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Lack of Correlation Between Serum Anti-HBcore Detectability and Hepatocellular Carcinoma in Patients With HCV-Related Cirrhosis

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BACKGROUND: While the likelihood of developing hepatocellular carcinoma (HCC) in patients coinfected with both HBV and HCV is increased, the role of previous exposure to HBV as a risk factor associated with tumor occurrence in subjects with HCV-related cirrhosis has not been fully investigated.

AIM: To assess whether serum anti-HBc positivity, as a marker of previous HBV exposure, is associated with HCC development in HCV-related positive, hepatitis B surface antigen (HBsAg) negative patients with cirrhosis treated with alfa-interferon (IFN) monotherapy.

PATIENTS AND METHODS: A database including 883 consecutive patients (557 men, mean age 54.7 yr) with histologically proven cirrhosis treated with IFN between 1992 and 1997 was analyzed. All subjects have been surveilled every 6 months by ultrasound. Independent predictors of HCC were assessed by Cox multiple regression analysis.

RESULTS: Mean follow-up was 96.1 months. Anti-HBc testing was available in 693 cases and, among them, 303 patients (43.7%) were anti-HBc seropositive. Anti-HBc positive patients were more often men (67.0% *vs* 58.7%, $P = 0.03$), had lower transaminase levels (3.3 ± 2.0 *vs* 3.8 ± 2.5 u.l.n., $P = 0.004$), and had higher rate of alcohol intake (38.3% *vs* 22.5%, $P < 0.001$) than anti-HBc negative patients. Overall, the incidence rates of HCC per 100 person-years were 1.84 (95% CI 1.34–2.47) in the anti-HBc positive patients and 1.86 (95% CI 1.41–2.42) in anti-HBc negative ones. By Cox multiple regression, there was no association of serum anti-HBc with HCC development (HR 1.03, 95% CI 0.69–1.52) or liver-related deaths incidence (HR 1.21; 95% CI 0.76–1.95).

CONCLUSIONS: In comparison with anti-HBc negative subjects, serum anti-HBc positive patients with HCV-related/HBsAg negative cirrhosis treated with IFN monotherapy did not show a greater risk of HCC.

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INTRODUCTION

Liver cirrhosis is a major risk factor for hepatocellular carcinoma (HCC) worldwide irrespective of etiology. In Italy, more than 90% of HCC occurs in patients with established cirrhosis (1, 2). Because cirrhosis and HCC share the same risk factors, the identification of predictors independently associated with the development of the tumor is particularly hard. However, it has been described that the presence of HBsAg positivity alone or anti-HCV (hepatitis C virus) positivity alone increases the risk of HCC in patients with coexisting cirrhosis by twofold (3), while case-control (4, 5) and prospective studies (6, 7) have shown an additive interaction between the two viruses. Moreover, it has recently been shown that patients with HCV-related cirrhosis and concomitant HCC had higher prevalence of HBV (hepatitis B virus) "occult" infection, which is defined by the presence of liver HBV-DNA but lacking serum HBsAg, in comparison to patients with HCV-related chronic liver disease with no HCC (8).

It is still debated whether the detectability of antibodies to hepatitis B core antigen (anti-HBc positivity), a marker of prior exposure to HBV infection, in patients with HCV-related cirrhosis, may be linked with a greater risk of HCC development (9–11).

We have, therefore, assessed the association of serum anti-HBc positivity and the risk of HCC occurrence, by reanalyzing a large cohort of patients with HCV-related, HBsAg negative histologically proven cirrhosis, who had previously experienced alfa-interferon (IFN) treatment and had been submitted to surveillance with periodically ultrasound examinations.

MATERIALS AND METHODS

Patients

Study design has been described elsewhere (12). Briefly, from February to December 2002, tertiary liver centers associated to the Italian Association for the Study of the Liver (AISF) were invited to participate in a questionnaire-based investigation aimed at assessing the impact of IFN therapy on patients with HCV-related cirrhosis. HCV-related cirrhosis was defined by the presence of serum HCV-RNA detected by polymerase chain reaction. Between January 1992 and December 1997, IFN was offered to all patients with a diagnosis of cirrhosis certified by histology (Ishak score of 6 or Knodell score of 4). A liver biopsy had to be carried out in the 18 months preceding IFN treatment, the diagnosis of cirrhosis being confirmed in each participating center, by an independent pathologist. Patients were not included into the study if they were older than 70 yr, lacked histological diagnosis of cirrhosis, had gastroesophageal varices or had shown previous episodes of decompensation or bleeding, were Child-Pugh class B or C, had HCC or extra-hepatic tumors or HBsAg/human immunodeficiency virus (HIV) seropositivity. Alcohol exposure was defined as described elsewhere (12): briefly, we considered positive a consuming intake of more than 40 g/day in women or 60 g/day for men for at least 10 yr.

