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Clinical Studies

Clinical characteristics and outcome of patients with cirrhosis and refractory ascites

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Abstract: *Background:* In patients with cirrhosis, refractory ascites is associated with a poor prognosis and is an indication for liver transplantation. However, factors that determine prognosis remain unclear. *Aims:* To investigate the predictive factors of prognosis in patients with refractory ascites. *Methods:* Seventy-five patients with refractory ascites were followed-up for 18 ± 13 months (mean ± SD) and survival was analyzed. *Results:* The 1-year probability of survival was 52%. Univariate analyses showed that older patients, hepatocellular carcinoma and diabetes, all assessed at entry, were associated with significantly increased risk ratios of death. The risk ratio of death was significantly lower in abstinent alcoholics than in patients with nonalcoholic cirrhosis. The risk ratio of death did not significantly differ between patients with nonalcoholic cirrhosis and nonabstinent alcoholics. Child–Pugh score at entry had no prognostic value. Multivariate analysis showed that older age, hepatocellular carcinoma, diabetes and abstinence were independent prognostic factors. *Conclusions:* In patients with cirrhosis and refractory ascites, older age, hepatocellular carcinoma and diabetes, but not Child–Pugh score at entry, were independent predictive factors of poor survival while abstinence was an independent predictive factor of good survival. These findings should be taken into account when deciding on liver transplantation in patients with refractory ascites.

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In patients with cirrhosis and ascites, diuretic therapy (associated with a restricted sodium intake) is used to mobilize ascites (1, 2) or prevent its reaccumulation following therapeutic (i.e., total) paracentesis (2, 3). However, ascites may be refractory to diuretics because these drugs induce complications (i.e., hyponatremia or renal failure) or cannot mobilize ascites (or prevent its reaccumulation after paracentesis) (4). Thus, there are two types of refractory ascites: 'diuretic-intractable ascites' and 'diuretic-resistant ascites', respectively (4). Refractory ascites is associated with poor survival (5). Different treatments have been proposed in patients with refractory ascites: paracentesis and plasma volume expansion (2, 3), peritoneovenous shunt (6, 7) or transjugular intrahepatic portosystemic shunt (TIPS) (8–11). These procedures, however, have not been shown to improve survival, and thus liver transplantation has been recommended for patients with refractory ascites (1, 2).

The mechanisms that cause refractory ascites have not been completely clarified (4). In particular, the role of liver failure is unclear. In addition, the outcome of ascites in relation to the course of underlying chronic liver disease, and the prognostic factors have not been determined. These issues are of major importance when deciding to perform liver transplantation or alternative therapy. Thus, the aim of the present study was to investigate the clinical characteristics, outcome and predictive prognostic factors in a large series of patients with refractory ascites.

Patients and methods

Patients

All patients admitted to our Liver Unit for chronic refractory ascites from January 1 to

Abbreviations: SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.

December 31, 1997 were studied. Included patients met the following criteria: older than 18 years with confirmed cirrhosis based on liver-biopsy findings or typical clinical signs and refractory ascites. Our criteria of refractory ascites were a modification of those of the International Ascites Club (4). Patients were considered having refractory ascites when they had either diuretic-resistant ascites or diuretic-intractable ascites. Diuretic-resistant ascites was ascites that cannot be mobilized or whose early recurrence cannot be prevented because of a lack of response to dietary sodium restriction and intensive diuretic therapy. Diuretic-intractable ascites was ascites that cannot be mobilized or whose early recurrence cannot be prevented because of (i) development of diuretic-induced metabolic disturbances that preclude continuing dietary sodium restriction and intensive diuretic therapy, or (ii) spontaneous occurrence of metabolic disturbances that preclude beginning dietary sodium restriction and intensive diuretic therapy. Metabolic disturbances were as follows: (a) hyponatremia was defined as a drop in serum sodium concentration by more than 10 mmol/l or a decrease in sodium concentration to a value below 125 mmol/l; (b) renal impairment was defined as an increase in serum creatinine concentration by more than 100% or an increase in creatinine concentration to a value above 176 μmol/l; and (c) hypokalemia was a decrease in serum potassium concentration to less than 3 mmol/l and hyperkalemia was an increase in potassium concentration to more than 6 mmol/l despite appropriate measures to normalize potassium levels.

