REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**Title:**
**Diabetes is not associated with an increased risk of hepatocellular carcinoma in patients with alcoholic or hepatitis C virus cirrhosis**

Authors:
Carlos Rodriguez-Escaja, Carmen Álvarez Navascués, María Luisa González-Diéguez, Valle Cadahia, María Varela , Miguel Angel de Jorge , Andrés Castaño-García, Manuel Rodríguez García

DOI: 10.17235/reed.2020.6953/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Rodriguez-Escaja Carlos, Álvarez Navascués Carmen, González-Diéguez María Luisa, Cadahia Valle, Varela María, de Jorge Miguel Angel, Castaño-García Andrés, Rodríguez García Manuel. Diabetes is not associated with an increased risk of hepatocellular carcinoma in patients with alcoholic or hepatitis C virus cirrhosis. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.6953/2020.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**OR 6953**

# Diabetes is not associated with an increased risk of hepatocellular carcinoma in patients with alcoholic or hepatitis C virus cirrhosis

Carlos Rodríguez-Escaja[#] (1); Carmen A. Navascués[#] (1); Luisa González-Diéguez (1); Valle Cadahía (1); María Varela (1,2,3); Miguel Ángel de Jorge (1); Andrés Castaño-García (1); Manuel Rodríguez* (1,3).

1. Liver Unit. Division of Gastroenterology and Hepatology. Hospital Universitario Central de Asturias. Oviedo, Asturias. Spain.

2. Instituto Universitario de Oncología del Principado de Asturias (IUOPA).

3. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA).

[#] These authors have contributed equally to this work

*Correspondence: Manuel Rodríguez, M.D. Liver Unit. Division of Gastroenterology and Hepatology. Hospital Universitario Central de Asturias. Avda. Roma s/n, 33011 Oviedo, Asturias, Spain.

Email: manurodrigg@gmail.com

## ABSTRACT

### Background and aims

Diabetes has been reported as a risk factor for hepatocellular carcinoma (HCC) in population based studies but there are controversial data in patients with cirrhosis. Otherwise, metformin could have a protective role in HCC development**.** The aim of this study was to know the influence of diabetes on the risk of developing HCC in patients with alcohol- and hepatitis C virus (HCV)-related cirrhosis.

### Methods

We analyzed 982 Caucasian patients with alcoholic or HCV cirrhosis included from 1992 to 2014 in a HCC surveillance program and prospectively followed. The influence of diabetes on the development of HCC was analyzed by Kaplan-Meyer and adjusted with Cox regression for relevant co-factors.

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

**Results**

At a median follow-up of 49.5 (24.0-96.0) months, 156 patients (15.8 %) developed HCC. There were no differences in the cumulative incidences of HCC after 20 years between diabetic and non-diabetic patients in the global series (53.5 % vs. 45.4 %; *P* =0.26), alcoholic (50.4 % vs. 45.4 %; *P*=0.21) or HCV (60 % vs. 43.1 %; *P*=0.57) cirrhosis. After adjusting for other potential co-factors, diabetes did not constitute a risk factor neither in the whole series (HR: 1.12, 95 % IC: 0.78-1.51; *P*=0.26) nor in alcoholic (HR: 1.160, 95 % CI: 0.74-1.82; *P*=0.50) or HCV cirrhosis (HR: 1.17, 95 % CI: 0.63-2.19; *P* =0.60). These figures did not change after excluding patients treated with metformin.

**Conclusions**

In Caucasian patients with alcoholic or HCV cirrhosis, diabetes is not a risk factor for developing HCC. This lack of association does not seem to be consequence of the protective effect of metformin.

**Keywords**

Primary liver cancer; Alcohol-related liver disease; Hepatitis C virus infection; End-stage liver disease; Diabetes mellitus; Metformin.

**Abbreviations**

HCC: Hepatocellular Carcinoma; HCV: Hepatitis C virus; HBV: Hepatitis B Virus

aUS: Abdominal Ultrasound; AFP: Alpha-feto protein; SVR: Sustained Virological Response; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; IQR: Interquartile Range; BMI: Body Mass Index; GGT: Gamma-Glutamyl Transferase; ULN: Upper Limit of Normal; ALT: Alanine Aminotrasnferase; AST: Aspartate Aminotransferase; HR: Hazard Ratio; NAFLD: Non Alcoholic Fatty Liver Disease; US: United States; IFN: Interferon.