Participating centers were required to run surveillance programs for HCC during and after stopping IFN treatment. In order to ensure that all eligible, consecutive patients were included in the database, all centers had to guarantee the preexisting registration of the cohort of patients treated during the study period. Sustained virological response (SVR) was defined as undetectable serum HCV-RNA 24 wk after discontinuation of IFN.

An Excel database including demographic, virological, and clinical data was set up between February 2002 and December 2002. All main outcomes occurring up to June 2005 were recorded. The study was approved by the ethical committees of all participating centers.

Follow-Up

The length of the study was calculated from the starting date of IFN therapy and ended at death or at the last follow-up visit. Liver function tests and a complete physical examination were performed every 6 months. The alpha-fetoprotein (AFP) assay and ultrasound (US) scan were repeated at 6-month intervals.

End Point

Whenever possible, patients with US detected node compatible with an HCC underwent an US-guided fine-needle biopsy, using a 21-gauge needle (Tru-Cut, TSK Laboratories, Tokyo, Japan) (13). Diagnostic criteria for HCC were: (a) histology, based on internationally accepted criteria (14); (b) clinical, in patients with AFP value greater than 400 ng/mL and a focal liver lesion at imaging techniques. After 2002, the diagnosis of HCC was based according to guidelines established by the Barcelona Conference (15).

Statistical Analysis

Continuous variables were summarized as mean and standard deviation, and categorical variables as absolute and relative frequencies. The unpaired Student's *t*-test was used to compare the mean, and the χ^2 test was applied to categorical variables. The receiver operating characteristic (ROC) curve was used to identify the best cutoff point to categorize continuous variables.

The main outcome of the study was the assessment of HCC incidence. Since viral replication of HCV may increase the risk of HCC occurrence in patients with anti-HCV positive cirrhosis, in the attempt to avoid confounding, we planned a three-step analysis. First, we analyzed the overall population, while the second and third step provided a separate analyses which included patients who did not achieve (high-risk group, with persistent viral activity) or who achieved SVR (lower-risk group, with sustained HCV-RNA undetectable after IFN therapy).

Cumulative incidence curves of HCC occurrence and the proportion of liver-related deaths according to anti-HBc status were plotted using the Kaplan–Meier method (16). The difference between groups was assessed using log-rank tests.

The time frame for each outcome was defined as the time from starting IFN treatment until the onset of the event. Data were censored when individuals died from nonliver-related causes, received a liver transplant, or were lost during follow-up. The variables which proved to be significant at univariate analysis were tested by the multivariate Cox proportional hazards regression model to assess their independent effect on the development of HCC during the follow-up (17). The results were expressed as hazard ratio (HR) and their 95% confidence interval (CI).

Data handling and analysis were performed with the Statistical Package for Social Sciences (SPSS 13.0; SPSS Inc., Chicago, IL). All tests was 2-sided and P value <0.05 was considered to be statistically significant.

Sample Size Calculation

Assuming an HCC incidence rate of 2 per 100 person-years in the lower-risk group (*i.e.*, subjects anti-HBc negative) and an HCC incidence rate of 3 per 100 person-years in subjects anti-HBc positive, regardless of the efficacy of IFN treatment, a sample size of 315 subjects in each group was needed to detect a relative risk of 1.5, with $\alpha = 0.05$ and $\beta = 0.20$.

RESULTS

Flowchart of the study is reported in Figure 1.

