LIVER

Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications

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Background and aims: The natural history of initially compensated cirrhosis due to hepatitis B (HBV) or hepatitis C (HCV) virus is only partially defined. We have investigated morbidity and mortality rates and the hierarchy of complications in compensated viral cirrhosis over a long follow up period.

Patients and Methods: A cohort of Italian patients with initially compensated cirrhosis of viral aetiology were followed up at six monthly intervals with laboratory tests to identify major complications (ascites, gastrointestinal bleeding, portal-systemic encephalopathy, hepatocellular carcinoma) and to assess the progression of Child's stage and mortality rate due to liver related causes.

Results: Between 1986 and 1996, 312 patients (43 HBV positive, 254 HCV positive, and 15 HBV and HCV coinfected) were included. During a median follow up of 93 (range 14–194) months, 102 (32.6%) patients developed at least one complication (HCV positive 31.1%; HBV positive 34.8%; HBV and HCV coinfected 53.3%). Overall, the most frequent complication was hepatocellular carcinoma which occurred in 65 (20.8%) cases, followed by ascites (61 cases, 19.5%), gastrointestinal bleeding (14 cases, 4.5%), and portal-systemic encephalopathy (six cases, 1.9%). Progression of Child's stage was observed in 62 patients (19.8%). Death from liver disease occurred in 58 (18.6%) cases and in 70.7% this was due to hepatocellular carcinoma. Hepatocellular carcinoma was the first complication to develop in 59 cases and represented the most frequent first complication in both HCV and HBV/ HCV related cirrhosis.

Conclusions: These results indicate significant morbidity and mortality during the first decade after diagnosis of compensated cirrhosis due to HBV and/or HCV, and identify hepatocellular carcinoma as the most frequent and life threatening complication, particularly in HCV positive cases.

Chronic infection with hepatotropic viruses is the main cause of chronic liver disease and cirrhosis worldwide, with a predominant role of the hepatitis B virus (HBV) in the Far East and of the hepatitis C virus (HCV) in Western countries.[1–5] Approximately 10–20% of patients with chronic HBV or HCV infection have cirrhosis at first clinical presentation, and as many as 20–30% of those who do not have cirrhosis will eventually develop this condition and its complications within one or more decades.[4–11] Many of these patients die as a consequence of end stage liver disease. The natural history of initially compensated cirrhosis due to HBV or HCV has been only partially defined. The disease often remains asymptomatic for many years, allowing a normal quality of life. Previous studies, often conducted in rather heterogeneous cohorts of patients, indicated an annual risk of developing hepatocellular carcinoma (HCC) of 1–6%, and similar or higher risk of decompensation of liver function.[12–18] Other complications, such as ascites, upper gastrointestinal bleeding, and encephalopathy, have been less frequently evaluated and reported in this specific setting.[16 17] Patients with well compensated cirrhosis due to HBV or HCV are often treated with antiviral therapy, in particular HCV patients may be treated with interferon (IFN) or IFN plus ribavirin combination therapy, in the attempt to prevent or delay disease progression.[19–26] Treatment with pegylated IFN alpha has created a new perspective for cirrhotic patients with HCV because of the high rate of sustained virological response recently reported.[27–30]

A better understanding of the natural history of compensated cirrhosis of viral aetiology would greatly improve our strategies of surveillance and intervention. We describe here the incidence and hierarchy of liver related complications seen during a long term prospective study conducted in the last 15 years in a large and homogeneous cohort of patients. Patients were initially included with early well compensated cirrhosis due to HBV or HCV.

PATIENTS AND METHODS

Study design

This study was initiated in 1986 as a prospective study aimed at investigating the natural history of cirrhosis and obtaining an early diagnosis of HCC. Criteria for inclusion in our follow up programme were: (a) histological or clinical diagnosis of cirrhosis (presence of irregular margins on ultrasound, portal hypertension with laboratory evidence of chronic liver disease); (b) presence of compensated disease (stage A or B according to the Child-Pugh classification); and (c) absence of clinical and ultrasonographic evidence of liver cancer at entry, with α-fetoprotein levels <200 ng/ml. In December 1997, using these criteria 573 patients with compensated cirrhosis were seen for the first time at our institute and 442 were followed up for at least 24 months. A total of 368 patients had Child-Pugh stage A cirrhosis and 312 had evidence of chronic HBV and/or chronic HCV infection with asymptomatic liver disease, anamnestic exclusion of previous episodes of decompensation, ascites, portal-systemic encephalopathy, gastrointestinal bleeding due to portal hypertension, and absence of focal lesion of the liver on abdominal US examination. In this subgroup of patients, we assessed prospectively the incidence and hierarchy of major complications during a prolonged follow up period.

