**Name of journal:** *World Journal of* *Gastroenterology*

**ESPS Manuscript NO: 18312**

**Columns: TOPIC HIGHLIGHTS**

2015 Advances in Hepatitis B virus

**Role of occult hepatitis B virus infection in chronic hepatitis C**

Coppola N *et al.* Occult HBV infection in HCV patients

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**Conflict-of-interest statement**: All the authors of the manuscript declare that they have no conflict of interest in connection with this paper

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**Received:** April 15, 2015

**Peer-review started:** April 18, 2015

**First decision:** June 2, 2015

**Revised:** June 28, 2015

**Accepted:** September 13, 2015

**Article in press:**

**Published online:**

**Abstract**

The development of sensitive assays to detect small amounts of hepatitis B virus (HBV) DNA has favored the identification of occult hepatitis B infection (OBI), a virological condition characterized by a low level of HBV replication with HBV DNA detectable in liver tissue in the absence of HBsAg in serum. The gold standard to diagnose OBI is the detection of HBV DNA in the hepatocytes by highly sensitive and specific techniques, a diagnostic procedure requiring liver tissue to be tested and the use of non-standardized homemade techniques. Consequently, in everyday clinical practice the detection of anti-HBc in serum of HBsAg-negative subjects is used as a surrogate marker to identify the subjects with OBI. In patients with chronic hepatitis C (CHC), occult HBV infection has been identified in nearly one-third of the cases. Considerable data suggest that occult HBV infection favors the increase of liver damage and the development of hepatocellular carcinoma (HCC) in patients with CHC. The data from other studies, however, indicate no influence of occult HBV infection on the natural history of CHC, particularly regarding the risk of developing HCC.

**Key words**: Occult hepatitis B virus infection; Silent hepatitis B virus infection; Anti-HBc; Hepatitis B virus infection; cirrhosis; Hepatocellular carcinoma

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**Core tip:** Occult hepatitis B infection is a virological condition characterized by a low level of hepatitis B virus (HBV) replication with HBV DNA detectable in liver tissue in the absence of HBsAg in serum. Some studies indicate that occult HBV infection may favor the increase of liver fibrosis and the development of hepatocellular carcinoma in patients with chronic hepatitis C, whereas other investigations refute this. This review article traces all the available data on this topic and discusses the possible influence of occult HBV infection on the natural course of chronic hepatitis C.

Coppola N, Onorato L, Pisaturo M, Macera M, Sagnelli C, Martini S, Sagnelli E. Role of occult hepatitis B virus infection in chronic hepatitis C. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Approximately 170 million individuals are chronically infected with hepatitis C virus (HCV) worldwide[1-4]. HCV is a small, enveloped, positive-sense, single-stranded RNA virus of the genus Hepacivirus of the Flaviviridae family. Phylogenetic analysis of HCV isolates has enabled the viral classification into six major genotypes (from 1 to 6) and more than 100 subtypes[5,6].HCV is transmitted by percutaneous exposure to infected blood through intravenous drug injection and invasive medical procedures, and by permucosal exposure through unprotected intercourse with multiple partners[7,8], particularly in HIV-positive men who have sex with men[9-12].

HCV causes acute hepatitis that is frequently asymptomatic and in its symptomatic form is characterized by nausea, malaise and jaundice. The acute HCV infection resolves spontaneously in about one-third of the cases[13,14], whereas the remaining two-thirds remain infected, circulate anti-HCV and HCV RNA, and usually show an indolent course or a slow progression to liver cirrhosis and hepatocellular carcinoma[15]. In some cases, however, spontaneous acute exacerbations may develop, characterized by one or more peaks of the aminotransferase serum level above the previous values[16-22], which can frequently induce a deterioration of the liver disease. In some cases the progression to liver cirrhosis and HCC is rapid[15], particularly when co-morbidities, an unfavorable genetic background and unsafe lifestyle factors are present. Indeed, the outcome of chronic hepatitis C (CHC) is influenced by associated host factors (sex, age at infection, routes of transmission, immune response, genetic background), viral factors (HCV genotype and viral quasispecies), co-morbidities (viral co-infection, insulin-resistance, liver steatosis, immunosuppressive clinical condition) and lifestyle factors (alcohol intake)[23-30].

 The development of sensitive assays to detect small amounts of HBV DNA has favored the identification of occult hepatitis B infection, a virological condition characterized by a low level of HBV replication with HBV DNA detectable in the liver cells in the absence of HBsAg in serum. In patients with CHC, occult HBV infection has been identified in about one-third of HBsAg-negative/anti-HCV- positive subjects in the Mediterranean Basin and in more than 50% in East Asian countries[31-36]. Considerable data suggest that in patients with CHC, occult HBV infection may contribute to chronic liver damage and to the development of hepatocellular carcinoma[24,31,37-40]. Other studies, however, indicate that occult HBV infection does not influence the natural history of HCV infection, particularly as regards the risk of HCC development[41-43]. In this review article, which takes into account all the available literature data, the possible role of occult HBV infection in modifying the clinical course of CHC is evaluated and discussed.

**DEFINITION OF OCCULT HBV INFECTION**

Occult hepatitis B infection (OBI) has been defined as the presence of viral DNA in the liver tissue (regardless of HBV DNA detectability in serum) of individuals testing negative for serum HBsAg[36]. The gold standard to diagnose OBI is the detection of HBV DNA in the hepatocytes by highly sensitive and specific techniques (real-time polymerase chain reaction (PCR), nested PCR and the use of oligonucleotide primers specific for different HBV genomic regions), a diagnostic procedure requiring liver tissue to be tested and the use of non-standardized homemade techniques. Consequently, in everyday clinical practice the detection of anti-HBc in serum of HBsAg-negative subjects, a sign of previous acute hepatitis B (AHB), is used as a surrogate serum marker to identify subjects with OBI[39,43-49]. This option is supported by the observation that in patients experiencing immunosuppression, OBI, as defined by the presence of HBV DNA in liver tissue, mostly occurs in HBsAg-negative/anti-HBc-positive patients[44,50,51]. The data from a previous investigation on 89 HBsAg-negative patients with CHC showed the presence of HBV DNA in plasma, peripheral blood mononuclear cells and/or liver tissue in 60% of the anti-HBs/anti-HBc-positive, in 80% of the anti-HBs-negative/anti-HBc-positive and in 10% of those lacking both antibodies[44].

**MECHANISMS OF LIVER DAMAGE BY OCCULT HBV INFECTION**

An underhand activity of HBV genome and in some cases mild hepatocellular necrosis may persist for years after the resolution of self-limiting AHB[52,53]. The mechanism of liver damage of OBI is still unclear, but there is some suggestion that viral factors may play a role in its development and in the related liver damage. In fact, the persistent synthesis of minute undetectable amounts of the virus or other viral transcripts produced by the HBV covalently closed circular DNA (cccDNA) seems capable of maintaining the HBV-specific memory T-cell response[33,54] and the production of cytokines such as tumor necrosis factor-α and interferon-γ[55,56]. In addition, mutations in the X region of HBV may reduce the ability of the X protein to transactivate host cellular proteins essential for viral replication, which may lead to the reduction of HBV DNA replication and the lack of HBsAg serum expression[57].

We should remember, however, that a rare escape mutation in the S region decreases the reactivity in the HBsAg detection assays[58] and is responsible for an “overt” HBsAg-negative infection that might mimic OBI.

