Journal of Hepatology 1994; **21**: 656–666
Printed in Denmark . All rights reserved
Munksgaard . Copenhagen

Journal of Hepatology
ISSN 0168-8278

Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study

Giuseppe Realdi[1], Giovanna Fattovich[2], Stephanos Hadziyannis[3], Solko W. Schalm[4], Piero Almasio[5], Josè Sanchez-Tapias[6], Erik Christensen[7], Giuliano Giustina[2], Franco Noventa[2] and The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP)*

[1]*Istituto di Clinica Medica, University of Sassari, Italy;* [2]*Istituto di Medicina Clinica, University of Padova, Italy;* [3]*Academic Department of Medicine, Hippokration General Hospital, Athens, Greece;* [4]*Internal Medicine II, University Hospital Rotterdam, The Netherlands;* [5]*Cattedra di Clinica Medica R, University of Palermo, Italy;* [6]*Liver Unit, Hospital Clinic, University of Barcelona, Spain and* [7]*Department of Medicine B, Bispebjerg University Hospital, Copenhagen, Denmark*

(Received 9 December 1993)

A multicenter longitudinal study was performed to assess the survival of hepatitis B surface antigen positive compensated cirrhosis, primarily in relation to hepatitis B virus replication and hepatitis delta virus infection, and to construct a prognostic index based on entry characteristics. This cohort study involved nine university medical centers in Europe. Three hundred and sixty-six Caucasian HBsAg positive patients with cirrhosis who had never had clinical manifestations of hepatic decompensation were enrolled and followed for a mean period of 72 months (6 to 202 months). Inclusion criteria were biopsy-proven cirrhosis, information on serum hepatitis B e antigen and antibody to hepatitis D virus at the time of diagnosis and absence of complications of cirrhosis. At entry 35% of the patients were HBeAg positive, 48% of the patients tested were HBV-DNA positive and 20% anti-HDV positive. Death occurred in 84 (23%) patients, mainly due to liver failure (45 cases) or hepatocellular carcinoma (23 cases). The cumulative probability of survival was 84% and 68% at 5 and 10 years, respectively. Cox's regression analysis identified six variables that independently correlated with survival: age, albumin, platelets, splenomegaly, bilirubin and HBeAg positivity at time of diagnosis. According to the contribution of each of these factors to the final model, a prognostic index was constructed that allows calculation of the estimated survival probability. No difference in survival of hepatitis D virus infected and uninfected patients was observed. Termination of hepatitis B virus replication and/or biochemical remission during follow up correlated with a highly significant better survival. These data show that in compensated cirrhosis B, hepatitis B virus replication, age and indirect indicators of poor hepatic reserve and established portal hypertension significantly worsen the clinical course of the disease, whereas hepatitis D virus infection does not influence the prognosis. The highly significant improvement in life expectancy following cessation of hepatitis B virus replication and biochemical remission favors antiviral therapy in those patients with a guarded prognosis, as estimated by a prognostic index. © Journal of Hepatology.

Key words: Cirrhosis; Clinical course; Hepatitis B virus infection; Hepatitis D virus infection; Longitudinal study; Prognostic index

Correspondence to: Giuseppe Realdi, MD, Istituto di Clinica Medica, Viale San Pietro , 07100 Sassari, Italy.

* The following institutions and investigators have contributed to the collection of the data presented in this report: Academic Department of Medicine, Hippokration General Hospital, Athens Greece (Hadziyannis SJ, Savvas S); Internal Medicine II, University Hospital Rotterdam, The Netherlands (Schalm SW, Quero C); Istituto Medicina Clinica, Clinica Medica 2a, University of Padova, Italy (Fattovich G, Giustina G); Clinica Medica R, University of Palermo, Italy (Almasio P, Craxì A); Liver Unit, Hospital Clinic, University of Barcelona, Spain (Sanchez-Tapias JM, Mas A); Istituto di Clinica Medica and Istituto di Patologia Speciale Medica, University of Sassari, Italy (Realdi G, Solinas A, Tocco A); University Hospital, Rigshospitalet, Copenhagen, Denmark (Krogsgaard K, Olsen JF); Unité d'Hépatologie, Hopital Beaujon, Paris, France (Degos F, Delarocque E); Servico de Medicina II, Medical School of Lisbon, Portugal (Carneiro de Moura M, Rocha P).

Chronic hepatitis B virus (HBV) carriage is common, with as many as 280 million carriers world wide. HBV infection is responsible for at least 30% of non-alcoholic cirrhosis, and chronic liver disease due to HBV is one of the leading causes of death throughout the world, linked mainly to cirrhosis and hepatocellular carcinoma.

Most studies on the clinical outcome of cirrhosis have focused mainly on patients with decompensated alcoholic or cryptogenetic cirrhosis (1–3). Few data are available concerning the clinical course of compensated cirrhosis, especially with HBV etiology, and at present the survival rate of hepatitis B surface antigen (HBsAg) positive compensated cirrhosis is not well defined. Cirrhosis type B is generally thought to be a progressive disease, but prognostic factors have been incompletely defined. Studies on the natural history of chronic HBV infection have shown that persistent HBV replication is an important determinant of progressive liver damage (4), while spontaneous or therapeutically induced termination of viral replication usually leads to remission of liver disease activity (5,6). Thus the clinical course and prognosis of compensated cirrhosis B may vary markedly depending on the presence or absence of HBV replication. Hepatitis delta virus (HDV) infection can also modify the course of HBsAg positive liver disease (7), but to our knowledge no studies are available comparing the course of compensated patients with cirrhosis and without HDV infection.

