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Effect of Hepatitis B and C Virus Infections on the Natural History of Compensated Cirrhosis: A Cohort Study of 297 Patients

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OBJECTIVES: The aim of this study was to compare the prognosis of patients with hepatitis B surface antigen (HBsAg) positive and those with antibody to hepatitis C (anti-HCV) positive cirrhosis.

METHODS: This was a retrospective cohort study of 297 untreated Western European patients with compensated viral cirrhosis (Child class A; 161 patients with hepatitis type B and 136 with type C) who were followed for a median period of 6.6 yr.

RESULTS: At diagnosis, median age was lower (48 *vs* 58 yr, respectively) in HBsAg-positive cirrhotic patients. The Kaplan-Meier 5-yr probability of hepatocellular carcinoma (HCC) was 9% and 10% in HBsAg and anti-HCV-positive cirrhotic patients, respectively; the corresponding figures for decompensation unrelated to HCC were 16% and 28% and for survival were 86% and 84%, respectively. After adjustment for clinical and serological differences at baseline, the relative risk (95% CI) for HCC, decompensation and mortality was 1.53 (CI = 0.81–2.89), 0.59 (CI = 0.37–0.94), and 1.44 (CI = 0.85–2.46) respectively, in HBsAg-positive patients compared with anti-HCV-positive cirrhotic patients. Among HBsAg-positive cirrhotic patients, the relative risk for HCC, decompensation, and mortality was 0.89 (CI = 0.30–2.63), 4.05 (CI = 1.09–15.1), and 5.9 (CI = 1.64–21.3), respectively, in HBV-DNA positive (HBeAg positive or negative) compared with HBV-DNA negative (HBeAg negative) patients at entry.

CONCLUSIONS: Patients with HBV infection may present with cirrhosis about 10 yr earlier than those with HCV infection. HCV infection tends to be associated with a higher risk of decompensation, but these data should take into consideration the heterogeneity of HBV-related cirrhosis in terms of viremia levels and risk of hepatic failure. Survival shows no significant differences according to HBV or HCV etiology in Western European cirrhotic patients.

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INTRODUCTION

The hepatitis B virus (HBV) and hepatitis C virus (HCV) infect, respectively, more than 350 and 170 million persons worldwide (1, 2). Infection with HBV and HCV are leading causes of chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC). The clinical course and long-term prognosis of HBV- and HCV-related compensated cirrhosis have been investigated in a number of longitudinal studies from the western world. However these studies have evaluated a heterogeneous study population in relation to the severity of stage of cirrhosis at enrollment, have included both patients treated with interferon-α and untreated controls, and do not provide a separate analysis of the clinical outcome in untreated patients according to HBV or HCV etiology (3–12). The aim of this study was to assess the long-term course of untreated Western European patients with compensated cirrhosis type B or type C, and to evaluate predictors of clinical outcome. The incidence of complications of cirrhosis and of mortality was compared between patients infected with HBV and HCV.

MATERIALS AND METHODS

Study Patients

The patients were part of a multicenter study of compensated cirrhosis type B and C, which involved 11 tertiary referral university hospitals in Europe participating in a European Concerted Action on Viral Hepatitis (EUROHEP). Details of the overall design of the study have been described previously (5, 7). A total of 297 consecutive patients were included in this study who fulfilled the following criteria: 1) HBsAg positivity or anti-HCV positivity; 2) biopsy-proven cirrhosis according to international criteria

(13); 3) no history or clinical evidence of complications of cirrhosis (*i.e.,* ascites, variceal bleeding, encephalopathy, or jaundice; and 4) no evidence of HCC at entry on the basis of ultrasonography, alfa-fetoprotein levels (<400 μg/L), and or histology. According to these entry criteria, all patients had cirrhosis in Child-Pugh class A. Patients with serological evidence of hepatitis delta virus (HDV) infection or HBV/HCV concurrent infection were excluded from this analysis. None had clinical or serological evidence of autoimmune or metabolic liver disease, and none had a history of alcohol abuse, defined as alcohol intake of ≥80 g/day for >5 yr.

The starting time for evaluation of morbidity and mortality was the time of histological diagnosis of compensated cirrhosis. The time of observation was calculated from the date of entry until death, liver transplantation, or the last observation. Patients were followed at least every 12 months or at shorter intervals. Follow-up of patients with HCV-related cirrhosis was updated through 1997 by review of clinical records or consultation of population registries; in addition, attempts were made to contact all patients to return for evaluation (14). HCC was recognized either on the basis of liver biopsy findings or if alfa-fetoprotein levels exceeded 400 μg/L and liver ultrasonography showed findings consistent with this diagnosis. Decompensation was defined as the appearance of at least one episode of ascites, jaundice, encephalopathy, or variceal bleeding. Biochemical remission was defined as the normalization of serum ALT and AST levels on at least two consecutive determinations obtained at least 3 wk apart and persisting at last observation.

Virology

Serum HBV and HCV markers were obtained from medical records or were retrospectively tested using stored serum samples. HBsAg, Hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), antibody to HDV (anti-HDV), and antibody to HIV were tested by commercial radioimmunoassays or ELISA. Serum HBV-DNA was measured by a spot hybridization or by a solution hybridization assay. Anti-HCV was assessed using second generation ELISA (ELISA-2) or reassessed using third generation ELISA on stored serum samples (14).

Statistical Analysis

Data are expressed as median (range). Mann-Whitney *U* and χ^2 tests were used to compare differences between medians and proportions, respectively. The cumulative incidence of HCC occurrence, hepatic decompensation appearance, and cumulative probability of survival were calculated using the Kaplan-Meier method (15) and were compared between the two groups of HBV- and HCV-related cirrhosis using the log rank test (16). Patients who died of non–liver-related causes and those who were lost to follow-up were censored at the time of death or at the time of drop-out in this analysis.