**OCCULT HBV INFECTION AND THE PROGRESSION OF LIVER FIBROSIS**

***The impact of OBI, as detected by the presence of serum anti-HBc, on the progression of liver fibrosis in patients with CHC***

As mentioned above, the detection of serum anti-HBc has been used as a surrogate marker of the presence of liver HBV DNA to detect OBI in numerous investigations exploring the correlation between this virological condition and liver fibrosis in patients with CHC (Table 1). In the year 2000, our group[24] published a cross-sectional, case-control study on 174 Caucasian HBsAg-negative CHC patients which showed a significantly higher prevalence of cases with cirrhosis in the anti-HBc-positive subgroup than in the anti-HBc-negative, thus suggesting a role of OBI in fibrosis progression. Similar data were obtained in a cross-sectional study performed in the same period by De Maria *et al*[37] on 285 HCV-infected patients. A few years later a cross-sectional study[38] confirmed the relationship between the presence of anti-HBc and liver cirrhosis in 119 Italian anti-HCV- positive/HBsAg-negative patients. A study on 129 Portuguese anti-HCV-positive patients published in 2005 found an independent association between previous HBV infection and biopsy-proven liver cirrhosis[59]. Subsequent studies further confirmed the unfavorable influence of OBI, as detected by the presence of anti-HBc in HBsAg-negative patients, on the clinical course of CHC. A cross-sectional Brazilian study[60] found OBI as predictive of significant necroinflammation and fibrosis; El-Sherif *et al*[61] demonstrated a higher prevalence of cases with advanced liver disease in patients with OBI than in those without, and Coppola *et al*[62] found OBI as an independent predictor of HCV-related cirrhosis in a cross-sectional study on 222 patients from southern Italy.

Instead, conflicting data have been published by other Authors. Verbaan *et al*[63] did not find any association of OBI with the progression to cirrhosis in 99 CHC patients, whereas patients with OBI, more frequently than those without, showed HCV-related cirrhosis in an Egyptian study[64], and no association was observed between serum anti-HBc and the degree of liver fibrosis in a study from Spain[65] or between anti-HBc and the entity of necroinflammation or fibrosis in a French study[66].

***The impact of OBI, as detected by the presence of HBV DNA in liver tissue, plasma or PBMC, on the progression of liver fibrosis in patients with CHC***

Table 2 shows the data from several studies on the relationship between the degree of liver fibrosis and the presence of OBI demonstrated by detecting HBV DNA in the liver tissue, plasma or PBMC of HBsAg-negative patients with CHC (Table 2). One of the first studies to suggest a clinical impact of OBI was a cross-sectional study published in 1999 by Cacciola *et al*, which showed that in 200 CHC patients one-third of those with detectable liver HBV DNA had cirrhosis versus 19.4% of the HBV-DNA-negative[31]. Similar data were observed in 203 HCV-infected patients in a French study published in 2007[67], in which those with plasma HBV-DNA showed more advanced fibrosis (*P <* 0.001) than the HBV-DNA-negative. In 2008, Matsuoka *et al*[68] tested 468 Japanese HBsAg-negative patients with CHC for the presence of plasma HBV DNA and found over a mean follow-up period of 6.7 years a more frequent occurrence of cirrhosis and HCC in those with OBI than in those without. These data were confirmed in a prospective study in which HBV DNA was detected in the liver tissue of 326 Italian CHC patients[69], of whom those who progressed to cirrhosis or developed HCC were more frequent in those with OBI than in those without.

Conflicting data, however, come from several studies, all but one detecting HBV DNA only in plasma. In a Japanese study on 65 HCV-infected patients, liver cirrhosis was detected with a similar frequency in CHC patents with or without OBI[35]. In 2004 Toberson *et al*[70] reported no association between OBI and the grading or staging in 180 anti-HCV-positive drug users. A cross-sectional study published in the same year on 59 Brazilian patients[71] showed a similar degree of liver fibrosis in those with or without OBI. Hui *et al*[72,73] published in 2006 two retrospective cohort studies on 74 CHC patients and 118 subjects with a recurrent HCV infection after liver transplantation, respectively; in both studies liver fibrosis, detected by comparing two consecutive liver biopsies, showed a similar increase in patients with or without OBI. In addition, Sagnelli *et al*[44] did not find any association between the degree of liver fibrosis and OBI in a prospective study where OBI was assessed through the detection of HBV DNA in plasma, PBMC and liver tissuein 89 patients with CHC. Finally, Emara *et al*[74] studied 155 Egyptian CHC patients and found a significantly lower prevalence of cases with cirrhosis in patients with circulating HBV DNA than in those without.

**OCCULT HBV INFECTION AND THE OCCURRENCE OF HCC**

There is biological, epidemiological and clinical evidence proving that the oncogenic potential of HBV may induce the development of HCC both in patients with cirrhosis and in those with a milder liver disease. Chronic HBV infection accounts for approximately 50% of the total cases and for virtually all childhood HCC, and prospective cohort studies showed a 5- to 100-fold increase in the risk of developing HCC among HBsAg carriers compared with uninfected subjects[75]. In spite of this, the role of OBI in the development of HCC in patients with chronic hepatitis due to etiological agents other than HBV, firstly HCV, is still a matter of debate in the scientific community. Using anti-HBc positivity or the presence of HBV DNA in plasma or liver tissue as a sign of OBI, several research groups have investigated the role of occult HBV infection in the development of HCC in HBsAg-negative patients with CHC.

***The impact of OBI, as detected by the presence of serum anti-HBc, on the development of HCC in patients with CHC***

The studies that evaluated the impact of OBI, as detected by the presence of anti-HBc in serum, on the development of HCC are listed in Table 3. In 1996 Chiba *et al*[76] published data from a cohort study on 412 Japanese patients with CHC with or without cirrhosis and showed a higher incidence of HCC in those with OBI than in those without (23.7% *vs* 7.5%, *P* = 0.02). The same Authors reported similar results in a cross-sectional study on 204 cirrhotic patients[77]. In 1999 a case-control study on 51 Australian patients with CHC with or without cirrhosis showed a correlation between the occurrence of HCC and male gender, lower serum albumin level and anti-HBc positivity[78]. In the same year Marusawa *et al*[34] published a study on 2,014 patients with CHC with or without cirrhosis which showed a significantly higher rate of patients with HCC in those with OBI than in those without (34.7% *vs* 18.8%). Similar results were reported in a cohort study[79] on 459 Japanese patients followed up for a mean period of 6.6 years, where the incidence of HCC correlated with the age of the patients, the degree of liver fibrosis, ALT levels and anti-HBc positivity. Another Japanese cohort study[80] on 74 CHC patients showed a correlation between the incidence of HCC and anti-HBc positivity. Ikeda *et al*[81] performed a prospective study on 872 Japanese CHC patients and observed in those with liver cirrhosis a significantly higher occurrence of HCC in those with OBI than in those without, a difference not observed in patients with a lower degree of liver fibrosis. Adachi *et al*[82] followed up 123 Japanese cirrhotic patients for a mean period of 53.3 months and identified as independent predictors of HCC development male gender, higher α-FP and ALT serum values and the presence in serum of anti-HBc but not of HBV DNA. A case-control study recently conducted by Reddy *et al*[83] in North America on 459 anti-HCV-positive patients with CHC showed a significantly higher frequency of HCC in those with OBI than in those without.

Several studies, however, produced different results. A prospective investigation[84] on 61 CHC patients found no difference in HCC occurrence between groups of patients with or without previous exposure to HBV. The cohort study conducted in 1998 by the Italian IFN-α Hepatocellular Carcinoma Study Group[85] on 451 anti-HCV-positive subjects showed a similar incidence of HCC in anti-HBc-positive and -negative cases. In 1997*,* a Japanese study on 502 patients demonstrated a similar frequency of HCC in anti-HBc-positive and anti-HBc-negative patients[86]. Hiraoka *et al*[48] in 2003 and Hasegawa *et al*[87] in 2005 also published similar data. Likewise, Bruno *et al*[49] demonstrated that anti-HBc positivity was not independently associated with HCC occurrence in 163 Italian consecutive cirrhotic patients with HCV infection followed up for a median period of 10.7 years. Similarly, Stroffolini *et al*[47] found no association of serum anti-HBc positivity with HCC development in a multicenter retrospective cohort study of 693 Italian cirrhotic patients. This association was not found also in two cross-sectional studies, one conducted in Lebanon[88] and one in Brazil[89]. In a cohort study[90] on 1,262 Japanese HCV patients, anti-HBc positivity was associated with the development of HCC in a univariate analysis and not associated in a multivariate analysis considering age and gender as confounding factors. Finally, Tsubouchi *et al*[91] in 2013 published the results of a prospective study on 400 anti-HCV-positive patients which showed no difference in the incidence of HCC and of cumulative liver-related mortality in patients with and without OBI.