The following data were obtained from the patients file: demography, cause of cirrhosis, alcohol consumption during follow-up, outcome (transplantation or death), clinical and laboratory data at entry and at follow-up year 1 and 2, ascites status at the time of death, liver transplantation, or last follow-up visit in patients who survived and did not receive liver transplants. Associated conditions at entry were recorded: any associated disease of abdominal organs; abdominal surgery immediately preceding the development of refractory ascites; hepatocellular carcinoma diagnosed on the basis of typical histological features or because of one or several hypervascular liver nodules with serum α-fetoprotein levels above 500 ng/ml; portal vein thrombosis documented by Doppler-ultrasound, computed tomography, magnetic resonance imaging, or abdominal angiography; overt diabetes, i.e., diabetes requiring treatment with oral agents or insulin; and any significant chronic condition requiring treatment and follow-up. At each visit, information on alcohol consumption was systematically sought and recorded by the attending physician, using an informal interview with the patient and the family. Excessive alcohol intake was defined as alcohol consumption >3 U a day for males and >2 U a day for females (12).

All data used in the present study (including definitions of refractory ascites and data retrieved from patients file) were prospective, i.e., they had been defined before the study and were routinely collected when the study begun.

Statistical analysis

Date of entry into the study was the date at which the criteria for refractory ascites were first fulfilled. One-way ANOVA, unpaired Student *t*-tests and Fisher exact test were used where appropriate. Survival was assessed according to the Kaplan–Meier method and survival curves were compared using the log-rank test. Univariate and multivariate Cox models were used to assess the prognostic value of the following variables: age, sex, cause of cirrhosis (defined as nonalcoholic, alcoholic/abstinent, alcoholic/nonabstinent), acute alcoholic hepatitis, a composite of previous and present spontaneous bacterial peritonitis (SBP), a composite of previous or present portal hypertensive bleeding, Child–Pugh grade (B vs. C), protein concentration in ascitic fluid, serum creatinine, arterial hypertension, diabetes, and hepatocellular carcinoma. A complication was defined as recent when this complication was present at the beginning of the hospitalization during which the patient was included in the study. Variables with a P value lower than 0.10 in univariate analyses were included in a stepwise backward selection analysis. Patients who received transplants were censored on the date of transplantation. Results are shown as mean $\pm$ SD.

Results

Patient characteristics at entry

Seventy-five patients were enrolled (Table 1). The cause of cirrhosis was alcohol in 50 patients (66.6%), chronic hepatitis C virus infection in 12 (16.0%), a combination of alcohol and chronic viral hepatitis in 11 (14.7%), and chronic hepatitis B virus infection in 2 (2.7%). Ascites had been present for 16 ± 21 months (range: 2–98 months).

At entry, 93% of the patients had diuretic-intractable ascites and the remaining 7% had diuretic-resistant ascites (Fig. 1). The main reason for not treating ascites with diuretics was: decreased serum sodium in 46 patients; renal impairment in 16; both hyponatremia and renal

Table 1. Characteristics at enrollment of patients with cirrhosis and refractory ascites

Age (year)	57 ± 9 (30–82)
Male	60 (80%)
Alcohol etiology	61 (81%)
Acute alcoholic hepatitis	12 (16%)
Hepatitis C infection	19 (25%)
Portal hypertensive bleeding	
Previous	18 (24%)
Recent*	10 (13%)
Previous or recent†	27 (36%)
Spontaneous bacterial peritonitis	
Previous	9 (12%)
Recent*	18 (24%)
Previous or recent‡	22 (29%)
Child–Pugh score	10.0 ± 0.6 (7–13)
Child–Pugh grade B	35 (47%)
Serum bilirubin (μmol/l)	45 ± 24 (10–100)
Serum albumin (g/l)	28 ± 5 (18–48)
Prothrombin time (% of control)	53 ± 16 (19–95)
Serum creatinine (μmol/l)	112 ± 57 (48–500)
Protein concentration in ascitic fluid (g/l)	15 ± 7 (4–41)
Arterial hypertension	16 (21%)
Diabetes	22 (29%)
Treated with insulin	15 (20%)
Treated with oral agents	7 (9%)
Hepatocellular carcinoma	13 (17%)
With portal vein obstruction	9 (12%)
Recent abdominal surgery	2 (3%)
Chylous ascites	2 (3%)
Portal vein thrombosis	2 (3%)
Heart disease	1 (1.5%)

Data are presented as mean ± SD (with range) or *n* (%). *A complication was defined as recent when this complication was present at the beginning of the hospitalization during which the patient was included in the study. †Patients who have had past and recent portal hypertensive bleeding were counted only once. ‡Patients who have had past and recent spontaneous bacterial peritonitis were counted only once.