First-step analysis included the overall population irrespective of the response to IFN. Among 883 patients, 693 subjects had anti-HBc tested at baseline. Table 1 shows the comparison between patients with or without anti-HBc testing. Out of 693 patients, 303 (43.7%) tested anti-HBc serum positive. At baseline, anti-HBc positive subjects were more likely men (67.0% *vs* 58.7%, $P = 0.03$), had lower transaminase levels (3.2 ± 1.9 *vs* 3.8 ± 2.4 u.l.n., $P = 0.004$), and higher rate of alcohol intake (38.3% *vs* 22.5%, $P < 0.001$) (Table 1). In addition, the achievement of SVR was not associated with the anti-HBc status. The overall mean length of follow-up was 97.4 months, without difference between anti-HBc positive and anti-HBc negative patients (97.3 *vs* 97.5 months, respectively). Forty-four patients (14.5%) of the former group and 57 (14.6%) of the latter one developed HCC during surveillance, with an incidence rate per 100 person-years of 1.84 (95% CI 1.34–2.47) and 1.86 (95% CI 1.41–2.42), respectively (Table 2), while the cumulative incidence in the 190 patients in whom anti-HBc test was missed was 1.98 (95% CI 1.32–2.86). Kaplan–Meier curves of HCC development according to anti-HBc status are shown in Figure 2 ($P = 0.8$ by log-rank test). The incidence rate of liver-related death without development of HCC was 0.49/100 person-years (95% CI 0.25–0.85) in anti-HBc positive patients and 0.44 (95% CI 0.24–0.74) in negative subjects. The incidence rate of nonliver-related death was 0.45/100 person-years (95% CI 0.22–0.80) in anti-HBc positive patients and 0.60 (95% CI 0.22–0.80) in negative ones. By Cox multiple regression analysis, there was no association between serum anti-HBc positivity and HCC development (HR 1.03, 95% CI 0.69–1.52) or liver-related deaths incidence (HR 1.21, 95% CI 0.76–1.95).

Second-step analysis included patients who did not achieve SVR. Table 3 shows the baseline characteristics of the two groups. Anti-HBc positive subjects were more frequently men (67.2% *vs* 55.2%, $P = 0.003$) with mean lower levels of transaminases value and platelet count. The incidence rate of HCC in this group of patients was similar among anti-HBc

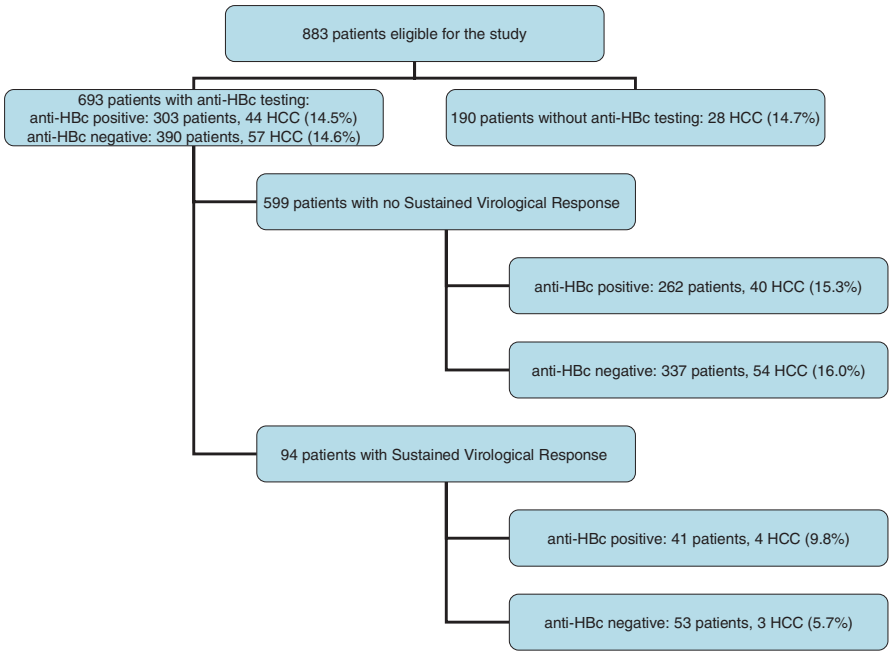

Figure 1. Flowchart of the study.

Table 1. Main Characteristics of 883 Patients With HCV-Related Cirrhosis Stratified According to Serum Anti-HBc Test