Prognostic factors for HCC, decompensation unrelated to HCC, and survival were analyzed by Cox regression analysis, both univariate and multivariate, with backward elimination of insignificant variables (17). The following clinical and serological variables at baseline were evaluated as potential prognostic factors: sex, age, $\log_{10}$ (bilirubin concentration), levels of albumin, gammaglobulins, and platelets, $\log_{10}$ (ALT times upper limit of normal [ULN]) and $\log_{10}$ (AST/ALT ratio), HBV and HCV status, HBV-DNA status (only for subgroup analysis of HBsAg-positive cirrhosis, *i.e.,* HBV-DNA positive, which included both HBeAg-positive and negative patients, and HBV-DNA negative, which included HBeAg-negative patients). Sex (male = 1, female = 0) and viral status (HBV = 1; HCV = 0; HBV-DNA positive = 1; HBV-DNA negative = 0) were introduced as dichotomous variables. Normalization of aminotransferase levels during follow-up was evaluated as a time-dependent variable, taking into account the time of biochemical remission. The Cox model included at all stages, whether significant or not, the indicator term of viral status (HBV = 1, HCV = 0 or HBV-DNA positive = 1, HBV-DNA negative = 0) and in the model, obtained *p* value for the viral status shows directly the significance of the viral type adjusted for the influence of all other prognostic variables included. The adjusted relative risk (RR) (HBV positive/HCV positive or HBV-DNA positive/HBV-DNA negative) with 95% CI of liver-related complications and mortality were estimated from the regression coefficient (and SE) for the viral status in models including variables, the influence of which was to be adjusted for. The estimated adjusted curves for the cumulative incidence of HCC, decompensation and for the probability of survival were calculated from the regression model as previously reported (18). All data were analyzed using the SPSS for Windows 10, software package (SPSS, North Chicago, IL).

RESULTS

Features at Entry According to HBV/HCV Status

Of the 297 white patients, 161 had HBV- and 136 HCV-related compensated cirrhosis. The series of 161 HBsAg-positive patients represents all untreated patients enrolled in a previous study evaluating survival of compensated cirrhosis B (5), except 17 of Asian or African ethnicity, 36 with HCV concurrent infection and/or anti-HIV positivity, 39 with anti-HDV positivity, and 113 who had received antiviral (n = 87) or steroid treatment (n = 26). The 136 anti-HCV-positive untreated patients represent all untreated subjects enrolled in a study evaluating survival of compensated cirrhosis C (7), with the exclusion of 14 patients of Asian or African ethnicity, 22 with lack of information on serum anti-HCV, and 212 who had received antiviral (n = 193) or steroid (n = 19) therapy. The probable source of HBV infection was undefined in 132 (82%) patients, perinatal or intrafamily transmission in 18 (11.4%), blood transfusion in five (3%), medical exposure in five (3%), or drug abuse in one (0.6%); among HCV-infected, patients the

Table 1. Baseline Characteristics of 297 Patients With Cirrhosis (Child A) According to HBsAg and Anti-HCV Status

Characteristic	HBsAg Positive (n = 161)	Anti-HCV Positive (n = 136)	*p* Value
Patient features			
Men*	143 (89)	81 (60)	< 0.0001
Median age (range), yr	48 (17–78)	58 (22–79)	< 0.0001
Splenomegaly (n = 290)*			
Present	46 (29)	61 (47)	< 0.001
Absent	115 (71)	68 (53)	
Hepatic stigmata (n = 287)*			
Present	44 (27)	46 (36)	ns
Absent	117 (73)	80 (64)	
Esophageal varices (n = 140)*			
Present	21 (38)	44 (52)	ns
Absent	34 (62)	41 (48)	
Referral pattern*			
Diagnosis of cirrhosis during follow-up for chronic hepatitis	39 (24)	37 (27)	< 0.001
Incidental finding of abnormal transaminases or viral markers	68 (42)	33 (24)	
Diagnosis of cirrhosis previously made elsewhere	16 (10)	32 (24)	
Symptoms	38 (24)	34 (25)	
Biochemistry*			
ALT (n = 293)			
<3 ULN	87 (55)	66 (49)	ns
≥3 ULN	71 (45)	69 (51)	
AST/ALT ratio (n = 290)			
>1	44 (28)	37 (28)	ns
≤1	114 (72)	95 (72)	
Bilirubin (n = 285)			
≤ 17 μmol/L	106 (68)	68 (53)	0.009
> 17 <51 μmol/L	50 (32)	61 (47)	
Albumin (n = 263)			
≥ 35 g/L	114 (81)	104 (85)	ns
< 35 g/L	27 (19)	18 (15)	
Gammaglobulin (n = 258)			
≤ 20 g/L	105 (72)	67 (59)	0.027
> 20 g/L	40 (28)	46 (41)	
Platelets (n = 267)			
> 130 × 10^9/L	89 (66)	47 (35)	< 0.0001
≤ 130 × 10^9/L	45 (34)	86 (65)	

* Data expressed as number of patients (percentage).
n values are total number of patients with analyzable data.
p value derived from Mann-Whitney or χ^2 test.

source of infection was unknown in 49 (36%); blood transfusion in 42 (31%); drug abuse in three (2%); or medical exposure, major surgery, or family member with chronic liver disease in 42 (31%).

Stored serum samples were available for HCV-RNA testing in 87 (64%) of 136 anti-HCV patients, and all of these patients were confirmed to be viremic (14). At enrollment, the 161 patients with HBV-related cirrhosis included 45 HBeAg-positive and 116 HBeAg-negative, anti-HBe-positive patients. Of 116 HBeAg-negative patients, 79 were tested for HBV-DNA at entry, and 24 (30%) had evidence of HBV-DNA detectable in the serum, whereas 55 (70%) tested HBV-DNA negative. Thus, overall, 124 patients had available data on both HBeAg and HBV-DNA status at enrollment.

The clinical and serological baseline characteristics of the patients according to HBV and HCV status are shown in Table 1. HBsAg-positive patients were younger and were more frequently male than those infected with HCV. A higher proportion of HBsAg-positive patients had normal serum bilirubin concentrations, gammaglobulin levels, and platelet counts, and did not have splenomegaly on physical examination and/or ultrasound (<13 cm in longitudinal diameter) compared with anti-HCV-positive patients. A similar proportion of patients with HBV- or HCV-related cirrhosis were referred to the enrolling center because of nonspecific symptoms such as dyspepsia, asthenia, or upper abdominal discomfort. Clinical and serological features at entry showed no significant differences among the three subgroups of HBeAg-positive (n = 45), HBeAg-negative/HBV-DNA-positive (n = 24), and HBeAg-negative/HBV-DNA-negative (n = 55) patients with HBV-related cirrho-

Table 2. Clinical Outcome of 297 Patients With Cirrhosis (Child A) According to HBsAg and Anti-HCV Status

Outcome	HBsAg Positive (n = 161)	Anti-HCV Positive (n = 136)
HCC	22 (14)	23 (17)
Decompensation	33 (20)	49 (36)
Liver-related death or OLT	35 (22)	35 (26)
Cause of death or OLT		
HCC	14	17
Liver failure	21	18
Unrelated	5	17
Lost to follow-up	8	15
Median follow-up (range), mo	77 (6–191)	82 (6–191)

Values are the number of patients (percentage).
HCC = hepatocellular carcinoma; OLT = orthotopic liver transplantation.

sis, with the exception of baseline ALT values, which were significantly higher in patients with serological evidence of active HBV replication (median × ULN [range]: 4.1 [1.5–23.2], 3.8 [1.83–25], and 1.5 [0.51–8.4], $p < 0.0001$, respectively).