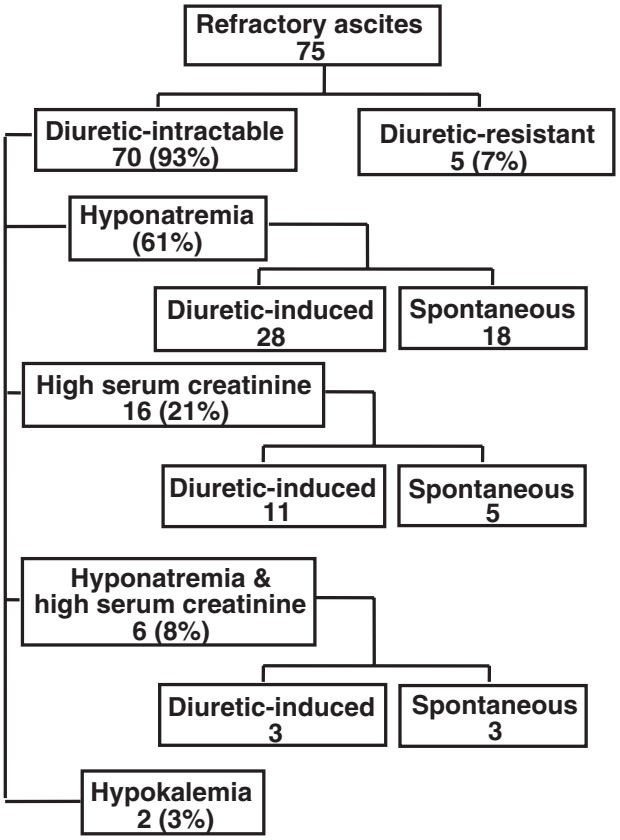

Fig. 1. Characteristics of refractory ascites in 75 patients with cirrhosis.

impairment in six and decreased serum potassium in two patients. Hyponatremia or renal impairment spontaneously occurred in 26 patients, while metabolic anomalies followed diuretic administration in 44 patients.

There were 35 (47%) Child–Pugh grade B patients. These patients differed from grade C patients by older age (60 ± 9 years vs. 53 ± 10 years, respectively; $P = 0.004$) and greater frequency of hepatocellular carcinoma (31% vs. 5%, respectively; $P = 0.003$) and diabetes (46% vs. 15%, respectively; $P = 0.004$).

Outcome

The mean follow-up period was 18 ± 13 months (range: 3–46 months). Two patients were lost to follow-up because they returned to their native country and were censored at the time they went abroad (i.e., at months 12 and 15, respectively). In surviving patients, mean follow-up was 30 ± 8 months (range: 6–46 months). Hepatorenal syndrome developed in 19 patients (25%). Cirrhotic hydrothorax developed in nine patients, six of whom were treated with regular thoracentesis. During follow-up, ascites was treated with paracentesis and plasma volume expansion on a regular basis.

Forty-two (56%) patients died. Death was caused by terminal liver failure. A precipitating factor was identified in 21 patients (gastrointestinal bleeding in eight; sepsis in 12; surgery in one). Thirty-three (44%) patients were alive at the end of follow-up. Eight (11%) underwent liver transplantation and 25 (33%) survived without transplantation. For the whole group, the probability of survival was 52% (95% confidence interval (CI), 40 to 63) at 1 year and 45% (95% CI, 33 to 49) at 2 years (Fig. 2).

In the 67 (89%) patients who did not receive liver transplants, the main reason for not performing liver transplantation was as follows: age over 60 years ($n = 18$); improvement with alcohol abstinence ($n = 14$); advanced hepatocellular carcinoma ($n = 10$); high risk of recurrence of initial disease ($n = 7$) including persistent hepatitis B virus replication and continued alcoholism; severe associated extrahepatic disease ($n = 7$); death on the waiting list ($n = 4$); unspecified reason ($n = 4$); patient's refusal ($n = 2$); or portal vein thrombosis ($n = 1$).