Variable	Anti-HBc Missing (N = 190)	Anti-HBc Positive (N = 303)	Anti-HBc Negative (N = 390)	*P*
Age, yr (mean ± S.D.)	54.1 ± 8.6	54.6 ± 8.6	55.1 ± 8.7	0.5
Gender				
Male	125 (65.8%)	203 (67.0%)	229 (58.7%)	0.03
Female	65 (34.2%)	100 (33.0%)	161 (41.3%)	
Serum bilirubin, mg/dL	0.9 ± 0.3	0.9 ± 0.4	0.9 ± 0.4	0.5
Serum albumin, g/L	40.1 ± 5.0	40.0 ± 4.8	40.4 ± 4.8	0.3
Prothrombin time, %	86.1 ± 11.0	86.9 ± 10.7	87.1 ± 11.6	0.8
ALT x u.l.n.	3.6 ± 2.0	3.3 ± 2.0	3.8 ± 2.5	0.004
Platelets $\times 10^9$/L	142.4 ± 38.6	138.8 ± 38.4	144.9 ± 46.6	0.06
Alpha-FP, ng/mL	16.0 ± 30.7	17.4 ± 40.3	16.8 ± 50.7	0.7
HCV Genotype*				
1, 4	80 (69.6%)	195 (75.6%)	201 (73.1%)	0.5
2, 3	35 (30.4%)	63 (24.4%)	74 (26.9%)	
SVR	30 (15.8%)	41 (13.5%)	53 (13.6%)	0.7
Follow-up (months)	91.3 ± 39.0	97.3 ± 36.3	97.5 ± 39.6	0.1
Alcohol intake	33/159 (20.8%)	108/282 (38.3%)	78/347 (22.5%)	<0.001

*HCV genotypes not available in 238 patients. u.l.n.: upper limit of normal.

positive and negative subjects (Table 4). By Cox regression analysis, serum anti-HBc was not associated with the likelihood of HCC development (HR = 1.13, 95% CI 0.75–1.72) (Table 5).

Third-step analysis incorporated only patients who had attained SVR. No significant differences of the baseline features were found across the two groups according to anti-HBc status (Table 6). We observed a greater incidence rate, although nonsignificant, of HCC in anti-HBc positive patients as compared to negative ones (Table 7). Due to few observed outcomes in the model, coefficients of Cox regression analysis did not converge.

Table 2. Incidence Rate of HCC in Patients With HCV-Related Cirrhosis Stratified According to Serum Anti-HBc

Strata	Number of Patients	Person-Years	Number of Events	Rate/100 Person-Years (95% CI)	*P*
Anti-HBc positive	303	2,387.4	44	1.84 (1.34–2.47)	0.9
Anti-HBc negative	390	3,058.6	57	1.86 (1.41–2.42)	
Anti-HBc missing	190	1,414.6	28	1.98 (1.32–2.86)	

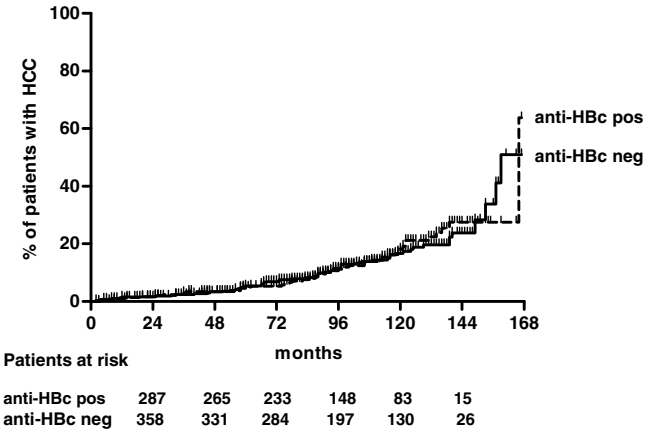

Figure 2. Cumulative incidence of HCC in patients with HCV-related histologically proven cirrhosis stratified according to anti-HBc status. The comparison was not significant by log-rank test.

Table 3. Baseline Characteristics of Patients With HCV-Related Cirrhosis Without SVR, Stratified According to Serum Anti-HBc

Variable	Anti-HBc Positive (N = 262)	Anti-HBc Negative (N = 337)	*P*
Age, yr (mean ± S.D.)	54.7 ± 8.3	55.3 ± 8.6	0.4
Gender			
Male	176 (67.2%)	186 (55.2%)	0.003
Female	86 (32.8%)	151 (44.8%)	
Serum bilirubin, mg/dL	0.9 ± 0.4	0.9 ± 0.4	0.3
Serum albumin, g/L	39.9 ± 4.8	40.3 ± 4.7	0.5
Prothrombin time,%	86.8 ± 10.7	86.9 ± 11.4	0.9
ALT × u.l.n.	3.2 ± 1.9	3.8 ± 2.4	0.002
Platelets $\times 10^9$/L	136.9 ± 39.1	144.4 ± 46.3	0.03
Alpha-FP, ng/mL	17.7 ± 42.1	16.5 ± 45.6	0.7
HCV genotype*			
1, 4	185 (81.5%)	191 (76.7%)	0.2
2, 3	42 (18.5%)	58 (23.2%)	

*HCV genotypes not available in 186 patients. u.l.n.: upper limit of normal.
SVR = sustained virologic response.

