

# Impact of occult hepatitis B virus infection on the outcome of chronic hepatitis C

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**Background & Aims:** Occult hepatitis B virus infection (OBI) frequently occurs in patients with hepatitis C virus (HCV) related chronic hepatitis (CHC), but the influence of OBI on the CHC outcome is still uncertain. This observational cohort study evaluated the clinical evolution of CHC patients according to their OBI status. **Methods:** From 1991 to 2000, 326 hepatitis B surface antigen negative CHC patients were tested for OBI by the analysis of liver biopsy DNA extracts. A total of 128/326 cases (39.2%) tested OBI positive and 198/326 (60.8%) OBI negative. Ninety-four of 326 patients (37 OBI positive, 57 OBI negative) were followed-up for a median time of 11 years (range 5–19 years). During the follow-up, 79/94 patients underwent anti-HCV treatments and 26 achieved a sustained virological response that occurred independently of their OBI status.

**Results:** Eighteen patients (13/37 OBI positive, 5/57 OBI negative,  $p < 0.01$ ) developed hepatocellular carcinoma (HCC). Among the 76 non-HCC individuals, 15 subjects (8/24 OBI positive, 7/52 OBI negative,  $p < 0.05$ ) developed advanced forms of cirrhosis. Eighteen patients died during follow-up and 2 underwent liver transplantation. OBI positive individuals had a cumulative survival rate significantly shorter than OBI negative individuals ( $p = 0.003$ ). Liver-related deaths were more frequently found in OBI positive than OBI negative patients (12/37 OBI positive vs. 6/57 OBI negative patients respectively,  $p < 0.01$ ). Finally, non-response to anti-HCV therapy was significantly associated with lower survival ( $p = 0.02$ ).

**Keywords:** HBsAg-negative; Liver biopsy; HBV DNA; Cirrhosis; Hepatocellular carcinoma.

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**Abbreviations:** OBI, occult HBV infection; HCV, hepatitis C virus; CHC, chronic hepatitis C; SVR, sustained virological response; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; IFN $\alpha$ , interferon- $\alpha$ ; LDW, liver disease worsening.

**Conclusions:** Among CHC patients, occult HBV co-infected individuals are a category at high risk of progression toward cirrhosis, HCC development, and lower survival.

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## Introduction

The long-lasting persistence of hepatitis B virus (HBV) genomes in the liver of individuals testing negative for the HBV surface antigen (HBsAg) is termed occult HBV infection (OBI) [1]. OBI is highly prevalent in chronic hepatitis C virus (HCV) carriers and it has been previously reported that, in the Mediterranean area, about one third of individuals with HCV-related chronic liver disease are occult HBV co-infected [2–4]. Whether OBI might negatively influence the chronic hepatitis C (CHC) clinical outcome, favoring its progression toward cirrhosis, has been a largely debated argument for many years [5]. In analogy, some controversies still exist on the possible pro-oncogenic role exerted by OBI, particularly in CHC patients [6–11]. In fact, compared with a recent meta-analysis confirming the impact of OBI on hepatocellular carcinoma (HCC) development [12], other studies failed to find any association between OBI and HCC in a North-American population of HCV patients who had undergone orthotopic liver transplantation (OLT) [13,14]. Of note, the same studies reported that a large number of those patients with end stage liver disease were OBI positive in spite of the very low general prevalence of HBV infection among North Americans of Caucasian origin [13,15]. One main reason for the persisting doubts about the possible contribution of OBI to the severe evolution of CHC remaining unsolved is the lack of longitudinal studies evaluating the clinical outcome of HCV patients according to their occult HBV status over an adequately long period of time.

During the last decade of the past century, liver biopsy specimens from a large cohort of CHC patients attending the Liver Unit of the University Hospital of Messina were tested for OBI and we report here the results of the observational study aimed at



**Table 1. Demographic, virological, and histological characteristics of 326 HCV positive patients tested for occult HBV infection.**

Median age, yr (range)	52 (20-73)
Men/women	211/115
HBcAb positive/negative	129/197
HCV genotypes 1/non-1	142/89 <sup>†</sup>
OBI positive (%)	128 (39.2)
Histology	No. of cases (OBI positive/negative)
Minimal changes	55 (12/43)*
Chronic hepatitis	216 (86/130)*
Cirrhosis	55 (30/25)*

<sup>†</sup>HCV genotype available in 231/326 cases.

\* $p < 0.01$ .

comparing OBI-positive and OBI-negative patients of that cohort with respect to the clinical outcome in long term follow-ups.

## Patients and methods

Between January 1991 and December 2000, 326 HBsAg negative and HCV RNA positive individuals (211 males; median age 52 years, range 20–73 years; 129 positive for antibody to HBV core antigen, anti-HBc) who had undergone needle liver biopsy at our Liver Unit were tested for OBI by molecular analysis of liver DNA extracts (Table 1). As a note, all these cases had been included in previously published studies by our team where the methods to detect HBV genomic sequences were reported in detail [16–18]. None of the patients had received any antiviral therapy before liver biopsy was performed, none was infected with human immunodeficiency virus, and none had evidence of alcoholic or autoimmune liver disease.

