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The Prognosis of Liver Cirrhosis in Recent Years in Korea

The survival of a recent series of 823 cirrhosis patients who were followed up for a mean of 48 months was analyzed. Cirrhosis was ascribed to alcohol (26%), hepatitis virus B (58%), hepatitis virus C (11%) or both (2%), or was cryptogenic (3%). Features of decompensation were observed in 51% of the patients at entry, and newly developed in 44% of compensated patients within 5 yr. The 5-yr survival after decompensation was 25%. The leading causes of death were liver failure (53%), hepatocellular carcinoma (HCC, 23%), and variceal bleeding (10%). Early detection of HCC significantly improved the survival of cirrhosis patients. Biannual ultrasonography increased the detection rate of small HCC. Mortality of variceal hemorrhage was much lower in patients with Child-Pugh scores from 5 to 8 than in those with scores above 8 (5% vs. 52%). Endoscopic prophylaxis significantly decreased the incidence of first variceal hemorrhage, but the effect was insufficient to improve the rate of survival. Mortality of first spontaneous bacterial peritonitis was 18%. These data suggest that the mortality of major complications of liver cirrhosis has considerably decreased during the last two decades, while there was no remarkable improvement in long-term survival. More efficient management of etiologic factors would be required.

Key Words : *Liver Cirrhosis; Liver Cirrhosis, Alcoholic; Prognosis; Survival Rate; Survival Analysis; Carcinoma, Hepatocellular; Esophageal and Gastric Varices; Hemorrhage*

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INTRODUCTION

Liver cirrhosis is a major public health problem in Korea, where it is the fourth most common cause of death (1), and is probably linked to the high prevalence of hepatitis B virus (HBV) infection (2) and to the culture that encourages high alcohol consumption. According to the reports from western countries in the 1980s (3-5), the prognosis of cirrhosis was generally poor; the patients with compensated cirrhosis decompensated at a rate of 5-10% per year, and the 5-yr survival rate after decompensation was roughly 20%. Over the last 20 yr, noticeable progress has been made in the management of fatal complications, such as variceal bleeding and hepatocellular carcinoma (6, 7), and this might have considerably altered the survival of cirrhosis patients. Updated prognostic information is necessary for appropriate decision-making in the management of cirrhosis patients.

This study analyzed the prognosis of patients with cirrhosis who were managed during the last 10 yr. The aims of this study were 1) to evaluate survival rates and prognostic factors, 2) to investigate the pattern of development of major complications and their impact on survival, and 3) to assess the benefits of two active measures designed to counter fatal complications: surveillance for hepatocellular carcinoma (HCC) and endoscopic prophylaxis against first variceal hemorrhage.

MATERIALS AND METHODS

Selection of Patients

The study examined a retrospective cohort of 823 adult patients with liver cirrhosis. This figure represents all the cirrhosis patients who were followed up in our department between September 1991 and July 1999, except those who had HCC at first presentation (n=623) or had certain types of cirrhosis, including primary biliary cirrhosis (n=5), Budd-Chiari syndrome (n=4), hemochromatosis (n=1), Wilson's disease (n=1), and cardiac cirrhosis (n=1). In 675 patients, liver cirrhosis was newly diagnosed during this period, and the entry point was defined as the date of diagnosis of cirrhosis. For the remaining 148 patients who had been managed for previously diagnosed cirrhosis, the entry point was defined as the first follow-up date after September 1, 1991. Ninety-seven patients (11.7%) dropped out during the study period, but all of their survival data were available from the National Death Index. For the entire cohort, the mean follow-up duration was 48 (1-94) months.

Patient Assessments

The diagnosis of liver cirrhosis was made during admission.

At admission, all the patients gave a full history, and underwent a complete physical and laboratory examinations including routine blood biochemistry, prothrombin time, blood cell count, and viral markers. Furthermore, upper gastrointestinal endoscopy, abdominal ultrasonography, and if needed, computerized tomography (CT) were performed. The diagnosis was biopsy-proven in 450 patients by using the histological criteria, proposed by Scheuer (8). In the remaining 373 patients, the recognition of ascites and an irregular liver surface on imaging studies, in addition to esophageal varices on endoscopy, was considered sufficient for the diagnosis.

HBV infection was recognized by identifying hepatitis B surface antigen (HBsAg) in the serum, and was further evaluated by checking hepatitis B e antigen (HBeAg), anti-HBe antibody, and HBV DNA in serum. Hepatitis C virus (HCV) infection was recognized by detecting anti-HCV antibody in serum, and by confirming HCV RNA in serum with the polymerase chain reaction. The etiology of liver cirrhosis was classified as follows: HBV- or HCV-related cirrhosis was diagnosed in patients seropositive for HBsAg or anti-HCV, respectively. Alcoholic cirrhosis was diagnosed in patients with a habit of alcohol abuse who were seronegative for HBsAg and anti-HCV. Alcohol abuse was defined as the consumption of more than 80 g of alcohol per day for more than 5 yr. Cryptogenic cirrhosis was diagnosed in nonalcoholic patients who were seronegative for viral markers.

Decompensation was defined as the presence of ascites, jaundice, encephalopathy, or variceal bleeding. Jaundice was defined as serum bilirubin levels >2 mg/dL. Ascites was detected by ultrasonography and confirmed by paracentesis. Spontaneous bacterial peritonitis (SBP) was diagnosed according to Runyon (9). Encephalopathy was recognized using standard criteria (10). The prothrombin time was expressed as the activity percentage. The degree of overall hepatic decompensation was assessed using the Child-Turcotte-Pugh score (11). Esophageal varices were described using Japanese guidelines with some modifications (12). In this study, varices were divided into two size categories: small (F1) or large (F2 or F3). Similarly, the red color (RC) sign was also categorized into two levels: positive or negative. When death occurred within 6 weeks of gastrointestinal bleeding, it was regarded as a bleeding-related death (13). HCC was diagnosed by ultrasound- or CT-guided biopsy, or by the combination of typical angiographic findings with an alpha-fetoprotein level over 400 ng/mL. Small HCC was defined as a single tumor <5 cm, or 2-3 tumors <3 cm without invasion of major veins larger than sub-segmental branches. These criteria are the same one applied to define the early stage HCC in BCLC staging scheme (14). The tumors exceeding these limits were regarded as advanced HCC. Cholelithiasis was detected by ultrasonography.

