hepatol*. 2008;49:831–44.
18. Bernsmeier C, Heim MH. Insulin resistance in chronic hepatitis C: mechanisms and clinical relevance. *Swiss Med Wkly*. 2009;139:678–84.
19. Negro F, Alaei M. Hepatitis C virus and type 2 diabetes. *World J Gastroenterol*. 2009;15:1537–47.
20. Naing C, Mak JW, Ahmed SI, Maung M. Relationship between hepatitis C virus infection and type 2 diabetes mellitus: meta-analysis. *World J Gastroenterol*. 2012;18:1642–51.
21. Ruhl CE, Menke A, Cowie CC, Everhart JE. Relationship of hepatitis C virus infection with diabetes in the U.S. population. *Hepatology*. 2014;60:1139–49.
22. Antonelli A, Ferrari SM, Giuggioli D, Di Domenicantonio A, Ruffilli I, Corrado A, et al. Hepatitis C virus infection and type 1 and type 2 diabetes mellitus. *World J Diabetes*. 2014;5:586–600.
23. Prummel MF, Laurberg P. Interferon-alpha and autoimmune thyroid disease. *Thyroid*. 2003;13:547–51.

24. Antonelli A, Ferri C, Fallahi P, Ferrari SM, Ghinoi A, Rotondi M, et al. Thyroid disorders in chronic hepatitis C virus infection. *Thyroid*. 2006;16:563–72.
25. Ozyilkan E, Arslan M. Increased prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection. *Am J Gastroenterol*. 1996;91:1480–1.
26. Mangia A, Schiavone G, Lezzi G, Marmo R, Bruno F, Villani MR, et al. HCV and diabetes mellitus: evidence for a negative association. *Am J Gastroenterol*. 1998;93:2363–7.
27. Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. *Mayo Clin Proc*. 2000;75:355–9.
28. Antonelli A, Ferri C, Fallahi P, Sebastiani M, Nesti C, Barani L, et al. Type 2 diabetes in hepatitis C-related mixed cryoglobulinaemia patients. *Rheumatology (Oxford)*. 2004;43:238–40.
29. Antonelli A, Ferri C, Fallahi P, Pampana A, Ferrari SM, Goglia F, et al. Hepatitis C virus infection: evidence for an association with type 2 diabetes. *Diabetes Care*. 2005;28:2548–50.
30. Grimbert S, Valensi P, Lévy-Marchal C, Perret G, Richardet JP, Raffoux C, et al. High prevalence of diabetes mellitus in patients with chronic hepatitis C. A case–control study. *Gastroenterol Clin Biol*. 1996;20:544–8.
31. Caronia S, Taylor K, Pagliaro L, Carr C, Palazzo U, Petrik J, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology*. 1999;30:1059–63.
32. Labropoulou-Karatza C, Goritsas C, Fragopanagou H, Repandi M, Matsouka P, Alexandrides T. High prevalence of diabetes mellitus among adult beta-thalassaemic patients with chronic hepatitis C. *Eur J Gastroenterol Hepatol*. 1999;11:1033–6.
33. Mason AL, Lau JY, Hoang N, Qian K, Alexander GJ, Xu L, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. *Hepatology*. 1999;29:328–33.
34. Ryu JK, Lee SB, Hong SJ, Lee S. Association of chronic hepatitis C virus infection and diabetes mellitus in Korean patients. *Korean J Intern Med*. 2001;16:18–23.
35. Arao M, Murase K, Kusakabe A, Yoshioka K, Fukuzawa Y, Ishikawa T, et al. Prevalence of diabetes mellitus in Japanese patients infected chronically with hepatitis C virus. *J Gastroenterol*. 2003;38:355–60.
36. Lecube A, Hernández C, Genescà J, Esteban JI, Jardí R, Simó R. High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. *Diabetes Care*. 2004;27:1171–5.
37. Imazeki F, Yokosuka O, Fukai K, Kanda T, Kojima H, Saisho H. Prevalence of diabetes mellitus and insulin resistance in patients with chronic hepatitis C: comparison with hepatitis B virus-infected and hepatitis C virus-cleared patients. *Liver Int*. 2008;28:355–62.
38. Nwokediuko SC, Oli JM. Hepatitis C virus infection in Nigerians with diabetes mellitus. *Niger J Clin Pract*. 2008;11:94–9.
39. Rouabhia S, Malek R, Bounecer H, Dekaken A, Bendali Amor F, Sadelaoud M, et al. Prevalence of type 2 diabetes in Algerian patients with hepatitis C virus infection. *World J Gastroenterol*. 2010;16:3427–31.
40. Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. *J Hepatol*. 1994;21:1135–9.
41. Guerreo Igea FJ, Garrido Serrano A, Lepe Jiménez JA, Palomo Gil S. [High prevalence of diabetes mellitus in patients with chronic hepatitis C virus infection]. *Med Clin (Barc)*. 1998;111:676–7.
42. Bigam DL, Pennington JJ, Carpentier A, Wanless IR, Hemming AW, Croxford R, et al. Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatology*. 2000;32:87–90.

43. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. *J Hepatol.* 2000;32:209–17.
44. Baid S, Cosimi AB, Farrel ML, Schoenfeld DA, Feng S, Chung RT, et al. Posttransplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. *Transplantation.* 2001;72:1066–72.
45. Garrido Serrano A, Guerrero Igea FJ, Lepe Jiménez JA, Palomo Gil S, Grilo Reina A. [Hyperinsulinemia in cirrhotic patients infected with hepatitis C virus]. *Gastroenterol Hepatol.* 2001;24:127–31.
46. Thuluvath PJ, John PR. Association between hepatitis C, diabetes mellitus, and race. a case-control study. *Am J Gastroenterol.* 2003;98:438–41.
47. Parolin MB, Zaina FE, Araújo MV, Kupka E, Coelho JC. Prevalence of new-onset diabetes mellitus in Brazilian liver transplant recipients: association with HCV infection. *Transplant Proc.* 2004;36:2776–7.
48. Simó R, Hernández C, Genescà J, Jardí R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. *Diabetes Care.* 1996;19:998–1000.
49. Rudoni S, Petit JM, Bour JB, Aho LS, Castaneda A, Vaillant G, et al. HCV infection and diabetes mellitus: influence of the use of finger stick devices on nosocomial transmission. *Diabetes Metab.* 1999;25:502–5.
50. Chen HF, Li CY, Chen P, See TT, Lee HY. Seroprevalence of hepatitis B and C in type 2 diabetic patients. *J Chin Med Assoc.* 2006;69:146–52.
51. Ocak S, Duran N, Kaya H, Emir I. Seroprevalence of hepatitis C in patients with type 2 diabetes mellitus and non-diabetic on haemodialysis. *Int J Clin Pract.* 2006;60:670–4.
52. Gulcan A, Gulcan E, Toker A, Bulut I, Akcan Y. Evaluation of risk factors and seroprevalence of hepatitis B and C in diabetic patients in Kutahya, Turkey. *J Investig Med.* 2008;56:858–63.
53. Sjöberg K, Widell A, Verbaan H. Prevalence of hepatitis C in Swedish diabetics is low and comparable to that in health care workers. *Eur J Gastroenterol Hepatol.* 2008;20:135–8.
54. Kaabia N, Ben Jazia E, Slim I, Fodha I, Hachfi W, Gaha R, et al. Association of hepatitis C virus infection and diabetes in central Tunisia. *World J Gastroenterol.* 2009;15:2778–81.
55. Jadoon NA, Shahzad MA, Yaqoob R, Hussain M, Ali N Seroprevalence of hepatitis C in type 2 diabetes: evidence for a positive association. *Virology.* 2010;7:304.
56. Chehadeh W, Kurien SS, Abdella N, Ben-Nakhi A, Al-Arouj M, Almuaili T, et al. Hepatitis C virus infection in a population with high incidence of type 2 diabetes: impact on diabetes complications. *J Infect Public Health.* 2011;4:200–6.
57. Korkmaz H, Kesli R, Onder Pamuk B, Ipekci SH, Terzi Y, Kebapcilar L. Assessment of evidence for positive association and seroprevalence of hepatitis B and C in diabetic patients in a developing country. *J Investig Med.* 2015;63:251–7.
58. Younossi ZM, McCullough AJ. Metabolic syndrome, non-alcoholic fatty liver disease and hepatitis C virus: impact on disease progression and treatment response. *Liver International.* 2009;29:3–12.
59. Negro F. Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. *J Hepatol.* 2014;61 Suppl 1:S69–78.
60. Guo X, Jin M, Yang M, Liu K, Li JW. Type 2 diabetes mellitus and the risk of hepatitis C virus infection: a systematic review. *Sci Rep.* 2013;3:2981.