**INTRODUCTION**

Curative treatments for HCC are only applicable if the diagnosis is made at an early stage, so efforts should be directed to identify its predisposing factors and to include patients at greatest risk in surveillance programs. Liver cirrhosis, hepatitis C virus (HCV) and hepatitis B virus (HBV) are well known predisposing factors(1), but other conditions such as alcohol consumption, metabolic syndrome and diabetes have also been implicated(2).

Diabetes, an increasing worldwide health problem, has been associated with the development of different malignancies, including liver, breast, pancreatic or gastrointestinal tract cancers(3). Several population studies reported an association between diabetes and HCC(4,5), although there is controversy in areas with a high prevalence of HCV and HBV infection(6). In addition, in patients with liver cirrhosis the relationship between diabetes and HCC may be influenced by confounding factors(7). On the other hand, the usefulness of metformin as a chemopreventive agent for HCC development has been suggested in several studies(8,9).

The aim of this study was to determine if diabetes constitutes a risk factor for developing HCC in Caucasian patients with alcohol- or HCV-related liver cirrhosis.

## PATIENTS AND METHODS

### Patients

A cohort of 982 Caucasian patients with Child-Pugh class A or B, alcoholic or HCV liver cirrhosis, included between 1992 and 2014 in a surveillance program for early detection of HCC and prospectively followed, was analyzed. The program was based on the performance of abdominal ultrasound (aUS) and alpha-fetoprotein (AFP) every six months.

Twelve patients who developed HCC during the first six months from the inclusion and 8 non-Caucasian patients were excluded.

Cirrhosis was diagnosed by liver biopsy in 263 patients (26.8 %), liver decompensation in 397 patients (40.4 %), presence of esophageal varices in 121 patients (12.3 %), and aUS showing a nodular liver and signs of portal hypertension in 201 patients (20.5 %).

Alcoholic liver cirrhosis was considered with daily ethanol consumption >60 g in men and >40 g in women during a period ≥10 years and in the absence of other causes of

liver disease. HCV cirrhosis was diagnosed when serum anti-HCV antibodies and HCV-RNA were present at inclusion or there was a previous history of HCV-RNA positivity followed by sustained virological response (SVR) with antiviral therapy.

The diagnosis of diabetes was established by two blood glucose determinations ≥126 mg/dL or when the patient was receiving anti-diabetic treatment at inclusion.

Demographic data, clinical background and biochemical parameters were collected at the time of inclusion and they were considered as baseline data (Table 1).

The study was approved by the hospital ethics committee as per guidelines set forth by the Declaration of Helsinki.

**Follow-up**

All patients were followed up prospectively every 6 months with physical examination, aUS, AFP level, blood count and routine biochemical tests. Patients were followed until June, 30$^{th}$ 2015 or until the date of one of the following events: HCC (n=156), progression to Child-Pugh class C (n=36), development of a severe co-morbidity (n=68), liver transplantation (n=41), death (n=121) or loss to follow-up (n=87).

Diagnostic criteria for HCC evolved along the study period and were based on the International guidelines. These criteria as well as the recall procedures have already been reported elsewhere(10). The Barcelona Clinic Liver Cancer (BCLC) staging system(11) was used for tumor classification.

**Statistical Analysis**

The Mann–Whitney and the $\chi 2$-test tests were used to compare continuous and categorical variables respectively. A two-tailed *P* value <.05 was considered to be statistically significant. Incidence rates of HCC are presented per 100 person years.

Univariate and multivariate logistic regression analyses were carried out to identify factors associated with diabetes. The Kaplan–Meier method was used to determine the cumulative probability of HCC occurrence during follow-up. The comparison of the survival curves obtained was made by the log-rank test. Patients who progressed to Child–Pugh class C or were transplanted and those who were lost, developed severe co-morbidity, or died, were censored at that time. Those variables associated with a *P*

value <0.10 in the univariate analysis, together with diabetes, were included in the multivariate analysis which was performed by the Cox proportional hazards model. Data analysis was performed using the SPSS statistical package 17.0 (Chicago, IL).

## RESULTS

### Baseline characteristics of patients

A total of 982 patients with Child-Pugh class A or B cirrhosis were analyzed. Most were male (78.7 %) and median age at inclusion was 54 years. Etiology of cirrhosis was alcohol in 603 (61.4 %) and HCV in 379 (38.6 %) patients. At inclusion, only 18 patients with HCV cirrhosis had been successfully treated with interferon-based therapies and subsequently were HCV-RNA negative. Twenty-five percent of the patients had diabetes, 81.2 % were Child-Pugh class A and 51.5 % had had a prior liver decompensation. Baseline features are reported in Table 1.