***The impact of OBI, as detected by the presence of HBV DNA in serum or liver tissue, on the development of HCC in patients with CHC***

The studies listed in Table 4 investigated the correlation between HBV-DNA positivity in plasma or in liver tissue and the development of HCC in CHC patients (Table 4). Pollicino *et al*[39] tested for HBV DNA the tumorous tissue of 73 patients with CHC and HCC and a liver sample of 153 CHC patients used as controls and observed a significant association between OBI and HCC, irrespective of age or gender. In a cross-sectional study published in 2004 Tanaka *et al*[92] demonstrated a significantly higher frequency of cases with HCC in CHC patients with plasma HBV-DNA positivity than in those without. Branco *et al*[93] studied 26 Brazilian CHC patients, 20 with HCV-related HCC and 20 healthy controls for HBV DNA in serum and for HBsAg and HBcAg immunochemistry in liver tissue and found a higher prevalence of HCC in the 10 patients with OBI than in the 56 without (70% *vs* 23%). Seeking HBV DNA in the liver tissue of 124 CHC patients followed up for a mean period of 82.8 months, Squadrito *et al*[40] found a significant association between OBI and HCC occurrence, a finding confirmed in a study they published more recently[69]. In 2008, a cohort study[94] enrolling 141 Japanese CHC patients identified OBI as an independent predictor of HCC development.

Some published studies, however, report conflicting data. A prospective study by Obika *et al*[41] on 167 patients with CHC showed a similar incidence rate of HCC over a mean follow-up of 42.5 months in patients with or without HBV DNA in liver tissue (8% *vs* 7%, respectively). In 2008, Shetty *et al*[42] published a study on 56 patients selected for orthotopic liver transplantation (OLT), 44 of whom underwent OLT. Serum HBV DNA was detected in 28% of the 56 and liver HBV DNA in 50% of the 44; explant-proven HCC was found in 12 of the 22 (54.5%) patients with OBI and in 8 of the 22 (36.3%) without, a difference not significant to the statistical analysis. Lastly, Lok *et al*[43] tested for HBV DNA in frozen liver samples of 83 CHC patients, 28 with HCC and 55 controls, and found no association between OBI and HCC.

**CONCLUSION**

The clinical impact of OBI on the natural history of CHC has been extensively investigated, but the resulting data are conflicting and do not allow conclusions to be drawn on this topic, one of the main reasons being the heterogeneity of the methods used to detect OBI. In fact, the detection of HBV DNA in liver tissue of HBsAg-negative subjects can be considered of high sensitivity and high specificity, and that of HBV DNA in plasma of high specificity and moderate sensitivity. In addition, the detection of anti-HBc in serum should be considered of moderate specificity and moderate sensitivity in this setting, although anti-HBc-negative subjects may show HBV DNA in the liver tissue. Furthermore, the variety of diagnostic molecular assays of different sensitivity used to identify HBV DNA in plasma and liver tissue of HBsAg-negative subjects has brought about considerable heterogeneity in the results. Indeed, in the majority of the studies, anti-HBc in serum or HBV DNA in plasma was applied to detect OBI, since this method is cheaper, less invasive and less time-consuming than the detection of HBV DNA in the liver tissue.

Other reasons for the substantial variability in the prevalence of OBI in published studies may be the different extent of the spread of HBV infection in the various geographical areas, the variability in the viral characteristics and the heterogeneity of the enrolment criteria regarding the age, gender, immunological and ethnic background and social habits of the subjects examined.

In addition, OBI itself is a virological condition of different origins; most patients having a self-limiting acute hepatitis B and a minority from the pool of HBsAg chronic carriers, of whom nearly 1% per year clear serum HBsAg. Subjects with OBI of different origins may be present in different proportions in the studies published, and OBI itself may have a different outcome and a different impact on the clinical course of CHC in relation to its origin.

In light of this, we should conclude that the present knowledge on the clinical impact of OBI on the progression of liver fibrosis and on the development of HCC is still insufficient.

In order to reduce the effect of the different sensitivity and specificity of the methods used to detect OBI in the published studies, we performed a comprehensive analysis of the studies in which OBI was identified by the detection of HBV DNA in the liver tissue, but the results remained conflicting. In fact, as regards the progression to cirrhosis we have only 3 studies, two from the same Italian group[31,69] showing a higher rate of patients with cirrhosis in CHC with OBI than in those without, and one from another Italian group[44] showing no difference. As regards the development of HCC, six studies were analyzed, three of which from the same Italian research group[39,40,69] showing a higher rate of patients with HCC in the group of patients with OBI than in those without, whereas the other three studies, one from Japan[41] and two from the USA[42,43], showed no difference. The selection criteria were certainly different from one study to another but the methods to detect HBV DNA in the liver were similar, albeit not identical. Therefore, the question whether OBI might influence the natural course of CHC remains unanswered.

A strong contribution to defining the clinical impact of OBI could come from a prospective international study considering a large number of HBsAg-negative patients with CHC selected with pre-established criteria and using as sign of OBI the detection of HBV DNA in the liver tissue performed with a highly sensitive technique in a single, high standard laboratory.

No standardized strategy, at least to our best knowledge, is at present recommended for the management of OBI in patients with CHC. In particular, because of the uncertainty surrounding the clinical impact of OBI, it is not clear whether close monitoring is an adequate measure or whether the administration of an anti-HBV nucleot(s)ide to prevent both the progression of fibrosis and the onset of HCC is necessary. In this case, the low cost the anti-HBV nucleoside lamivudine, which is now obsolete in other HBV treatment settings because of its low genetic barrier and the consequent high risk of inducing viral resistance, might be the drug of choice to suppress the low level of HBV replication characterizing occult HBV infection.

In conclusion, some studies indicate that occult HBV infection unfavorably affects the progression of liver fibrosis and the development of HCC in patients with CHC, an observation not confirmed in other investigations. The data from prospective studies applying a careful selection of patients and a highly sensitive, standardized method to identify HBV DNA in the liver tissue may help clarify this important issue.

**REFERENCES**

1 **Shepard CW**, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005; **5**: 558-567 [PMID: 16122679]

2 **Mohd Hanafiah K**, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; **57**: 1333-1342 [PMID: 23172780 DOI: 10.1002/hep.26141]

3 **Global Burden Of Hepatitis C Working Group**. Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 2004; **44**: 20-29 [PMID: 14681338]

4 **McHutchison JG**, Bacon BR. Chronic hepatitis C: an age wave of disease burden. *Am J Manag Care* 2005; **11**: S286-S95; quiz S286-S95; [PMID: 16232012]

5 **Lauer GM**, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41-52 [PMID: 11439948 DOI: 10.1056/NEJM200107053450107]

6 **Moradpour D**, Penin F, Rice CM. Replication of hepatitis C virus. *Nat Rev Microbiol* 2007; **5**: 453-463 [PMID: 17487147]

7 **Daniels D**, Grytdal S, Wasley A. Surveillance for acute viral hepatitis - United States, 2007. *MMWR Surveill Summ* 2009; **58**: 1-27 [PMID: 19478727]

8 **Santantonio T**, Medda E, Ferrari C, Fabris P, Cariti G, Massari M, Babudieri S, Toti M, Francavilla R, Ancarani F, Antonucci G, Scotto G, Di Marco V, Pastore G, Stroffolini T. Risk factors and outcome among a large patient cohort with community-acquired acute hepatitis C in Italy. *Clin Infect Dis* 2006; **43**: 1154-1159 [PMID: 17029134]

9 **Götz HM**, van Doornum G, Niesters HG, den Hollander JG, Thio HB, de Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men--results from contact tracing and public health implications. *AIDS* 2005; **19**: 969-974 [PMID: 15905679]

10 **van de Laar TJ**, van der Bij AK, Prins M, Bruisten SM, Brinkman K, Ruys TA, van der Meer JT, de Vries HJ, Mulder JW, van Agtmael M, Jurriaans S, Wolthers KC, Coutinho RA. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. *J Infect Dis* 2007; **196**: 230-238 [PMID: 17570110]