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; US, ultrasound; CT, computed tomography; MR, magnetic resonance; HBsAg, hepatitis B surface antigen; ELISA, enzyme linked immunosorbent assay; HCC, hepatocellular carcinoma; IFN, interferon

Patients

There were 192 (61.5%) males and 120 (38.5%) females with a median age at entry of 60 (range 30–78) years. Diagnosis of cirrhosis was obtained by liver biopsy in 283 (90.7%) patients and on the basis of clinical criteria in 29 (9.3%) cases. Median known duration of cirrhosis was 0 years (0–6) at inclusion. In total, 254 patients (81.4%) were anti-HCV positive in serum using first and second generation enzyme linked immunosorbent assay (ELISA) kits; 131 (58.2%) were infected with genotype 1, 89 (39.6%) with genotype 2, four (1.8%) with genotype 4, and one (0.4%) with genotype 3, while 29 (11.4%) were HCV-RNA negative and could not be genotyped. Forty three patients (13.8%) were hepatitis B surface antigen (HBsAg) positive by ELISA and three (6.9%) were coinfected with hepatitis D virus (HDV); 26 (60.5%) were HBV-DNA positive in serum at inclusion. Fifteen (4.8%) patients were both anti-HCV and HBsAg positive and three (20.0%) had evidence of HDV coinfection; six (40.0%) were HCV-RNA positive and six (40.0%) were HBV-DNA positive at inclusion. A past history of heavy alcohol abuse (more than 80 g/day for males and more than 50 g/day for females) was recorded in 46 (14.7%) patients.

Follow up of patients and events assessment

All patients underwent evaluations at six monthly intervals for: (a) clinical signs and symptoms of liver disease; (b) laboratory parameters, including alanine aminotransferase, aspartate aminotransferase, bilirubin, prothrombin time, serum albumin, platelets and leucocyte count, haemoglobin, and alpha-fetoprotein; and (c) abdominal US examination of the liver, followed by computerised tomography (CT) or magnetic resonance (MR), when indicated. The development of major complications of cirrhosis during follow up was defined according to the following criteria: (1) HCC was diagnosed by US, CT, or MR, and US assisted fine needle biopsy; (2) ascites was identified by US examination of the abdomen; (3) gastrointestinal bleeding due to portal hypertension was confirmed by endoscopy in the presence of oesophageal or gastric varices or hypertensive gastropathy; (4) portal-systemic encephalopathy was established by clinical parameters and confirmed by electroencephalogram and psychometric tests; (5) worsening of disease with decompensation was defined according to transition from Child A to Child B or Child C cirrhosis; and (6) death due to liver related causes. Each of these events was recorded when first seen during the observation period. Recurrence of the same complication during further follow up was not considered for the purpose of this analysis.

Statistical analysis

The χ^2 test and Fisher's exact test were used, when appropriate, to compare sex distribution, alcohol abuse, and hierarchy of complications among patients with and without alcohol abuse. The Kruskal-Wallis one way analysis of variance was used to compare follow up time, duration of cirrhosis, age, and baseline laboratory parameters in the different aetiological subgroups. Kaplan-Meier product limit survival analysis was performed to evaluate the cumulative probability of each complication. Univariate analysis by Kaplan-Meier product limit survival and the log rank test were used (with 95% confidence intervals (CI)) to compare the cumulative probability of developing ascites in relation to the appearance of HCC during follow up, incidence of each event in relation to treatment with IFN during follow up, and incidence of major complications according to the presence or absence of a history of alcohol abuse. All statistical tests were two sided, and a type 1 error probability was set at 0.05. Data analysis was performed using the BMDP statistical package.[31]

RESULTS

Baseline features of cirrhotic patients in relation to aetiology of cirrhosis

The main baseline characteristics of the 312 patients considered for this analysis in relation to aetiology of cirrhosis are described in table 1. HBsAg positive patients without anti-HCV were significantly younger than those with anti-HCV (with or without HBsAg) ($p<0.0001$) and were significantly more likely to be male ($p<0.0001$). Median prothrombin time was significantly higher in anti-HCV positive cases compared with those with HBsAg alone or coinfected with HCV ($p<0.0001$). Alcohol abuse was more prevalent in HBsAg and in HBV and HCV coinfected patients but the difference was not statistically significant. In contrast, the three aetiological subgroups were similar with regard to known duration of cirrhosis, other liver function tests, and haematological profiles. Duration of follow up was also similar in the three subgroups.