The primary objective of this study was to evaluate the survival of HBsAg positive histologically documented cirrhosis in patients who had never had clinical manifestation of decompensation, such as jaundice, ascites, variceal bleeding or encephalopathy. The outcome of the disease was considered primarily in relation to the presence or absence of HBV replication and the presence or absence of HDV infection. We therefore performed a multicenter retrospective study based on longitudinally collected data with a long-term follow up. The viral markers investigated in relation to outcome were hepatitis B e antigen (HBeAg) and antibody to hepatitis delta virus (anti-HDV), both established by routine tests and therefore easily available in all participating centers.

In addition to the study of survival, the value of a set of serological and clinical variables was assessed for predicting survival of the disease based on multivariate analysis. A prognostic index was developed.

Materials and Methods

Study design

This retrospective study was initiated by the European concerted action on viral hepatitis B (EUROHEP) and involved all centers participating in the Eurohep project who wished to take part. Data collection was performed by electronic proforma according to a protocol defining the study population, time of entry, referral pattern and follow up. To facilitate the input of data and to provide quality control, an investigator from each participating center was trained by the coordinating center at the Istituto di Medicina Clinica, University of Padova, to enter patient data correctly into the electronic proforma and also to apply the correct methodology for consecutively entering patients into the study, as well as for doing a complete follow up on mortality.

Study population

All consecutive patients, regardless of sex or race, seen at each Institution and fulfilling the following criteria were considered eligible for the study:

1) HBsAg positivity;
2) Biopsy proven cirrhosis according to accepted international criteria, including the diagnosis of active, inactive, probable and early cirrhosis (8);
3) Absence of complications of cirrhosis, i.e. present or past ascites, gastrointestinal hemorrhage, encephalopathy and jaundice (diagnosed on physical examination and confirmed by serum bilirubin above 51.7 μmol/l);
4) Information on serum HBeAg and anti-HDV at presentation;
5) Follow up at the enrolling center for a minimum of 6 months.

Patients with hemochromatosis, Wilson's disease or any type of biliary cirrhosis were excluded from this study on the basis of serological and histological parameters.

Information on alcohol abuse, defined as more than 80 g/day for more than 5 years, were evaluated at enrollment.

Enrollment of patients could be started from 1973 onwards when routine HBsAg testing by sensitive methods was introduced.

Time of entry into the study and referral pattern

Entry into the study (time zero) was defined as the time of diagnosis of HBsAg positive compensated cirrhosis, provided that the patients fulfilled the inclusion critera, including availability of information on test results of serum HBeAg and anti-HDV. Patients diagnosed as having HBsAg positive cirrhosis prior to the introduction of routine HBeAg and anti-HDV testing could be enrolled if retrospective testing on stored sera had been performed at the time of histological diagnosis of cirrhosis.

The following four referral patterns were defined at the enrolling center: 1) the incidental finding of HBsAg positivity and/or elevated transaminases; 2) the presence of non-specific symptoms; 3) diagnosis of cirrhosis made at the enrolling center during follow up for HBsAg positive

chronic hepatitis; in this case the start of follow up (time zero) was established as the time of histological diagnosis of cirrhosis; 4) referral to the enrolling center for evaluation after the histological diagnosis had previously been made elsewhere; in this case the start of follow up was established as the time of referral to the enrolling center.

Follow up

According to the protocol, survival from entry into the study was evaluated until December 31, 1991. Death was classified as caused by liver failure if progressive impairment of liver function with neurological disturbances occurred, or if it occurred within 40 days of gastrointestinal bleeding, regardless of the severity (9), or as caused by hepatocellular carcinoma (HCC). Patients who died of conditions not related to liver disease were censored at the time of death. Follow up information on survival was obtained at each enrolling center where patients were seen for care, or were obtained through telephone interviews with the patient or by consulting population registries.

Biochemical remission was defined as the normalization of amino-transaminases in at least two consecutive tests taken at least 3 weeks apart and persisting at the time of the last observation. Clearance of HBeAg or HBV-DNA was defined as the loss of these markers during follow up, after the diagnosis of compensated cirrhosis, and persisting at the last observation.

Laboratory studies

Virological data were available from the records of patients or were retrospectively tested on stored serum samples.

HBsAg, antibody to HBsAg (anti-HBs), HBeAg, antibody to HBeAg (anti-HBe), anti-HDV and anti-HIV were detected using commercially available solid-phase radioimmunoassays (RIA) or enzyme-linked immunosorbent assays (ELISA). Serum HBV-DNA was measured by a spot hybridization technique or by a solution hybridization assay.

Laboratory analysis, which included alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, albumin, gammaglobulin, alphafetoprotein and platelets, were determined by routine laboratory procedures.

Statistical analysis

Results were expressed as mean±standard deviation. Statistical analysis included Fisher's exact test, chi-square test and Student's *t*-test.

The cumulative survival probability was calculated using the Kaplan and Meier method (10). A total of 20 virological, biochemical and clinical variables were considered as possible predictors of survival (Table 1). Univariate analysis of survival was performed by computing survival curves according to the Kaplan and Meier method. For continuous variables, the cut-off level chosen was its median value; if the median value was close to the upper normal limit of laboratory measurements, the latter was used as cut off. For each variable, the differences in the survival curves were determined using the log-rank test (11) and Breslow test.

TABLE 1

Variables at entry tested as predictors of survival

Clinical	Biochemical	Virological
Sex	aspartate aminotransferase	HBeAg
Age	alanine aminotransferase	anti-HDV
Referral pattern	bilirubin	HBV-DNA
Symptoms	albumin	
Hepatic stigmata	gammaglobulin	
Liver firmness*	platelets	
Splenomegaly	alphafetoprotein*	
Esophageal varices*		
Histology		
Therapy**		

HBeAg=hepatitis B e antigen; anti-HDV=antibody to hepatitis delta virus; HBV-DNA=hepatitis B virus deoxyribonucleic acid.

* These variables were not included in the step-wise Cox regression model, as measurements were available only in a minority of patients.

