

The impact of outpatient clinical care on the survival and hospitalisation rate in patients with alcoholic liver cirrhosis

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Background. In the study, we aimed to determine whether regular outpatient controls in patients with alcoholic liver cirrhosis have an impact on their survival and hospitalisation rates.

Patients and methods. We included patients with liver cirrhosis and regular outpatient controls as a prospective study group and patients with liver cirrhosis who were admitted to hospital only in cases of complications as a retrospective control group. The study was conducted between 2006 and 2011.

Results. We included 98 patients in the study group and 101 patients in the control group. There were more outpatient controls in the study group than in the control group (5.54 examinations vs. 2.27 examinations, $p = 0.000$). Patients in the study group had 25 fewer hospitalisations (10.2%; $p = 0.612$). The median survival rate was 4.6 years in the study group and 2.9 years in the control group ($p = 0.021$). Patients with Child A classification had an average survival of one year longer in the study group ($p = 0.035$). No significant difference was found for Child B patients. Patients with Child C classification had longer survival by 1.6 years in the study group ($p = 0.006$). Alcohol consumption was lower in the study group than in the control group ($p = 0.018$).

Conclusions. We confirmed that patients with regular outpatient controls had lower alcohol consumption, a lower hospitalisation rate and significantly prolonged survival time. We confirmed the necessity for the establishment of regular outpatient controls in patients with alcoholic liver cirrhosis.

Key words: liver cirrhosis; survival rate; regular outpatient controls; Child-Pugh classification

Introduction

Liver cirrhosis is characterised by the destruction of liver structures and the formation of regenerative nodules. It is a morphologically uniform response to chronic and recurring liver damage, and it represents the final, irreversible stage of various chronic liver diseases. Patients with liver cirrhosis are prone to many complications, have significantly shorter survival times and require frequent medical care and hospitalisations.¹ Excess alcohol consumption is the most frequent cause of cirrhosis in Europe.²

Liver failure is most commonly caused by chronic alcohol consumption (60–70%) and can manifest

as fatty liver disease, alcoholic hepatitis and alcoholic liver cirrhosis. Liver cirrhosis is responsible for 32 deaths per 100,000 population each year and is also the 8th leading cause of death in Slovenia.^{3,4,5} Liver cirrhosis is an important public health concern and a significant cause of morbidity and mortality worldwide.⁶

Not all patients who consume large amounts of alcohol will develop liver cirrhosis; 80% of them develop liver steatosis, 10% to 35% develop alcoholic hepatitis and 10% develop liver cirrhosis.⁷

Liver cirrhosis can be diagnosed in different ways. Patients may seek medical help because of symptoms; diagnosis may be made incidentally through a routine blood test or check-up, and

sometimes a diagnosis is made randomly during surgery, life-threatening conditions (such as bleeding varices, spontaneous bacterial peritonitis, portosystemic encephalopathy), or at autopsy.

Patients and methods

The study included a group of patients with alcoholic liver cirrhosis and regular outpatient controls (study group) and a group of patients with alcoholic liver cirrhosis who were admitted to hospital only in cases of complications (control group). We observed both groups between 2006 and 2011.

We included 99 patients in the study group and 101 patients in the control group. All consecutive patients with liver cirrhosis hospitalised in the Department of Gastroenterology of Murska Sobota General Hospital in 2006 were included in the study group. After discharge, patients were systematically monitored 3 to 4 times during the first year and then every 6 to 12 months for up to 5 years.

The National Medical Ethics Committee approved the survey protocol (85/01/09). All patients gave their informed consent prior to participation. Patient records were anonymized and de-identified prior to analysis. The study was conducted in accordance with the requirements of the Declaration of Helsinki and agreed with all the provisions set forth in the International Conference of Harmonization and Good Clinical Practice Guidelines.

The control group encompassed patients, who were admitted to hospital in 2006 and treated in other departments of the hospital. After discharge, they were not under regular outpatient control. Data for the control group were collected retrospectively from the hospital informatics programme Birpis.