Follow-up was usually conducted in the outpatient clinic at 3-month intervals, but was more frequent for those with decompensated cirrhosis. On each occasion, the patients underwent physical and laboratory examinations to assess possible alterations in hepatic function and the development of complications. For early detection of HCC, the serum alpha-fetoprotein level and ultrasonography were checked in every 3 and 6 months, respectively, as a rule.

Treatments

Ascites, SBP, and encephalopathy were treated following textbook guidelines. If a subject had a sign of gastrointestinal bleeding, he or she was hospitalized immediately for emergency endoscopy and adequate hemostatic treatment. For variceal bleeding, the patients underwent an emergency endoscopic band ligation or sclerotherapy, or supportive management using balloon tamponade or somatostatin or vasopressin followed by elective endoscopic treatment. Endoscopic treatment aimed to eradicate the varices, and was repeated, if needed. Once HCC was diagnosed, hepatic resection was recommended for the patients with operable tumors and compensated cirrhosis. For inoperable HCC, non-surgical treatments were considered, including transarterial oily chemo-embolization, local ablative therapies involving percutaneous ethanol injection or radiofrequency wave ablation, or combined modalities. Local ablation was generally used for small HCC.

Data Analysis

The cumulative survival rates and cumulative incidences of major complications were computed using the Kaplan-Meier method (15). The prognostic role of various clinical parameters for death and the development of HCC or variceal hemorrhage was assessed using univariate and multivariate analyses. In the univariate analysis, Kaplan-Meier curves were compared using the log rank test for each variable. Multivariate analyses were conducted using Cox's regression model (16) with the variables for which $p<0.1$ in the univariate analyses. The variables yielding continuous values were categorized into two levels in the univariate analysis using their median value, while they were introduced intact as continuous values in the multivariate analysis. Chi-square or Fisher's exact tests were used to compare ratios, and ANOVA or Student's t-test to compare averages. All the analyses were performed using the program SAS. The significance level was set at 0.05, and two-tailed tests were used.

RESULTS

Initial Characteristics of the Patients

The initial characteristics of the patients at entry are summarized in Table 1. In the entire series, 603 (73%) of 823 patients were men. The mean age was 50 yr (range: 16-82). Cirrhosis was compensated in 401 (49%) patients and decompensated in 422 (51%). Fifty patients in the compensated

Table 1. Initial characteristics of patients in the series and the results of the univariate analysis of survival

Factors	No. of Patients	5-yr Survival	*p*-value
Gender			
Male	603	57%	0.06
Female	220	63%	
Age (yr)			
≤50	427	65%	<0.0001
≥51	396	50%	
Cause of cirrhosis			
Alcohol	211	59%	
HBV*-related			
HBV	376	59%	
HBV & Alcohol	105	47%	0.06
HCV†-related			
HCV	65	65%	
HCV & Alcohol	24	55%	
HBV & HCV-related	14	62%	
Cryptogenic	28	69%	
Varix			
Absent	241	78%	<0.0001
Present	582	50%	
Albumin (g/dL)			
≤3.6	413	43%	<0.0001
>3.6	410	74%	
Bilirubin (mg/dL)			
≤1.4	383	70%	<0.0001
>1.4	440	48%	
Prothrombin (%)			
≤80	412	47%	<0.0001
>80	411	70%	
Ascites			
Absent	540	71%	<0.0001
Controllable	200	44%	
Intractable	83	7%	
Encephalopathy			
Absent	778	60%	<0.0001
Present	45	22%	
Platelets ($10^3/\mu L$)			
≤920	407	50%	<0.0001
>920	416	66%	
AST‡ (IU/L)			
≤67	415	63%	0.001
>67	408	53%	
ALP§ (IU/L)			
≤81	417	67%	<0.0001
>81	406	50%	
GGT‖ (IU/L)			
≤62	414	62%	0.19
>62	409	55%	
BUN¶ (mg/dL)			
≤13	477	61%	0.12
>13	346	55%	
Creatinine (mg/dL)			
≤0.8	572	59%	0.70
>0.8	251	56%	
Diabetes mellitus			
Present	127	46%	0.09
Absent	696	60%	
Hypertension			
Present	32	50%	0.71
Absent	791	59%	
Gall bladder stone			
Present	39	63%	0.75
Absent	784	58%	

*hepatitis virus B, †hepatitis virus C, ‡aspartate aminotransferase, §alkaline phosphatase, ‖gamma glutamyl transpeptidase, ¶blood urea nitrogen.

Table 2. Patient characteristics at diagnosis of cirrhosis according to etiology

	Alcoholic	HBV	HCV	B&C*	Cryptogenic
Number of patients	211	481	89	14	28
Age (Mean±SD)	52±10	46±10	60±9	51±10	57±11
Male patients (%)	200 (95)	331 (69)	53 (60)	12 (86)	7 (25)
Decompensated cirrhosis (%)	161 (76)	250 (52)	34 (38)	9 (64)	18 (64)
Esophageal varices (%)	182 (86)	311 (65)	53 (60)	8 (57)	19 (68)

*Coinfection with HBV and HCV.

group at entry had a previous history of decompensation. In the decompensated group at entry, ascites was found in 281 (67%), jaundice in 207 (49%), variceal bleeding in 119 (28%), and encephalopathy in 45 (11%). Esophageal varices were found in 582 (71%). The main comorbid conditions were diabetes mellitus in 127 (15%), cholelithiasis in 39 (5%), and hypertension in 32 (4%).