Table 4. Incidence Rate of HCC in Patients With HCV-Related Cirrhosis Without SVR, Stratified According to Serum Anti-HBc

Strata	Number of Patients	Person-Years	Number of Events	Rate/100 Person-Years (95% CI)	*P*
Anti-HBc positive	262	2,044.5	40	1.96 (1.39–2.66)	0.8
Anti-HBc negative	337	2,590.1	54	2.08 (1.57–2.72)	

SVR = sustained virologic response.

Table 5. Univariate and Multivariate Analysis of Factors Associated With HCC in Patients With HCV-Related Cirrhosis Without SVR

Variable	Strata	Univariate HR (95% CI)	Multivariate HR (95% CI)	*P*
Age	>58 *vs* ≤58 yr	2.10 (1.33–3.32)	2.36 (1.48–3.76)	<0.001
Sex	Male *vs* female	1.85 (1.18–2.89)	2.29 (1.15–3.62)	<0.001
Platelets	<110.0 *vs* $\geq 110.0 \times 10^9$/L	1.78 (1.15–2.75)	1.64 (1.05–2.54)	0.029
Alpha-FP	≥ 40 *vs* < 40 ng/mL	2.46 (1.36–4.42)	2.26 (1.24–4.11)	0.008
Anti-HBc	Positive *vs* negative	1.05 (0.69–1.58)	1.13 (0.75–1.72)	0.5
HCV Genotype	1–4 *vs* 2—3	1.01 (0.59–1.71)	1.18 (0.70–1.89)	0.5
Alcohol intake	Yes *vs* no	1.06 (0.65–1.74)	1.01 (0.61–1.66)	0.9

SVR = sustained virologic response.

DISCUSSION

The analysis of this large cohort of Italian patients, with histologically proven HCV-related cirrhosis treated with IFN, clearly demonstrated the lack of correlation between serum anti-HBc and risk of HCC development.

The proportion of anti-HBc positivity among patients with HCV-related cirrhosis in the present survey (43.7%) matches with the figure of 45.7%, as previously reported (18), while the HCC incidence per 100 person-years of follow-up is similar to that observed in previous reports in our geographical area (6, 7). Although the retrospective nature of this study may have potentially introduced a selection bias, strength of the present analysis included the large number of patients studied, the consecutive enrolment of all patients treated with IFN at each center, the inclusion of sole subjects with histologically proven cirrhosis, the long-term prospective follow-up, and the availability of an adequate number of events which allowed us to stratify patients according to the response to IFN, thus avoiding the impact of this variable as confounding.

Several epidemiological studies have found that patients with both HBV and HCV infections have higher risk of HCC (4–7), while the contribution of past exposure to HBV infection (anti-HBc positive but HBsAg negative) in increasing the risk of HCC is still debated. The possible link between the presence of anti-HBc positivity and the occurrence of HCC was previously described in a large retrospective study in our geographical area, in which serum anti-HBc was shown to be marginally associated with HCC development (18). However, in this study, the greater risk was restricted to the subgroup of patients who had been treated with IFN but not in the untreated ones. The lack of the assessment of response to IFN when interpreting results, together with the wide heterogeneity of disease stages of patients included in that study, may account for the discrepancies with our results.

More recently, a slight significant association between anti-HBc positivity and HCC risk was also prospectively observed in a Japanese population (19). In this study, however, the incidence of HCC per 100 person-year was exceedingly high and possibly related with racial characteristics of the population and with differences in the viral genome of both HCV and HBV. Of major interest, in agreement with our findings, in the subgroup of patients with chronic hepatitis without cirrhosis in whom the rate of HCC was comparable with those reported in the present study, anti-HBc positivity did not emerge as a risk factor for HCC. It also should be noted that the authors did not assess the effect of response of treatment at multivariate analysis thus hampering the interpretation of the results.

An interesting finding that emerged from our study deserves further comment. Although not significant, a trend toward difference of HCC occurrence between anti-HBc positive and negative patients who achieved SVR was detected. This suggests that HCV clearance may up-regulate HBV replication later on.