61. García-Compeán D, González-González JA, Lavallo-González FJ, González-Moreno EI, Villarreal-Pérez JZ, Maldonado-Garza HJ. Current Concepts in Diabetes Mellitus and Chronic Liver Disease: Clinical Outcomes, Hepatitis C Virus Association, and Therapy. *Dig Dis Sci*. 2016;61:371–8.
62. Fabrizi F, Lampertico P, Lunghi G, Mangano S, Aucella F, Martin P. Review article: hepatitis C virus infection and type-2 diabetes mellitus in renal diseases and transplantation. *Aliment Pharmacol Ther*. 2005;21:623–32.
63. Knobler H, Stagnaro-Green A, Wallenstein S, Schwartz M, Roman SH. Higher incidence of diabetes in liver transplant recipients with hepatitis C. *J Clin Gastroenterol*. 1998;26:30–3.
64. Boschi-Pinto C, Stuver S, Okayama A, Trichopoulos D, Orav EJ, Tsubouchi H, et al. A follow-up study of morbidity and mortality associated with hepatitis C virus infection and its interaction with human T lymphotropic virus type I in Miyazaki, Japan. *J Infect Dis*. 2000;181:35–41.
65. Howard AA, Klein RS, Schoenbaum EE. Association of hepatitis C infection and antiretroviral use with diabetes mellitus in drug users. *Clin Infect Dis*. 2003;36:1318–23.
66. Butt AA, Fultz SL, Kwok CK, Kelley D, Skanderson M, Justice AC. Risk of diabetes in HIV infected veterans pre- and post-HAART and the role of HCV coinfection. *Hepatology*. 2004;40:115–9.
67. Delgado-Borrego A, Casson D, Schoenfeld D, Somsouk M, Terella A, Jordan SH, et al. Hepatitis C virus is independently associated with increased insulin resistance after liver transplantation. *Transplantation*. 2004;77:703–10.
68. Wilson C. Hepatitis C infection and type 2 diabetes in American-Indian women. *Diabetes Care*. 2004;27:2116–9.
69. Brar I, Shuter J, Thomas A, Daniels E, Absalon J; Minorities and Women's Task Force of Terry Bein Community Programs for Clinical Research on AIDS. A comparison of factors associated with prevalent diabetes mellitus among HIV-Infected antiretroviral-naïve individuals versus individuals in the National Health and Nutritional Examination Survey cohort. *J Acquir Immune Defic Syndr*. 2007;45:66–71.
70. Jain MK, Aragaki C, Fischbach L, Gibson S, Arora R, May L, et al. Hepatitis C is associated with type 2 diabetes mellitus in HIV-infected persons without traditional risk factors. *HIV Med*. 2007;8:491–7.
71. Ledergerber B, Furrer H, Rickenbach M, Lehmann R, Elzi L, Hirschel B, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. *Clin Infect Dis*. 2007;45:111–9.
72. Stapleton JT, Bennett K, Bosch RJ, Polgreen PM, Swindells S. Effect of antiretroviral therapy and hepatitis c co-infection on changes in lipid levels in HIV-Infected patients 48 weeks after initiation of therapy. *HIV Clin Trials*. 2007;8:429–36.
73. Taura N, Ichikawa T, Miyaaki H, Yatsunami H, Ishibashi H, Nakao K. Prevalence of type 2 diabetes mellitus in Japanese patients with hepatocellular carcinoma. *Exp Ther Med*. 2011;2:81–4.
74. Visnegarwala F, Chen L, Raghavan S, Tedaldi E. Prevalence of diabetes mellitus and dyslipidemia among antiretroviral naïve patients co-infected with hepatitis C virus (HCV) and HIV-1 compared to patients without co-infection. *J Infect*. 2005;50:331–7.
75. Younossi Z, Stepanova M, Saab S, Trimble G, Mishra A, Henry L. The association of hepatitis C virus infection and post-liver transplant diabetes: data from 17 000 HCV-infected transplant recipients. *Aliment Pharmacol Ther*. 2015;41:209–17.

76. el-Zayadi AR, Selim OE, Hamdy H, Dabbous H, Ahdy A, Moniem SA. Association of chronic hepatitis C infection and diabetes mellitus. *Trop Gastroenterol.* 1998;19:141–4.
77. alDosary AA, Ramji AS, Elliott TG, Sirrs SM, Thompson DM, Erb SR, et al. Post-liver transplantation diabetes mellitus: an association with hepatitis C. *Liver transp.* 2002;8:356–61.
78. Yildiz A, Tutuncu Y, Yazici H, Akkaya V, Kayakan SM, Sever MS, et al. Association between hepatitis C virus infection and development of post-transplantation diabetes mellitus in renal transplant recipients. *Transplantation.* 2002;74:1109–13.
79. Huang JF, Dai CY, Hwang SJ, Ho CK, Hsiao PJ, Hsieh MY, et al. Hepatitis C viremia increases the association with type 2 diabetes mellitus in a hepatitis B and C endemic area: an epidemiological link with virological implication. *Am J Gastroenterol.* 2007;102:1237–43.
80. Wang CS, Wang ST, Yao WJ, Chang TT, Chou P. Hepatitis C virus infection and the development of type 2 diabetes in a community-based longitudinal study. *Am J Epidemiol.* 2007;166:196–203.
81. Schnier C, Wild S, Kurdi Z, Povey C, Goldberg DJ, Hutchinson SJ. Matched population-based study examining the risk of type 2 diabetes in people with and without diagnosed hepatitis C virus infection. *J Viral Hepat.* 2016;23:596–605.
82. Brischetto R, Corno C, Amore MG, Leotta S, Pavone S, Bonsignore L, et al. [Prevalence and significance of type-2 diabetes mellitus in chronic liver disease, correlated with hepatitis C virus]. *Ann Ital Med Int.* 2003;18:31–6.
83. Montenegro L, De Michina A, Misciagna G, Guerra V, Di Leo A. Virus C hepatitis and type 2 diabetes: a cohort study in southern Italy. *Am J Gastroenterol.* 2013;108:1108–11.
84. Amarapurkar DN, Patel ND. Increased prevalence of type II diabetes mellitus in hepatitis C virus infection in western India. *Trop Gastroenterol.* 2008;29:148–52.
85. Elhawary EI, Mahmoud GF, El-Daly MA, Mekky FA, Esmat GG, Abdel-Hamid M. Association of HCV with diabetes mellitus: an Egyptian case-control study. *Virology.* 2011;8:367.
86. Ratzu V, Heurtier A, Bonyhay L, Poynard T, Giral P. Review article: an unexpected virus-host interaction--the hepatitis C virus-diabetes link. *Aliment Pharmacol Ther.* 2005;22 (suppl 2):56–60.
87. Masini M, Campani D, Boggi U, Menicagli M, Funel N, Pollera M, et al. Hepatitis C virus infection and human pancreatic beta-cell dysfunction. *Diabetes Care.* 2005;28:940–1.
88. Fallahi P, Ferri C, Ferrari SM, Corrado A, Sansonno D, Antonelli A. Cytokines and HCV-Related Disorders. *Clin Dev Immunol.* 2012;2012:468107.
89. Kita Y, Mizukoshi E, Takamura T, Sakurai M, Takata Y, Arai K, et al. Impact of diabetes mellitus on prognosis of patients infected with hepatitis C virus. *Metabolism.* 2007;56:1682–8.
90. Wang CS, Yao WJ, Chang TT, Wang ST, Chou P. The impact of type 2 diabetes on the development of hepatocellular carcinoma in different viral hepatitis statuses. *Cancer Epidemiol Biomarkers Prev.* 2009;18:2054–60.
91. Alter MJ, Margolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, et al. The natural history of community-acquired hepatitis C in the United States. The Sentinel Counties Chronic non-A, non-B Hepatitis Study Team. *N Engl J Med.* 1992;327:1899–905.
92. Colombo M, Kuo G, Choo QL, Donato MF, Del Ninno E, Tommasini MA, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet.* 1989;2:1006–8.

93. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med*. 1993;328:1797–801.
94. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology*. 2004;126:460–8.
95. Gao C, Yao SK. Diabetes mellitus: a “true” independent risk factor for hepatocellular carcinoma? *Hepatobiliary Pancreat Dis Int*. 2009;8:465–73.
96. Elgouhari HM, Zein CO, Hanouneh I, Feldstein AE, Zein NN. Diabetes mellitus is associated with impaired response to antiviral therapy in chronic hepatitis C infection. *Dig Dis Sci*. 2009;54:2699–705.
97. Nasrollah L, Backstedt DW, Pedersen MR, Choi M, Seetharam AB. Tu1022 Diabetes and Hyperlipidemia Compromise Practical Effectiveness of Direct Acting Antiviral HCV Therapy in Minority Populations. *Gastroenterology*. 2015;148 Suppl 1:S–1087.
98. Knobler H, Malnick S. Hepatitis C and insulin action: An intimate relationship. *World J Hepatol*. 2016;8:131–8.
99. Premji R, Roopnarinesingh N, Qazi N, Nylén ES. New-Onset Diabetes Mellitus With Exposure to Ledipasvir and Sofosbuvir. *J Investig Med High Impact Case Rep*. 2015; 3:2324709615623300.
100. Pattullo V, Heathcote J. Hepatitis C and diabetes: one treatment for two diseases? *Liver Int*. 2010;30:356–64.
101. Milner KL, Jenkins AB, Trenell M, Tid-Ang J, Samocha-Bonet D, Weltman M, et al. Eradicating hepatitis C virus ameliorates insulin resistance without change in adipose depots. *J Viral Hepat*. 2014;21:325–32.
102. Kawaguchi T, Ide T, Taniguchi E, Hirano E, Itou M, Sumie S, et al. Clearance of HCV improves insulin resistance, beta-cell function, and hepatic expression of insulin receptor substrate 1 and 2. *Am J Gastroenterol*. 2007;102:570–6.
103. Tallón de Lara P, Himschoot T, Frossard JL, Negro F. Does telaprevir possess a direct antidiabetic effect? *Liver Int*. 2014;34:967–9.
104. Vanni E, Bugianesi E, Saracco G. Treatment of type 2 diabetes mellitus by viral eradication in chronic hepatitis C: Myth or reality? *Dig Liver Dis*. 2016;48:105–11.
105. Younossi Z, Park H, Henry L, Adeyemi A, Stepanova M. Extrahepatic Manifestations of Hepatitis C: A Meta-analysis of Prevalence, Quality of Life, and Economic Burden. *Gastroenterology*. 2016;150:1599–608.

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- Karatzas 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=0.0000

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	RR
							2.32	2.11
							1.78–2.69	1.66–2.69
							p=0.0000	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
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