Cirrhosis was related to HBV in 481 (58%) patients, HCV in 89 (11%), and HBV and HCV co-infection in 14 (2%); alcohol abuse was recognized in 346 (42%) patients, including 211 (26%) with alcoholic cirrhosis; cirrhosis was cryptogenic in 28 (3%). The patients with alcoholic cirrhosis were predominantly male, while most of the patients with cryptogenic cirrhosis were female as shown in Table 2. At the time of diagnosis of cirrhosis, the mean age of patients was significantly different ($p<0.001$) depending on the etiologies of cirrhosis; lowest in HBV-related cirrhosis and highest in HCV-related cirrhosis. Also, there were significant differences ($p<0.001$) in the incidence of decompensation or esophageal varices; highest in the patients with alcoholic cirrhosis and lowest in those with HCV-related cirrhosis (Table 2).

Causes of Deaths

A total of 362 patients died during the study period, and the causes of death were identified from 310. Liver failure accounted for 165 deaths (53%), progression of HCC for 73 (23%), variceal bleeding for 28 (10%), infection for 13 (5%),

other digestive bleeding for 6 (2%), other malignancy for 4 (1%), and other causes for 21 (7%). Variceal bleeding was a terminal event in 12 of the patients who died of advanced HCC. Among the patients who died of liver failure, 55 (33%) and 29 (18%) were combined with SBP or hepatorenal syndrome, respectively. In patients with alcoholic cirrhosis, variceal bleeding was a more frequent cause of death than HCC (18% vs. 8%).

Survival and Prognostic Indicators at Entry

The cumulative survival rates in the whole series were 94, 76, 58, and 46% at 1, 3, 5, and 7 yr after inclusion, respectively. Survival was much better in patients with compensated cirrhosis than in the decompensated group, with respective 5-yr survival rates of 74% and 43%. The Child-Turcotte-Pugh scoring system allowed a more detailed prediction of survival depending on the severity of decompensation (Fig. 1). In this series, the 1-yr survival rate was 96% for patients with a Child-Turcotte-Pugh score of 6 to 8, and 40% for those with scores above 11.

In the univariate analysis of the entire series (Table 1), 13 of 18 variables at entry were linked to survival with $p<0.1$. Ten of them had independent ($p<0.05$) relationships with survival in the multivariate analysis (Table 3). The rate of survival was reduced for patients with male gender, older age, varix, ascites, prolonged prothrombin time (PT), lower platelet count, low serum albumin levels, and high levels of serum bilirubin or alkaline phosphatase (ALP). The patients with alcoholic cirrhosis had significantly better survival rate than those with HBV-related cirrhosis. In the multivariate analysis for subgroups, varix and ALP had a prognostic significance specifically for compensated cirrhosis, while bilirubin and PT were significant for decompensated cirrhosis.

Table 3. Prognostic factors for survival at entry in the multivariate analysis for the entire series using the Cox regression model

Variables	Hazard ratio (95% confidence interval)	*p* value
Gender (female/male)	0.687 (0.527-0.896)	0.0056
Age (yr)	1.037 (1.026-1.049)	<0.0001
Varices (present/ absent)	1.552 (1.147-2.102)	0.0045
Albumin (g/dL)	0.581 (0.461-0.731)	<0.0001
Bilirubin (mg/dL)	1.166 (1.076-1.264)	0.0002
PT (%)	0.990 (0.983-0.998)	0.0116
Ascites (intractable/ absent)	3.443 (2.517-4.710)	<0.0001
Platelet count ($10^3/\mu L$)	0.962 (0.937-0.988)	0.0045
ALP (IU/L)	1.003 (1.001-1.004)	0.0006
Etiology of cirrhosis (HBV-related/alcoholic)	1.608 (1.214-2.130)	0.0009

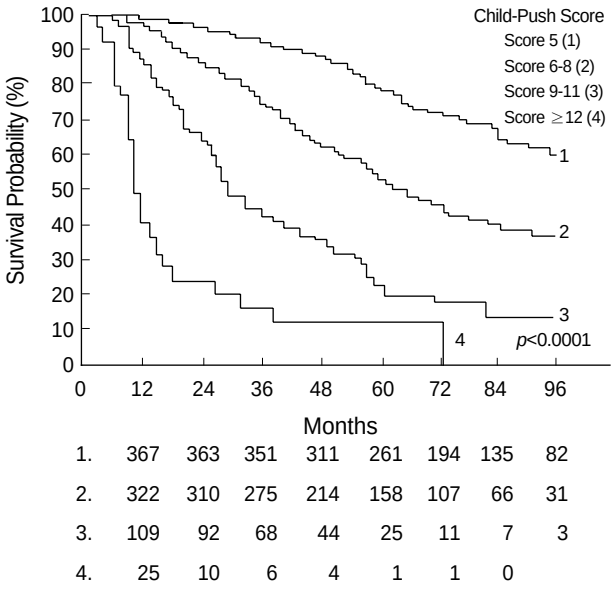

Fig. 1. Survival probability (Kaplan-Meier plot) in four subgroups based on the Child-Turcotte-Pugh scores. The numbers at the bottom of the figure are the numbers of patients at risk.