Clinical Outcome of Patients With Cirrhosis in Relation to HBV/HCV Status

The 297 patients of European white ethnicity with compensated viral cirrhosis were followed longitudinally for a median period of 79 months (range 6–191 months). As shown in Table 2, no difference was observed in the duration of follow-up ($p = 0.22$) and in the drop-out rates ($p = 0.079$) between patients with HBV- and HCV-related cirrhosis. The analysis of the baseline clinical and serological features of the patients dropping out indicated that these patients were not in any aspect more ill than those being followed-up in each of the two groups of HBV- or HCV-related cirrhosis. Sustained biochemical remission occurred in 38 (24%) and five (3.7%) of HBsAg-positive and anti-HCV-positive patients, respectively.

Development of Hepatocellular Carcinoma

During the study period, HCC was diagnosed in 22 (14%) HBsAg-positive and 23 (17%) anti-HCV-positive patients with cirrhosis. In a similar proportion of HBsAg-positive and anti-HCV-positive patients, liver cancer was detected because of symptoms (ascites or jaundice): four of 22 (18%) and four of 23 (17%) HCC, respectively. The median interval between the time of entry into the study and the diagnosis of HCC was 44 mo (range 6–180 mo) for patients infected with HBV and 59 mo (range 7–125 mo) for those infected with HCV ($p = 0.69$).

The cumulative 5-yr incidence of HCC was 9% and 10% for HBsAg-positive and anti-HCV-positive cirrhotic patients, respectively ($p = 0.66$) (Fig. 1A); the incidence per 100 person-years was 2.2 and 2.5, respectively. Among HBsAg-positive cirrhotic patients, the cumulative 5-yr incidence of liver cancer was 8%, 14%, and 9% in HBeAg-negative/HBV-DNA-negative, HBeAg-negative/HBV-DNA-positive, and HBeAg-positive patients at entry, respectively ($p = 0.4$) (Fig. 2A).

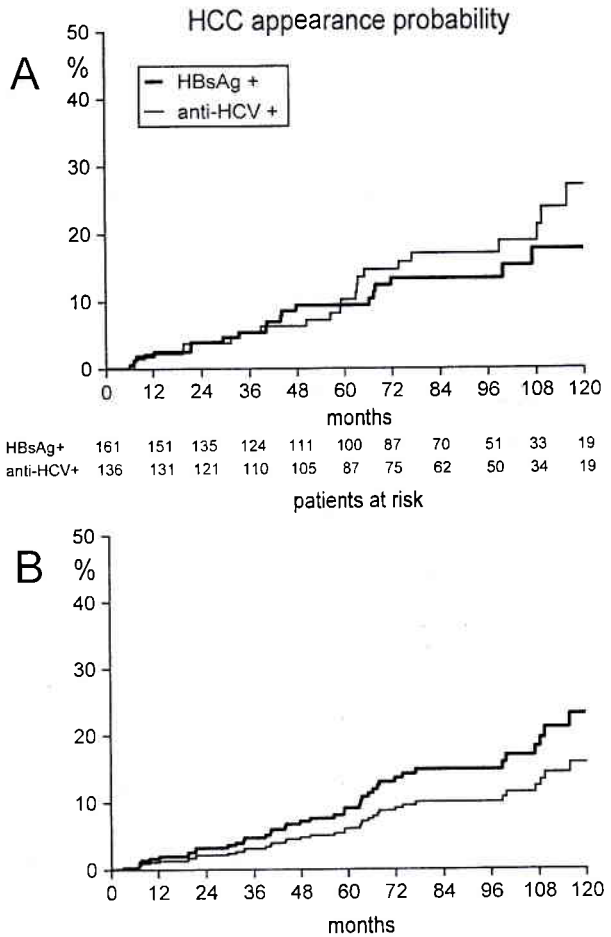

Figure 1. Cumulative probability of hepatocellular carcinoma (HCC) appearance in patients with compensated cirrhosis type B (thick line) or type C (thin line). The 5-yr appearance rate was 9% and 10% for HBsAg-positive and anti-HCV-positive cirrhotic patients, respectively ($p = 0.66$, log rank test) (*A*). The estimated 5-yr probability adjusted for prognostic variables by Cox model was 9% and 6% for HBsAg-positive and anti-HCV-positive patients, respectively (*B*).

Risk Factors for Development of Hepatocellular Carcinoma

By univariate Cox analysis, the following variables were associated with a higher risk of HCC: older age ($p = 0.0004$), higher bilirubin concentration ($p = 0.0008$), higher AST/ALT ratio ($p = 0.004$), lower albumin levels ($p = 0.0098$) and lower platelet count ($p = 0.035$). Multivariate Cox regression analysis identified the following variables that independently correlated with HCC development; age, bilirubin, and albumin (Table 3). Biochemical remission did not influence HCC occurrence in the multivariate analysis ($p = 0.99$). As shown in Table 4, the adjusted RR (95% CI) for HCC was 1.53 (0.81–2.89) in HBsAg-positive relative to anti-HCV-positive patients. The adjusted estimated 5-yr risk