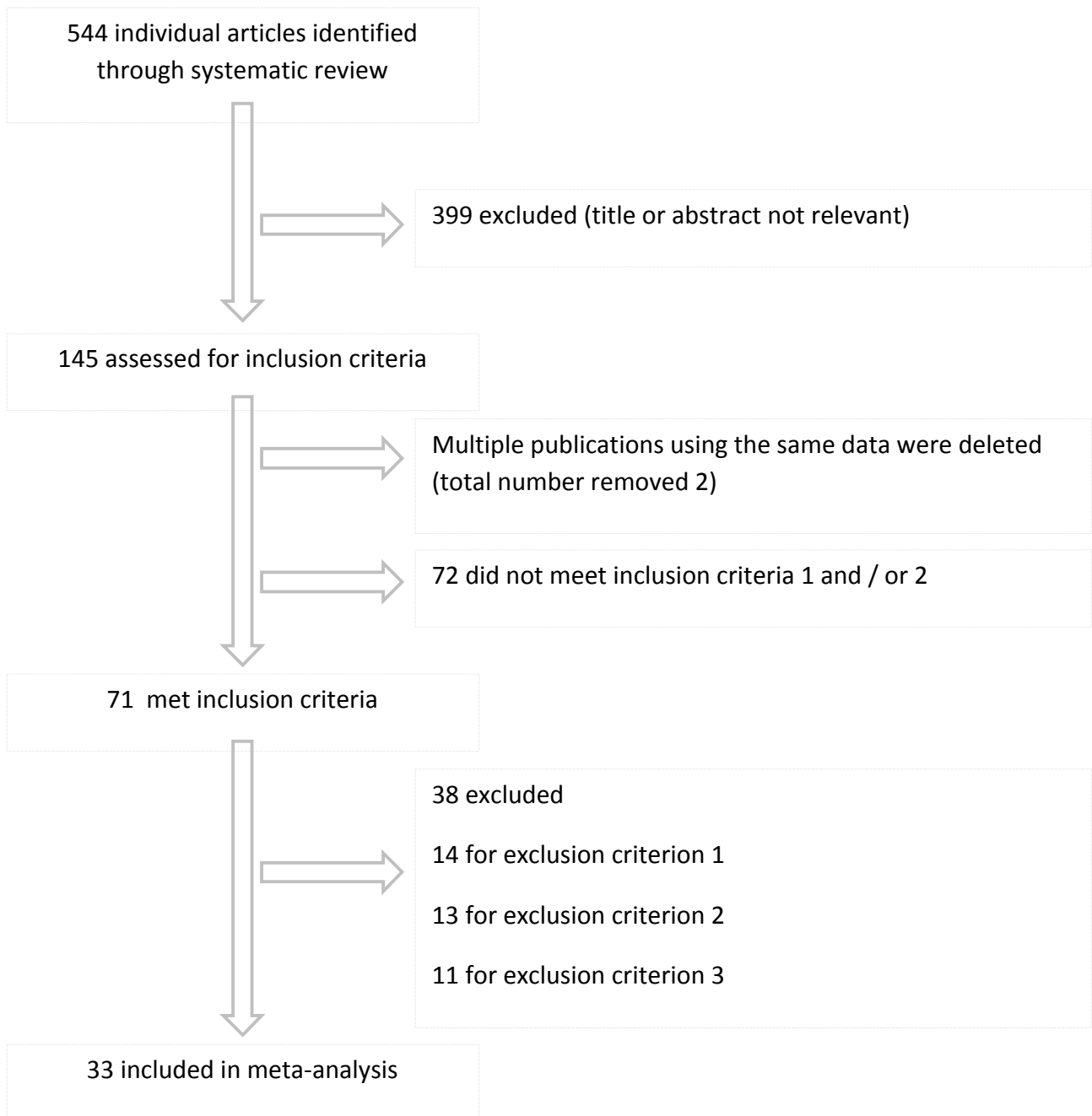
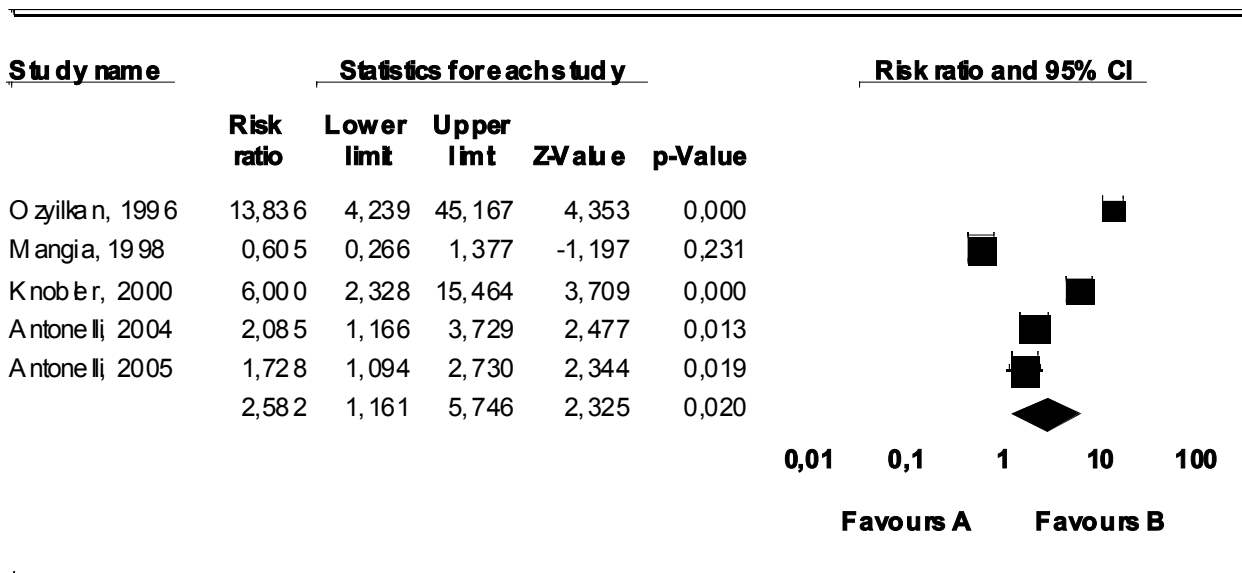