### Analysis of factors related with the presence of diabetes

Overall, 239 patients (24.3 %) had diabetes at inclusion; this proportion was similar along the study period (27.1 % in 1992-1998; 23.6 % in 1999-2004; 28 % in 2005-2010) except in the last years (2011-2016) in which it was slightly lower (19.5 %)

Prevalence of diabetes was 28.8 % among patients with alcoholic cirrhosis and 17.1 % among those with HCV cirrhosis. The median follow-up of patients with and without diabetes was 60 (IQR 24-96) and 48 months (IQR 18-96) respectively (*P*=.17). Table 1 shows the comparison between patients with and without diabetes as well as the univariate analysis of factors associated with the presence of diabetes. Variables associated with diabetes at the multivariate analysis were age (OR: 1.03; 95 % CI: 1.02-1.05, per year increase; *P*=0.003), Body Mass Index (BMI) (OR: 1.05; 95 % CI: 1.01-1.08, per Kg/m$^2$; *P*=0.002), GGT (OR: 1.01; 95 % CI: 1.00-1.02, per IU/ml; *P*=0.013) and history of prior decompensation (OR: 1.49; 95 % CI: 1.02-2.16; (*P*=0.035). There were no differences in survival between diabetic and non-diabetic patients at 20 years (*P*= 0.094).

### Treatment of diabetes

At inclusion, 135 out of 239 (56.5 %) diabetic patients were receiving pharmacological treatment for diabetes; 46 of them were on treatment with metformin (21 as the only therapy, 10 with insulin, and 13 with other oral anti-diabetic drugs). The remaining 89 patients received diverse anti-diabetic treatments, without metformin.

**Hepatocellular carcinoma incidence and characteristic of the tumors**

During a median follow-up of 49.5 months, 156 patients (15.9 %) developed HCC, with an average annual incidence of 2.70 % and a cumulative incidence at 10 and 20 years of 25.8 % and 48.1 % respectively.

HCC was diagnosed after detection of a hepatic focal lesion together with an AFP ≥400 ng/mL in six patients (3.8 %), by biopsy in 35 patients (22.4 %), and by non-invasive criteria in 115 patients (73.7 %). According to the BCLC staging system, 23 tumors were diagnosed at stage 0 (14.7 %), 96 at stage A (61.5 %), 16 at stage B (10.2 %), 15 at stage C (9.6 %) and 6 at stage D (3.8 %).

**Factors associated with HCC in the whole series**

The cumulative incidence of HCC was similar among diabetic and non-diabetic patients (Fig1A). By univariate Cox regression, seven baseline variables were associated with development of HCC, namely, age, gender, cause of cirrhosis, ALT, AST, Child-Pugh class, platelets and esophageal varices. In the multivariate analysis, four variables were independently associated with the risk of HCC, age (HR= 2.34; 95 % CI 1.68-3.25; $P < 0.001$), male sex (HR= 2.45; 95 % CI 1.55-3.90; $P < 0.001$), high AST values (HR= 1.86; 95 % CI 1.29-2.68; $P = 0.001$) and low platelet count (HR= 2.58; 95 % CI 1.58-4.19; $P < 0.001$), After adjusting with other factors, diabetes was not associated with HCC development (HR 1.12, 95 % IC: 0.78-1.61).

***Factors associated with HCC in alcohol-related cirrhosis***

Among the 603 patients with alcoholic cirrhosis, 88 (14.6 %) developed HCC (annual incidence rate of 2.44 %). The cumulative incidence of HCC was similar among diabetic and non-diabetic patients (Fig1B). Factors associated with HCC are shown in Table 2. In the multivariate analysis, age >55 years, male gender, high GGT values, platelet count

<150x10³/mm³ and a history of previos liver decompensation were independently associated with the risk of HCC. After adjusting with other factors, diabetes was not associated with HCC (HR 1.16, 95 % IC: 0.74-1.82).

***Factors associated with HCC in HCV-related cirrhosis***

Among the 379 patients with HCV cirrhosis, 68 (17.9 %) developed HCC yielding an annual incidence rate of 3.42 %. There were no differences in the annual incidence of HCC between diabetic and non-diabetic patients, 3.92 % and 3.30 % respectively (*P* =.57), neither in HCC cumulative incidence (Fig1C).