11 **Danta M**, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, Fisher M, Johnson AM, Dusheiko GM. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviours. *AIDS* 2007; **21**: 983-991 [PMID: 17457092]

12 **Bottieau E**, Apers L, Van Esbroeck M, Vandenbruaene M, Florence E. Hepatitis C virus infection in HIV-infected men who have sex with men: sustained rising incidence in Antwerp, Belgium, 2001-2009. *Euro Surveill* 2010; **15**: 19673 [PMID: 20929655]

13 **Micallef JM**, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006; **13**: 34-41 [PMID: 16364080]

14 **Orland JR**, Wright TL, Cooper S. Acute hepatitis C. *Hepatology* 2001; **33**: 321-327 [PMID: 11172332]

15 **Seeff LB**. Natural history of chronic hepatitis C. *Hepatology* 2002; **36**: S35-S46 [PMID: 12407575]

16 **Sheen IS**, Liaw YF, Lin DY, Chu CM. Acute exacerbations in chronic hepatitis C: a clinicopathological and prognostic study. *J Hepatol* 1996; **24**: 525-531 [PMID: 8773906]

17 **Hiraga N**, Suzuki F, Akuta N, Suzuki Y, Sezaki H, Hosaka T, Someya T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Matsuda M, Watabiki S, Satoh J, Kumada H. Clinical and virological characteristics of untreated patients with chronic hepatitis C who develop serum alanine aminotransferase flare-up. *J Med Virol* 2005; **75**: 240-248 [PMID: 15602722]

18 **Rumi MG**, De Filippi F, La Vecchia C, Donato MF, Gallus S, Del Ninno E, Colombo M. Hepatitis C reactivation in patients with chronic infection with genotypes 1b and 2c: a retrospective cohort study of 206 untreated patients. *Gut* 2005; **54**: 402-406 [PMID: 15710990]

19 **Sagnelli E**, Coppola N, Marrocco C, Coviello G, Battaglia M, Messina V, Rossi G, Sagnelli C, Scolastico C, Filippini P. Diagnosis of hepatitis C virus related acute hepatitis by serial determination of IgM anti-HCV titres. *J Hepatol* 2005; **42**: 646-651 [PMID: 15826712]

20 **Coppola N**, Vatiero LM, Sagnelli E. HCV genotype 2 as a risk factor for reactivation of chronic HCV infection. *Gut* 2005; **54**: 1207 [PMID: 16009701]

21 **Sagnelli E**, Pisaturo M, Stanzione M, Messina V, Alessio L, Sagnelli C, Starace M, Pasquale G, Coppola N. Clinical presentation, outcome, and response to therapy among patients with acute exacerbation of chronic hepatitis C. *Clin Gastroenterol Hepatol* 2013; **11**: 1174-1180.e11 [PMID: 23591280 DOI: 10.1016/j.cgh.2013.03.025]

22 **Sagnelli E**, Sagnelli C, Pisaturo M, Coppola N. Hepatic flares in chronic hepatitis C: spontaneous exacerbation vs hepatotropic viruses superinfection. *World J Gastroenterol* 2014; **20**: 6707-6715 [PMID: 24944463 DOI: 10.3748/wjg.v20.i22.6707]

23 **Sagnelli E**, Pasquale G, Coppola N, Scarano F, Marrocco C, Scolastico C, Santantonio T, Gentile A, Piccinino F. Influence of chronic coinfection with hepatitis B and C virus on liver histology. *Infection* 2004; **32**: 144-148 [PMID: 15188073]

24 **Sagnelli E**, Coppola N, Scolastico C, Filippini P, Santantonio T, Stroffolini T, Piccinino F. Virologic and clinical expressions of reciprocal inhibitory effect of hepatitis B, C, and delta viruses in patients with chronic hepatitis. *Hepatology* 2000; **32**: 1106-1110 [PMID: 11050062]

25 **Sagnelli E**, Coppola N, Pisaturo M, Masiello A, Tonziello G, Sagnelli C, Messina V, Filippini P. HBV superinfection in HCV chronic carriers: a disease that is frequently severe but associated with the eradication of HCV. *Hepatology* 2009; **49**: 1090-1097 [PMID: 19263473 DOI: 10.1002/hep.22794]

26 **Coppola N**, Zampino R, Bellini G, Macera M, Marrone A, Pisaturo M, Boemio A, Nobili B, Pasquale G, Maione S, Adinolfi LE, Perrone L, Sagnelli E, Miraglia Del Giudice E, Rossi F. Association between a polymorphism in cannabinoid receptor 2 and severe necroinflammation in patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2014; **12**: 334-340 [PMID: 23707465 DOI: 10.1016/j.cgh.2013.05.008]

27 **Coppola N**, Zampino R, Sagnelli C, Bellini G, Marrone A, Stanzione M, Capoluongo N, Boemio A, Minichini C, Adinolfi LE, Maione S, Del Giudice EM, Sagnelli E, Rossi F. Cannabinoid receptor 2-63 QQ variant is associated with persistently normal aminotransferase serum levels in chronic hepatitis C. *PLoS One* 2014; **9**: e99450 [PMID: 24940753 DOI: 10.1371/journal.pone.0099450]

28 **Coppola N**, Marrone A, Pisaturo M, Starace M, Signoriello G, Gentile I, Adinolfi LE, Sagnelli E, Zampino R. Role of interleukin 28-B in the spontaneous and treatment-related clearance of HCV infection in patients with chronic HBV/HCV dual infection. *Eur J Clin Microbiol Infect Dis* 2014; **33**: 559-567 [PMID: 24081499 DOI: 10.1007/s10096-013-1985-7]

29 **Coppola N**, Rosa Z, Cirillo G, Stanzione M, Macera M, Boemio A, Grandone A, Pisaturo M, Marrone A, Adinolfi LE, Sagnelli E, Miraglia Del Giudice E. TM6SF2 E167K variant is associated with severe steatosis in chronic hepatitis C, regardless of PNPLA3 polymorphism. *Liver Int* 2015; **35**: 1959-1963 [PMID: 25581573 DOI: 10.1111/liv.12781]

30 **Zampino R**, Coppola N, Cirillo G, Boemio A, Pisaturo M, Marrone A, Macera M, Sagnelli E, Perrone L, Adinolfi LE, Miraglia del Giudice E. Abdominal fat interacts with PNPLA3 I148M, but not with the APOC3 variant in the pathogenesis of liver steatosis in chronic hepatitis C. *J Viral Hepat* 2013; **20**: 517-523 [PMID: 23808989 DOI: 10.1111/jvh.12053]

31 **Cacciola I**, Pollicino T, Squadrito G, Cerenzia G, Orlando ME, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. *N Engl J Med* 1999; **341**: 22-26 [PMID: 10387938 DOI: 10.1056/NEJM199907013410104]

32 **Torbenson M**, Thomas DL. Occult hepatitis B. *Lancet Infect Dis* 2002; **2**: 479-486 [PMID: 12150847 DOI: 10.1016/S1473-3099(02)00345-6]

33 **Raimondo G**, Caccamo G, Filomia R, Pollicino T. Occult HBV infection. *Semin Immunopathol* 2013; **35**: 39-52 [PMID: 22829332 DOI: 10.1007/s00281-012-0327-7]

34 **Marusawa H**, Osaki Y, Kimura T, Ito K, Yamashita Y, Eguchi T, Kudo M, Yamamoto Y, Kojima H, Seno H, Moriyasu F, Chiba T. High prevalence of anti-hepatitis B virus serological markers in patients with hepatitis C virus related chronic liver disease in Japan. *Gut* 1999; **45**: 284-288 [PMID: 10403743]

35 **Fukuda R**, Ishimura N, Niigaki M, Hamamoto S, Satoh S, Tanaka S, Kushiyama Y, Uchida Y, Ihihara S, Akagi S, Watanabe M, Kinoshita Y. Serologically silent hepatitis B virus coinfection in patients with hepatitis C virus-associated chronic liver disease: clinical and virological significance. *J Med Virol* 1999; **58**: 201-207 [PMID: 10447413]