Among the 13 patients with hepatocellular carcinoma, 12 (92%) died within 2 years and none of the patients received liver transplant. Among the 22 patients with diabetes, 19 (86%) died within 2 years. None of the patients with diabetes underwent liver transplantation.

Among the 14 patients with nonalcoholic cirrhosis, 12 (86%) died within 2 years and two received liver transplants 24 and 30 months after inclusion, respectively. Among the 61 patients with alcoholic cirrhosis, 11 patients continued drinking (thereafter referred to as nonabstinent) and 50 became totally or partially abstinent (thereafter referred to as abstinent). All of the 11 nonabstinent patients died, and none received liver transplant. Among the abstinent patients, six (12%) received liver transplants (28 ± 9 months (range: 12–42 months) after inclusion), and 19 (38%) died.

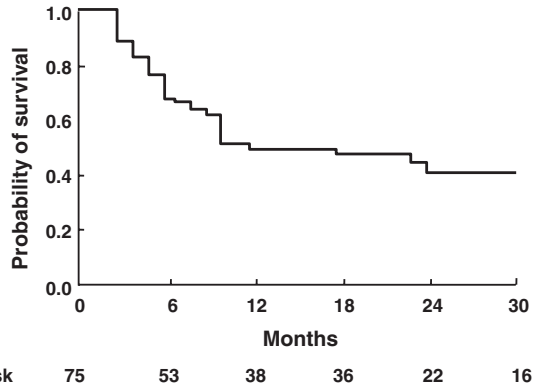

Fig. 2. Probability of survival in patients with cirrhosis and refractory ascites.

Twenty-five (50%) abstinent patients survived without transplantation. In these patients, Child–Pugh grade improved from C to B or A or from B to A within 2 years. Ascites disappeared or became easy-to-treat in 17 of these 25 patients. Ascites remained refractory in the eight other patients and was treated with a peritoneovenous shunt.

Univariate survival analysis

Nonsurvivors were significantly older than survivors (Table 2). Compared with patients 50 years old or younger, the risk ratio of death was significantly higher in patients older than 60 and in patients between 51 and 60 years (Table 3 and Fig. 3).

The frequency of hepatocellular carcinoma at enrollment was significantly higher in nonsurvivors than in survivors (Table 2). The risk ratio of death was significantly higher in patients with hepatocellular carcinoma than in those without (Table 3 and Fig. 4).

The frequency of diabetes at enrollment was significantly higher in nonsurvivors than in survivors (Table 2). The risk ratio of death was significantly higher in patients with diabetes than in those without (Table 3 and Fig. 5).

Table 2. Characteristics at enrollment of patients who survived and those who did not

Variable	Survivors ($n = 33$)	Nonsurvivors ($n = 42$)	*P* value
Age (year)	53 ± 10 (30–75)	60 ± 8 (46–82)	0.0005
Male	27 (82%)	33 (79%)	0.954
Alcoholic etiology	31 (94%)	30 (71%)	0.029
Acute alcoholic hepatitis	8 (33%)	4 (10%)	0.159
Portal hypertensive bleeding			
Previous	7 (21%)	11 (26%)	0.819
Recent*	3 (9%)	7 (17%)	0.538
Previous or recent†	10 (30%)	14 (33%)	0.547
Spontaneous bacterial peritonitis			
Previous	2 (6%)	7 (17%)	0.296
Recent*	7 (21%)	11 (26%)	0.819
Previous or recent‡	8 (24%)	14 (33%)	0.547
Child–Pugh score	10.4 ± 1.6	9.7 ± 1.8	0.097
Child–Pugh grade B	11 (33%)	24 (57%)	0.069
Serum bilirubin (μmol/l)	53 ± 25 (10–100)	40 ± 23 (13–96)	0.023
Serum albumin (g/l)	28 ± 4 (21–37)	28 ± 6 (18–48)	0.697
Prothrombin time (% of control)	51 ± 14 (33–90)	57 ± 17 (19–95)	0.126
Serum creatinine (μmol/l)	113 ± 40 (63–240)	112 ± 68 (48–500)	0.915
Protein concentration in ascitic fluid (g/l)	18 ± 8 (7–41)	13 ± 7 (4–30)	0.005
Arterial hypertension	4 (12%)	12 (29%)	0.149
Diabetes	3 (9%)	19 (45%)	0.002
Hepatocellular carcinoma	1 (3%)	12 (29%)	0.010