** Therapy during follow up was scored as a baseline feature for statistical purposes.

Multivariate analysis of survival was performed using the step-wise forward Cox regression model (12). The statistical software used was BMDP (13). In this process, the order of entry of any variable is determined by the maximum log-likelihood value and the statistical significance is assessed by the likelihood ratio test (14).

Missing data were replaced by the regression method because this analysis requires all patients to be represented by a complete set of variables and in order not to reduce the number of patients (15). The percentages of missing values for each variable ranged from 0.8% to 15%. To assess the validity of the model, a split-sample procedure was used (16). The proportionality assumption of the model was also tested by log minus log hazard plots.

Results

Three hundred and sixty-six patients fulfilling the inclusion criteria were enrolled at nine European centers from 1973 to 1990.

Features at presentation

The main initial clinical features of the patients included in the study are shown in Table 2. The 366 patients consisted of 315 men and 51 women and the age ranged from 17 to 74 years. Three hundred and forty-nine (95%)

TABLE 2

Initial clinical features of HBsAg positive patients with compensated cirrhosis

Mean age (years) (n=366)*	44±12	
Men (n=366)	315	(86%)
Homosexual (n=366)	24	(7%)
Alcohol abuse (<80 g/day) (n=366)	14	(4%)
Referral pattern (n=366)		
– diagnosis of cirrhosis during follow up for chronic hepatitis B	88	(24%)
– incidental finding of HBsAg and/or abnormal transaminases	139	(38%)
– diagnosis of cirrhosis made elsewhere previously	50	(14%)
– symptoms	89	(24%)
Symptoms (n=366)		
present	152	(42%)
absent	214	(58%)
Hepatic stigmata (n=363)		
present	101	(28%)
absent	262	(72%)
Liver firmness (n=222)		
present	175	(79%)
absent	47	(21%)
Splenomegaly (n=361)		
present	105	(29%)
absent	256	(71%)
Esophageal varices on endoscopy (n=143)		
present	51	(36%)
absent	92	(74%)
Histology (n=360)		
probable cirrhosis	40	(11%)
early cirrhosis	47	(13%)
active cirrhosis	225	(63%)
inactive cirrhosis	48	(13%)

* In parentheses are the total numbers of patients with analyzable data.

TABLE 3

Biochemical and virological baseline features of HBsAg positive patients with compensated cirrhosis

		No. of patients (%)	
AST (n=366)*	normal value	72	(20)
	1–2 u.n.v.**	111	(30)
	>2 u.n.v.	183	(50)
ALT (n=349)	normal value	53	(15)
	1–2 u.n.v.	62	(18)
	>2 u.n.v.	234	(67)
Bilirubin (n=342)	≤17 μmol/l	234	(68)
	>17<51 μmol	108	(32)
Albumin (n=313)	>35 g/l	246	(79)
	≤35 g/l	67	(21)
Gammaglobulin (n=311)	≤20 g/l	206	(66)
	>20 g/l	105	(34)
Platelets (n=309)	>120×10⁹/l	208	(68)
	≤120×10⁹/l	101	(32)
Alphafetoprotein (n=162)	≤10 μg/l	105	(65)
	>10 μg/l	57	(35)
HBeAg (n=366)	positive	126	(35)
	negative	240	(65)
Anti-HDV (n=366)	positive	73	(20)
	negative	293	(80)
HBV-DNA (n=265)	positive	126	(48)
	negative	139	(52)

* In parentheses are the total numbers of patients with analyzable data.

** u.n.v.=upper limit of normal value.

patients were Caucasian and only nine (3%) and eight (2%) were oriental or black, respectively.

The probable source of HBV infection was undefined in 247 (69%) patients and due to household contact in 20 (5%), vertical transmission in 14 (4%), sexual transmission in 27 (7%), medical exposure in 18 (5%), blood transfusion in 14 (4%) or drug addiction in 26 (6%).

At presentation, more than half (58%) the patients were completely asymptomatic, while the remainder complained of minor, non specific symptoms such as dyspepsia, asthenia and/or upper abdominal discomfort. On physical examination hepatic stigmata (spider nevi and/or palmar erythema) and splenomegaly were present in only 28% and 29% of the patients, respectively.

Liver biopsy at entry (blind percutaneous biopsy in 281 and laparoscopic biopsy in 79) showed histological activity in a large proportion of patients (63%). Of the 50 patients in whom the histological diagnosis of cirrhosis was made elsewhere before being referred to the enrolling center, 44 had the liver biopsy taken within 12 months (range 1–12 months) of enrollment, while six had a histological diagnosis of cirrhosis from 2 to 9 years before entry into the study. At entry, these six patients fulfilled the inclusion criteria, including absence of jaundice, ascites, variceal bleeding and/or encephalopathy in the period between the diagnosis of cirrhosis until the time of referral to the enrolling center.

As shown in Table 3, at presentation most patients had increased serum levels of alanine aminotransferase (85%) and/or aspartate aminotransferase (80%) and/or normal values of serum bilirubin (68%), albumin (79%), gammaglobulin (66%) and platelets (68%).

At the time of diagnosis of compensated cirrhosis, 126 (35%) patients were HBeAg positive. The 73 (20%) patients found anti-HDV positive included 11 (15%) HBeAg positive and 62 (85%) HBeAg negative cases. HBV-DNA was positive in 126 (48%) of 265 patients tested, including 78 (62%) HBeAg positive and 48 (38%) HBeAg negative cases. Six of 84 cases tested were anti-HIV positive and all six patients were asymptomatic.