36 **Raimondo G**, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, Craxì A, Donato F, Ferrari C, Gaeta GB, Gerlich WH, Levrero M, Locarnini S, Michalak T, Mondelli MU, Pawlotsky JM, Pollicino T, Prati D, Puoti M, Samuel D, Shouval D, Smedile A, Squadrito G, Trépo C, Villa E, Will H, Zanetti AR, Zoulim F. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol* 2008; **49**: 652-657 [PMID: 18715666]

37 **De Maria N**, Colantoni A, Friedlander L, Leandro G, Idilman R, Harig J, Van Thiel DH. The impact of previous HBV infection on the course of chronic hepatitis C. *Am J Gastroenterol* 2000; **95**: 3529-3536 [PMID: 11151889]

38 **Giannini E**, Ceppa P, Botta F, Fasoli A, Romagnoli P, Ansaldi F, Durando P, Risso D, Lantieri PB, Icardi GC, Testa R. Previous hepatitis B virus infection is associated with worse disease stage and occult hepatitis B virus infection has low prevalence and pathogenicity in hepatitis C virus-positive patients. *Liver Int* 2003; **23**: 12-18 [PMID: 12640722]

39 **Pollicino T**, Squadrito G, Cerenzia G, Cacciola I, Raffa G, Craxi A, Farinati F, Missale G, Smedile A, Tiribelli C, Villa E, Raimondo G. Hepatitis B virus maintains its pro-oncogenic properties in the case of occult HBV infection. *Gastroenterology* 2004; **126**: 102-110 [PMID: 14699492]

40 **Squadrito G**, Pollicino T, Cacciola I, Caccamo G, Villari D, La Masa T, Restuccia T, Cucinotta E, Scisca C, Magazzu D, Raimondo G. Occult hepatitis B virus infection is associated with the development of hepatocellular carcinoma in chronic hepatitis C patients. *Cancer* 2006; **106**: 1326-1330 [PMID: 16453330]

41 **Obika M**, Shinji T, Fujioka S, Terada R, Ryuko H, Lwin AA, Shiraha H, Koide N. Hepatitis B virus DNA in liver tissue and risk for hepatocarcinogenesis in patients with hepatitis C virus-related chronic liver disease. A prospective study. *Intervirology* 2008; **51**: 59-68 [PMID: 18349544 DOI: 10.1159/000121363]

42 **Shetty K**, Hussain M, Nei L, Reddy KR, Lok AS. Prevalence and significance of occult hepatitis B in a liver transplant population with chronic hepatitis C. *Liver Transpl* 2008; **14**: 534-540 [PMID: 18324677 DOI: 10.1002/lt.21284]

43 **Lok AS**, Everhart JE, Di Bisceglie AM, Kim HY, Hussain M, Morgan TR. Occult and previous hepatitis B virus infection are not associated with hepatocellular carcinoma in United States patients with chronic hepatitis C. *Hepatology* 2011; **54**: 434-442 [PMID: 21374690 DOI: 10.1002/hep.24257]

44 **Sagnelli E**, Imparato M, Coppola N, Pisapia R, Sagnelli C, Messina V, Piai G, Stanzione M, Bruno M, Moggio G, Caprio N, Pasquale G, Del Vecchio Blanco C. Diagnosis and clinical impact of occult hepatitis B infection in patients with biopsy proven chronic hepatitis C: a multicenter study. *J Med Virol* 2008; **80**: 1547-1553 [PMID: 18649338 DOI: 10.1002/jmv.21239]

45 **Koike K**, Kobayashi M, Gondo M, Hayashi I, Osuga T, Takada S. Hepatitis B virus DNA is frequently found in liver biopsy samples from hepatitis C virus-infected chronic hepatitis patients. *J Med Virol* 1998; **54**: 249-255 [PMID: 9557290]

46 **Jilg W**, Sieger E, Zachoval R, Schätzl H. Individuals with antibodies against hepatitis B core antigen as the only serological marker for hepatitis B infection: high percentage of carriers of hepatitis B and C virus. *J Hepatol* 1995; **23**: 14-20 [PMID: 8530804 DOI: 10.1016/0168-8278(95)80305-X]

47 **Stroffolini T**, Almasio PL, Persico M, Bollani S, Benvegnù L, Di Costanzo G, Pastore G, Aghemo A, Stornaiuolo G, Mangia A, Andreone P, Stanzione M, Mazzella G, Saracco G, Del Poggio P, Bruno S. Lack of correlation between serum anti-HBcore detectability and hepatocellular carcinoma in patients with HCV-related cirrhosis. *Am J Gastroenterol* 2008; **103**: 1966-1972 [PMID: 18637087 DOI: 10.1111/j.1572-0241.2008.01912.x]

48 **Hiraoka T**, Katayama K, Tanaka J, Ohno N, Joko K, Komiya Y, Kumagai J, Mizui M, Hino K, Miyakawa Y, Yoshizawa H. Lack of epidemiological evidence for a role of resolved hepatitis B virus infection in hepatocarcinogenesis in patients infected with hepatitis C virus in Japan. *Intervirology* 2003; **46**: 171-176 [PMID: 12867755]

49 **Bruno S**, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology* 2007; **46**: 1350-1356 [PMID: 17680653]

50 **Bréchot C**, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Bréchot P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely "occult"? *Hepatology* 2001; **34**: 194-203 [PMID: 11431751]

51 **Raimondo G**, Navarra G, Mondello S, Costantino L, Colloredo G, Cucinotta E, Di Vita G, Scisca C, Squadrito G, Pollicino T. Occult hepatitis B virus in liver tissue of individuals without hepatic disease. *J Hepatol* 2008; **48**: 743-746 [PMID: 18314221 DOI: 10.1016/j.jhep.2008.01.023]

52 **Bläckberg J**, Kidd-Ljunggren K. Occult hepatitis B virus after acute self-limited infection persisting for 30 years without sequence variation. *J Hepatol* 2000; **33**: 992-997 [PMID: 11131464]

53 **Yuki N**, Nagaoka T, Yamashiro M, Mochizuki K, Kaneko A, Yamamoto K, Omura M, Hikiji K, Kato M. Long-term histologic and virologic outcomes of acute self-limited hepatitis B. *Hepatology* 2003; **37**: 1172-1179 [PMID: 12717399]

54 **Mason AL**, Xu L, Guo L, Kuhns M, Perrillo RP. Molecular basis for persistent hepatitis B virus infection in the liver after clearance of serum hepatitis B surface antigen. *Hepatology* 1998; **27**: 1736-1742 [PMID: 9620351]

55 **Martin CM**, Welge JA, Shire NJ, Shata MT, Sherman KE, Blackard JT. Cytokine expression during chronic versus occult hepatitis B virus infection in HIV co-infected individuals. *Cytokine* 2009; **47**: 194-198 [PMID: 19625194 DOI: 10.1016/j.cyto.2009.06.005]

56 **Guidotti LG**, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. *Annu Rev Immunol* 2001; **19**: 65-91 [PMID: 11244031]

57 **Uchida T**, Saitoh T, Shinzawa H. Mutations of the X region of hepatitis B virus and their clinical implications. *Pathol Int* 1997; **47**: 183-193 [PMID: 9103208]

58 **El Chaar M**, Candotti D, Crowther RA, Allain JP. Impact of hepatitis B virus surface protein mutations on the diagnosis of occult hepatitis B virus infection. *Hepatology* 2010; **52**: 1600-1610 [PMID: 20815025 DOI: 10.1002/hep.23886]

59 **Dinis-Ribeiro M**, Ramalho F, Glória H, Marinho R, Raimundo M, Serejo F, Velosa J, Carneiro-de-Moura M. Factors associated with the development of cirrhosis in patients with HCV chronic infection. *Hepatogastroenterology* 2005; **52**: 176-179 [PMID: 15783023]