The Status of Etiologic Factors during Follow-up and Their Impact on Survival

Sixty-one (28%) of 211 patients with alcoholic cirrhosis and 75 (56%) of 135 alcohol abusers with viral cirrhosis permanently stopped drinking during the study period. They had a significantly better survival than those who continued to abuse alcohol (Table 4). In the subgroup analysis based on the Child-Turcotte-Pugh score, however, the benefit of abstinence was recognized only for patients with a fairly good hep-

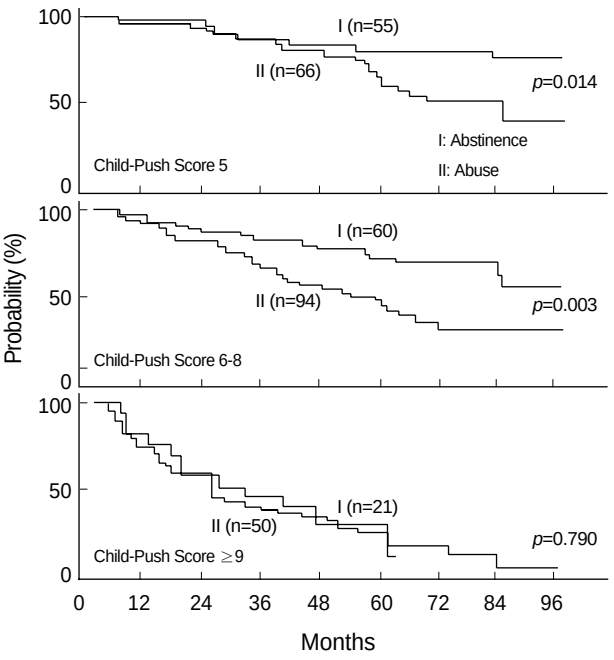

Fig. 2. Survival probability (Kaplan-Meier plot) in alcoholic patients who continued to abuse or stopped abusing alcohol. The survival benefit of abstinence was significant only in patients with Child-Turcotte-Pugh scores of 5 to 8 at entry.

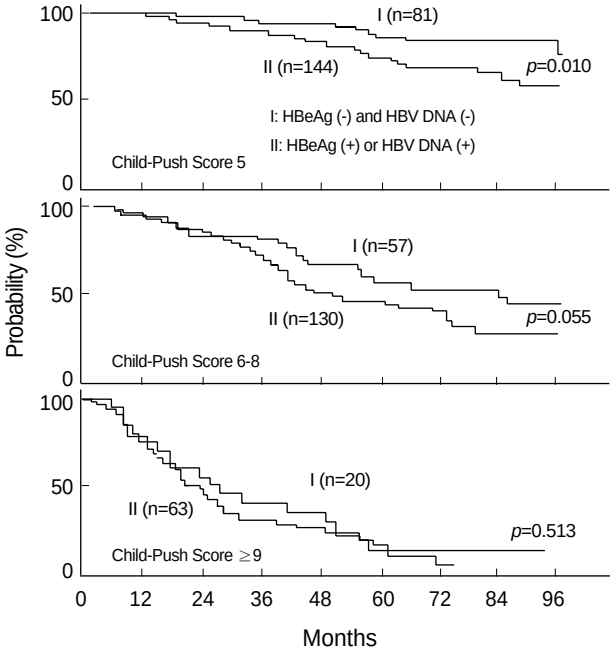

Fig. 3. Survival probability (Kaplan-Meier plot) in patients with HBV-related cirrhosis according to the HBeAg status and HBV DNA in the serum during follow-up. A significant difference in survival was observed between groups I and II only for the patients with a Child-Turcotte-Pugh score of 5 at entry.

atic reserve, but not in those with advanced decompensation features, as shown in Fig. 2.

Of the 495 patients with HBsAg, 143 (29%) were seronegative for both HBeAg and HBV DNA at entry, but 12 (8%) of them reverted to seropositive state thereafter. By contrast, 27 (8%) of 352 patients who had been seropositive for HBeAg or HBV DNA at entry became seronegative for both markers during follow-up. Overall, viral replication was suppressed in a total of 158 (32%) patients during the study period, and they showed a significantly improved survival rate compared to those with active viral replication (Table 4). However, this benefit was also significant only for the patients with compensated cirrhosis at entry (Fig. 3).

Development of Decompensation

Of the 351 patients who had never experienced decompensation at entry, 140 became decompensated during follow-up, with cumulative incidences of 13% and 44% at 1 and 5 yr after inclusion, respectively. The first sign of decompensation was ascites in 110 (79%), jaundice in 81 (58%), encephalopathy in 20 (14%), and variceal bleeding in 19 (14%). The 5-yr survival rate from entry was 97% in patients who did not develop decompensation, but 41% in those who decompensated. The survival rates after the initial episode of decompensation were 68% at 1 yr and 25% at 5 yr. Of note, the 5-yr survival after the appearance of ascites was 16%.

Table 4. Univariate analysis of survival in relation to important clinical events during follow-up

Events	No. of patients	Survival		*p* value
		3-yr	5-yr	
Alcohol abuse				
Stop	136	82%	71%	<0.0001
Continue	210	69%	48%	
Clearance of HBeAg and HBV DNA				
Absent	337	71%	52%	0.0002
Present	158	83%	66%	
Hepatocellular carcinoma				
Absent	705	78%	67%	<0.0001
Small*	69	77%	37%	
Advanced	49	57%	22%	
Upper GI bleeding				
Absent	687	79%	64%	<0.0001
Present	136	64%	40%	
SBP				
Absent	674	82%	68%	<0.0001
Present	149	50%	26%	

*Hepatocellular carcinoma consisting of a single nodule <5 cm or 2-3 nodules <3 cm without invasion of major veins.

Table 5. Risk factors for HCC using the Cox regression model

Variables	Hazard ratio (95% confidence interval)	*p* value
Gender (female/male)	0.444 (0.278-0.712)	0.0007
Age (yr)	1.061 (1.040-1.082)	<0.0001
Etiology of cirrhosis		
(HBV-related/alcoholic)	11.598 (5.322-25.274)	<0.0001
(HCV-related/alcoholic)	7.248 (3.004-17.486)	<0.0001
Varices (present/absent)	1.823 (1.164-2.855)	0.0087
ALP (IU/L)	1.005 (1.002-1.008)	0.0018

Development of Hepatocellular Carcinoma

One hundred and eighteen patients developed HCC during follow-up, with a cumulative incidence of 3% at 1 yr and 19% at 5 yr after inclusion. HBV- or HCV-related cirrhosis was more frequently complicated by HCC than alcoholic cirrhosis, with the 5-yr cumulative incidence in each group being 24%, 28% and 5%, respectively. In addition, male gender, older age, esophageal varices, and high serum alkaline phosphatase level were independently associated ($p<0.05$) with a higher risk of HCC (Table 5).