Incidence and hierarchy of hepatic complications during follow up

During a median follow up period of 93 (range 14–194) months, 101 (32.3%) cirrhotic patients developed at least one complication, 13 (4.2%) died from causes not related to liver disease (six patients from cancer, three from ischaemic stroke, three from heart failure, and one from myocardial infarction) after 25–148 (median 60) months and 35 (11.2%) were lost to follow up after 36–128 (median

Table 1 Baseline clinical and laboratory characteristics of 312 patients with Child A cirrhosis in the different aetiological subgroups

	HCV+/HBsAg− (n = 254)	HCV−/HBsAg+ (n = 43)	HCV+/HBsAg+ (n = 15)	p Value
Age (y)*	61 (36–78)	52 (30–74)	60 (43–68)	<0.0001†
Sex				
Males	142 (55.9%)	38 (88.4%)	12 (80.0%)	<0.0001‡
Females	112 (44.1%)	5 (11.6%)	3 (20.0%)	
Duration of cirrhosis (y)*	0 (0–6)	0 (0–5)	0 (0–6)	0.92†
Alcohol abuse	34 (13.4%)	8 (18.6%)	4 (26.7%)	0.25‡
Albumin (g/l)*	42 (32–53)	42 (30–54)	40 (35–47)	0.49†
Prothrombin time (%)*	85 (50–100)	76 (55–100)	70 (63–92)	<0.0001†
Total bilirubin (μmol/l)*	14 (3–44)	15 (3–39)	17 (4–34)	0.53†
Platelets count ($\times 10^9$/l)*	131 (31–294)	140 (61–239)	122 (89–257)	0.80†
Leucocytes count ($\times 10^9$/l)*	5.0 (2.0–9.8)	5.4 (2.7–8.3)	6.0 (3.8–9.2)	0.22†
ALT (U/l)*	130 (18–973)	116 (14–750)	127 (37–613)	0.82†
Follow up (months)*	91 (14–194)	112 (39–175)	82 (50–177)	0.12†

*Values are median (range).
HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase.
†Kruskal-Wallis test; ‡χ^2 test.

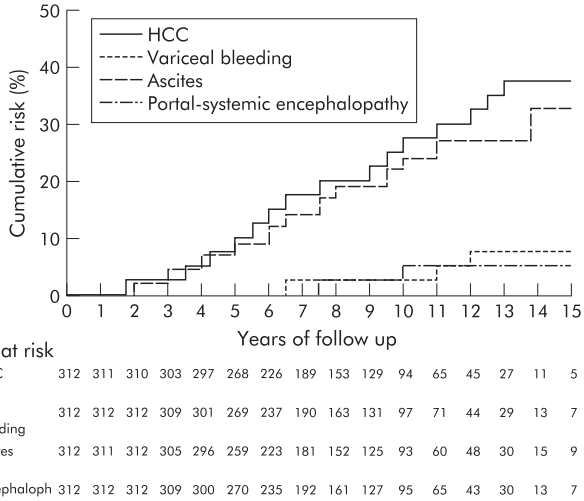

Figure 1 Cumulative probability of hepatocellular carcinoma (HCC), ascites, variceal bleeding, and portal-systemic encephalopathy during follow up in 312 patients with initially compensated cirrhosis of viral aetiology (Kaplan-Meier method).

72) months from inclusion. The most frequent complication was HCC, seen in 65 cases (20.8%), followed by ascites (61 cases, 19.5%), gastrointestinal bleeding (14 cases, 4.5%), and portal systemic encephalopathy (six cases, 1.9%). Using the Kaplan-Meier method (fig 1), the cumulative incidences of HCC, ascites, gastrointestinal bleeding, and encephalopathy were 8%, 7.5%, 0%, and 0% at five years, and 28%, 25%, 5%, and 5% at 10 years, respectively. Worsening of Child stage occurred in 62 patients (19.8%), and seven (2.3%) patients underwent liver transplantation for liver failure. Fifty eight patients (18.6%) died of liver related causes, and HCC was the first cause of death (41 cases: 70.7%) followed by liver failure without HCC (15 cases) and massive gastrointestinal bleeding (two cases). As shown in fig 2, mortality rates during the first decade after diagnosis of cirrhosis closely paralleled the rate of HCC development. With regard to the hierarchy of complications, HCC was the first to develop in 59 cases and was therefore the most frequent first complication, followed by ascites, seen as the first complication in 34 cases, bleeding (five cases), and encephalopathy (three cases). Patients who developed HCC had a significantly higher incidence of ascites that usually developed after the tumour, compared with patients who remained free of HCC during follow up ($p<0.0001$) (fig 3).