Factors associated with HCC are shown in Table 3. In the multivariate analysis, age >55 years, male gender, Child-Pugh class B and presence of esophageal varices were independently associated with the risk of HCC. After adjusting with other factors, diabetes was not associated with HCC (HR 1.17, 95 % CI: 0.63-2.19)

**Factors associated with HCC after excluding patients treated with metformin**

The analysis was repeated after excluding the 46 patients who were on metformin at inclusion (34 in the alcohol group and 12 in the HCV group), 6 of whom had developed HCC. No changes in the factors associated with HCC were observed in the whole series or in the subsets of alcohol- or HCV-related cirrhosis. Again, presence of diabetes was not associated with HCC in the whole series (HR 1.03, 95 % CI: 0.68-1.55), in alcohol-related cirrhosis (HR 1.21, 95 % CI: 0.73-2.01) neither in HCV-related cirrhosis (HR 1.59, 95 % CI: 0.77-3.22).

**DISCUSSION**

Liver cirrhosis is the main risk factor for the development of HCC, and surveillance is recommended in Child-Pugh class A and B patients with cirrhosis of any etiology and in those Child-Pugh class C awaiting liver transplantation(12,13). However, risk of HCC is not uniform among cirrhotic patients(14) and a better knowledge of factors implicated in its development would be useful to refine the target population for implementing

effective HCC screening.

We analyzed the influence of diabetes on the risk of developing HCC among patients with alcohol- or HCV-related cirrhosis. The relationship between cirrhosis and diabetes is complex. Diabetes contributes to cirrhosis promoting non-alcoholic fatty liver disease (NAFLD)(15). On the other hand, progression of liver dysfunction is accompanied by insulin resistance and higher prevalence of diabetes(16). In addition, HCV infection has a direct role in promoting insulin resistance and diabetes(17). In our series, the prevalence of diabetes was higher among patients with alcoholic cirrhosis than in those with HCV cirrhosis. Nevertheless, etiology of cirrhosis was not independently associated with the presence of diabetes. Factors associated with diabetes were older age, higher BMI, higher GGT values and a history of previous hepatic decompensation. While age and BMI are well-known risk factors for diabetes in the general population, the association with previous decompensation is probably reflecting a relationship between more advanced liver disease and diabetes. The reasons to explain higher GGT levels among diabetic patients are less clear but it could be speculated that high GGT levels are a surrogate marker of the coexistence of NAFLD. At the present time, it is impossible to know the proportion of liver disease attributable to NAFLD in patients with other causes for liver cirrhosis, but most likely there is a degree of overlap, especially among patients with alcoholic cirrhosis.

Several population-based studies have reported diabetes as a risk factor for HCC development(4,5). Insulin resistance has been postulated as the key pathophysiological factor due to the release of multiple pro-inflammatory agents and to the increase in circulating insulin-like growth factor-1(18). In our study, the presence of diabetes was not associated with an increase in HCC risk, and this lack of link was observed in the whole cohort as well as in the subsets of alcohol- and HCV-related cirrhosis. If the relationship between diabetes and cirrhosis is complex, the situation is even more bizarre when HCC is incorporated into the equation. In our series, older age and factors linked to a more advanced disease were independently associated with HCC as well as with diabetes, illustrating the existence of confounding factors when the association of diabetes with HCC is explored in patients with cirrhosis.

In a recent meta-analysis of 23 cohort studies, diabetes was associated with increased HCC risk(19). However, just 5 of the 23 studies included only cirrhotic patients and, although diabetic patients had a two-fold increase in HCC risk, there was significant heterogeneity among the studies. A French study analyzed risk factors for HCC in 771 patients with well-compensated alcohol- or HCV-related cirrhosis and found a positive association between diabetes and HCC(20), but an adjustment for variables related with the degree of liver dysfunction was not performed. Ioannou et al(21) investigated the predictors of HCC in a large cohort of patients with cirrhosis of several etiologies and diabetes was not a predictor in the multivariate model. A more recent study, also from US, did not find an association between diabetes and HCC in 739 patients with cirrhosis of different etiologies(7).