At the initial diagnosis of HCC, 69 (59%) patients had small HCC, while 80 (68%) patients were in a decompensated state. Hepatic resection was performed in 7 (6%) patients, local ablation combined with chemo-embolization in 36 (31%), chemo-embolization alone in 37 (31%), and conservative management in 35 (30%); 3 patients dropped out after the diagnosis. Active treatment of HCC was attempted in 80% of the cases with small HCC and in only 55% of advanced

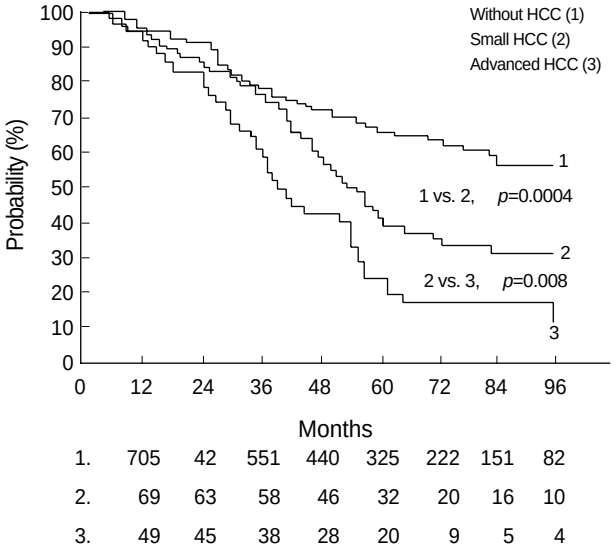

Fig. 4. Survival probability (Kaplan-Meier plot) of patients with or without hepatocellular carcinoma (HCC) during follow-up. The patients who developed HCC were divided into two subgroups according to the tumor status when diagnosed: small or advanced HCC. The numbers at the bottom of the figure are the numbers of patients at risk.

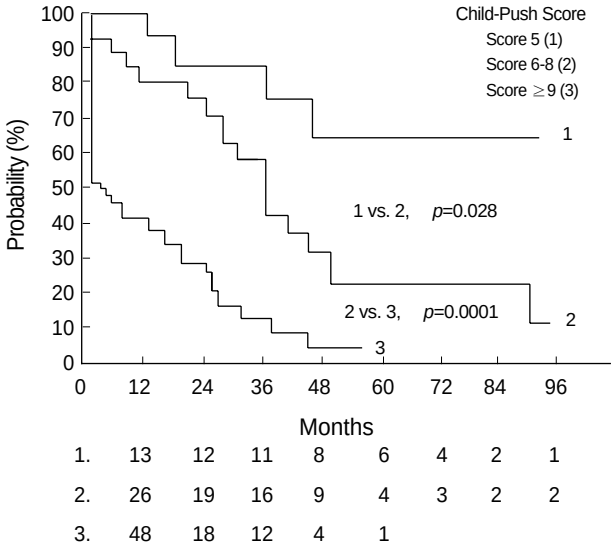

Fig. 5. Survival probability (Kaplan-Meier plot) after developing a first variceal hemorrhage according to the Child-Turcotte-Pugh score at the time of bleeding. The numbers at the bottom of the figure are the numbers of patients at risk.

cases. The life expectancy following entry was longer in patients in whom HCC was detected at the stage of small HCC than in those with HCC detected at advanced stage, although both groups had shorter survival times than those who did not develop HCC (Table 4, Fig. 4).

Development of Upper Gastrointestinal Bleeding

During follow-up, 163 upper gastrointestinal (GI) bleeds developed in 136 patients. The origins of the bleeding were identified in 157 cases by endoscopy: esophago-gastric varices in 138 (87.9%), gastric ulcer in 13 (8.3%), hemorrhagic gastropathy in 2 (1.3%), duodenal ulcer in 2 (1.3%), esophageal ulcer in 1 (0.6%), and esophagitis in 1 (0.6%).

The patients who developed upper GI hemorrhages during follow-up had a lower survival rate than those without bleeding (Table 4). The overall mortality of variceal bleeding was 29% (40/138), and was almost the same in initial (25/87) and recurrent (15/51) episodes. By contrast, the mortality from non-variceal upper GI bleeding was 11% (2/19). The cumulative survival rate after the first variceal bleed was 71% at 6 weeks, 58% at 1 yr, and 20% at 5 yr, but there were significant differences ($p<0.0001$) depending on the severity of hepatic decompensation at the time of bleeding (Fig. 5). For example, the 6-week survival rate was 95% (37/39) in patients with Child-Turcotte-Pugh scores from 5 to 8, but 52% (25/48) in those with scores above 8. The cumulative incidence of recurrent variceal bleeding was 11% at 6 weeks, 25% at 1 yr, and 54% at 5 yr.

Development of Spontaneous Bacterial Peritonitis (SBP)

At least one episode of SBP occurred in 149 (30%) of the 502 patients with ascites during the investigation. The cumulative incidence of the first episode of SBP was 27% at 1 yr and 44% at 5 yr after developing ascites in 194 patients who experienced ascites for the first time during follow-up. At first presentation of SBP, most patients had advanced liver dysfunction, and their mean (±SD) Child-Turcotte-Pugh score was 10.5±2.3. As expected, the patients who developed SBP during follow-up had reduced survival from entry (Table 4). Twenty-seven (18%) of 146 patients died shortly after their first episode of SBP, while still in hospital. Of the 119 patients discharged alive, 58 (50%) developed recurrent SBP with a cumulative incidence of 44% at 1 yr and 68% at 5 yr. The survival rate after first SBP was 46% at 1 yr and 10% at 5 yr.