Incidence and hierarchy of complications in relation to aetiology of cirrhosis

As shown in table 2, at least one complication of cirrhosis occurred in 78/254 (30.7%) anti-HCV positive cases, in 15/43 (34.8%) HBsAg positive cases, and in 8/15 (53.3%) HBsAg and anti-HCV positive patients. HCC was the most frequent and first complication in anti-HCV positive patients and in HCV/HBV coinfected cases while ascites predominated as the most frequent and first complication among HBsAg positive cases without anti-HCV. Worsening of cirrhosis stage and death due to liver related causes occurred with similar frequencies in anti-HCV positive and HBsAg positive cases while the incidence of these events was twofold higher in patients with HBV and HCV coinfection. Kaplan-Meier analysis on the development of different complications during follow up in the three aetiological subgroups is shown in fig 4. The cumulative incidences of HCC at five and 10 years were 7.8% and 28% in patients with HCV alone, 10% and 18% in patients with HBsAg alone, and 13% and 50% in

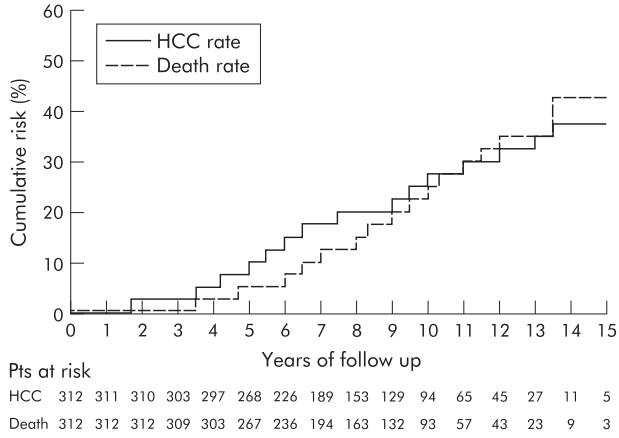

Figure 2 Incidence of hepatocellular carcinoma (HCC) and liver related mortality rate during follow up in the whole population (Kaplan-Meier method).

HBV/HCV coinfected cases. The cumulative incidences of ascites at five and 10 years were 7% and 20% in patients with HCV alone, 11% and 30% in patients with HBsAg alone, and 11% and 40% in HBV/HCV coinfected cases. The cumulative probabilities of bleeding and encephalopathy were 2.5%/0% at five years and 5%/2.5% at 10 years in patients with anti-HCV alone, and 0%/0% and 5%/5% in patients with HBsAg alone, respectively, while none of the patients coinfected with HBV and HCV developed these complications during follow up. When HCV genotype distribution was taken into consideration, no significant difference was observed concerning frequency and hierarchy of the major complication, worsening of stage of cirrhosis, or mortality rate between genotype 1 and genotype 2 infected patients. HDV coinfection, which was present in few HBV positive cases, did not significantly affect the outcome of HBsAg positive patients or HBV/HCV coinfected cases. HBV-DNA positivity in HBV infected patients was associated with a higher incidence of ascites (30.7% *v* 11.7%), worsening of stage of cirrhosis (30.7% *v* 5.9%), and death or liver transplant (42.3% *v* 11.7%) during follow up. These differences were not statistically significant using the Kaplan-Meier method and the log rank test, most likely due to the small numbers of patients in each

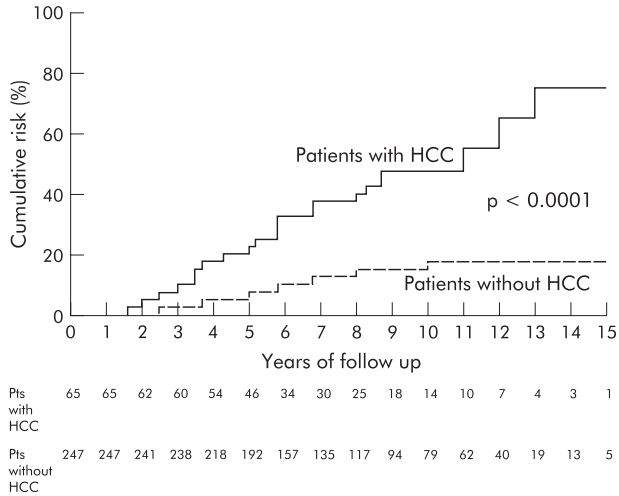

Figure 3 Cumulative incidence of ascites appearance in relation to development of hepatocellular carcinoma (HCC) during follow up (Kaplan-Meier method and log rank test).