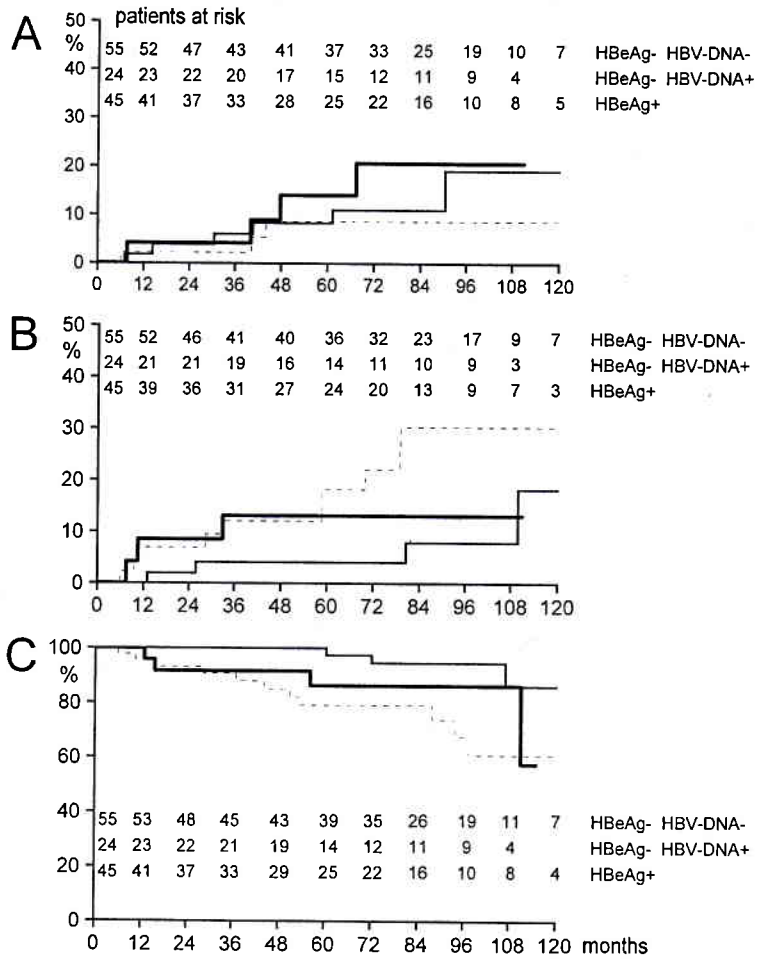

Figure 2. Cumulative probability of hepatocellular carcinoma (HCC) appearance (*A*), decompensation occurrence (*B*), and survival (*C*) among HBsAg-positive patients in relation to hepatitis B e antigen (HBeAg) and HBV-DNA status at entry. The 5-yr HCC appearance rate was 8%, 14%, and 9% for HBeAg-negative/HBV-DNA-negative (thin line), HBeAg-negative/HBV-DNA-positive (thick line), and HBeAg-positive (dashed line) patients, respectively (p = 0.4, log rank test) (*A*); the corresponding figures for the probability of decompensation were 4%, 13%, and 18% (p = 0.04, log rank test) (*B*) and for survival were 97%, 86%, and 79% (p = 0.01, log rank test) (*C*), respectively.

for HCC, based on Cox model for median values of age, bilirubin, and albumin, was 9% and 6% for cirrhotic patients infected with HBV and HCV, respectively (Fig. 1B).

In the subgroup of 124 HBsAg-positive cirrhotic patients with known HBeAg/HBV-DNA status at entry, multivariate Cox regression analysis showed age (p = 0.0004) as the only variable predicting HCC. The adjusted RR (95% CI) for HCC was 0.89 (0.30–2.63) in HBV-DNA-positive relative to HBV-DNA-negative patients (Table 5).

Developement of Decompensation

The worsening of cirrhosis with development of at least one episode of ascites, jaundice, hepatic encephalopathy, or variceal bleeding unrelated to HCC occurred in 33 (20%) and 49 (36%) patients with HBV- and HCV-related cirrhosis, respectively (Table 2). The median interval between the time of entry into the study and the occurrence of the first episode of decompensation was 31 mo (range 6–109 mo) for HBsAg-positive patients and 29 mo (range 6–126 mo)

Table 3. Significant Prognostic Variables (and Viral Status) for Prediction of Hepatocellular Carcinoma (HCC) Occurrence, Decompensation Appearance and Survival in Multivariate Cox Analysis

Outcome	Variable	β Regression Coefficient	SE	p Value*
HCC	Age	0.061	0.017	0.000
	Bilirubin	1.899	0.715	0.008
	Albumin	−0.064	0.030	0.034
	Viral status†	0.425	0.324	0.189
Decompensation	Platelets	−0.005	0.002	0.024
	Albumin	−0.083	0.023	0.000
	Gammaglobulin	0.043	0.018	0.018
	AST/ALT ratio	1.525	0.486	0.002
	Viral status	−0.523	0.234	0.026
Survival	Age	0.061	0.014	0.000
	Sex	0.627	0.303	0.038
	Platelets	−0.006	0.003	0.018
	Albumin	−0.110	0.024	0.000
	Viral status	0.367	0.271	0.176

* p Value derived from the likelihood ratio test.
† HCV = 0, HBV = 1.

Table 4. Effect of Viral Status (HBsAg Positive Relative to Anti-HCV Positive) on Hepatocellular Carcinoma (HCC) Occurrence, Decompensation, and Mortality

	HCC		Decompensation		Mortality	
	β Regression Coefficient (SE)	RR (95% CI)	β Regression Coefficient (SE)	RR (95% CI)	β Regression Coefficient (SE)	RR (95% CI)
Univariate analysis	−0.1290 (0.2994)	0.88 (0.49–1.58)	−0.5761 (0.2253)	0.56 (0.36–0.87)	−0.0311 (0.2409)	0.97 (0.60–1.55)
Multivariate analysis						
A	0.4250 (0.3240)	1.53 (0.81–2.89)	−0.5230 (0.2340)	0.59 (0.37–0.94)	0.3670 (0.2710)	1.44 (0.85–2.46)
B	0.3310 (0.3310)	1.39 (0.73–2.66)	−0.6050 (0.2640)	0.55 (0.33–0.92)	0.3780 (0.2710)	1.46 (0.86–2.48)

A = relative risk (RR) estimates (95% CI) adjusted for significant prognostic variables by Cox model (see Table 3); B = RR estimates (95% CI) adjusted for all potential prognostic variables by Cox model (age, sex, $\log_{10}$ (bilirubin), albumin, gammaglobulins, $\log_{10}$ (ALT × ULN), AST/ALT ratio, platelets, and biochemical remission.

for those who were anti-HCV positive. The first episode of decompensation was caused by ascites in 16 (49%) and 25 (51%) of patients infected with HBV and HCV, respectively. Variceal bleeding, encephalopathy, jaundice, or more than one complication occurred in three (9%), none (0%), four (12%), and 10 (30%) of HBsAg-positive patients and in 10 (20%), three (6%), none (0%), and 11 (23%) of anti-HCV-positive patients.