Survival and relation to HBV and HDV markers at entry

The 366 patients with HBsAg positive compensated cirrhosis were followed longitudinally for 6 to 202 months

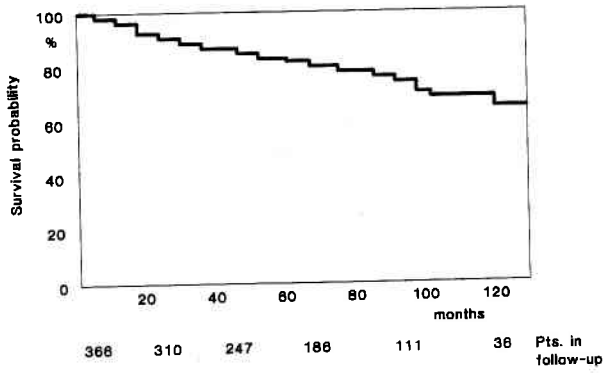

Fig. 1. Cumulative probability of survival in patients with compensated cirrhosis type B.

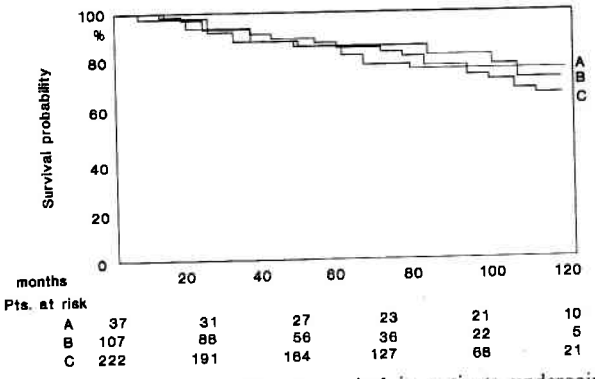

Fig. 2. Cumulative probability of survival in patients undergoing treatment with steroids (A), antivirals (B) and in untreated patients (C). No statistically significant difference was found among the three groups of patients.

(mean±DS 72±40 months). Fifteen (4%) patients were lost to follow up. One hundred and forty-four patients received immunosuppressive or antiviral therapy during follow up. In fact, 72 (19%) patients were treated with interferon, 25 (7%) with acyclovir and 10 (3%) with adenine arabinoside, usually for periods not exceeding 6 months, and 37 (10%) patients received steroids.

Death occurred in 84 (23%) patients, due to liver failure in 45 (54%), HCC in 23 (27%) and to non-liver-related causes in 16 (19%).

The probability of survival after diagnosis of compensated cirrhosis was 84% and 68% at 5 and 10 years, respectively (Fig. 1). No differences in the probability of survival were observed among the subgroups of patients who had received steroid or antiviral therapy or remained untreated (Fig. 2).

As shown in Table 4, among the virological markers studied at presentation only HBeAg significantly predicted survival at univariate analysis.

Survival was also studied in the following four subgroups of patients: 1) HBeAg and HBV-DNA positive and anti-HDV negative (HBV wild type replication); 2) HBeAg negative, HBV-DNA positive and anti-HDV negative (precore mutant replication); 3) HBeAg, HBV-DNA and anti-HDV negative (no viral replication); 4) HBeAg, HBV-DNA negative and anti-HDV positive (delta infection). The probability of survival was significantly (p=0.02) different among these four subgroups of patients, with the worst survival observed in HBeAg and HBV-DNA positive patients without delta infection (Table 4).

TABLE 4

Univariate analysis of survival in relation to viral markers at presentation

Variable	No. of patients	Survival		p
		5 yrs (SE)*	10 yrs (SE)	
HBeAg status (n=366)**				
HBeAg positive	126	0.77 (0.04)	0.68 (0.06)	0.039[a]
HBeAg negative	240	0.88 (0.02)	0.68 (0.05)	
HDV status (n=366)				
HDV positive	73	0.89 (0.03)	0.65 (0.10)	n.s.[b]
HDV negative	293	0.82 (0.02)	0.67 (0.03)	
HBV-DNA status (n=265)				
HBV-DNA positive	126	0.82 (0.03)	0.70 (0.07)	n.s.[b]
HBV-DNA negative	139	0.90 (0.02)	0.70 (0.06)	
HBeAg/HBV-DNA/anti-HDV status (n=239)				
HBeAg+DNA+HDV−	70	0.75 (0.05)	0.61 (0.08)	
HBeAg−DNA+HDV−	45	0.90 (0.04)	0.68 (0.19)	0.02[b]
HBeAg−DNA−HDV+	47	0.91 (0.04)	0.74 (0.07)	
HBeAg−DNA−HDV−	77	0.91 (0.03)	0.77 (0.07)	

* SE=Standard error.

** In parentheses are the total numbers of patients with analyzable data.

[a] p-value significant by Breslow test.

[b] p-value derived from log-rank test and Breslow test.

TABLE 5

Clinical, biochemical and histological variables showing prognostic significance by log-rank test