Figure Legend

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

Meta Analysis

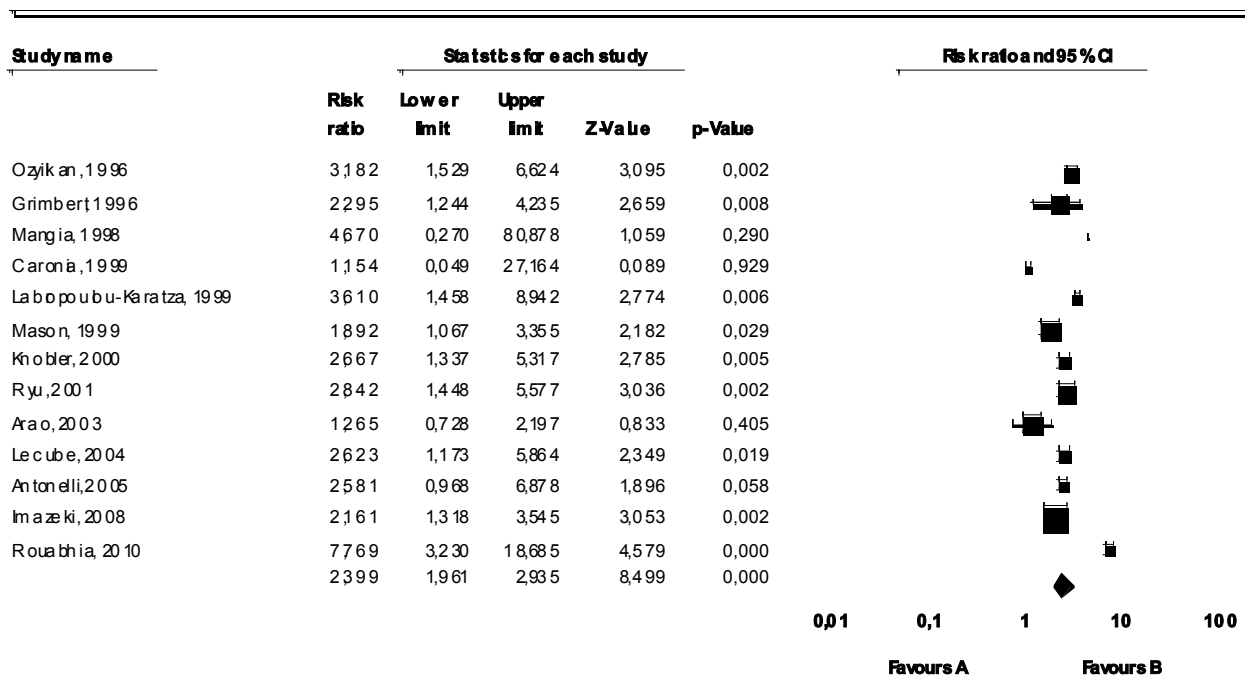


Meta Analysis

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)