Data are presented as mean ± SD (with range) or *n* (%). *A complication was defined as recent when this complication was present at the beginning of the hospitalization during which the patient was included in the study. †Patients who have had past and recent portal hypertensive bleeding were counted only once. ‡Patients who have had past and recent spontaneous bacterial peritonitis were counted only once.

Table 3. Prognostic factors in patients with cirrhosis and refractory ascites

Variable	Univariate Cox analysis*		Multivariate Cox analysis		
	Risk ratio of death	*P* value	Risk ratio of death	95% CI	*P* value
Age (year)					
$\leq$ 50 ($n = 19$)	1		1		
$>$50 and $\leq$ 60 ($n = 30$)	2.9	0.02	4.4	1.6 to 12	0.004
>60 ($n = 26$)	3.0	0.02	2.1	0.8 to 5.6	0.12
Hepatocellular carcinoma					
Absent ($n = 62$)	1		1		
Present ($n = 13$)	3.2	0.0008	2.8	1.0 to 4.8	0.05
Diabetes					
Absent ($n = 53$)	1		1		
Present ($n = 22$)	2.6	0.002	2.2	1.1 to 4.5	0.03
Cause of cirrhosis					
Nonalcoholic ($n = 14$)	1		1		
Alcoholic/abstinent ($n = 50$)	0.3	0.0008	0.34	0.14 to 0.84	0.02
Alcoholic/nonabstinent ($n = 11$)	1.17	0.7	1.3	0.5 to 3.3	0.5
Ascitic fluid protein concentration (g/l)					
$\leq$ 15 ($n = 43$)	1		–		
$>$15 ($n = 32$)	0.5	0.03	–	–	–

*Only variables with a *P* value of less than 0.10 are shown.

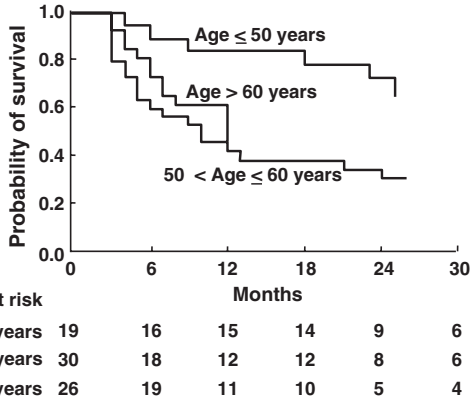

Fig. 3. Probability of survival in patients with cirrhosis and refractory ascites according to the age ($P = 0.043$ for the overall comparison, by the log-rank test).

The risk ratio of death was significantly lower in abstinent alcoholics than in nonabstinent alcoholics and in patients with nonalcoholic cirrhosis (Table 3 and Fig. 6). The proportion of patients free of hepatocellular carcinoma or diabetes (a composite criterion) and that of patients free of diabetes alone were significantly lower in abstinent alcoholics than in the other two groups (Table 4).

At entry, protein concentration in ascitic fluid was significantly lower in nonsurvivors than in survivors (Table 2). The risk ratio of death was two times lower in patients with an ascitic fluid concentration >15 g/l than in patients with a concentration below or equal to 15 g/l (Table 3).

There were no significant differences between nonsurvivors and survivors in terms of: sex, frequency of previous or recent portal hypertensive bleeding, frequency of previous or recent SBP, Child–Pugh grade at entry, frequency of acute alcoholic hepatitis at entry, serum creatinine at entry, and frequency of arterial hypertension at entry (Table 2).

Multivariate survival analysis

The five variables with a *P* value lower than 0.10 in univariate Cox analysis (i.e., age, hepatocellular carcinoma, diabetes, cause of cirrhosis, ascitic fluid protein concentration) were entered in the multivariate Cox model. Among these five variables, four had independent effects on death: older age; the presence of hepatocellular carcinoma; the presence of diabetes; and etiology of cirrhosis (Table 3).