60 **Carvalho-Filho RJ**, de Lucca Schiavon L, Narciso-Schiavon JL, Sampaio JP, Lanzoni VP, Gomes Ferraz ML, Benedito Silva AE. Clinical and histological impact of previous hepatitis B virus infection in patients with chronic hepatitis C. *Liver Int* 2009; **29**: 133-140 [PMID: 18507759 DOI: 10.1111/j.1478-3231.2008.01786.x]

61 **El-Sherif A**, Abou-Shady M, Abou-Zeid H, Elwassief A, Elbahrawy A, Ueda Y, Chiba T, Hosney AM. Antibody to hepatitis B core antigen as a screening test for occult hepatitis B virus infection in Egyptian chronic hepatitis C patients. *J Gastroenterol* 2009; **44**: 359-364 [PMID: 19271112 DOI: 10.1007/s00535-009-0020-3]

62 **Coppola N**, Gentile I, Pasquale G, Buonomo AR, Capoluongo N, D'Armiento M, Borgia G, Sagnelli E. Anti-HBc positivity was associated with histological cirrhosis in patients with chronic hepatitis C. *Ann Hepatol* 2014; **13**: 20-26 [PMID: 24378262]

63 **Verbaan H**, Widell A, Bondeson L, Andersson K, Eriksson S. Factors associated with cirrhosis development in chronic hepatitis C patients from an area of low prevalence. *J Viral Hepat* 1998; **5**: 43-51 [PMID: 9493516]

64 **Helmy A**, Al-Sebayel MI. Isolated antibody to hepatitis B core antigen in patients with chronic hepatitis C virus infection. *World J Gastroenterol* 2006; **12**: 4406-4410 [PMID: 16865787]

65 **Laguno M**, Larrousse M, Blanco JL, Leon A, Milinkovic A, Martínez-Rebozler M, Loncá M, Martinez E, Sanchez-Tapias JM, de Lazzari E, Gatell JM, Costa J, Mallolas J. Prevalence and clinical relevance of occult hepatitis B in the fibrosis progression and antiviral response to INF therapy in HIV-HCV-coinfected patients. *AIDS Res Hum Retroviruses* 2008; **24**: 547-553 [PMID: 18393687 DOI: 10.1089/aid.2007.9994]

66 **Levast M**, Larrat S, Thelu MA, Nicod S, Plages A, Cheveau A, Zarski JP, Seigneurin JM, Morand P, Leroy V. Prevalence and impact of occult hepatitis B infection in chronic hepatitis C patients treated with pegylated interferon and ribavirin. *J Med Virol* 2010; **82**: 747-754 [PMID: 20336715 DOI: 10.1002/jmv.21695]

67 **Mrani S**, Chemin I, Menouar K, Guillaud O, Pradat P, Borghi G, Trabaud MA, Chevallier P, Chevallier M, Zoulim F, Trépo C. Occult HBV infection may represent a major risk factor of non-response to antiviral therapy of chronic hepatitis C. *J Med Virol* 2007; **79**: 1075-1081 [PMID: 17596829]

68 **Matsuoka S**, Nirei K, Tamura A, Nakamura H, Matsumura H, Oshiro S, Arakawa Y, Yamagami H, Tanaka N, Moriyama M. Influence of occult hepatitis B virus coinfection on the incidence of fibrosis and hepatocellular carcinoma in chronic hepatitis C. *Intervirology* 2008; **51**: 352-361 [PMID: 19127078 DOI: 10.1159/000187720]

69 **Squadrito G**, Cacciola I, Alibrandi A, Pollicino T, Raimondo G. Impact of occult hepatitis B virus infection on the outcome of chronic hepatitis C. *J Hepatol* 2013; **59**: 696-700 [PMID: 23751755 DOI: 10.1016/j.jhep.2013.05.043]

70 **Torbenson M**, Kannangai R, Astemborski J, Strathdee SA, Vlahov D, Thomas DL. High prevalence of occult hepatitis B in Baltimore injection drug users. *Hepatology* 2004; **39**: 51-57 [PMID: 14752822]

71 **Silva Cd**, Gonçales NS, Pereira JS, Escanhoela CA, Pavan MH, Gonçales FL. The influence of occult infection with hepatitis B virus on liver histology and response to interferon treatment in chronic hepatitis C patients. *Braz J Infect Dis* 2004; **8**: 431-439 [PMID: 15880234]

72 **Hui CK**, Lau E, Wu H, Monto A, Kim M, Luk JM, Lau GK, Wright TL. Fibrosis progression in chronic hepatitis C patients with occult hepatitis B co-infection. *J Clin Virol* 2006; **35**: 185-192 [PMID: 16103008]

73 **Hui CK**, Lau E, Monto A, Kim M, Luk JM, Poon RT, Leung N, Lo CM, Fan ST, Lau GK, Wright TL. Natural history of patients with recurrent chronic hepatitis C virus and occult hepatitis B co-infection after liver transplantation. *Am J Transplant* 2006; **6**: 1600-1608 [PMID: 16827860]

74 **Emara MH**, El-Gammal NE, Mohamed LA, Bahgat MM. Occult hepatitis B infection in egyptian chronic hepatitis C patients: prevalence, impact on pegylated interferon/ribavirin therapy. *Virol J* 2010; **7**: 324 [PMID: 21083926 DOI: 10.1186/1743-422X-7-324]

75 **El-Serag HB**. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; **142**: 1264-1273.e1 [PMID: 22537432 DOI: 10.1053/j.gastro.2011.12.061]

76 **Chiba T**, Matsuzaki Y, Abei M, Shoda J, Tanaka N, Osuga T, Aikawa T. The role of previous hepatitis B virus infection and heavy smoking in hepatitis C virus-related hepatocellular carcinoma. *Am J Gastroenterol* 1996; **91**: 1195-1203 [PMID: 8651170]

77 **Chiba T**, Matsuzaki Y, Abei M, Shoda J, Aikawa T, Tanaka N, Osuga T. Multivariate analysis of risk factors for hepatocellular carcinoma in patients with hepatitis C virus-related liver cirrhosis. *J Gastroenterol* 1996; **31**: 552-558 [PMID: 8844477]

78 **Dutta U**, Byth K, Kench J, Khan MH, Coverdale SA, Weltman M, Lin R, Liddle C, Farrell GC. Risk factors for development of hepatocellular carcinoma among Australians with hepatitis C: a case-control study. *Aust N Z J Med* 1999; **29**: 300-307 [PMID: 10868491]

79 **Imazeki F**, Yokosuka O, Fukai K, Hiraide A, Saisho H. Significance of prior hepatitis B virus infection in the development of hepatocellular carcinoma in patients with chronic hepatitis C. *Dig Dis Sci* 2003; **48**: 1786-1792 [PMID: 14561002]

80 **Tanaka K**, Nagao Y, Ide T, Kumashiro R, Sata M. Antibody to hepatitis B core antigen is associated with the development of hepatocellular carcinoma in hepatitis C virus-infected persons: a 12-year prospective study. *Int J Mol Med* 2006; **17**: 827-832 [PMID: 16596267]

81 **Ikeda K**, Marusawa H, Osaki Y, Nakamura T, Kitajima N, Yamashita Y, Kudo M, Sato T, Chiba T. Antibody to hepatitis B core antigen and risk for hepatitis C-related hepatocellular carcinoma: a prospective study. *Ann Intern Med* 2007; **146**: 649-656 [PMID: 17470833]

82 **Adachi S**, Shibuya A, Miura Y, Takeuchi A, Nakazawa T, Saigenji K. Impact of occult hepatitis B virus infection and prior hepatitis B virus infection on development of hepatocellular carcinoma in patients with liver cirrhosis due to hepatitis C virus. *Scand J Gastroenterol* 2008; **43**: 849-856 [PMID: 18584524 DOI: 10.1080/00365520801935459]

83 **Reddy A**, May E, Ehrinpreis M, Mutchnick M. Latent hepatitis B is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C. *World J Gastroenterol* 2013; **19**: 9328-9333 [PMID: 24409059 DOI: 10.3748/wjg.v19.i48.9328]