Meta Analysis

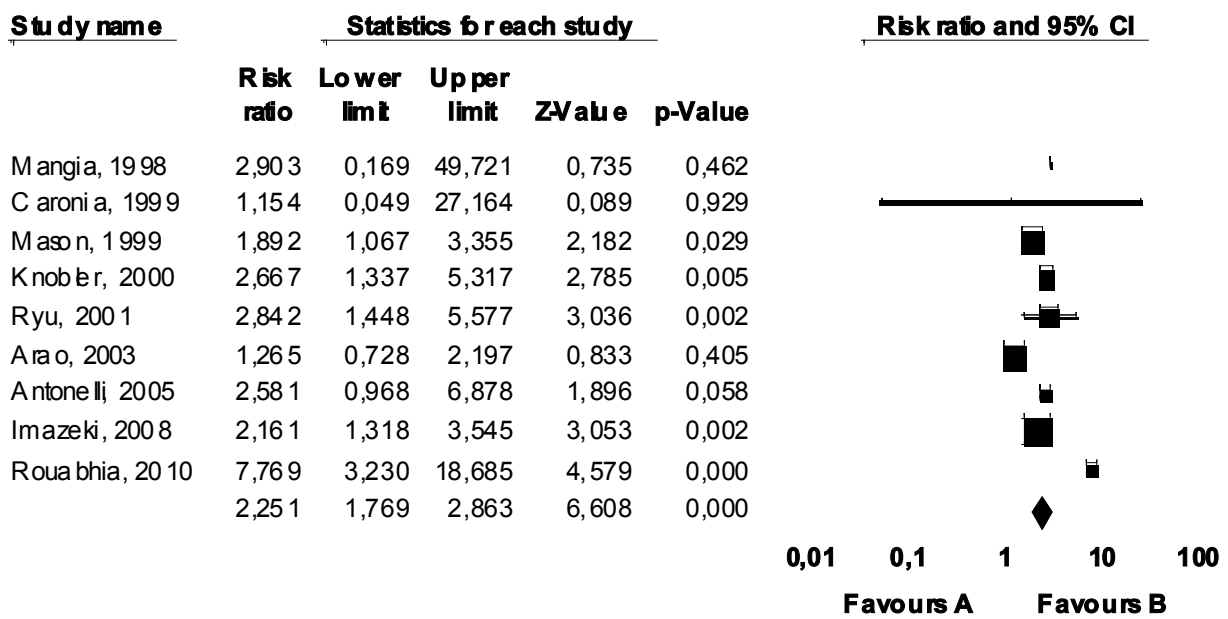


Meta Analysis

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

Meta Analysis

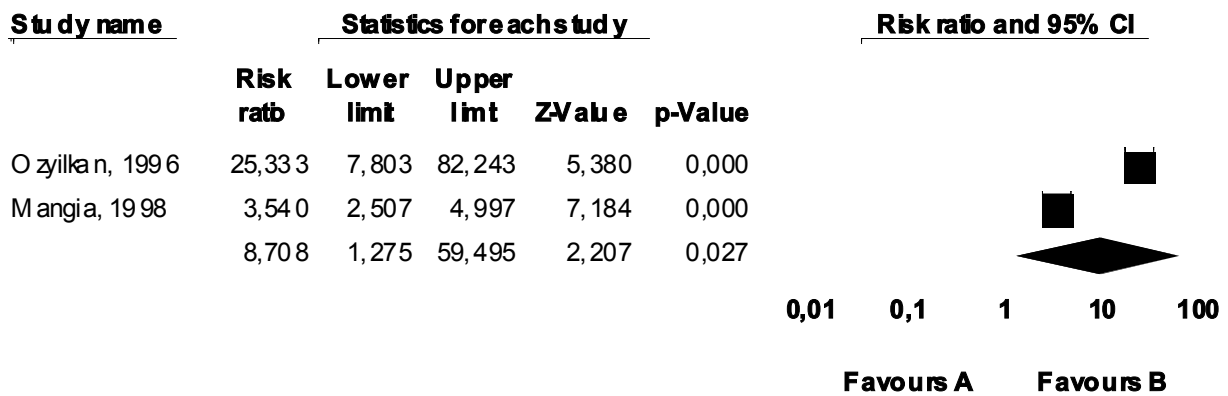


Meta Analysis

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)

Meta Analysis



Meta Analysis

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)

Meta Analysis

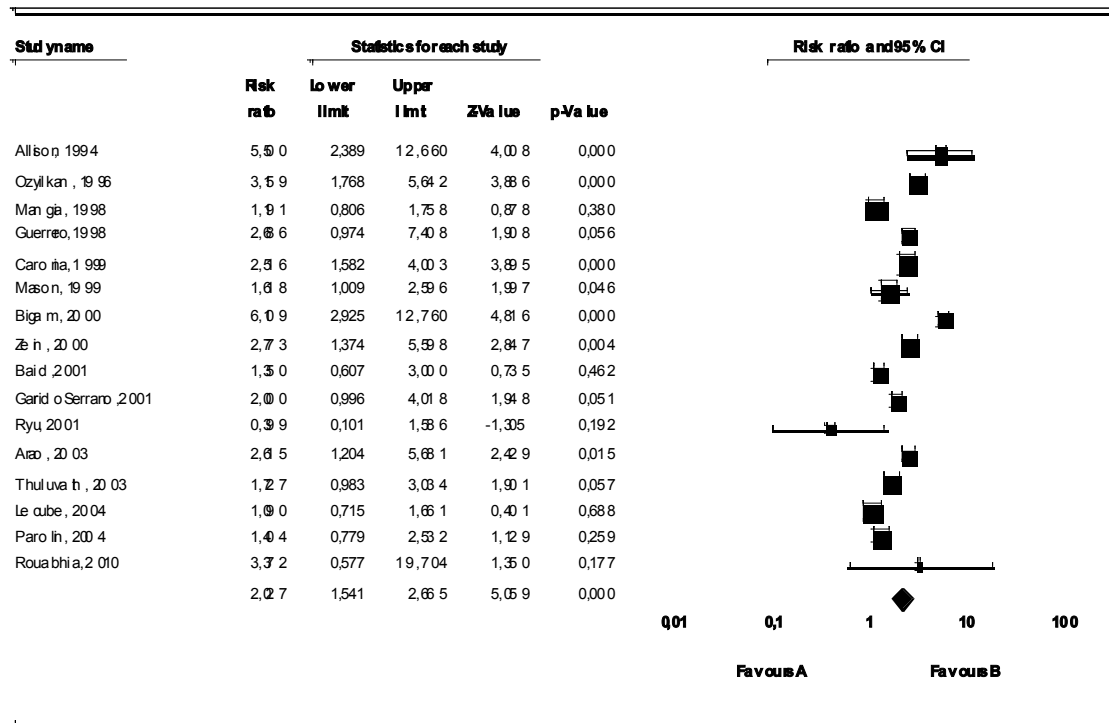
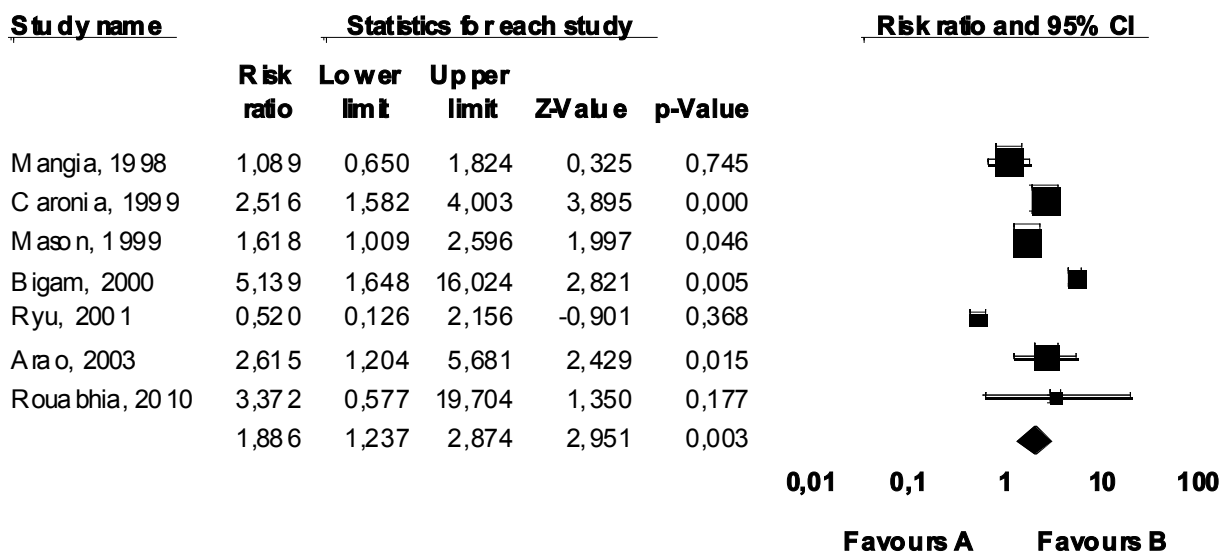