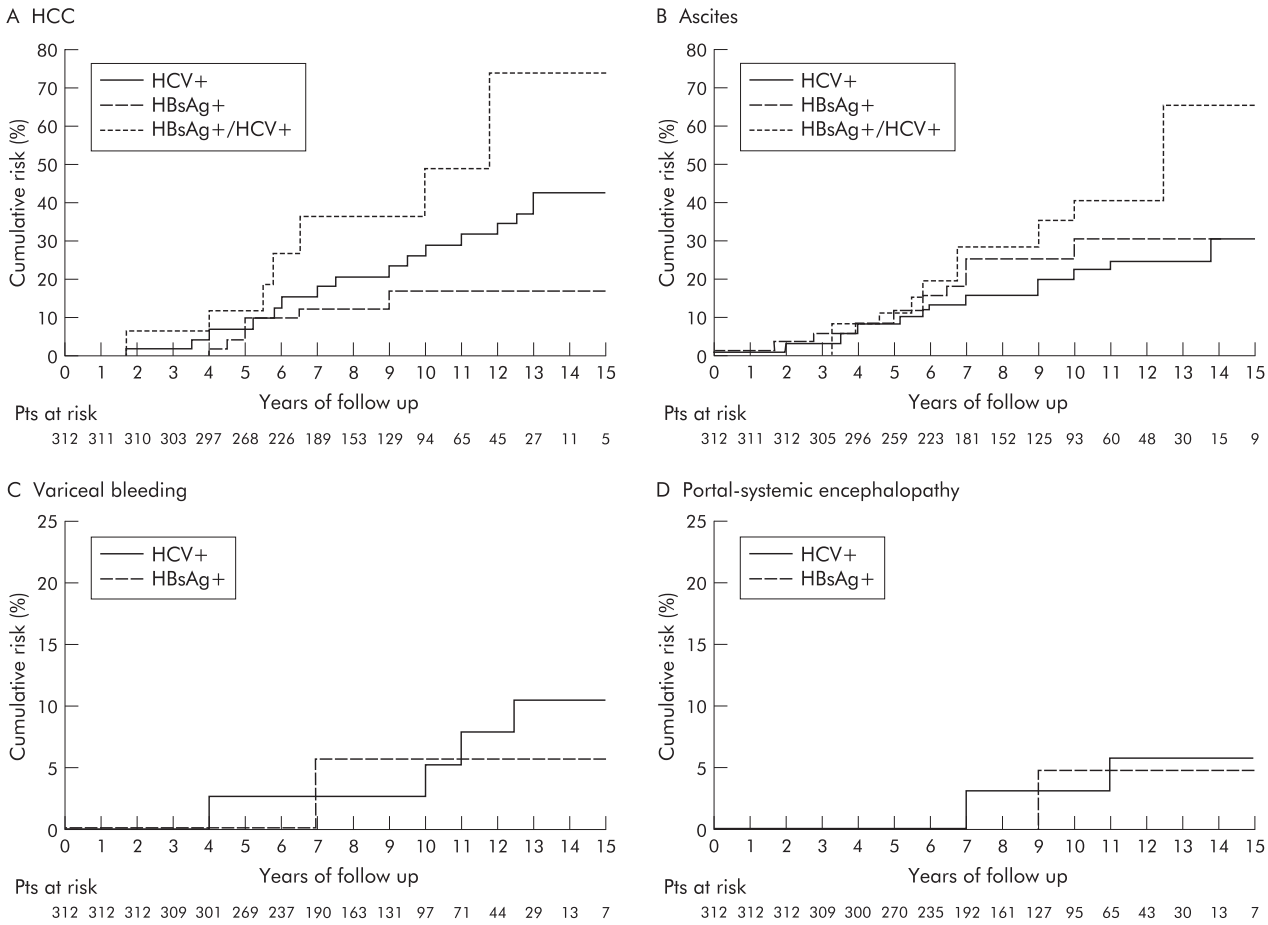

Figure 4 Cumulative probability of hepatocellular carcinoma (HCC) (A), ascites (B), variceal bleeding (C), and portal-systemic encephalopathy (D) during follow up in the different aetiological subgroups (Kaplan-Meier method). HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen.

group. Ascites was the first complication to occur in HBV-DNA positive cases while HCC was the earliest event in HBV-DNA negative patients.

Incidence and hierarchy of complications in relation to alcohol abuse

Using the Kaplan-Meier method and the log rank test, previous history of alcohol abuse was found to be significantly associated with a higher incidence of ascites ($p<0.05$) and mortality from liver related causes ($p<0.05$) during the observation period while no significant differences were observed concerning HCC development ($p = 0.44$), gastrointestinal bleeding ($p = 0.62$), encephalopathy occurrence ($p = 0.70$), or worsening of stage of cirrhosis ($p = 0.18$). The same values were observed in anti-HCV positive cases which showed a significantly higher frequency of ascites ($p<0.05$) and liver related death ($p<0.05$) among patients with a history of alcohol abuse. No significant differences in the incidence of major complications in relation to alcohol abuse were observed in HBsAg or HBsAg/anti-HCV positive cases.