In the subset of 603 patients with alcohol-related cirrhosis we observed an HCC incidence rate of 2.44 per 100 patient-years, which is similar to that observed in a recent multicenter study from Belgium and France(22) and to the one we have previously reported(23). Factors associated with the development of HCC were older age, male gender, high GGT values, lower platelet count and a history of previous liver decompensation. HCC incidence was similar among diabetic and non-diabetic patients and the lack of association remained after adjustment with other risk factors. Few studies have addressed this issue in patients with alcoholic cirrhosis. The French report previously outlined(18) found an association between diabetes and HCC in the subgroup of 478 patients with alcoholic cirrhosis, but variables related with the extent of liver dysfunction were not included in the analysis. Yang et al(7) also observed a significant association between diabetes and HCC among patients with non-HCV cirrhosis, but it was not maintained after adjustment with other variables; in addition, in this group of non-HCV cirrhosis, alcohol, NAFLD and other etiologies were included.

Regarding HCV cirrhosis, we detected an HCC incidence rate of 3.42 per 100 patient-years, almost identical to that previously observed among patients with advanced fibrosis and treatment failure(24). Factors associated with HCC were older age, male gender, Child-Pugh class B and presence of esophageal varices, while diabetes was not associated. It should be remarked that most of our patients with HCV-cirrhosis had active HCV infection at the time of their inclusion and only a small proportion of them

achieved SVR during follow-up. Other studies that mainly consisted of patients with active HCV infection have displayed discordant results regarding the association between diabetes and HCC(7,18,21,25). Nevertheless, the situation may be different after achieving SVR. In a study from US that included a large series of patients with chronic hepatitis C who had achieved SVR with IFN-based therapies, diabetes was an independent risk factor for HCC(26). It could be hypothesized that diabetes, and consequently NAFLD, increase their role in the pathogenesis of liver disease after HCV eradication. Although another study, that included 7495 patients with cirrhosis who achieved SVR with Direct-acting Antiviral Agents, did not find an independent association between diabetes and HCC(27), but the follow-up was shorter than 24 months in all patients, and probably a longer follow-up is required to see the effect observed after IFN-based HCV eradication.

A body of evidence now suggests that diabetic medication may impact HCC risk. In a recent meta-analysis involving 550.882 diabetic subjects, metformin was associated with a 48 % reduction in HCC risk(28). Although the number of patients taking metformin in our series was low, the analysis after their exclusion did not detect any modification in the factors associated with the risk of HCC neither in the whole series nor in the subsets of patients with alcohol- or HCV-related cirrhosis.

Probably, the greatest strength of our study is that it comprises a large cohort of patients with cirrhosis included in a HCC screening program, with a long follow-up and a low loss rate. Nevertheless, there are also some limitations that need consideration. First, only Caucasian patients were included, so these results may be not reproducible in different populations. Second, our cohort was constituted basically by patients with advanced cirrhosis and the results could be different in patients with earlier stages of the disease. Third, we did not consider the time from diabetes diagnosis to inclusion and we did not either take into account the new-onset diabetes cases during the follow-up. Finally, the dose and duration of treatment with metformin were not explored.

In conclusion, we have not found that diabetes increases the risk of developing HCC among patients with alcohol- or HCV-related cirrhosis. Moreover, this lack of association cannot be attributable to the use of metformin. There are several

confounding factors that interact between diabetes, cirrhosis and HCC that may explain the discrepancy observed in the literature. Nevertheless, diabetes and other metabolic factors can play a role in patients with HCV cirrhosis after SVR and it could be worthy to analyze their function in patients with alcohol-related cirrhosis who maintain alcohol abstinence.

**DISCLOSURES**

Carmen A. Navascués: Consultant: AbbVie, Bayer; Sponsored Lectures: AbbVie, Gilead.

Luisa González-Diéguez: Sponsored Lectures: Gilead and Novartis

María Varela: Consultant and Sponsored lectures: Bayer

Manuel Rodríguez: Consultant: Gilead; Sponsored Lectures: AbbVie, Gilead, Merck Sharp & Dohme.

**AUTHOR'S CONTRIBUTION IS AS FOLLOWS**

1. Carlos Rodríguez-Escaja: acquisition of data, analysis and interpretation of data, drafting of the article.

2. Carmen A. Navascués: acquisition of data, analysis and interpretation of data, critical revision of the article for important intellectual content.

3. Luisa González-Diéguez: analysis and interpretation of data, critical revision of the article for important intellectual content.

4. Valle Cadahía: analysis and interpretation of data, critical revision of the article for important intellectual content.

5. María Varela: analysis and interpretation of data, critical revision of the article for important intellectual content.