The 5-yr cumulative incidence of developing decompensated cirrhosis after diagnosis was significantly higher in patients infected with HCV compared with those infected with HBV (28% and 16%, respectively, $p = 0.0094$) (Fig. 3A); the incidence per 100 person-yr was 5.3 and 3.3, respectively. In the subgroup of HBsAg-positive cirrhotic patients, the 5-yr cumulative probability of decompensation was 4%, 13%, and 18% in HBeAg-negative/HBV-DNA-negative, HBeAg-negative/HBV-DNA-positive, and HBeAg-positive patients at entry, respectively ($p = 0.04$) (Fig. 2B).

Risk Factors for Decompensation

Among the clinical and biochemical characteristics evaluated by univariate analysis, higher bilirubin concentration ($p = 0.0001$), lower albumin levels ($p = 0.00001$), higher gammaglobulin levels ($p = 0.00001$), lower platelet count ($p = 0.00001$), higher AST/ALT ratio ($p = 0.00001$), and viral status ($p = 0.01$) were associated with a higher risk of decompensation. Multivariate analysis identified the following variables that independently correlated with decompensation: platelet, albumin, gammaglobulins, AST/ALT ratio, and viral status (Table 3). Biochemical remission did not influence the development of decompensation in multivariate analysis ($p = 0.8$). HBV-related cirrhosis was associated with a decreased risk of decompensation compared with HCV-related cirrhosis (adjusted RR = 0.59) (Table 4). The adjusted estimated 5-yr probability of decompensation, based on the Cox model for median values of albumin, platelet, AST/ALT ratio, and gammaglobulins, were 20% and 12% for anti-HCV-positive and HBsAg-positive patients, respectively (Fig. 3B).

In the subgroup of 124 HBsAg-positive cirrhotic patients with known HBeAg/HBV-DNA status at entry, multivariate Cox regression analysis identified AST/ALT ratio ($p = 0.0002$), albumin ($p = 0.002$), and viral status ($p = 0.004$) as independent prognostic variables for decompensation. The adjusted RR (95% CI) for decompensation was 4.05 (1.09–15.1) in HBV-DNA-positive relative to HBV-DNA-negative patients (Table 5).

Survival

Liver-related death or liver transplantation occurred in 35 (22%) patients with HBV-related cirrhosis, caused by HCC in 14 and liver failure in 21, and in 35 (26%) patients with HCV-related cirrhosis, caused by HCC in 17 and liver failure in 18 (Table 2). Three HBsAg-positive and three anti-HCV-positive patients underwent liver transplantation for end-stage liver disease. The cumulative 5-yr probability of survival was 86% and 84% in HBV-related and HCV-related cirrhotic patients, respectively ($p = 0.89$) (Fig. 4A); the incidence per 100 person-yr of liver-related death was 3.5 and 3.8, respectively. Among HBV-related cirrhotic

Table 5. Effect of Viral Status (HBV-DNA Positive Relative to HBV-DNA Negative) on Hepatocellular Carcinoma (HCC) Occurrence, Decompensation, and Mortality in the Subgroup of 124 HBsAg-Positive Cirrhotic Patients With Known HBeAg/HBV-DNA Status at Study Entry

	HCC		Decompensation		Mortality	
	β Regression Coefficient (SE)	RR (95% CI)	β Regression Coefficient (SE)	RR (95% CI)	β Regression Coefficient (SE)	RR (95% CI)
Univariate analysis	−0.1509 (0.5350)	0.86 (0.30–2.45)	1.1168 (0.5675)	3.06 (1.00–9.29)	1.5013 (0.6330)	4.49 (1.30–15.5)
Multivariate analysis						
A	−0.1125 (0.5505)	0.89 (0.30–2.63)	1.3990 (0.6700)	4.05 (1.09–15.1)	1.7757 (0.6538)	5.90 (1.64–21.3)
B	−0.5494 (0.6229)	0.58 (0.17–1.96)	1.4948 (0.6800)	4.46 (1.18–16.9)	1.9416 (0.7353)	6.97 (1.65–29.4)

A = relative risk (RR) estimates (95% CI) adjusted for significant prognostic variables by Cox model; B = RR estimates (95% CI) adjusted for all potential prognostic variables by Cox model (age, sex, $\log_{10}$ (bilirubin), albumin, gammaglobulins, $\log_{10}$ (ALT × ULN), AST/ALT ratio, platelets, and biochemical remission.

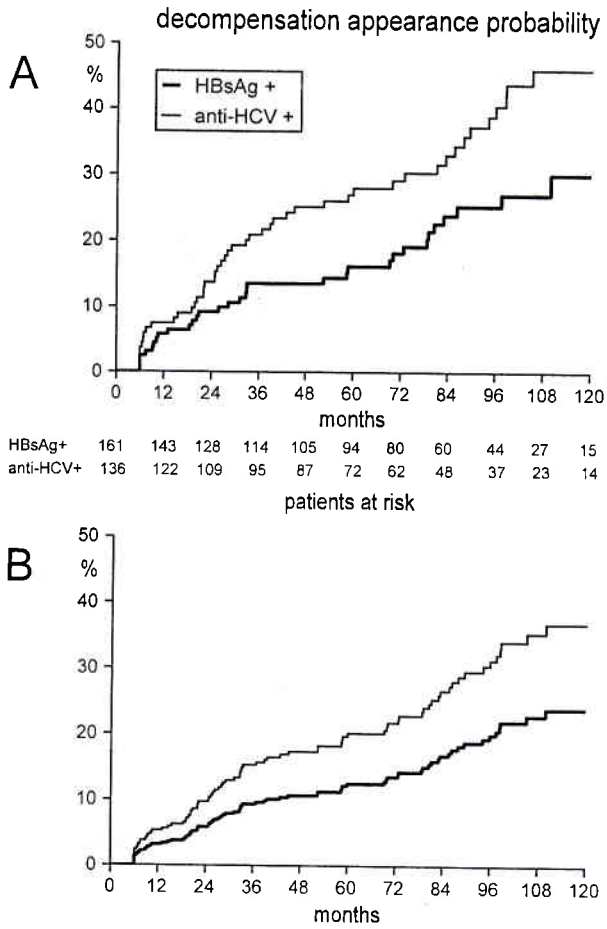

Figure 3. Cumulative probability of developing decompensation in patients with compensated cirrhosis type B (thick line) or type C (thin line). The 5-yr probability of decompensation was 16% and 28% for HBsAg-positive and anti-HCV-positive cirrhotic patients, respectively (p = 0.0094, log rank test) (*A*). The estimated 5-yr probability adjusted for prognostic variables by Cox model was 12% and 20% for HBsAg-positive and anti-HCV-positive patients, respectively (*B*).