The study was performed according to the principles of the Declaration of Helsinki and written informed consent was obtained in every case.

### Statistical analysis

The numerical data were expressed as median and range and the categorical variables as number and percentage. Variables did not present normal distribution by Kolmogorov Smirnov test, and a non-parametric approach was applied. Mann Whitney test was used for each parameter to compare OBI positive and negative patients and to compare HCC and non-HCC patients. The non-parametric Spearman correlation test was applied to assess the existence of any significant interdependence between numerical parameters. Chi square test was utilized to evaluate the association between categorical variables. Kaplan Meier curves were plotted to describe the decrease in cumulative survival in years. In particular, OBI positive and negative curves were compared by Log-rank test. Cox regression models were estimated to assess the possible dependence of the survival times. Finally, for patients who did not develop HCC, univariate logistic regression models were estimated to assess the possible dependence of the events worsening the liver disease on age, sex, HCV genotype, fibrosis staging, steatosis, OBI status, anti-HCV therapy, and response to therapy. Variables significant at univariate analyses were entered into the final multivariate model, estimated by the stepwise procedure of backward elimination, Spearman correlation test was applied to assess the interdependence between OBI and other parameters. Statistical analyses were performed using SPSS 11.0 for Windows package.  $p < 0.05$  was considered to be statistically significant.

## Results

### Baseline characteristics

The liver histology examination showed minimal changes (F0-F1 at Metavir score) in 55 cases, chronic hepatitis (F2-F3) in 216 cases, and cirrhosis (F4) in 55 cases (Table 1). One-hundred twenty-eight out of the 326 cases (39.2%) were found to be OBI

positive and showed a significant association with cirrhosis ( $p < 0.01$ ) (Table 1). Like all the patients attending our Liver Unit, the 326 individuals were invited to a clinical/biochemical/instrumental follow-up: 94 of them regularly attended our out-patients clinic for a median time of 11 years (range: 5–19 years) and make up the population of the present study. Considering the age of the patients when the liver biopsy was performed, these 94 patients were significantly older than the 232 individuals who dropped out at follow-up, whereas the two subsets were comparable in terms of sex distribution, liver histology, HCV genotype, anti-HBc positivity, and OBI prevalence (37 OBI positive, 57 OBI negative) (Table 2). The followed-up patients were unselected, and we have no explanation for justifying the different mean age between these patients and those lost to follow-up. We can only imagine that younger people tend to be less likely to undergo long-term periodic visits in the hospital than older ones. Fifty-six were teetotalers, whereas 38 (17 OBI positive, 21 OBI negative) reported occasional consumption of alcohol and always in an amount lower than 25 gr/die. Forty-six (20 OBI positive, 26 OBI negative) were smokers of cigarettes. Of note, during the follow-up 79/94 patients underwent anti-HCV treatments based on either interferon- $\alpha$  (IFN $\alpha$ ) alone or IFN $\alpha$  + ribavirin or Peg-IFN + ribavirin, in accordance with the available therapeutic schedules over time. Twenty-five of these 79 individuals (31.6%) achieved a sustained virological response (SVR) and this occurred independently of their OBI status (Table 3).

### Events during follow-up

Primarily, we took into account the development of HCC as a main clinical event occurring in the study population (HCC-pts). Secondly, we stratified the subgroup of patients who did not develop HCC on the basis of clear liver disease worsening (LDW-pts) as documented by development of gastro-esophageal varices, and/or gastro-esophageal bleeding, and/or ascites decompensation, and/or encephalopathy. Finally, we evaluated the events of death or OLT in the overall population.

Eighteen patients developed HCC after a median time of 8.8 years (range 2–16 years) following the liver biopsy. Thirteen were males and 5 females, their median age at the time of HCC diagnosis was 65 years (range 45–83 years). Fifteen additional individuals had evidence of severe evolution of their liver disease [9 males, 6 females; median age at the time of the first evidence of liver disease deterioration 70 years (range 49–80 years)]. As a note, 4 among the patients who developed HCC and 6 among those who developed LDW had cirrhosis at liver biopsy (2/4 and 3/6 OBI positive, respectively). Finally, a total number of 18 patients died during follow-up, all of liver-related deaths (14 HCC-pts and 4 LDW-pts), whereas 2 (1 HCC-pts, 1 LDW-pts) underwent OLT.

### Clinical events according to OBI status

Of the 18 HCC-pts, 13 were OBI positive and 5 OBI negative, thus revealing a statistically significant association between OBI status and HCC occurrence ( $p < 0.05$ ) (Fig. 1). In addition, OBI positive HCC-patients were significantly younger than OBI negative ones [60 years (range 45–76) vs. 74 (range 58–83),  $p < 0.05$  Mann Whitney]. Apart from occult infection, HCC occurrence was significantly associated with the lack of response to anti-HCV therapy ( $p < 0.01$ ), whereas no association was found with age

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