Variable	No. of patients	Probability of survival		p-value
		5 yrs (SE)*	10 yrs (SE)	
Age (n=366)**				
≤44 yrs	185	0.88 (0.02)	0.72 (0.06)	0.0077
>44 yrs	181	0.80 (0.03)	0.63 (0.05)	
Referral pattern (n=366)				
Diagnosis of cirrhosis during follow up for chronic hepatitis B	88	0.93 (0.03)	0.73 (0.09)	0.003
Incidental finding of HBsAg and/or abnormal transaminases	139	0.89 (0.03)	0.72 (0.057)	
Diagnosis of cirrhosis made elsewhere previously	50	0.77 (0.06)	0.62 (0.08)	
Symptoms	89	0.73 (0.05)	0.59 (0.06)	
Splenomegaly (n=361)				
Present	105	0.73 (0.05)	0.57 (0.06)	0.0003
Absent	256	0.89 (0.02)	0.75 (0.04)	
Esophageal varices (n=143)				
Present	51	0.60 (0.08)	0.42 (0.11)	0.00001
Absent	92	0.94 (0.02)	0.70 (0.12)	
Histology (n=360)				
Probable cirrhosis	40	0.93 (0.04)	0.81 (0.09)	0.007
Early cirrhosis	47	1.00 (0.00)	0.90 (0.06)	
Active cirrhosis	225	0.79 (0.03)	0.58 (0.05)	
Inactive cirrhosis	48	0.84 (0.05)	0.74 (0.07)	
Bilirubin (n=342)				
≤17 μmol/l	234	0.88 (0.02)	0.77 (0.04)	0.00001
>17<51 μmol/l	108	0.74 (0.04)	0.46 (0.09)	
Albumin (n=313)				
>35 g/l	246	0.90 (0.02)	0.78 (0.04)	0.00001
≤35 g/l	67	0.67 (0.06)	0.44 (0.08)	
Gammaglobulin (n=311)				
≤20 g/l	206	0.90 (0.02)	0.75 (0.05)	0.0004
>20 g/l	105	0.74 (0.05)	0.49 (0.09)	
Platelets (n=309)				
>120×10 /l	208	0.91 (0.02)	0.81 (0.05)	0.00001
≤120×10 /l	101	0.71 (0.05)	0.49 (0.08)	
Alphafetoprotein (n=162)				
≤10 μg/l	105	0.90 (0.03)	0.78 (0.06)	0.00001
10–50 μg/l	43	0.73 (0.08)	0.62 (0.10)	
>50	14	0.52 (0.15)	0.26 (0.15)	

* SE=standard error.

** Numbers in parentheses represent the total number of patients on which survival calculation is based, as initial data were not available in all patients.

Clinical and biochemical baseline factors correlating with survival

Among the clinical and biochemical features studied at presentation, ten variables significantly predicted survival at univariate analysis: age, the referral pattern, esophageal varices, splenomegaly, platelets, bilirubin, albumin, gammaglobulin, alphafetoprotein and histologic diagnosis (Table 5).

Variables studied during follow up correlating with survival

The serological events observed during follow up are illustrated in Table 6.

The percentage of patients in whom biochemical remission could be assessed was 98% (287 out of 294 patients with abnormal transaminases at entry).

Moreover HBeAg, HBV-DNA and HBsAg clearance

TABLE 6

Serologic events during follow up of HBsAg positive compensated cirrhosis

	No. of patients (%)	
Biochemical remission (n=287)*	75	(26)
HBeAg clearance (n=116)	64	(55)
HBV-DNA clearance (n=97)	52	(53)
HBsAg clearance (n=323)	35	(11)

* In parentheses are the total numbers of patients in whom the event could be assessed.

TABLE 7

Variables studied during follow up showing prognostic significance

	Alive	Dead	*p*-value*
Biochemical remission (n=287)**			
Present	74	1	0.00001
Absent	146	66	
HBeAg clearance (n=116)			
Present	60	4	0.0001
Absent	32	20	
HBV-DNA clearance (n=97)			
Present	47	5	0.019
Absent	32	13	

* Fisher's exact test.
** In parentheses are the total numbers of patients in whom the event could be assessed.

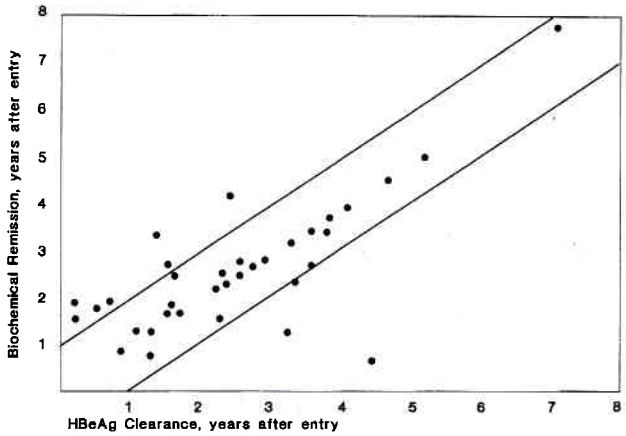

Fig. 3. Linear relationship between the time of HBeAg clearance and the time of biochemical remission in patients with compensated cirrhosis type B ($p<0.001$). The data refer to 36 HBeAg positive patients with elevated transaminases at entry undergoing biochemical remission and HBeAg clearance during follow up.

could be studied in 92% (116 out of 126 HBeAg positive patients), 77% (97 out of 126 HBV-DNA positive patients) and 88% (323 out of 366 HBsAg positive patients), respectively.

Seventy-five (26%) of 287 patients with elevated transaminases at entry showed complete and persistent normalization of liver enzymes. Moreover, 64 (55%) patients became HBeAg negative, 52 (53%) cleared HBV-DNA from serum and 35 (11%) became HBsAg negative during follow up.

As shown in Table 7, biochemical remission, HBeAg or HBV-DNA loss from serum were significantly associated with a higher rate of survival. No differences in initial ALT values and histological diagnosis were observed between patients in biochemical remission, HBeAg or HBV-DNA clearance and those with sustained biochemical activity, HBeAg or HBV-DNA positivity during the observation period (Table 8). The duration of follow up was significantly longer for patients with normalization of liver enzymes, HBeAg or HBV-DNA loss from serum compared with patients without these events (Table 8).

A close temporal association was observed between biochemical remission and clearance of HBeAg or HBV-DNA in patients in whom both these parameters were available (Fig. 3 and 4).

Multivariate analysis and calculation of a prognostic index

Multivariate analysis with Cox's model showed that six variables studied at presentation independently maintained their prognostic significance: age, albumin, platelets, splenomegaly, bilirubin and HBeAg (Table 9).

In this study population, therapy did not influence survival either in the univariate or the multivariate analysis.