Discussion

The relationship of refractory ascites with impaired liver function has been disputed (13). In this study, poor liver function was an isolated finding in Child–Pugh grade C patients. In these patients, unlike in grade B patients (see below), no associated disorders were found to be additional factors contributing to the difficulty in controlling ascites. Thus, our findings suggest that liver failure was probably sufficient for refractory ascites to develop in grade C patients. Interestingly, in two-thirds of the patients in whom liver function improved during follow-up, ascites became easy to treat with sodium restriction and diuretic therapy.

On the other hand, this study shows that almost 50% of the patients in this series had only slight impairment in liver function tests, and

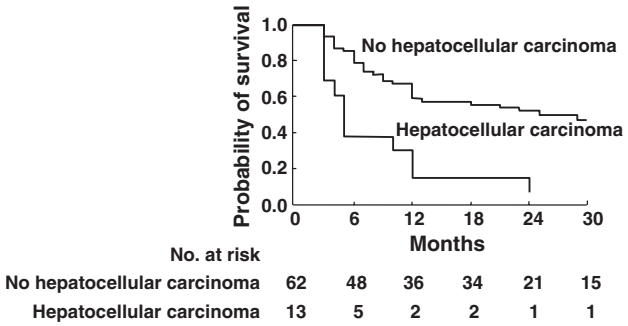

Fig. 4. Probability of survival in patients with cirrhosis and refractory ascites who did or did not have advanced hepatocellular carcinoma ($P = 0.0002$ for the overall comparison, by the log-rank test). The probability of survival at 1 and 2 years was 15% and 8%, respectively, in patients with hepatocellular carcinoma and 61% and 54%, respectively, in patients without.

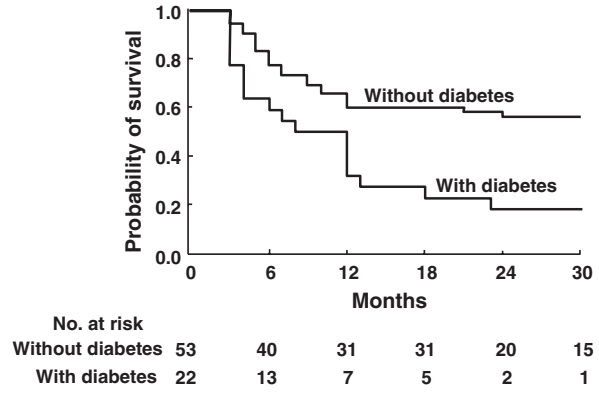

Fig. 5. Probability of survival in patients with cirrhosis and refractory ascites who did or did not have diabetes ($P = 0.0004$ for the overall comparison, by the log-rank test). The probability of survival at 1 and 2 years was 32% and 18%, respectively, in patients with diabetes and 62% and 58%, respectively, in patients without.

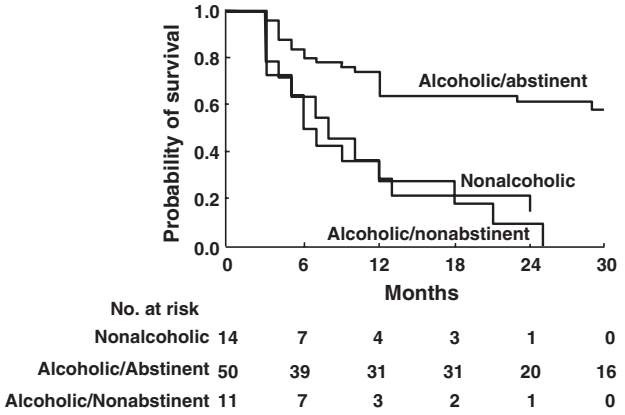

Fig. 6. Probability of survival in patients with cirrhosis and refractory ascites according to the cause of chronic liver disease ($P < 0.0001$ for the overall comparison, by the log-rank test). The probability of survival at 1 and 2 years was: 66% and 63%, in abstinent alcoholics; 27% and 9%, in nonabstinent alcoholics; 29% and 24%, in patients with nonalcoholic cirrhosis.

were ascribed to Child–Pugh grade B because of tense ascites alone. In other words, refractory ascites may occur even in the absence of poor liver function. Our 'grade B group' differed from our 'grade C group' by older age at inclusion, and a greater frequency of hepatocellular carcinoma and diabetes. Thus, these factors may be important for the development of refractory ascites in patients with preserved liver function.