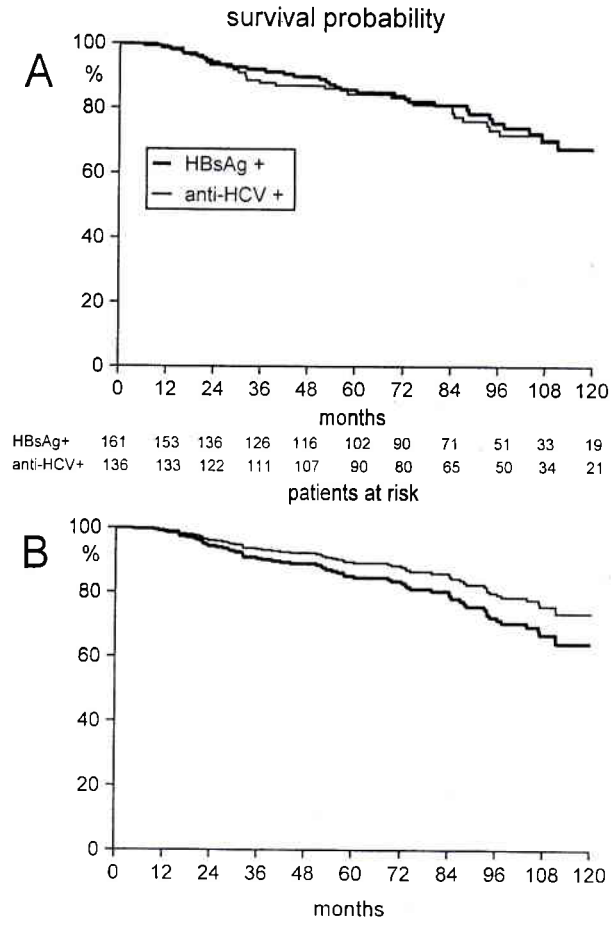

Figure 4. Cumulative survival probability in patients with compensated cirrhosis type B (thick line) or type C (thin line). The 5-yr survival probability was 86% and 84% for HBsAg-positive and anti-HCV-positive cirrhotic patients, respectively (p = 0.89, log rank test) (*A*). The estimated 5-yr survival probability adjusted for prognostic variables by Cox model was 85% and 89% for HBsAg-positive and anti-HCV-positive patients, respectively (*B*).

patients, the cumulative 5-yr survival probability was 97%, 86%, and 79% in HBeAg-negative/HBV-DNA-negative, HBeAg-negative/HBV-DNA-positive, and HBeAg-positive patients at entry, respectively (p = 0.01) (Fig. 2C).

Prognostic Factors for Survival

By univariate analysis, more advanced age (p = 0.0001), higher bilirubin concentration (p = 0.0038), lower albumin levels (p = 0.00001), higher gammaglobulin values (p = 0.0065), lower platelet count (p = 0.0043), and higher AST/ALT ratio (p = 0.001) were associated with a decreased survival.

The following variables independently correlated with survival in multivariate analysis: age, sex, albumin, and platelets (Table 3). Biochemical remission did not influence survival in multivariate analysis (p = 0.98). As shown in Table 4, the adjusted RR (95% CI) for liver-related mortality was 1.44 (0.86–2.48) in HBsAg-positive relative to anti-HCV-positive patients. The adjusted estimated 5-yr survival, based on Cox model for median values of age, sex (male), albumin, and platelets, were 85% and 89% for HBV- and HCV-related cirrhotic patients (Fig. 4B).

In the subgroup of 124 HBsAg-positive cirrhotic patients with known HBeAg/HBV-DNA status at entry, multivariate Cox regression analysis identified age (p = 0.0003), AST/ALT ratio (p = 0.02), and viral status (p = 0.006) as independent prognostic variables for survival. The adjusted RR (95% CI) for survival was 5.9 (1.64–21.3) in HBV-DNA-positive relative to HBV-DNA-negative patients (Table 5).

Survival After Hepatic Decompensation

The probability of survival after the onset of the first major complication of the disease was 71% and 82% at 1 yr for HBsAg- and anti-HCV-positive patients, respectively; the corresponding figures at 3 yr were 40% and 60% and at 5 yr were 28% and 47% (p = 0.09) (Fig. 5). The lowest survival rate was observed in patients with more than one complication (35% and 38% at 3 yr for HBV- and HCV-related

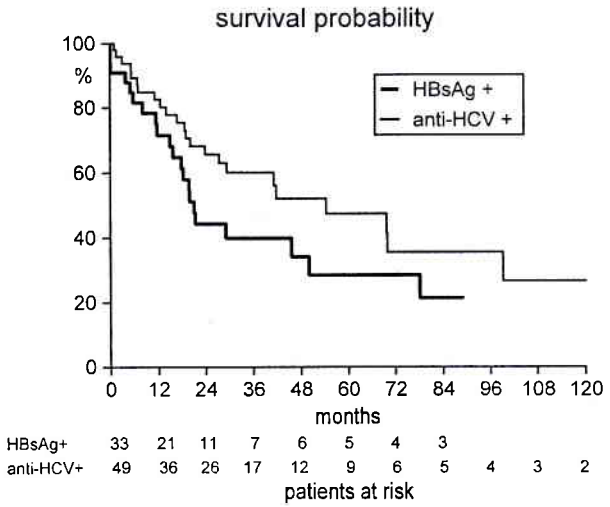

Figure 5. Cumulative survival probability after the appearance of the first complication of the disease in 33 HBsAg-positive (thick line) and 49 anti-HCV-positive (thin line) patients who developed decompensated cirrhosis. The 5-yr survival probability was 28% and 47% for HBsAg-positive and anti-HCV-positive cirrhotic patients, respectively ($p = 0.09$, log rank test).

cirrhosis, respectively), and the highest survival rate was in those who presented with ascites (50% and 62% at 3 yr and 38% and 55% at 5 yr for HBV- and HCV-related cirrhosis, respectively).