A prognostic index (PI) for survival was calculated according to the formula:

$$PI=0.0361\times age+(-0.0843)\times albumin+(-0.0059)\times platelets+0.549\times splenomegaly+0.021\times(bilirubin)+0.429\times HBeAg$$

In the formula, age, albumin, platelets and bilirubin are introduced as continuous variables. Splenomegaly (pres-

TABLE 8

Initial clinical features and duration of follow up according to presence or absence of serological events during the observation of HBsAg positive compensated cirrhosis

	Biochemical remission			HBeAg clearance			HBV-DNA clearance		
	Present (n=75)	Absent (n=212)	*p**-value	Present (n=64)	Absent (n=52)	*p**-value	Present (n=52)	Absent (n=45)	*p**-value
Mean ALT (×u.n.v.)**	5.1	4.4	n.s.	5.5	4.9	n.s.	5.5	5.6	n.s.
Histology (%)									
Probable cirrhosis	17	11		13	11		8	13	
Early cirrhosis	14	13	n.s.	11	11	n.s.	16	6	n.s.
Active cirrhosis	62	68		66	70		68	70	
Inactive cirrhosis	7	8		10	8		8	11	
Mean follow up (mo.)	82	62	0.001	77	42	0.001	70	48	0.0

* Student's t-test for comparison of alanine aminotransferase (ALT) and follow up; chi-square test in 2×4 table for comparison of histology.
** Times the upper limit of normal value.

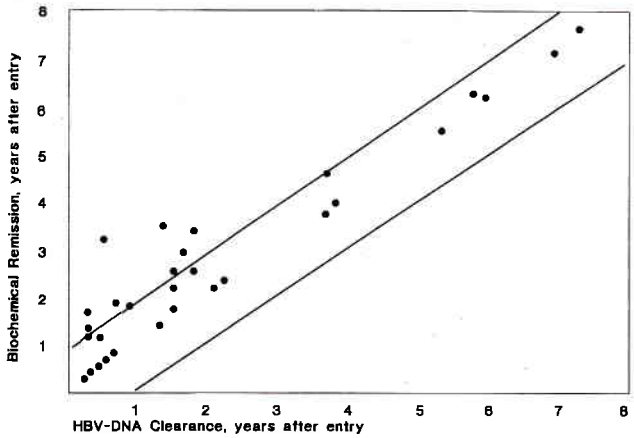

Fig. 4. Linear relationship between the time of HBV-DNA clearance and the time of biochemical remission in patients with HBsAg positive compensated cirrhosis ($p<0.001$). The data refer to 30 HBV-DNA positive patients with elevated transaminases at entry undergoing biochemical remission and HBV-DNA clearance during follow up.

ent=1, absent=0) and HBeAg (positive=1, negative=0) are introduced as dichotomous variables. The prognostic index of the patients enrolled in this study ranged between −4.62 to +0.97. The distribution of the prognostic index in this study population is shown in Fig. 5.

Validity of the final model was assessed using a split-sample technique. Among the 366 patients, 238 (65%) were randomly drawn and the regression coefficients corresponding to the variables in the final models were estimated. The regression coefficients obtained were used to calculate the individual prognostic indexes in the remaining 128 patients. These 128 patients were divided into two groups with PI higher or lower than the median PI value and the average estimated survivorship functions for the patients in the two classes were computed. No significant difference between expected and observed survival was found in either of the two groups of patients with different levels of prognostic indexes (log rank test: $p=0.8$).

Fig. 6 shows the estimated probability of 5-year and 10-year survival as a function of the prognostic index according to the final model.

TABLE 9

Significant prognostic variables for survival and their regression coefficient

Variables	Coefficient regression	Standard error	*p*-value*
Age	0.0361	0.0099	0.0002
Albumin	−0.0843	0.023	0.0002
Platelets	−0.0059	0.0025	0.0135
Splenomegaly	0.549	0.255	0.033
Bilirubin	0.021	0.011	0.061
HBeAg	0.429	0.243	0.083

* *p*-value derived from likelihood ratio test.

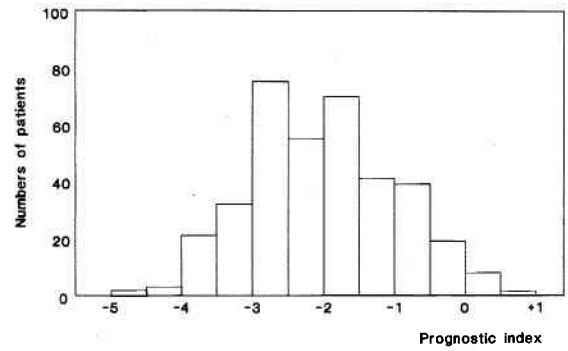

Fig. 5. Distribution of prognostic index in 366 patients with HBsAg positive compensated cirrhosis.

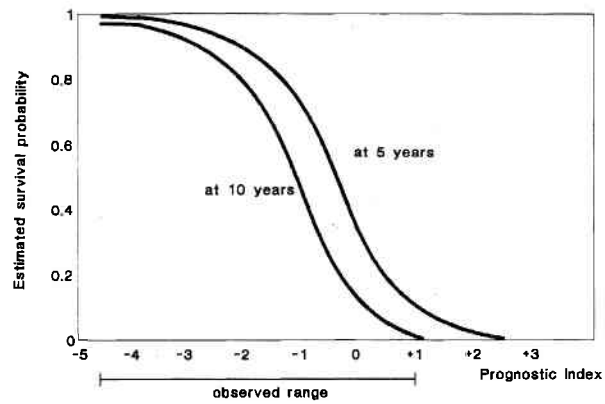

Fig. 6. Estimated probability of 5-year and 10-year survival as a function of the prognostic index according to the final model.

Discussion

Early studies have indicated that type B cirrhosis may be a progressive disease, often leading to liver failure or hepatocellular carcinoma (17–19). This study provides important information on the features and clinical course of a well-defined group of patients with HBsAg positive compensated cirrhosis.