In this study, the estimated probability of survival was only 45% at 2 years. These findings confirm that whatever the level of liver function, refractory ascites is a severe complication of cirrhosis and a marker of a poor prognosis (5, 14).

Multivariate analyses showed that four factors present at entry had prognostic significance. First, the risk of death was increased in older patients and in those with hepatocellular carcinoma. In this study, most patients had advanced hepatocellular carcinoma with portal vein invasion, which is known to be associated with a poor 2-year survival compared with patients with small tumors (15–17). Third, patients with diabetes had a shorter survival rate than those without. In the present study, the prevalence of diabetes was 29%, a figure that is identical to that in a previous study in hospitalized cirrhotic patients that showed that diabetes is an independent predictive factor of death from liver failure (18). Fourth, the risk of death was significantly decreased in abstinent alcoholics compared with patients with nonalcoholic cirrhosis. Interestingly, Child–Pugh score measured at enrollment was not a prognostic factor in this series of patients.

In the abstinent alcoholics in this study, the relatively high survival rate (60% at 2 years) may be due not only to the beneficial effect of abstinence but also to the high proportion (74%) of patients without any of the two important risk factors of death, i.e., hepatocellular carcinoma and diabetes. It should be emphasized that, in agreement with previous results (12, 19), a significant number of the abstinent alcoholics in this study survived without liver transplantation.

Table 4. Hepatocellular carcinoma and diabetes in patients with cirrhosis and refractory ascites according to the cause of chronic liver disease

Variable	Alcoholic/ abstinent ($n = 50$)	Alcoholic/ nonabstinent ($n = 11$)	Nonalcoholic cirrhosis ($n = 14$)	P value
Age (year)	55 ± 9	59 ± 9	58 ± 13	0.3417
Hepatocellular carcinoma	6 (12%)	2 (18%)	5 (36%)	0.1165
Diabetes	8 (16%)	6 (55%)	8 (57%)	0.0016
Presence of at least hepatocellular carcinoma or diabetes	13 (26%)	7 (64%)	10 (71%)	0.0002
Absence of hepatocellular carcinoma and diabetes	37 (74%)	4 (36%)	4 (29%)	

Data are presented as mean ± SD or n (%).

As expected (12), nonabstinent alcoholics had a very low survival rate (27% and 9% at 1 and 2 years). This may be due to continued drinking and to a high proportion of patients with diabetes. Patients with nonalcoholic cirrhosis also had a low probability of survival (29% and 24% at 1 and 2 years). Diabetes was very common in these patients and probably played a role in their poor outcome. It should be noted that in nonabstinent alcoholics and patients with nonalcoholic cirrhosis, the decrease in survival rate was marked during the first year of follow-up.

Although patients with cirrhosis and refractory ascites are candidates for liver transplantation (1, 2), most of patients in this study did not receive liver transplants. There are two obvious reasons for this. First, many abstinent alcoholics had progressive improvement in liver function. Thus, ascites became easy to control with medical treatment and these patients no longer fulfilled inclusion criteria for liver transplantation. These findings indicate that, in patients with alcoholic cirrhosis, refractory ascites may not be irreversible and consequently, should not be considered *per se* an indication for liver transplantation. Second, contraindications to liver transplantation were common: e.g., age over 60, lack of abstinence and presence of advanced hepatocellular carcinoma.

Severe limitations in liver graft availability make selection of recipients of utmost importance. Our findings suggest the following guidelines when making a decision of transplantation for refractory ascites. (a) Transplantation should always be considered in patients with refractory ascites because of their poor outcome. (b) Child–Pugh grade B patients should be carefully evaluated for an associated disorder that, besides explaining why ascites is difficult to control, might contraindicate liver transplantation. (c) To date, there is no medical treatment known to improve liver function and survival in patients with viral-induced cirrhosis with ascites (20). These patients should receive liver transplants as soon as possible because their chance of survival rapidly decreases during the first year of follow-up. (d) Liver transplantation may be postponed in abstaining alcoholics without hepatocellular carcinoma and diabetes.

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