The Effectiveness of Surveillance Programs for Hepatocellular Carcinoma

We evaluated the effectiveness of our surveillance program for HCC, which involves regular ultrasonography and measurement of serum alpha-fetoprotein levels. Of 118 patients with HCC in this series, the most recent ultrasound examination just before the diagnosis of HCC was 6 months or less in 35 patients (group I), 7 to 12 months in 46 patients (group II), and more than 1 yr in 37 patients (group III).

The frequency of small HCC in groups I or II was higher than in group III (69% or 63 vs. 43%, $p<0.05$). However, life expectancy after entry was similar in all three groups, as

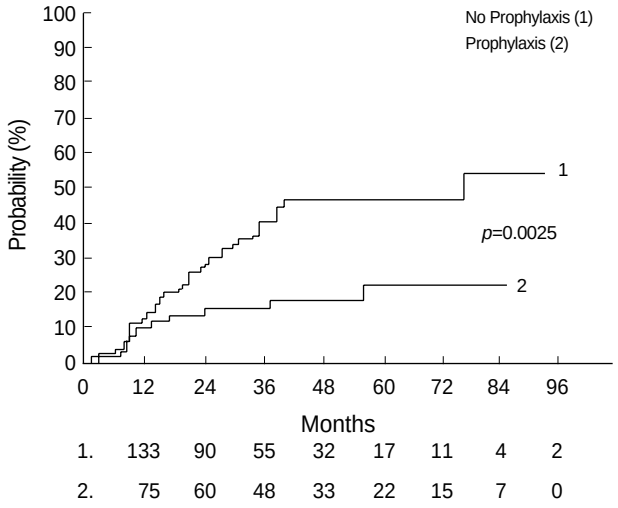

Fig. 6. Cumulative probability (Kaplan-Meier plot) of developing a first variceal hemorrhage in two subgroups of patients with large esophageal varices: those who did and did not receive endoscopic prophylaxis. The numbers at the bottom of the figure are the numbers of patients at risk.

indicated by the 5-yr survival rates, which were 30%, 33%, and 29% in groups I, II, and III, respectively. Although the prognostic factors at baseline were adjusted in the multivariate analysis, no significant benefit in survival was recognized.

The Benefit of Endoscopic Prophylaxis against First Variceal Bleed

We assessed the effect of endoscopic prophylaxis against first variceal bleeds for the patients who had large esophageal varices (Japanese classification F2 or F3) without coincident HCC or severe decompensated cirrhosis (Child-Turcotte-Pugh scores over 12). The effect of beta-blockers was not evaluated because there were too few cases and the schedule of medications was not consistent.

Throughout the study period, 441 patients were found to have large esophageal varices (Japanese classification F2 or F3). One hundred and eighty-seven of them, however, had previous or ongoing variceal bleedings at the time of diagnosis; 9 had coincident HCC; 8 presented the features of severe decompensation. Among the remaining 237 patients who met the above inclusion criteria, 75 underwent endoscopic prophylaxis (band-ligation in 50, sclerotherapy in 9, and a combination of the two methods in 16), 29 were given oral propranolol, and 133 were given no prophylaxis. At baseline, the endoscopy prophylaxis group had a higher prevalence of red color sign (67% vs. 44%, $p<0.01$), and had a slightly lower mean ($\pm$SD) value of Child-Turcotte-Pugh score (6.5 ± 1.7 vs. 7.1 ± 1.8, $p<0.05$) compared with the no-prophylaxis group.

The cumulative incidence of first variceal bleed after the diagnosis of large varices was significantly lower in the prophylaxis group than in the no-prophylaxis group, with 3-yr incidences of 18% and 42%, respectively (Fig. 6). This preventive effect still remained significant in multivariate analysis, which adjusted several potential risk factors of variceal hemorrhage at base line that had shown $p<0.1$ in univariate analysis, such as red color sign, serum bilirubin level, gender, aspartate aminotransferase, and gammaglutamyl transpeptidase (Table 6).

Table 6. Risk factors for first variceal hemorrhage in patients with large esophageal varices using the Cox regression model (n= 208)

Variables	Hazard ratio (95% confidence interval)	*p* value
Bilirubin (mg/dL)	1.371 (1.090-1.725)	0.007
Red color sign (present/absent)	4.683 (2.516-8.718)	0.000
Endoscopic prophylaxis (present/absent)	0.286 (0.151-0.542)	0.000

However, there was no significant difference in the cumulative survival rates between the prophylaxis and no-prophylaxis groups, with 3-yr survival rates of 68% and 58%, respectively. Furthermore, no survival benefit was observed in the univariate analysis considering the Child-Turcotte-Pugh scores at baseline or in the multivariate analysis adjusting the prognostic factors at baseline.

DISCUSSION

In the present study, the main causes of liver cirrhosis were HBV, HCV, and alcohol, which accounted for the origin of cirrhosis in 60%, 13%, and 26% of the whole patients, respectively. The predominant role of HBV in viral cirrhosis reflects the high prevalence of chronic HBV infection in this country (2).

Depending on the etiologies of cirrhosis some clinical features were distinctive. The patients with alcoholic cirrhosis were predominantly male (95%), presumably this being related with the cultural background in alcohol ingestion, and most of them (75%) showed decompensation features at first presentation, suggesting chronic alcoholics usually keep drinking without insight until decompensated. HBV-related cirrhosis was diagnosed in mid-forties on average, relatively earlier than in other types of cirrhosis. This presumably may be associated with the vertical transmission of HBV, the main route of HBV infection in this country, which elicits chronic hepatitis from earlier ages. In contrast, HCV-related cirrhosis was detected at the mean age of 60, and was compensated in 60% of cases. Compared with alcoholic cirrhosis, viral cirrhosis was complicated by HCC approximately 5-fold more in frequency. As a result, HCC was responsible for about one third of total deaths in viral cirrhosis, whereas only 8% of all deaths in alcoholic cirrhosis. Instead, variceal bleeding was a more dominant cause of death in alcoholic cirrhosis.