Figure Legend

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

Meta Analysis

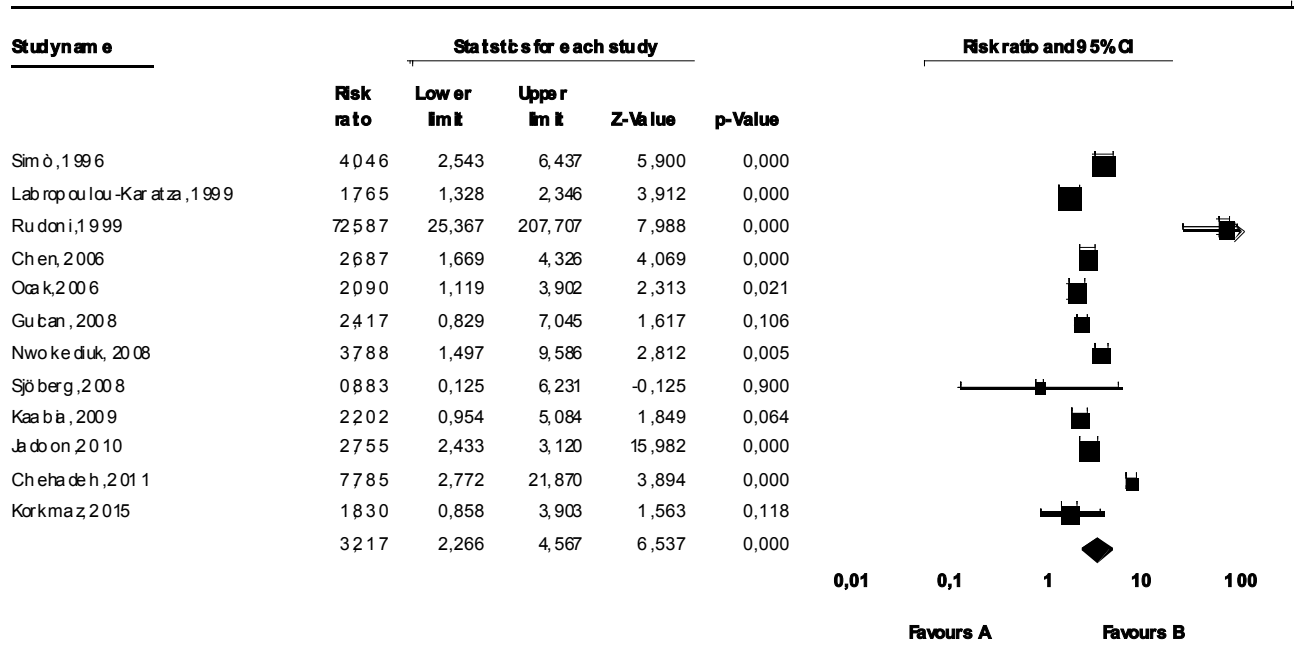


Meta Analysis

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

Meta Analysis



Meta-analysis

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