Table 2 Incidence and hierarchy of complications seen during long term follow up in cirrhotic patients according to aetiology

	HCV+/HBsAg− (n = 254)	HCV−/HBsAg+ (n = 43)	HCV+/HBsAg+ (n = 15)
Overall incidence			
At least one complication	78 (30.7%)	15 (34.8%)	8 (53.3%)
HCC	52 (20.5%)	6 (13.9%)	7 (46.7%)
Ascites	45 (17.7%)	10 (23.2%)	6 (40.0%)
Bleeding	12 (4.7%)	1 (2.3%)	0
Encephalopathy	5 (1.9%)	1 (2.3%)	0
Progression of Child stage	46 (18.1%)	9 (20.9%)	7 (46.7%)
Liver related death	42 (16.3%)	9 (20.9%)	7 (46.7%)
Hierarchy			
First event occurring			
HCC	47 (18.5%)	6 (13.9%)	6 (40.0%)
Ascites	24 (9.4%)	8 (18.6%)	2 (13.3%)
Bleeding	5 (1.9%)	0 (0%)	0 (0%)
Encephalopathy	2 (0.8%)	1 (2.3%)	0 (0%)

Table 3 Hierarchy of complications seen during long term follow up in cirrhotic patients according to aetiology and previous alcohol abuse

	All patients	HCV+/HBsAg−	HCV−/HBsAg+	HCV+/HBsAg+
No alcohol abuse				
No of patients	266	220	35	11
First event occurring				
HCC	52 (19.5%)*	42 (19.1%)	5 (14.2%)	5 (45.4%)
Ascites	24 (9.0%)*	17 (7.7%)	7 (20.0%)	0 (0%)
Bleeding	5 (1.9%)	5 (2.3%)	0 (0%)	0 (0%)
Encephalopathy	3 (1.1%)	2 (0.9%)	1 (2.8%)	0 (0%)
Alcohol abuse				
No of patients	46	34	8	4
First event occurring				
HCC	7 (15.2%)*	5 (14.7%)	1 (12.5%)	1 (25.0%)
Ascites	10 (21.7%)*	7 (20.5%)	1 (12.5%)	2 (50.0%)
Bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Encephalopathy	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*$p<0.05$ by Fisher's exact test.

As shown in table 3, HCC was the earliest complication in patients without alcohol abuse (52 cases; 19.5%) while ascites represented the first complication in patients with a history of alcohol abuse (10 cases; 21.7%) ($p<0.05$). The same findings were observed in anti-HCV positive patients alone and in HBV/HCV coinfected cases but in these subgroups the difference did not reach statistical significance.

Incidence and hierarchy of complications in anti-HCV positive cases with or without interferon treatment

During follow up, 115 patients with anti-HCV positive cirrhosis (45.3%) received IFN therapy for at least six months. Most patients were treated with 3 MU of IFN alfa given three times a week. The remaining 139 patients (54.7%) did not received IFN or other antiviral treatments. During the entire follow up period, at least one complication of cirrhosis developed in 29 (25.2%) IFN treated cases and in 50 (35.9%) untreated cases. HCC was the most frequent complication in untreated cases (24.5%), followed by ascites (20.1%), bleeding (5.7%), and encephalopathy (2.9%). In contrast, treated patients had the same incidence of HCC and ascites (15.6%), followed by bleeding (3.4%) and encephalopathy (0.9%). Worsening of Child stage was seen in 20.1% of untreated and 15.5% of treated cases. Death due to liver related causes occurred in 20.8% of the former and in 11.3% of the latter.

DISCUSSION

The natural history of compensated cirrhosis of viral aetiology, rate and type of complications occurring over time in different aetiological subgroups, and effect of IFN therapy in virus related cases have been matters of great interest and frequent controversy in recent years. Early studies conducted in patients recruited at different stages of cirrhosis usually identified portal hypertension and its main clinical consequence (that is, ascites and oesophageal bleeding) as the most frequent causes of transition from compensated to decompensated cirrhosis and of liver related death.[32–34] Furthermore such events were reported to have profound effects on survival rates.

In most studies, ascites was the first complication to occur and to mark decompensation of liver disease.[32–35] Recently, studies conducted in more homogeneous cohorts of cirrhotic patients with initially well compensated ''early'' cirrhosis of viral aetiology have clearly shown that HCC is another important complication that in these patients may frequently develop in the compensated phase of disease, as reported in studies from Japan and the Far East.[12–18 36] These observations were the basis for the increasing interest in surveillance programmes in cirrhotic patients, aimed at identifying HCC as early as possible, as well as of clinical studies evaluating the possibility of reducing or delaying the HCC risk with IFN therapy. However, the cost effectiveness of US screening and monitoring of cirrhotic patients, and the benefit of prolonged IFN therapy remain controversial and are currently being evaluated in large prospective trials conducted mainly in patients with HCV related cirrhosis.