As expected from the causes of death in the cirrhosis patients,

the clinical variables representing the severity of hepatic failure or portal hypertension, including the five variables used in the Child-Turcotte-Pugh system, esophageal varices, and thrombocytopenia, are reported as the key prognostic indicators of liver cirrhosis (4, 5, 11, 17, 18), and their importance was reconfirmed in the present study. Also, the variables such as age, gender, and serum alkaline phosphatase level had prognostic significance, as previously reported (4, 5, 17, 18). Of interest, these three factors had a significant correlation with the risk of developing HCC as well.

It is well known that efficient management of etiologic factors is closely correlated with survival in cirrhosis patients (3, 4, 17-20). In this study, we were able to confirm that the prognosis was far better in the patients who stopped drinking during follow-up than in those who continued to drink, and the patients with inactive HBV replication had a higher survival rate than those with consistent viral replication. Furthermore, we demonstrated that these benefits were seen only in patients with compensated or mildly decompensated cirrhosis in the subgroup analysis. This emphasizes that the control of etiologic factors must be attempted at an earliest stage of cirrhosis, if possible, to improve the rate of survival substantially. In addition, the better prognosis of alcoholic cirrhosis in our study compared with HBV-related cirrhosis might be explained by the differing intractability of etiologic factors, i.e., 28% of the patients with alcoholic cirrhosis succeeded in abstaining from alcohol after entry, while only 8% of the patients with HBV-related cirrhosis showed HBeAg seroconversion during follow-up. Indeed, we could not find any significant difference in survival between alcoholic and HBV-related cirrhosis when the patients who stopped drinking were excluded.

In this study, 44% of the patients with compensated cirrhosis developed decompensation signs within 5 yr after entry, and the 5-yr survival rate after decompensation was 25%. These data are similar to the figures reported in the 1980s (3-5); therefore, it is difficult to say that there has been a substantial improvement in the long-term survival of cirrhosis patients during the last 20 yr. Although the 5-yr survival rate in patients who had been decompensated at entry appears higher in the present series as compared with previous results (40% vs. 16-21%), it can be noted that our series included a relatively lower percentage of patients with ascites and no patients with HCC at entry.

However, the short-term prognosis of some major complications appears to have remarkably improved. For example, in this study, which took vigorous endoscopic measures to prevent variceal rebleeding, the rebleeding rate after a first variceal hemorrhage was 11% at 6 weeks and 25% at 1 yr. These values are much lower than the figures of 20-50% at 6 weeks and 47-84% at 1 yr in untreated cases in earlier studies (6). Correspondingly, the 6-week mortality after variceal hemorrhage was decreased to 29% (22% when terminal HCC patients were excluded) in our study, and to 5% in patients with Child-Turcotte-Pugh scores below 9, as compared to 33-71% in prior studies (6, 21). Similarly, the hospital mortality of SBP in this study was reduced to 18% compared with 40-50% in previous reports (22-24).

After considering tumor stage and functional hepatic reserve, a mere 6% of the patients with HCC underwent partial hepatectomy in this study, and another 62% were treated non-surgically. It is now evident that the development of non-surgical modalities has enlarged the range of therapeutic indications for HCC patients, especially for cases that are inoperable due to impaired liver function or multiple lesions. Particularly, patients with small HCC had more opportunities for treatment than those with advanced HCC (80% vs. 55%). In concert with these findings, it is noteworthy that the patients with small HCC had a significantly longer life expectancy from entry, as well as after the diagnosis of HCC, than those with advanced HCC. This indicates that early detection of HCC can lead to a genuine survival benefit in cirrhosis patients, and provides good grounds for regular surveillance for the early detection of HCC. As far as we know, this study will be the first to demonstrate that early detection of HCC can improve the survival of cirrhosis patients beyond the lead-time bias (25). Unfortunately, however, biannual ultrasonography in this study failed to achieve a significant improvement in survival, although it increased the detection rate of small HCC in the screened group by more than 20%. This is most likely because about 30% of cases of small HCC were still overlooked on ultrasound examination, probably due to limitations of sonography and the inexpertness of the examiners. Therefore, in order to improve the detection rate of small HCC in cirrhosis patients, it is necessary to introduce complementary imaging modalities with higher resolution and to develop highly sensitive tumor markers.

In this study, endoscopic prophylaxis for a first variceal bleed significantly reduced the bleeding rate, in spite of the higher incidence of the RC sign in the prophylaxis group at baseline. However, we did not find a significant improvement in survival, although there were fewer signs of decompensation in the prophylaxis group at baseline. This concurs with previous studies (26-29). Of course, the possibility of type II error still exists in our study, since the prophylaxis group had a higher survival rate than the non-prophylaxis group by 10% at 3 yr, although this was not significant. Nonetheless, the expected survival benefit of endoscopic prophylaxis does not seem very high, even if it has a statistical significance. This low potential benefit might be ascribed to the reduced bleeding-related mortality that has resulted from the progress in the management of variceal hemorrhage, and the development of means to prevent rebleeding, especially in patients with an otherwise good prognosis. Therefore, for endoscopic prophylaxis against a first variceal hemorrhage, a more discreet approach might be required that considers cost-effectiveness, and a stricter selection of target patients is desirable, since the 3-yr bleeding rate was only 42% in patients with large varices in this study.