6. Miguel Ángel de Jorge: analysis and interpretation of data.

7. Andrés Castaño-García: analysis and interpretation of data.

8. Manuel Rodríguez: study concept and design, acquisition of data, analysis and interpretation of the data, critical revision of the article for the important intellectual content, statistical analysis.

**REFERENCES**

1. Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. *Gastroenterology* 2004;127:S35–S50.
2. Ascha MS, Hanouneh IA, Lopez R, et al. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010;51:1972–1978.
3. Harding JL, Shaw JE, Peeters A, et al. Cancer risk among people with type 1 and type 2 diabetes: Disentangling true associations, detection bias, and reverse causation. *Diabetes Care* 2015;38:264–270.
4. Lai SW, Chen PC, Liao KF, et al. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: A population-based cohort study. *Am J Gastroenterol* 2012;107:46–52.
5. Davila JA, Morgan RO, Shaib Y, et al. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005;54:533–539.
6. Koh WP, Wang R, Jin A, et al. Diabetes mellitus and risk of hepatocellular carcinoma: findings from the Singapore Chinese Health Study. *Br J Cancer* 2013;108:1182–1188.
7. Yang JD, Mohamed HA, Civinar JL, et al. Diabetes mellitus heightens the risk of hepatocellular carcinoma except in patients with hepatitis C cirrhosis. *Am J Gastroenterol* 2016;111:1573–1580.
8. Chen HP, Shieh JJ, Chang CC, et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. *Gut* 2013;62:606–615.9. Donadon V, Balbi M, Mas MD, et al. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int* 2010;30:750–758.
9. Donadon V, Balbi M, Mas MD, et al. Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. *Liver Int* 2010;30:750–758.
10. Mancebo A, Varela M, González-Diéguez ML, et al. Incidence and risk factors associated with hepatocellular carcinoma surveillance failure. J Gastroenterol Hepatol 2018;33:1524-1529.

11. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. *Semin Liver Dis* 1999;19:329–338.
12. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018;69(1):182-236.
13. Heimbach JK, Kulik ML, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018;67:358–380.
14. Velázquez R, Rodríguez M, Navascues CA, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology 2003;37:520-527.
15. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: Implications for prognosis and clinical management. *J Hepatol* 2015;62:1148–1155.
16. Muller MJ, Willmann O, Rieger A, et al. Mechanism of insulin resistance associated with liver cirrhosis. *Gastroenterology* 1992;102:2033–2041.
17. Negro F. Facts and fictions of HCV and comorbidities: Steatosis, diabetes mellitus, and cardiovascular diseases. *J Hepatol* 2014;61:S69–S78.
18. Wojciechowska J, Krajewski W, Bolanowski M, et al. Diabetes and cancer: a review of current knowledge. *Exp Clin Endocrinol Diabetes* 2016;124:263–275
19. Wang C, Wang X, Gong G, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Int J Cancer* 2012;130:1639–1648.
20. N'Kontchou G, Paries J, Htar MTT, et al. Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis. *Clin Gastroenterol Hepatol* 2006;4:1062–1068.
21. Ioannou GN, Splan MF, Weiss NS, et al. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2007;5:938–945.
22. Ganne-Carrie N, Chaffaut C, Bourcier V, et al. Estimate of hepatocellular carcinoma incidence in patients with alcoholic cirrhosis. *J Hepatol* 2018;69:1274-1283.

23. Mancebo A, Gonzalez-Dieguez M, Cadahia V, et al. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. *Clin Gastroenterol Hepatol* 2013;11:95–101.
24. Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. *Clin Gastroenterol Hepatol* 2010;8:280–288.
25. Veldt BJ, Chen W, Heathcote EJ, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology* 2008;47:1856–1862.
26. El-Serag HB, Kanwal F, Richardson P, et al. Risk of hepatocellular carcinoma after sustained virologic response in veterans with HCV-infection running head: HCC after SVR. *Hepatology* 2017;64:130–137.
27. Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. *Gastroenterology* 2017;153:996–1005.
28. Ma S, Zheng Y, Xiao Y, et al. Meta-analysis of studies using metformin as a reducer for liver cancer risk in diabetic patients. *Medicine* 2017;96(19): e6888.