The major features of this study are: 1) a large series of patients with histologically documented compensated cirrhosis; 2) a long-term follow up with a low drop-out rate; 3) 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; 4) information on serum HBeAg and anti-HDV at entry into the study in all cases; 5) exclusion of major interfering cofactors, such as alcohol abuse in most patients or other known causes of liver damage in all cases.

Previous studies on the outcome of compensated cirrhosis have only included a small number of HBsAg positive patients and/or have not specifically analyzed the group of patients with HBV infection (20–23). On the other hand, most studies dealing with survival in chronic hepatitis B did not distinguish between compensated and

decompensated cirrhosis (24). Due to the low drop-out rate, we were able to trace the course of the disease in most patients and in our series the survival rate at 5 and 10 years was 84% and 68%, respectively. The probability of survival observed in our patient population was higher than that previously reported at 5 years (67%) and 10 years (46%) in a Spanish study including 268 HBsAg negative patients with histologically documented compensated cirrhosis (20). Two other studies, including mainly patients with compensated cirrhosis of etiology other than HBV, reported a 6-year survival of 54% (21) and 40% (23), respectively. These studies suggest a better prognosis for our HBsAg positive non-alcoholic cases. However, in the study of D'Amico et al. (21), HBsAg positivity appeared to be a significant indicator of death risk in compensated cirrhosis. This finding may be explained by differences in patient characteristics. Indeed, the low rate of splenomegaly (29%) and hepatic stigmata (28%) reported in our study suggests a relatively early stage of the cirrhosis in most cases. Moreover, the precise definition of the time of entry into the study of our patients allowed us to obtain a rather uniform population in relation to the zero time point of follow up. A lack of uniformity of this methodological aspect in other clinical studies may lead to different survival rates.

Our results, which are derived from a large series of patients, indicate that several clinical and serological data could predict survival. According to the univariate analysis, the type of referral pattern, namely symptoms or diagnosis of cirrhosis made elsewhere prior to referral to the enrolling center, the presence of esophageal varices and hypergammaglobulinemia were indicators of a bad prognosis, probably indicating a more advanced stage of the disease at presentation. Moreover, histological activity and baseline serum alpha-fetoprotein above the upper limit of normal value both reflect progressive liver damage and were also predictors of lower survival.

Multivariate analysis identified age, splenomegaly, platelets, albumin, bilirubin and HBeAg at entry as independent significant predictors of survival. It is not surprising that age is a very strong prognostic variable, and probably indicates a longer duration of liver disease. Both splenomegaly and low platelet value reflect advanced cirrhosis and were indicators of bad prognosis. Moreover, this report has pointed out that bilirubin, albumin and platelets are actually the most useful laboratory tests for monitoring prognosis in compensated cirrhosis type B. It is interesting to note that slightly increased serum concentrations of bilirubin and decreased serum albumin at presentation, which reflect decreased hepatocellular function, were of great value in predicting the prognosis in patients with compensated liver disease.

A major aim of this study was to assess the prognostic significance of the presence or absence of HBV replication and of HDV infection. Among the virological markers at diagnosis, only HBeAg positivity, irrespective of HDV infection, showed a prognostic significance in term of lower survival. The fact that in our study HBeAg negative patients had only a slightly better prognosis may be related to the heterogeneity of this subgroup of patients, which actually included cases with or without HBV replication according to serum HBV-DNA.

This study included enough patients to provide reasonable estimates of survival, and showed the absence of a significant difference in the course of HDV infected and uninfected patients, suggesting that HDV infection is not always a rapidly progressive disease, as previously reported (7, 25–27). Indeed, few studies have specifically investigated the clinical outcome in patients with cirrhosis and delta infection; moreover, no comparison of the course of anti-HDV positive or negative compensated cirrhosis has been reported so far. As anti-HDV positivity does not necessarily reflect ongoing HDV replication, our results may have been influenced by the actual rate of delta virus replication in our patients.

About half of our patients who were initially HBeAg and/or HBV-DNA positive underwent termination of HBV replication during follow up. This confirms that this event may occur after the development of cirrhosis and explains the low HBeAg positivity rate observed in our patients at entry, as well as in patients with advanced cirrhosis, compared to earlier phases of HBsAg positive chronic liver disease (28).

An outstanding finding of the present study was that termination of HBV replication and biochemical remission correlated with a highly significant better survival rate. These results were not influenced by differences in the initial biochemical or histological severity of liver disease between patients with HBeAg or HBV-DNA clearance or normalization of liver enzymes and patients without these events. Moreover, the longer follow up of patients undergoing these serologic events strengthens the observation of a higher rate of survival compared with patients showing sustained HBV replication and biochemical activity. As far as we know, this is the largest cohort of Caucasian patients so far indicating a favorable clinical outcome of compensated cirrhosis B after termination of virus replication and normalization of liver enzymes.

As normalization of liver enzymes was found to be closely temporally associated with termination of HBV replication, the use of drugs to suppress viral replication might also be expected to improve survival. In our study antiviral treatment did not significantly influence survival in either univariate and multivariate analysis; however,

this may be related to the relatively small number of patients receiving antiviral therapy and/or to the short follow up after treatment withdrawal.

In this report the investigation of independent predictors of survival allowed us to develop prognostic indices that can easily be estimated from clinical data and laboratory analysis. This study has shown that compensated cirrhosis type B has a 5-year mortality rate of less than 20% and that a favorable outcome of the disease may occur in most patients following termination of HBV replication and biochemical remission. These observations have important implications in medical decision making, for example, the rational application of therapeutic measures, specifically antiviral drugs.

Appendix

The prognostic index (PI) can be obtained in a simple way at the bedside by very simple algebra, using the pocket chart presented in the Appendix Table. Here the regression terms corresponding to different values of the variables have already been calculated. For example, for the age of 50 years the regression term would be $50 \times 0.0361 = 1.8$. In the Appendix Table, this has been multiplied by 10 to give the integer 18. The other regression terms have been calculated in a similar way.