DISCUSSION

The main findings of this study are those concerning the comparison of clinical characteristics between HBV- and HCV-infected patients with compensated cirrhosis on their presentation at tertiary referral European centers and the analysis of the clinical impact of HBV and HCV infection on the clinical course and long-term prognosis of untreated white patients with cirrhosis.

Our data indicate that infection by HBV or HCV is associated with different clinical and serological presentation of cirrhotic patients. In fact, HBsAg-positive patients were younger and were more frequently male compared with anti-HCV-positive cirrhotic patients. The average age of 48 and 58 yr of HBsAg-positive and anti-HCV-positive patients, respectively, at the time of initial presentation with cirrhosis is in agreement with several reports about chronic hepatitis B and C (6, 9, 19, 20). In one study of hepatitis C, the mean age of patients was 42 yr for those without cirrhosis, 55 yr for those with cirrhosis, and 66 yr for those with HCC (20). At the time of diagnosis of cirrhosis, a higher proportion of HBsAg-positive patients had normal serum bilirubin concentration, gammaglobulin levels, and platelet count, and a lower proportion had splenomegaly on physical examination compared with patients infected with HCV. Overall, these data suggest that patients with HBV infection may progress to cirrhosis about 10 yr earlier and may present with a less advanced stage of compensated cirrhosis compared with hepatitis C patients.

These clinical differences at presentation may be the consequence of an earlier acquisition in life of HBV infection by perinatal or intrafamily transmission, although these sources of infection were documented in a minority (11%) of our patients. In the absence of vertical transmission or of a history of acute hepatitis, the age at infection is most often unknown. However, in favor of the hypothesis of an earlier acquisition in life of HBV infection in our study population is the observation of a low rate of parenteral exposure in the adult age, namely 3% as opposed to 34% in anti-HCV-positive patients.

Unlike HCV infection, there is little information concerning the rate of liver fibrosis progression in chronic HBV carriers. It has been reported that persistence of active HBV replication as well as emergence of viral mutants are risk factors for cirrhosis development (21, 22). Approximately one half of patients tested for both serum HBeAg and HBV-DNA (69 of 124 [56%]) had evidence of high levels of HBV replication and severe biochemical activity at the time of diagnosis of cirrhosis, which may have caused rapid fibrosis progression and referral to the enrolling center at a younger age and at an earlier stage of cirrhosis. On the other hand, the fact that the majority of patients chronically infected with HCV are totally asymptomatic, and that the rate of disease progression is generally slow and requires decades before the emergence of clinically apparent chronic liver disease (23–25), may explain the observation that anti-HCV-positive patients present with clinical and serological features of a more severe stage of cirrhosis. In addition, in this study population, a higher proportion of patients with HCV-related cirrhosis were referred to the enrolling center after the diagnosis of cirrhosis was previously made elsewhere (24% *vs* 10%, respectively) (Table 1), thus suggesting a longer duration of the cirrhotic stage.

Longitudinal studies provide the optimal approach to evaluate the risk for HCC, decompensation, and mortality for patients with viral cirrhosis. However, in published series, referral biases in selection of patients and the lack of uniformity in the timing of initiation of follow-up make it difficult to estimate the incidence of liver-related complications and death (4, 9, 10, 12, 24, 26). In our study, there is an acceptable level of uniformity in the patient population by defining the zero-time point of follow-up as the time of histological diagnosis of cirrhosis, by including only untreated patients in Child class A, and by excluding major cofactors of disease progression such as concurrent HBV and HCV infections and excessive alcohol consumption. Nonetheless, it is likely that these patients enrolled at tertiary referral centers represent the more severe stage of the liver disease spectrum.

It should be pointed out that, in this retrospective study, the method of HCC surveillance may differ among all participating centers; however with follow-up intervals of 12 months instead of 6 months, the HCC detection may be delayed an average of 6 months, and the amount of bias in

the Kaplan-Meier analysis caused by this limited delay is rather small.

Morbidity and mortality were compared between the two groups of HBsAg-positive and anti-HCV-positive cirrhotic patients. The unadjusted Kaplan-Meier analysis of cumulative incidence of HCC and of survival probability showed no significant difference between the two groups of patients (Fig. 1A and 4A), whereas the incidence of decompensation was higher in HCV-related cirrhosis (Fig. 3A).

Taking into consideration that even small differences in baseline clinical and biochemical characteristics among patients reflecting the stage of liver disease can account for marked differences in patient outcome, we have estimated for all the three endpoints evaluated (HCC, decompensation, and liver-related death) the viral effect adjusted for significant prognostic variables by Cox model (Table 4). This analysis has confirmed that the estimated risk for decompensation occurrence decreases significantly by a factor of 0.59 in hepatitis B compared with hepatitis C patients; in other words, patients with HCV-related cirrhosis have an approximately 40% increased risk for decompensation compared with those infected with HBV. Accordingly, after adjusting for clinical and serological differences at baseline, the estimated 5-yr probability of decompensation was confirmed to be higher in patients infected by HCV (Fig. 3B). Furthermore, also assuming that all patients lost to follow-up had decompensation, the estimated risk for decompensation was confirmed to be decreased by a factor of 0.57 (95% CI = 0.38–0.85) in HBsAg-positive relative to anti-HCV-positive patients (data not shown).

The discordant results for decompensation compared with those for HCC and survival are interesting, and should be interpreted taking into consideration several issues. As previously emphasized, the rate of disease progression in hepatitis C is generally slow, and the clinical course is probably much more insidious than that of hepatitis B. Therefore, it makes sense that cirrhosis type C is diagnosed at a relatively later stage, closer to the stage of decompensation, which may be one explanation for the greater risk of developing decompensation in hepatitis C patients. However, the risk of liver-related complications in cirrhotic patients is related both to the duration of infection and to the duration and stage of cirrhosis; and a limitation of this study is that the presumed duration of infection is unknown in the majority of our patients.