**Table 1. Baseline characteristics and comparison between diabetic and non-diabetic patients.**

| Variable | Whole cohort (N= 982) | Diabetic (n= 239) | Non-diabetic (n= 743) | *P* Value |
|---|---|---|---|---|
| Age (years)* | 54 (48.7-61.0) | 56.0 (50.0-62.0) | 54.0 (48.0-60.0) | <0.001 |
| Male gender† | 773 (78.7) | 198 (82.8) | 575 (77.4) | 0.073 |
| Alcohol/HCV† | 603 (61.4)/379 (38.6) | 174 (72.8)/65 (27.2) | 429 (57.7)/314 (42.3) | <0.001 |
| BMI (Kg/m²)*‡ | 27.3 (24.4-30.6) | 28.3 (25.1-31.6) | 26.9 (24.2-30.4) | 0.001 |
| Tobacco smoking (ever)§* | 680 (72.9) | 161 (222 (69.4) | 519 (69.8) | 0.15 |
| ALT (IU/L)* | 36 (24-61) | 36 (25-61) | 37 (25-66) | 0.11 |
| AST (IU/L)* | 48 (33-75) | 45 (31-68) | 49 (34-77) | 0.12 |
| GGT (IU/L)* | 93 (52-180) | 118 (63-216) | 86 (49-168) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Bilirrubin (total), (mg/dl)* | 1.1 (0.8-1.9) | 1.2 (0.8-1.9) | 1.1 (0.8-1.8) | 0.45 |
| Albumin, (g/L)* | 40.0 (35.8-44.0) | 39.9 (35.9-43.8) | 40.0 (35.6-44.0) | 0.63 |
| Prothrombin activity ( %)*\|\| | 75 (65-88) | 74 (65-87) | 76 (65-88) | 0.21 |
| Platelet count (10$^3$/mm$^3$)†* | 113 (78-152) | 105 (74-146) | 114 (80-156) | 0.032 |
| Child-Pugh class A † | 797 (81.2) | 199 (83.2) | 598 (80.5) | 0.33 |
| Esophageal varices¶† | 682 (72.2) | 178 (76.7) | 504 (70.8) | 0.079 |
| Prior decompensation† | 506 (51.5) | 142 (59.4) | 364 (49.0) | 0.005 |
| AFP (ng/ml) * | 4.8 (3.0-9-7.7) | 4.6 (2.7-4.6) | 4.8 (3.1-7.8) | 0.63 |
| Follow-up (months) * | 49.5 (24.0-96.0) | 60.0 (24.0-96.0) | 48.0 (18.0-96.0) | 0.17 |

*Median (Q1; Q3)

†Number (percentage) of patients

‡Assessed in 885 patients

§Recorded in 932 patients

||32 patients were on warfarin therapy

¶Assessed in 944 patients

HCV, hepatitis C virus; BMI, body mass index; ALT, alanine transaminase; AST aspartate transaminase; GGT, gamma-glutamyl transferase; AFP, alpha-fetoprotein

**Table 2. Results of univariate and multivariate analysis for risk of HCC occurrence during follow-up in patients with alcohol-related cirrhosis (number of patients= 603; number of HCC= 88).**

| **Features** | Univariate HR (95 % CI) | ***P*** | Multivariate HR (95 % CI) | ***P*** |
|---|---|---|---|---|
| Age (>55 versus ≤55 years) | 2.39 (1.53-3.73) | <0.001 | 2.72 (1.73-4.28) | <0.001 |
| Gender (male versus female) | 2.78 (1.34-5.78) | 0.006 | 3.40 (1.61-7.17) | 0.001 |
| BMI (per Kg/m$^2$) | 0.97 (0.92-1.02) | 0.25 | | |
| Tobacco consumption (past/ongoing versus never) | 1.49 (0.87-2.57) | 0.14 | | |
| Diabetes (yes versus no) | 1.31 (0.84-2.04) | 0.22 | 1.16 (0.74-1.82) | 0.50 |
| ALT (elevated versus normal) | 1.46 (0.94-2.26) | 0.087 | | |

| | | | | |
|---|---|---|---|---|
| AST (elevated versus normal) | 1.47 (0.96-2.25) | 0.071 | | |
| GGT (elevated versus normal) | 1.57 (0.94-2.61) | 0.080 | 1.98 (1.18-3.34) | 0.009 |
| Child-Pugh class (B versus A) | 1.34 (0.84-2.13) | 0.20 | | |
| Platelet count (<150 versus ≥150x10$^3$) | 2.79 (1.48-5.27) | 0.001 | 2.78 (1.47-5.28) | 0.002 |
| Esophageal varices (yes versus no) | 1.33 (0.75-2.36) | 0.32 | | |
| Prior decompensation (yes versus no) | 1.55 (0.92-2.61) | 0.093 | 2.01 (1.19-3.41) | 0.009 |
| AFP (≥10 versus <10 ng/ml) | 1.07 (0.39-2.94) | 0.88 | | |

HCC, hepatocellular carcinoma; CI, confidence interval; HCV, hepatitis C virus; BMI, body mass index; ALT, alanine transaminase; AST aspartate transaminase; GGT, gamma-glutamyl transferase; AFP, alpha-fetoprotein; ULN, upper limit of normal; Ref, reference.