84 **Takano S**, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995; **21**: 650-655 [PMID: 7875662]

85 Effect of interferon-alpha on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. International Interferon-alpha Hepatocellular Carcinoma Study Group. *Lancet* 1998; **351**: 1535-1539 [PMID: 10326535]

86 **Shiratori Y**, Shiina S, Zhang PY, Ohno E, Okudaira T, Payawal DA, Ono-Nita SK, Imamura M, Kato N, Omata M. Does dual infection by hepatitis B and C viruses play an important role in the pathogenesis of hepatocellular carcinoma in Japan? *Cancer* 1997; **80**: 2060-2067 [PMID: 9392327]

87 **Hasegawa I**, Orito E, Tanaka Y, Hirashima N, Sakakibara K, Sakurai M, Suzuki S, Sugauchi F, Ohno T, Ueda R, Mizokami M. Impact of occult hepatitis B virus infection on efficacy and prognosis of interferon-alpha therapy for patients with chronic hepatitis C. *Liver Int* 2005; **25**: 247-253 [PMID: 15780046]

88 **Ramia S**, Sharara AI, El-Zaatari M, Ramlawi F, Mahfoud Z. Occult hepatitis B virus infection in Lebanese patients with chronic hepatitis C liver disease. *Eur J Clin Microbiol Infect Dis* 2008; **27**: 217-221 [PMID: 18071765]

89 **Alencar RS**, Gomes MM, Sitnik R, Pinho JR, Malta FM, Mello IM, Mello ES, Bacchella T, Machado MC, Alves VA, Carrilho FJ. Low occurrence of occult hepatitis B virus infection and high frequency of hepatitis C virus genotype 3 in hepatocellular carcinoma in Brazil. *Braz J Med Biol Res* 2008; **41**: 235-240 [PMID: 18097499]

90 **Ohki T**, Tateishi R, Goto E, Sato T, Masuzaki R, Imamura J, Goto T, Kanai F, Kato N, Shiina S, Yoshida H, Kawabe T, Omata M. Influence of anti-HBc seropositivity on the risk of hepatocellular carcinoma in HCV-infected patients after adjusting for confounding factors. *J Viral Hepat* 2010; **17**: 91-97 [PMID: 19566786 DOI: 10.1111/j.1365-2893.2009.01152.x]

91 **Tsubouchi N**, Uto H, Kumagai K, Sasaki F, Kanmura S, Numata M, Moriuchi A, Oketani M, Ido A, Hayashi K, Kusumoto K, Shimoda K, Stuver SO, Tsubouchi H. Impact of antibody to hepatitis B core antigen on the clinical course of hepatitis C virus carriers in a hyperendemic area in Japan: A community-based cohort study. *Hepatol Res* 2013; **43**: 1130-1138 [PMID: 23413835 DOI: 10.1111/hepr.12075]

92 **Tanaka T**, Inoue K, Hayashi Y, Abe A, Tsukiyama-Kohara K, Nuriya H, Aoki Y, Kawaguchi R, Kubota K, Yoshiba M, Koike M, Tanaka S, Kohara M. Virological significance of low-level hepatitis B virus infection in patients with hepatitis C virus associated liver disease. *J Med Virol* 2004; **72**: 223-229 [PMID: 14695663]

93 **Branco F**, Mattos AA, Coral GP, Vanderborght B, Santos DE, França P, Alexandre C. Occult hepatitis B virus infection in patients with chronic liver disease due to hepatitis C virus and hepatocellular carcinoma in Brazil. *Arq Gastroenterol* 2007; **44**: 58-63 [PMID: 17639185]

94 **Miura Y**, Shibuya A, Adachi S, Takeuchi A, Tsuchihashi T, Nakazawa T, Saigenji K. Occult hepatitis B virus infection as a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C in whom viral eradication fails. *Hepatol Res* 2008; **38**: 546-556 [PMID: 18179561 DOI: 10.1111/j.1872-034X.2007.00316.x]

**P-Reviewer:** Inoue K **S-Editor:** Yu J **L-Editor:** **E-Editor:**

**Table 1 The studies evaluating the role of anti-HBc in the development of cirrhosis in HBsAg-negative patients with chronic hepatitis C**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **First author, year**  | **No. of****patients** | **Country** | **Type of Study** | **Cirrhosis, positive/ tested, *n*/*n* (%)** | ***P* value** |
|  |  |  |  | **HBcAb+** | **HBcAb-** |  |
| Verbaan 1998[63] | 99 | Sweden | Cross-sectional | 10/44 (22.7) | 10/55 (18.2) | NS |
| De Maria 2000[37] | 285 | USA | Cross-sectional | 29/90 (32.2) | 41/195 (21.0) | < 0.05 |
| Sagnelli 2000[24] | 174 | Italy | Case-control | 9/76 (11.8) | 6/98 (6.1) | <0.005 |
| Giannini 2003[38] | 119 | Italy | Cross-sectional | 20/48 (41.6) | 15/71 (21.0) | 0.02 |
| Dinis-Ribeiro 2005[59] | 129 | Portugal | Cross-sectional | 14/30 (46.6) | 32/99 (32.3) | HR:1.35 (1.01-2.69)1 |
| Helmy 2006[64] | 169 | Saudi Arabia | Cross-sectional | 14/85 (16.5) | 45/84 (53.6) | 0.0001 |
| Laguno 2008[65] | 238 | Spain | Cross-sectional | 78/142 (55)2 | 49/96 (51)2 | 0.72 |
| Carvalho-Filho 2009[60] | 111 | Brazil | Cross-sectional | 24/31 (77.4)3 | 40/80 (50.0)3 | 0.017 |
| El-Sherif 2009[61] | 100 | Egypt | Cross-sectional | 68/71 (95.8) | 23/29 (79.3) | 0.009 |
| Levast 2010[66] | 140 | France | Cross-sectional | 5/45 (11.1) | 16/95 (16.8) | NS |
| Coppola 2014[62] | 222 | Italy | Cross-sectional | 21/77 (27.3) | 12/145 (8.3) | < 0.009 |

1Hazard ratio for progression to cirrhosis in HBsAb/HBcAb+ patients; 2Advanced fibrosis (Scheuer score > 2); 3Advanced fibrosis (Metavir score F2-F4). NS: Not significant.

**Table 2 The studies evaluating the role of HBV DNA in serum and/or liver tissue in the development of cirrhosis in HBsAg-negative patients with chronic hepatitis C**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **No. of****patients** | **Country** | **Type of study** | **Liver disease** | **Sample for HBV-DNA detection** | **Cirrhosis, positive/tested, *n*/*n* (%)** | ***P* value** |
|  |  |  |  |  |  | **OBI+** | **OBI-** |  |
| Cacciola 1999[31] | 200 | Italy | Cross-sectional | CH/cirrhosis | Liver | 22/66 (33.3) | 26/134 (19.4) | 0.04 |
| Fukuda 1999[35] | 65 | Japan | Cross-sectional | CH/cirrhosis | Serum | 5/34 (14.7) | 3/31 (9.7) | NS |
| Giannini 2003[38] | 119 | Italy | Cross-sectional | CH/cirrhosis | Serum | 2/8 (25.0) | 32/111 (28.8) | NS |
| Silva 2004[71] | 59 | Brazil | Cross-sectional | CH/cirrhosis | Serum | 2/10 (20.0) | 6/49 (12.0) | NS |
| Toberson 2004[70] | 180 | USA | Cross-sectional | CH/cirrhosis | Serum | 8/81 (9.9)1 | 11/99 (11.1)1 | NS |
| Hui 2006[72] | 74 | USA | Cohort | CH/cirrhosis | Serum | 6/31 (19.4)2 | 8/43 (18.6)2 | NS |
| Hui 2006[73] | 118 | USA | Cohort | Liver transplantation | Serum | 8/41 (19.5)2 | 13/77 (16.9)2 | NS |
| Mrani 2007[67] | 203 | France | Cross-sectional | CH/cirrhosis | Serum | 28/47 (60.0) | 52/156 (33.3) | < 0.001 |
| Laguno 2008[65] | 90 | Spain | Cross-sectional | CH/cirrhosis | Serum | 8/15 (53.3)3 | 37/75 (49.3)3 | NS |
| Matsuoka 2008[68] | 468 | Japan | Cross-sectional | CH/cirrhosis | Serum | 37/204 (18.1) | 28/264 (10.6) | 0.002 |
| Sagnelli 2008[44] | 89 | Italy | Cohort | CH/Cirrhosis | Serum/PBMC/liver | 10/37 (27.0)3 | 19/52 (36.5)3 | NS |
| Emara 2010[74] | 155 | Egypt | Cross-sectional | CH/cirrhosis | Serum | 0/6 (0.0) | 4/149 (2.7) | 0.02 |
| Squadrito 2013[69] | 326 | Italy | Cohort | CH/cirrhosis | Liver | 30/128 (23.4) | 25/198 (12.6) |  *<* 0.01 |