The results of our study strongly support the rationale of these approaches by showing that HCC is indeed a major and early complication of compensated cirrhosis of viral aetiology, being the most frequent first complication and cause of death in HCV positive patients. In our study, conducted in a large cohort of more than 300 patients followed from the very early phase of compensated cirrhosis to almost one decade later, the incidence and also the hierarchy of major clinical complications were analysed prospectively and separately in HCV positive and HBV positive patients, as well as in cases coinfected with both HBV and HCV. Development of HCC, which was investigated by periodic US examination of the liver, occurred in 20.5% of patients with HCV and in 46.7% of those with HCV and HBV, being the first complication of cirrhosis in 18.5% and 40%, respectively, of such cases. HCC often preceded the appearance of ascites and was the cause of death in 70.7% of our patients. The major clinical impact of HCC in the first decade of virus related cirrhosis was clearly evident from the close association between HCC appearance and death rate. As our patients were monitored by periodic US, leading to early detection of small HCC lesions, it would appear that early studies indicating that ascites was by far the most frequent first complication to develop in compensated cirrhosis could have underestimated small HCC that may have preceded and precipitated ascites, as often seen in our patients. In contrast, previous studies also included patients with non-viral forms of cirrhosis, mainly alcohol related, where the pathogenesis and pathophysiology of liver damage are quite different; haemodynamic changes prevail over inflammation and abnormal hepatocellular proliferation.[32–34] This assumption would also appear to be confirmed in our study where a significantly higher incidence of ascites and liver related deaths were observed among patients with previous alcohol abuse, independent of the aetiology of cirrhosis, while HCC represented the more frequent first complication in non-drinkers. Interestingly, in the Eurohep series by Fattovich and colleagues,[17] where only patients with HCV related compensated cirrhosis were included, the overall incidence of events occurring as the first complication was 8% for HCC, 8% for ascites, 3.6% for variceal bleeding, and 1.3% for encephalopathy, and the hierarchy of complications, although not reported in that series, would appear to have been similar to that seen in our series.

The risk of HCC in the compensated phase of cirrhosis was exaggerated in our patients by coinfection with HBV and HCV, confirming that this condition is extremely prone to malignant transformation and needs urgent priority in the development of surveillance and prevention strategies. In the absence of HBV/HCV coinfection, HBV cirrhotics showed a somehow different natural history of liver disease in relation to the hierarchy of complications compared with HCV infected patients, even if our observations were limited by the smaller size of the HBV infected group. Ascites seemed to be the more common early complication in HBsAg positive patients with evidence of HBV replication, while this feature was not observed in HBV-DNA negative cases. In our study, the presence of HDV coinfection, probably because of its small prevalence, did not influence the outcome of HBV related cirrhosis. The incidence and hierarchy of major complications in HCV positive patients was similar in those with different genotypes, particularly HCV-1 and HCV-2, in agreement with previous studies.[37 38]

Approximately half of our cirrhotics had received at least one course of IFN monotherapy during follow up. As the decision to treat was made on an individual patient basis, without randomisation, our findings cannot add much to what has already been described with regard to the controversial effect of IFN treatment in cirrhotic patients with HCV or HBV infection. A better understanding of the effect of IFN on liver cell proliferation and HCC development and on liver disease progression and decompensation will require new data from ongoing prospective randomised studies.

In summary, our results indicate that in compensated cirrhosis of viral aetiology and particularly in HCV infected patients, HCC is frequently the first complication to occur and a major cause of liver related death. Strategies for adequate assessment of the individual HCC risk and for better monitoring and prevention of malignant complications in these patients are urgently needed.