**Table 3. Results of univariate and multivariate analysis for risk of HCC occurrence during follow-up in patients with HCV-related cirrhosis (number of patients= 379; number of HCC= 68).**

| **Features** | Univariate HR (95 % CI) | ***P*** | Multivariate HR (95 % CI) | ***P*** |
|---|---|---|---|---|
| Age (>55 versus ≤55 years) | 2.14 (1.32-3.48) | 0.002 | 2.48 (1.49-4.14) | <0.001 |
| Gender (male versus female) | 1.74 (0.98-3.10) | 0.057 | 2.32 (1.25-4.29) | 0.007 |
| BMI (per Kg/m$^2$) | 1.02 (0.97-1.04) | 0.41 | | |
| Tobacco consumption (past/ongoing versus never) | 1.06 (0.64-1.75) | 0.82 | | |
| Diabetes (yes versus no) | 1.17 (0.66-2.05) | 0.58 | 1.17 (0.63-2.19) | 0.60 |
| ALT (>2 x ULN versus ≤ 2 x ULN) | 1.58 (0.96-2.60) | 0.067 | | |
| AST (elevated versus normal) | 5.09 (1.24-20.81) | 0.023 | | |
| GGT (elevated versus normal) | 0.82 (0.50-1.35 | 0.44 | | |
| Child-Pugh class (B versus A) | 2.15 (1.09-4.24) | 0.026 | 2.13 (1.05-4.29) | 0.034 |
| Platelet count (<150 versus ≥150x10$^3$/mm$^3$) | 2.69 (1.33-5.44) | 0.006 | | |
| Esophageal varices (yes versus no) | 2.02 (1.19-3.44) | 0.009 | 1.78 (1.02-3.08) | 0.040 |

| | | | |
|---|---|---|---|
| Prior decompensation (yes versus no) | 1.73 | (0.98-3.05) | 0.055 |
| AFP (≥10 versus <10 ng/ml) | 1.16 | (0.70-1.92) | 0.55 |

HCC, hepatocellular carcinoma; CI, confidence interval; HCV, hepatitis C virus; BMI, body mass index; ALT, alanine transaminase; AST aspartate transaminase, GGT, gamma-glutamyl transferase; AFP, alpha-fetoprotein; ULN, upper limit of normal; Ref, reference.

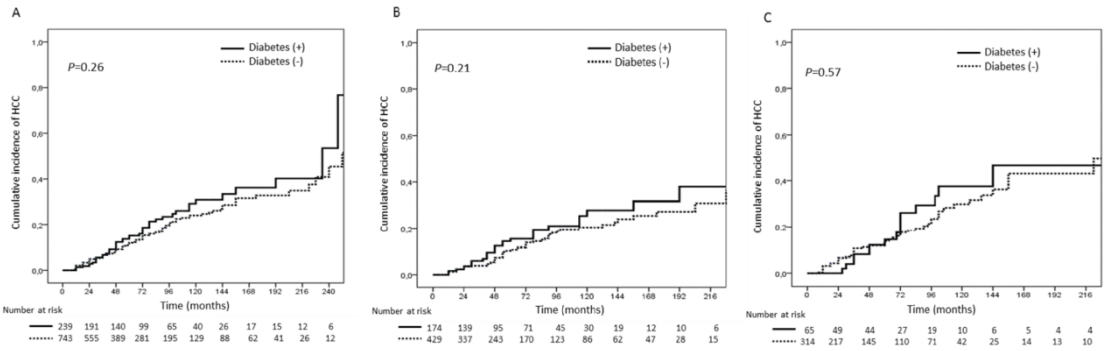


**Figure 1. Incidence of hepatocellular carcinoma (HCC) in diabetic and non-diabetic patients. (A): whole cohort; (B): alcohol-related cirrhosis; (C): HCV-related cirrhosis.**