1Advanced fibrosis (Ishak score 3-6); 2Severe fibrosis (Metavir score F3-F4); 3Advanced fibrosis (Scheuer score > 2); 4Severe fibrosis (Scheuer score 3-4). CH: Chronic hepatitis; PBMC: Peripheral blood mononuclear cells; NS: Not significant.

**Table 3 The studies evaluating the role of anti-HBc in the development of hepatocellular carcinoma in HBsAg-negative patients with chronic hepatitis C**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **No. of****patients** | **Country** | **Type of study** | **Liver disease** | **HCC, positive/tested, *n*/*n* (%)** | ***P* value** |
|  |  |  |  |  | **Anti-HBc+**  | **Anti-HBc-** |  |
| Takano 1995[84] | 61 | Japan | Cohort | CH | 9/36 (25.0) | 2/25 (8.0) | NS |
| Chiba 1996[76] | 412 | Japan | Cohort | CH/cirrhosis | 47/198 (23.7) | 16/214 (7.5) | 0.02 |
| Chiba 1996[77] | 204 | Japan | Cross-sectional | cirrhosis | 92/128 (71.9) | 36/76 (47.4) | 0.0005 |
| Shiratori 1997[86] | 502 | Japan | Case-control | CLD | 111/263 (42.2) | 81/239 (33.9) | NS |
| IIHCSG 1998[85] | 451 | Italy | Cohort | CLD | 34/206 (16.5) | 32/245 (13.1) | NS |
| Dutta 1999[78] | 51 | Australia | Case-control | CH/cirrhosis | 10/17 (58.8) | 7/34 (20.6) | 0.01 |
| Marusawa 1999[34] | 2366 | Japan | Cross-sectional | CH/cirrhosis | 363/1047 (34.7) | 248/1319 (18.8) | < 0.01 |
| Hiraoka 2003[48] | 202 | Japan | Case-control | CLD | 109/250 (43.6) | 93/342 (27.2) | NS |
| Imazeki 2003[79] | 459 | Japan | Cohort | CH/cirrhosis | 37/160 (23.1) | 26/299 (8.7) | < 0.05 |
| Hasegawa 2005[87] | 140 | Japan | Cohort | CH/cirrhosis | 9/64 (14.0) | 9/76 (11.8) | NS |
| Tanaka 2006[80] | 74 | Japan | Cohort | CLD | 13/53 (24.5) | 0/21 (0.0) | 0.012 |
| Bruno 2007[49] | 160 | Italy | Cohort | Cirrhosis | 29/86 (33.7) | 25/74 (33.8) | 0.39 |
| Ikeda 2007[81] | 846 | Japan | Cohort | CH/Cirrhosis | 130/392 (33.1) | 107/454 (23.6) | IRR:1.03 (0.66-1.56)1IRR:1.58 (1.12-2.22)2 |
| Adachi 2008[82] | 123 | Japan | Cohort | Cirrhosis | 57/96 (59.3) | 10/27 (37.0) | 0.0039 |
| Alencar 2008[89] | 50 | Brazil | Cross-sectional | Cirrhosis | 5/12 (41.7) | 12/38 (31.6) | NS |
| Miura 2008[95] | 141 | Japan | Cohort | CH | 22/83 (26.5) | 11/58 (19.0) | 0.7 |
| Ramia 2008[88] | 3364 | Lebanon | Cross-sectional | CH/cirrhosis/healthy controls | 7/408 (1.7) | 2/2956 (0.07) | 0.507 |
| Stroffolini 2008[47] | 693 | Italy | Cohort | Cirrhosis | 44/303 (14.5) | 57/390 (12.0) | 0.9 |
| Ohki 2010[90] | 1262 | Japan | Cohort | CLD | 160/522 (30.6) | 179/740 (24.2) | 0.63 |
| Lok 2011[43] | 273 | USA | Case-control | CH/Cirrhosis | 38/121 (31.4) | 53/152 (35.0) | 0.54 |
| Reddy 2013[83] | 459 | USA | Case-control | CLD | 95/229 (41.5) | 27/230 (11.7) | 0.01 |
| Tsubouchi 2013[91] | 400 | Japan | Cohort | CLD | 24/213 (11.3) | 14/187 (7.5) | 0.28 |

1Incidence Rate Ratio for HCC in patients with chronic hepatitis; 2Incidence Rate Ratio for HCC in patients with cirrhosis. CH: Chronic hepatitis; CLD: Chronic liver disease; NS: Not significant.

**Table 4 The studies evaluating the role of HBV DNA in serum and/or liver tissue in the development of hepatocellular carcinoma in HBsAg-negative patients with chronic hepatitis C**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **No. of****patients** | **Country** | **Type of study** | **Liver disease** | **Sample for HBV-DNA detection** | **HCC, positive/tested, *n*/*n* (%)** | ***P* value** |
|  |  |  |  |  |  | **OBI+** | **OBI-** |  |
| Pollicino 2004[39] | 226 | Italy | Case-control | CH/cirrhosis/ HCC | Liver | 45/101 (44.5) | 28/125 (22.4) | < 0.001 |
| Tanaka 2004[39] | 93 | Japan | Cross-sectional | CH/cirrhosis/ HCC | Serum | 25/32 (78.1) | 25/61 (41.0) | < 0.001 |
| Hasegawa 2005[87] | 140 | Japan | Cohort | CH/cirrhosis | Serum | 2/11 (18.2) | 16/129 (12.4) | NS |
| Squadrito 2006[40] | 134 | Italy | Cohort | CH/cirrhosis | Liver | 8/53 (15.1) | 1/81 (1.2) | 0.002 |
| Branco 2007[93] | 66 | Brazil | Cross-sectional | CH/HCC/health controls | Serum/liver1 | 7/10 (70.0) | 13/56 (23.2) | 0.029 |
| Adachi 2008[82] | 123 | Japan | Cohort | Cirrhosis | Serum | 6/14 (42.9) | 60/109 (55.0) | NS |
| Matsuoka 2008[68] | 468 | Japan | Cohort | CH/cirrhosis | Serum/liver1 | 29/204 (14.2) | 9/264 (3.4) | 0.0001 |
| Miura 2008[94] | 141 | Japan | Cohort | CH | Serum | 4/8 (50.0) | 29/133 (21.8) | 0.0036 |
| Obika 2008[41] | 167 | Japan | Cohort | CLD | Liver | 2/25 (8.0) | 10/142 (7.0) | NS |
| Shetty 2008[42] | 44 | USA | Cross-sectional | cirrhosis | Liver | 12/22 (54.5) | 8/22 (36.3) | NS |
| Lok 2011[43] | 83 | USA | Case-control | CH/Cirrhosis | Liver | 3/16 (18.7) | 25/67 (37.3) | NS |
| Squadrito 2013[69] | 94 | Italy | Cohort | CH/cirrhosis | Liver | 13/37 (35.1) | 5/57 (8.1) | < 0.01 |

1OBI assessed with immunochemistry for HBsAg and/or HBcAg. OBI: Occult HBV infection; CH: Chronic hepatitis; CLD: Chronic liver disease, HBV: Hepatitis C virus; HCC: Hepatocellular carcinoma.