Overall, since our results confirm the observations of two other prospective studies carried out in Italy which included a large cohort of patients with HCV-related cirrhosis, who had been surveilled for up to 17 yr (9, 20), we assume that serum anti-HBc positivity should not be considered as a marker of greater HCC risk in patients with cirrhosis, at least in subjects with persistent HCV replication.

The failure to demonstrate the association between serum anti-HBc and the risk of HCC in patients with HCV-related cirrhosis indicates that in some patients serum anti-HBc may simply signal resolved HBV infection, whereas in other subjects serum anti-HBc positivity may mark replicating "occult" HBV in the liver without the presence of serum HBsAg. Nevertheless, despite having recently been demonstrated in one cross-sectional study that the proportion of "occult" HBV

Table 6. Baseline Characteristics of Patients With HCV-Related Cirrhosis and SVR After IFN Mono-Therapy Stratified According to Serum Anti-HBc

Variable	Anti-HBc Positive (N = 41)	Anti-HBc Negative (N = 53)	*P*
Age, yr (mean ± S.D.)	53.8 ± 10.6	53.5 ± 9.4	0.8
Gender			
Male	27 (65.9%)	43 (81.1%)	0.09
Female	14 (34.1%)	10 (18.9%)	
Serum bilirubin, mg/dL	0.9 ± 0.3	0.9 ± 0.3	0.8
Serum albumin, g/L	40.5 ± 4.9	41.4 ± 5.5	0.6
Prothrombin time, %	87.0 ± 11.3	87.8 ± 12.5	0.7
ALT × u.l.n.	3.9 ± 2.4	4.0 ± 2.7	0.9
Platelets × 10^9/L	150.5 ± 31.9	147.9 ± 48.6	0.8
HCV genotype*			
1, 4	10 (32.3%)	10 (38.5%)	0.6
2, 3	21 (67.7%)	16 (61.5%)	

*HCV genotypes not available in 49 patients. u.l.n.: upper limit of normal.
SVR = sustained virologic response.

Table 7. Incidence Rate of HCC in Patients With HCV-Related Cirrhosis and SVR After IFN Mono-Therapy Stratified According to Serum Anti-HBc

Strata	Number of Patients	Person-Years	Number of Events	Rate/100 Person-Years (95% CI)	Rate Ratio (95% CI)	*P*
Anti-HBc Positive	41	343.03	4	1.17 (0.32–2.98)	1.72 (0.29–11.77)	n.s.
Anti-HBc Negative	53	468.6	3	0.64 (0.13–1.87)		

SVR = sustained virologic response.

in anti-HBc positive HCV-related cirrhosis is extremely high (8), it should be carefully taken into account that serum anti-HBc should not be considered a surrogate marker of ongoing "occult" HBV infection. Therefore, the linkage between HCC occurrence and "occult" HBV infection in this population of patients will be obtained only by prospective studies with the use of frozen liver sections and highly sensitive technique. Finally, the hypothesis that IFN treatment may have masked a potential oncogenic effect of "occult" HBV infection remains to be demonstrated.

The findings of the present study therefore do not challenge the general belief that concomitant HBV and HCV infections are additive with respect to the risk of developing HCC (21). The two viruses may interact by causing more severe inflammation and accelerated progression to cirrhosis. Alternatively, direct oncogenic effects of these two viruses may be cumulative or synergistic. Chronic HBV infection may exert a direct carcinogenic mechanism because of its capacity to integrate into the host's genome and to produce proteins (X proteins and truncated pre-S-S protein) having potential transforming properties (22).

In conclusion, this study clearly shows that serum anti-HBc positivity was not associated with a greater risk of HCC in patients with HCV-related cirrhosis at least in those who failed to achieved SVR after IFN therapy. Our results also indicate that in everyday clinical practice patients with HCV-related cirrhosis and anti-HBc positivity, which marks past exposure to HBV infection, do not require a tailored surveillance for HCC.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- Liver cirrhosis, irrespective of the etiology, is the main independent risk factor of hepatocellular carcinoma (HCC) development in western countries
- HCC risk is higher in patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection.
- Past exposure to HBV (anti-HBcore seropositivity) has previously been reported to be associated with high risk of HCC in patients with cirrhosis in Japan.

What Is New Here

- In this large cohort study carried out in western patients with HCV-related cirrhosis, serum anti-HBcore positivity is not associated with a greater risk of HCC development.

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CONFLICT OF INTEREST

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