Later, at the end of the calculation, the sum of the regression terms is divided by 10 and thus a precision of PI of one decimal is obtained. It is important to note that for each variable only one number should be used in the addition. If a patient has values between those in the table, interpolation should be used.

APPENDIX TABLE

Pocket chart for easy estimation of the prognostic index

Variable		Points to add
Age (years):	17	6
	28	10
	39	14
	50	18
	61	22
	72	26
	83	30
Albumin (g/l):	20	−17
	26	−22
	32	−27
	38	−32
	45	−38
	51	−43
	57	−48
Platelets (×10 g/l):	35	− 2
	85	− 5
	135	− 8
	205	−12
	270	−16
	340	−20
	405	−24
Splenomegaly: No		0
Yes		5
Bilirubin (μmol/l):	14	3
	38	8
	62	13
	86	18
	114	24
	138	29
	162	34
	190	40
HBeAg: No		0
Yes		4

Sum of added points (S)=
PI=S/10=

Note: For each variable only one number should be used in the addition. If a patient has values between those in the table, interpolation should be used.

Acknowledgements

We are indebted to Jan Vandenbroucke, Professor in Epidemiology, University of Leiden, The Netherlands, for his skilled and helpful advice in the preparation of the study design.

This work was supported in part by a contract (MR-0190/NL) from European Commission.

References

1. Garceau AJ, The Boston Inter-Hospital Liver Group. The natural history of cirrhosis. II. The influence of alcohol and prior hepatitis on pathology and prognosis. N Engl J Med 1964; 271: 1173–9.
2. Saunders JB, Walters JRF, Davies P, Paton A. A 20-year prospective study of cirrhosis. Br Med J 1981; 1: 263–6.
3. Christensen E, Schlichting P, Fauerholdt L, et al. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. Hepatology 1984; 430–5.
4. Fattovich G, Brollo L, Giustina G, et al. Natural history and prognostic factors for chronic hepatitis type B. Gut 1991, 32: 294–8.
5. Realdi G, Alberti A, Rugge M, et al. Seroconversion from hepatitis B e antigen to anti-HBe in chronic hepatitis B virus infection. Gastroenterology 1980; 79: 195–9.
6. Fattovich G, Rugge M, Brollo L, et al. Clinical, virologic and histologic outcome following seroconversion from HBeAg to anti-HBe in chronic hepatitis type B. Hepatology 1986; 6: 167–72.
7. Rizzetto M, Verme G, Recchia S, et al. Chronic hepatitis in carriers of hepatitis B surface antigen, with intrahepatic expression of the Delta antigen. An active and progressive disease unresponsive to immunosuppressive treatment. Ann Intern Med 1983; 98: 437–41.
8. Bianchi L, De Groote J, Desmet VJ, et al. Acute and chronic hepatitis revisited. Lancet 1977; ii: 914–9.
9. Sorensen TIA. Definition of death in relation to variceal bleeding. In: Burroughs AK, ed. Methodology and Reviews of Clinical Trials in Portal Hypertension. Amsterdam: Excerpta Medica; 1987: 31–5.

10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958; 53: 457–81.
11. Peto R, Pike MC. Conservatism of the approximation (O-E) /E in the logrank test for survival data on tumor incidence data. Biometrics 1973; 29: 579–84.
12. Cox DR. Regression models and life tables (with discussion). J R Stat Soc B 1972; 34: 187–220.
13. Dixon WH, ed. BMDP statistical software. Los Angeles: University of California Press, 1983.
14. Rao CR. Linear Statistical Inference and its Application. New York: Wiley, 1973.
15. Beale EML, Little RJA. Missing values in multivariate analysis. J R Stat Soc B 1975; 37: 129–45.
16. Schlichting P, Christensen E, Andersen PK, et al. Prognostic factors in cirrhosis identified by Cox's regression model. Hepatology 1983; 3: 889–95.
17. Dudley FJ, Scheuer PJ, Sherlock S. Natural history of hepatitis-associated antigen-positive chronic liver disease. Lancet 1972; ii: 1388–93.
18. De Groote J, Fevery J, Lepoutre L. Long-term follow-up of chronic active hepatitis of moderate severity. Gut 1978; 19: 510–3.
19. Lo KJ, Tong MJ, Chien MC, et al. The natural course of hepatitis B surface antigen-positive chronic active hepatitis in Taiwan. J Infect Dis 1982; 146: 205-10.
20. Ginès P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987; 7: 122–8.
21. D'Amico G, Morabito A, Pagliaro L, Marubini E, The Liver Study Group of "V. Cervello" Hospital. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci 1986; 31: 468–75.
22. Liaw YF, Lin DY, Chen TJ, Chu CM. Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Liver 1989; 9: 235–41.
23. Zoli M, Cordiani MR, Marchesini G, et al. Prognostic indicators in compensated cirrhosis. Am J Gastroenterol 1991; 86: 1508–13.
24. 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.
25. Hadziyannis SJ. Delta antigen positive chronic liver disease in Greece: clinical aspects and natural course. Progr Clin Biol Res 1983; 143: 209–17.
26. Lok ASF, Lindsay I, Scheuer PJ, Thomas HC. Clinical and histological features of delta infection in chronic hepatitis B virus carriers. J Clin Pathol 1985; 38: 530–3.
27. Fattovich G, Boscaro S, Noventa F, et al. Influence of hepatitis delta virus infection on progression to cirrhosis in chronic hepatitis type B. J Infect Dis 1987; 155: 931–5.
28. Liaw YF, Chu CM, Lin DY, Sheen IS, Yang C, Huang MJ. Age-specific prevalence and significance of HBeAg/anti-HBe in chronic HBV infection in Taiwan: a comparison among asymptomatic carriers, chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. J Med Virol 1984; 13: 385–91.