Chronic hepatitis B is a heterogeneous disease in terms of disease activity. We have shown that the risk of hepatic decompensation and mortality is different among HBV-infected patients according to the level of HBV replication, with a lower incidence of decompensation for patients who are HBeAg and HBV-DNA negative compared with those who are HBeAg positive or HBeAg negative/HBV-DNA positive at diagnosis. Thus, it is speculated that the relative proportion of individuals with or without high levels of HBV replication among HBsAg-positive patients might have influenced the results of a lower risk of decompensation compared with that for anti-HCV-positive patients. Furthermore, cofactors such as alcohol ingestion in amounts less than 80 g/day may contribute to hepatic decompensation, and may determine differences in the rate of decompensation. However, this detailed information is lacking in our study.

The slightly higher risk of developing HCC in HBV-related cirrhosis may be attributed to the fact that HBV may cause liver cancer, both through the development of cirrhosis and directly by early genetic alterations induced by HBV integration into the host genome, whereas the mechanisms by which HCV infection leads to HCC are not well defined, although cirrhosis plays a central role. In our study, HBeAg and HBV-DNA status at the time of diagnosis of cirrhosis did not influence the risk for liver cancer, in agreement with the hypothesis of a direct oncogenic potential of HBV. In addition, it has been recently reported that cirrhotic patients infected with HBV, compared with hepatitis C patients, are at higher risk for developing an infiltrative and a more aggressive type of HCC, which is independent of duration or stage of cirrhosis and may reflect more direct viral carcinogenesis (27).

Despite the more advanced stage of HCV-related cirrhosis, the rate of disease progression may still be very low, as also suggested by the relatively longer survival (although not significantly) after the appearance of the first episode of hepatic decompensation in anti-HCV-positive compared with HBsAg-positive patients (Fig. 5). These results may explain the similar life expectancy in hepatitis B and C patients after diagnosis of compensated cirrhosis, despite the higher rate of decompensation in hepatitis C.

Nevertheless, once an episode of decompensation occurs, the prognosis is poor, irrespective of etiology of liver disease. The 5-yr survival rate after the appearance of the first major complication of cirrhosis is only 28% and 47% for patients infected with HBV and HCV, respectively, considerably lower than the survival for compensated cirrhosis (5-yr probability of survival 86% and 84%, respectively). The type of decompensation correlates to some degree with the probability of survival, with a better prognosis in patients who present with ascites. Such analyses are helpful in guiding management decisions and timing of referral for liver transplantation.

In conclusion, our analysis suggests that the overall prognosis, in terms of survival after diagnosis of compensated cirrhosis, show no significant differences according to HBV or HCV etiology in Western European cirrhotic patients. The higher risk of decompensation unrelated to HCC observed in HCV-infected patients should take into account the lack of precise information on duration of infection and on cofactors such as moderate alcohol consumption, the heterogeneity of HBV-related cirrhosis in terms of level of viral replication and disease activity, and risk for hepatic failure.

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REFERENCES

1. Zuckerman AJ. More than third of world's population has been infected with hepatitis B. Br Med J 1999;318:1213.
2. World Health Organization technical consultation on hepatitis C. Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepatitis 1999;6:35–47.
3. Fattovich G, Giustina G, Schalm SW, et al. Occurrence of hepatocellular carcinoma and decompensation in Western European patients with cirrhosis type B. Hepatology 1995;21: 77–82.
4. De Jongh FE, Janssen HLA, De Man RA, et al. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. Gastroenterology 1992;103:1630–5.
5. Realdi G, Fattovich G, Hadziyannis S, et al. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: A multicenter study. J Hepatol 1994;21:656–66.
6. Mazzella G, Accogli E, Sottili S, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. J Hepatol 1996;24:141–7.
7. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis C: A retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463–72.
8. Bruno S, Silini E, Crosignani A, et al. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis; a prospective study. Hepatology 1997;25:754–8.
9. Serfaty L, Aumaître H, Chazouillères O, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998;27:1435–40.
10. Niederau C, Lange S, Heintges T, et al. Prognosis of chronic hepatitis C: Results of a large prospective cohort study. Hepatology 1998;28:1687–95.
11. Valla DC, Chevallier M, Marcellin P, et al. Treatment of hepatitis C virus-related cirrhosis: A randomized, controlled trial of interferon alfa-2b versus no treatment. Hepatology 1999;29:1870–5.
12. Hu KQ, Tong MJ. The long-term outcomes of patients with compensated hepatitis C virus-related cirrhosis and history of parenteral exposure in the United States. Hepatology 1999;29: 1311–6.
13. Bianchi L, De Groote J, Desmet VJ, et al. Acute and chronic hepatitis revisited. Lancet 1977;2:914–9.
14. Fattovich G, Ribero ML, Pantalena M, et al. Hepatitis C virus genotypes. distribution and clinical significance in patients with cirrhosis type C seen at tertiary referral centers in Europe. J Viral Hepatitis 2001;8:206–16.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–81.
16. Peto R, Pike MC. Conservatism of the approximation (0-E)/E in the log rank test for survival data on tumor incidence data. Biometrics 1973;29:579–84.
17. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972;34:187–220.
18. Christensen E. Multivariate survival analysis using Cox's regression model. Hepatology 1987;7:1346–58.
19. Tsai JF, Jeng JE, Ho MS, et al. Effect of hepatitis C and B virus infection on risk of hepatocellular carcinoma: A prospective study. Br J Cancer 1997;76:968–74.
20. Gordon SC, Bayati N, Silverman AL. Clinical outcome of hepatitis C as a function of mode of transmission. Hepatology 1998;28:562–7.
21. Fattovich G, Brollo L, Giustina G, et al. Natural history and prognostic factors of chronic hepatitis type B. Gut 1991;32: 294–8.
22. Brunetto MR, Oliveri F, Coco B, et al. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: A long term cohort study. J Hepatol 2002; 36:263–70.
23. Kiyosawa K, Sodeyama T, Tanaka E, et al. Interrelationship of blood transfusion, non-A. non-B hepatitis and hepatocellular carcinoma: Analysis by detection of antibody to hepatitis C virus. Hepatology 1990;12:671–5.
24. Tong MJ, El-Farra NS, Reikes AR, et al. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995; 332:1463–6.
25. Poynard T, Bedossa P, Opolon P, for the OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. Lancet 1997;349:825–32.
26. Weissberg JI, Andres LL, Smith CI, et al. Survival in chronic hepatitis B. An analysis of 379 patients. Ann Intern Med 1984;101:613–6.
27. Benvegnu L, Noventa F, Bernardinello E, et al. Evidence for an association between the aetiology of cirrhosis and pattern of hepatocellular carcinoma development. Gut 2001;48:110–5.