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REFERENCES

1 **Margolis HS**, Alter MJ, Hadler SC. Hepatitis B: evolving epidemiology and implication for controls. *Semin Liver Dis* 1991;**11**:84–92.
2 **Lok AS**, Heathcote EJ, Hoofnagle YH. Managment of hepatitis B: 2000—Summary of a Workshop. *Gastroenterology* 2001;**120**:1828–53.
3 Global surveillance, control of hepatitis C. Report of a WHO consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *J Viral Hepat* 1999;**6**:35–47.
4 National Institute of Health Consensus Development Conference Panel statement: management of hepatitis C. *Hepatology* 1997;**26**(suppl 1):2S–10.
5 EASL International Consensus Conference on Hepatitis C: Paris, 26–28 February 1999, consensus statement. *J Hepatol* 1999;**30**:956–61.
6 **Chen DS**. The natural history of chronic hepatitis B virus infection: disease progression and the transmission of infection. In:Zuckerman A, editor. *Hepatitis B in the Asian-Pacific region*. London: Royal College of Physicians, 1997:67–77.
7 **Liaw YF**, Tai DI, Chu CM, *et al*. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. *Hepatology* 1988;**8**:493–6.
8 **Di Marco V**, Lo Iacono O, Cammà C, *et al*. The long-term course of chronic hepatitis B. *Hepatology* 1999;**30**:257–64.
9 **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.
10 **Ikeda K**, Saitoh S, Suzuki Y, *et al*. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation of 2215 patients. *J Hepatol* 1998;**28**:930–8.
11 **Alberti A**, Chemello L, Benvegnù L. Natural history of hepatitis C. *J Hepatol* 1999;**31**(suppl 1):17–24.
12 **Colombo M**, De Franchis R, Del Ninno E, *et al*. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991;**325**:675–80.
13 **Ikeda K**, Saitoh S, Koida I, *et al*. A multivariate analysis of risk factors for hepatocellular carcinoma: a prospective observation of 795 patients with viral and alcoholic cirrhosis. *Hepatology* 1993;**18**:47–53.
14 **Tsukuma H**, Hiyama T, Tanaka S, *et al*. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993;**328**:1797–801.
15 **Benvegnù L**, Fattovich G, Noventa F, *et al*. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis: a prospective study. *Cancer* 1994;**74**:2442–8.
16 **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.
17 **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.
18 **Collier J**, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998;**27**:273–8.
19 **Sobesky R**, Mathurin P, Charlotte F, *et al*. Modeling the impact of interferon alfa treatment on liver fibrosis progression in chronic hepatitis C: a dynamic view. *Gastroenterology* 1999;**116**:378–86.
20 **Nishiguchi S**, Kuroki T, Nakatani S, *et al*. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995;**346**:1051–5.
21 **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.
22 **Benvegnù L**, Chemello L, Noventa F, *et al*. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis. *Cancer* 1998;**83**:901–9.
23 **Serfaty L**, Aumaitre H, Chazouilleres O, *et al*. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998;**27**:1435–40.
24 **International Interferon-alfa Hepatocellular Carcinoma Study Group**. Effect of interferon-α on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study. *Lancet* 1998;**351**:1535–9.
25 **Kasahara A**, Hayashi N, Mochizuki K, *et al*. Risk factors for hepatocellular carcinonma and its incidence after interferon treatment in patients with chronic hepatitis C. *Hepatology* 1998;**27**:1394–402.
26 **Poynard T**, McHutchison J, Davis GL, *et al*. Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 2000;**32**:1131–7.
27 **Zeuzem S**, Feinman SV, Rasenack J, *et al*. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;**343**:1666–72.
28 **Heathcote EJ**, Shiffman ML, Cooksley GE, *et al*. Peginterferon alfa-2a in patieitns with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000;**343**:1673–80.
29 **Manns MP**, McHutchinson JG, Gordon SC, *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;**358**:958–65.
30 **Lindsay KL**, Trepo C, Heintges T, *et al*. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology* 2001;**34**:395–403.
31 **Brown MB**, Engleman L, Jennrich RI. *BMDP statistical software manual*, In: Dixon WJ, e, eds. Berkeley: University of California Press, 1990.
32 **D'Amico G**, Morabito A, Pagliaro L, *et al*. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci* 1986;**31**:468–475.
33 **Gines P**, Quintero E, Arroyo V, *et al*. Compensated cirrhosis: natural history and prognostic factors. *Hepatology* 1987;**7**:122–8.
34 **Pagliaro L**, D'Amico G, Pasta L, *et al*. Portal hypertension in cirrhosis: natural history. In: Bosch J, Groszmann R, eds. *Portal hypertension: Pathophysiology and treatment*. Cambridge, MA: Blackwell Scientific, 1994:72–92.
35 **Hui AY**, Chan HL, Leung NW, *et al*. Survival and prognostic indicators in patients with hepatittis B virus-related cirrhosis after onset of hepatic decompensation. *J Clin Gastroenterol* 2002;**34**:569–72.
36 **Tanaka R**, Itoshima T, Nagashima H. Follow-up study of 582 liver cirrhosis patients for 26 years in Japan. *Liver* 1987;**7**:316–24.
37 **Takano S**, Yokosuka O, Imazeki F, *et al*. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995;**21**:650–5.
38 **Benvegnù L**, Pontisso P, Cavalletto D, *et al*. Lack of correlation between hepatitis C virus (HCV) genotypes and clinical course of HCV-related cirrhosis. *Hepatology* 1997;**25**:211–15.