In summary, this study provided a wide range of updated prognostic information that will be helpful for the appropriate management of cirrhosis patients. We found that 1) effective control of causative agents increased life expectancy in patients with compensated or mildly decompensated cirrhosis; 2) early detection of HCC led to a genuine survival benefit; 3) the short-term prognosis of some major complications, such as variceal hemorrhage and SBP, has considerably improved over the last two decades, while there was no remarkable improvement in the long-term survival of cirrhosis patients; and 4) biannual ultrasonography increased the detection rate of small HCC and endoscopic prophylaxis decreased the incidence of first variceal hemorrhage without improving survival. These results suggest that more efficient management of etiologic factors and complications is necessary to improve the prognosis of compensated or mildly decompensated cirrhosis. In severely decompensated cirrhosis, liver transplantation might be the only therapeutic option that alters the outcome.

REFERENCES

1. Korean National Statistical Office. *Annual Report on the Causes of Death Statistics. Seoul 1999: 25-7 (in Korean).*
2. Lee DH, Kim JH, Nam JJ, Kim HR, Shin HR. *Epidemiological findings of hepatitis B infection based on 1998 National Health and Nutrition Survey in Korea. J Korean Med Sci 2002; 17: 457-62.*
3. Saunders JB, Walters JRF, Davies AP, Paton A. *A 20-year prospective study of cirrhosis. Br Med J 1981; 282: 263-6.*
4. 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.*
5. Ginés P, Quintero E, Arroyo V, Terés J, Bruguera M, Rimola A, Caballería J, Rodés J, Rozman C. *Compensated cirrhosis: natural history and prognostic factors. Hepatology 1987; 7: 122-8.*
6. D'Amico G, Pagliaro L, Bosch J. *The treatment of portal hypertension: a meta-analytic review. Hepatology 1995; 22: 332-54.*
7. Farinati F, Gianni S, Marin G, Fagiuoli S, Rinaldi M, Naccarato R. *Does the choice of treatment influence survival of patients with small hepatocellular carcinoma in compensated cirrhosis? Eur J Gastroenterol Hepatol 2001; 13: 1217-24.*
8. Scheuer PJ. *Liver biopsy in the diagnosis of cirrhosis. Gut 1970; 11: 275-8.*
9. Runyon BA. *Spontaneous bacterial peritonitis: An explosion of information. Hepatology 1988; 8: 171-5.*
10. Sherlock S, Dooley J. *Disease of the liver and biliary system, 11th ed. Oxford: Blackwell Science, 2002: 93-109.*
11. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. *Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-9.*
12. Beppu K, Inokuchi K, Koyanagi N, Nakayama S, Sakata H, Kitano S, Kobayashi M. *Prediction of variceal hemorrhage by esophageal endoscopy. Gastrointest Endosc 1981; 27: 213-8.*
13. de Franchis R. *Updating consensus in portal hypertension: report of Baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. J Hepatol 2000; 33: 846-52.*
14. Llovet JM, Bru C, Bruix J. *Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19: 329-38.*
15. Kaplan GL, Meier P. *Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958; 53: 457-81.*
16. Cox DR. *Regression models and life tables. J R Stat Soc B 1972; 34: 187-220.*
17. Christensen E. *Prognostic models in chronic liver disease: validity, usefulness and future role. J Hepatol 1997; 26: 1414-24.*
18. Christensen E, Schlichting P, Andersen PK, Fauerholdt L, Schou G, Pedersen BV, Juhl E, Poulsen H, Tygstrup, N Copenhagen study group for liver disease. *Updating prognosis and therapeutic effect evaluation in cirrhosis with Cox's multiple regression model for time-dependent variables. Scand J Gastroenterol 1986; 21: 163-74.*
19. de Jongh FE, Janssen HL, de Man RA, Hop WC, Schalm SW, van Blankenstein M. *Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. Gastroenterology 1992; 103: 1630-5.*
20. Powell WJ Jr, Klatskin G. *Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease. Am J Med 1968; 44: 406-20.*
21. Burroughs AK, D'heygere F, McIntyre N. *Pitfalls in studies of prophylactic therapy for variceal bleeding in cirrhotics. Hepatology 1986; 6: 1407-13.*
22. Hoefs JC, Canawati HN, Sapico FL, Hopkins RR, Weiner J, Montgomerie JZ. *Spontaneous bacterial peritonitis. Hepatology 1982; 2: 399-407.*
23. Runyon BA, Hoefs JC. *Culture-negative neutrocytic ascites: a variant of spontaneous bacterial peritonitis. Hepatology 1984; 4: 1209-11.*
24. Tito L, Rimola A, Ginés P, Llach J, Arryo V, Rodés J. *Recurrence of spontaneous bacterial peritonitis in cirrhosis: Frequency and predictive factors. Hepatology 1988; 8: 27-31.*
25. Sherman M. *Screening for hepatocellular carcinoma. Baillière's Clinical Gastroenterology 1999; 13: 623-35.*
26. Piai G, Cipolletta L, Claar M, Marone G, Bianco MA, Forte G, Iodice G, Mattera D, Minieri M, Roccop P, *et al. Prophylactic sclerotherapy of high risk esophageal varices: Results of a multicentric prospective controlled trial. Hepatology 1988; 8: 1495-500.*
27. Kobe E, Zipprich B, Schentke KU, Nilius R. *Prophylactic endoscopic sclerotherapy of esophageal varices. A prospective randomized trial. Endoscopy 1990; 22: 245-8.*
28. Sarin SK, Guptan RK, Jain AK, Sundaram KR. *A randomized controlled trial of endoscopic variceal band ligation for primary prophylaxis of variceal bleeding. Eur J Gastroenterol Hepatol 1996; 8: 337-42.*
29. Lo GH, Lai KH, Cheng JS, Lin CK, Hsu PI, Chiang HT. *Prophylactic banding ligation of high-risk esophageal varices in patients with cirrhosis: a prospective, randomized trial. J Hepatol 1999; 31: 451-6.*