Patients in both groups were divided into classes according to the Child-Pugh classification. Based on this classification, we attempted to determine the frequency of hospitalisation and patients' survival. The diagnosis of alcoholic liver cirrhosis was based on data of alcohol consumption, heteroanamnesis, with Alcohol Use Disorders Identification Test (AUDIT) and CAGE questionnaires, laboratory tests, abdominal ultrasound and gastroscopy. Liver biopsy was not performed. We excluded the following other causes of liver cirrhosis: autoimmune hepatitis, primary biliary cholangitis, metabolic hepatitis (α -1-antitrypsin deficiency, hemochromatosis, Wilson's disease) and viral hepatitis infection.

Variables monitored in both patient groups were as follows: alcohol consumption, degree of hepatic failure, comorbidities, laboratory findings, pharmacological treatment, number of hospitalisations, survival according to the Child-Pugh classification and estimated median age at death according to the Child-Pugh classification.

Patients in the study group were educated about the importance of the abandonment of drinking alcohol, diet and adjusting diuretic therapy (monitoring of liquid input, diuresis and weight). We offered all of them alcoholism treatment. We asked family members to help them in the recovery process. We expected better cooperation, less alcohol consumption and better compliance in taking drugs in the study group. The goal of regular outpatient examinations was the timely prevention of complications of liver cirrhosis and the proper treatment of patients. Patients were educated, therapy was customised to each patient and additional diagnostic tests were performed if they were needed.

Statistical analysis

Numerical variables were presented as average values \pm standard deviations (SDs). Categorical variables were presented as absolute numbers and percentages. Survival of patients was monitored until December 31, 2011.

We used chi-square statistics to assess the relationship between variables and the t-test to test the hypothesis of equality of arithmetic means of the variables in both groups. Levene's test was used to assess the equality of a variables calculated in both groups. Survival probability was calculated with the Kaplan-Meier method and compared with the Breslow test and log-rank test. The time variable was set as the time between the date of hospitalisation and the event (death) or until December 31, 2011. The results were presented as risk ratios (RRs) and corresponding 95% confidence intervals (CIs). Statistical analysis was performed using IBM SPSS Statistics 20.0. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristic

One hundred and ninety-nine patients were included in the study, including 98 patients in the study group and 101 patients in the control group. Most of the patients were male (80.6% in the study

group and 79.2% in the control group). The average age of participants in the study group and control group was 58.2 and 59.1 years, respectively (Table 1).

In the study group, 66.3% of patients were unemployed, 24.5% of patients were retired and only 9.2% of patients were employed.

All patients consumed alcohol. Males had higher rates than females for all measures of drinking in the past month: any alcohol use (57.5% *vs.* 45%), binge drinking (30.8% *vs.* 15.1%), and heavy alcohol use (10.5% *vs.* 3.3%), and males were twice as likely as females to have met the criteria for alcohol dependence or abuse in the past year (10.5% *vs.* 5.1%).

Degree of hepatic impairment: comparison of both groups

According to the Child-Pugh classification, there were significant differences between groups (chi-square = 7.975, *sp* = 1, *p* = 0.019). Patients in the study group were classified into a higher Child-Pugh classification class (Child C 44.9% of patients in study group *vs.* 26.7% of patients in control group; *p* = 0.000; Table 1).

We monitored the presence of oesophageal varices, portal gastropathy, ascites, peripheral oedema, gastrointestinal bleeding and other possible aetiologic factors for liver cirrhosis in both groups.

There were no differences in the degree of oesophageal varices between the groups.

More patients in the study group had portal gastropathy (32.7% *vs.* 22.8%; *p* = 0.106), ascites (62.2% *vs.* 54.0%; *p* = 0.339) and peripheral oedema (54.6% *vs.* 33.7%; *p* = 0.100).

Concomitant diseases and comparison in both groups

We compared the most common comorbidities, hepatitis and gastrointestinal bleeding in patients of both groups. Statistically significant differences between the groups were not found (Table 2). Most of the patients had diabetes, hypertension and renal failure. More patients were on insulin in the control group than in the study group (11.9% *vs.* 6.1%; *p* = 0.198).

We compared cardiovascular diseases (stroke, heart failure, arterial hypertension, atrial fibrillation), kidney diseases and diabetes in both groups (Table 3).

TABLE 1. Demographic characteristics of patients with liver cirrhosis in the study group and the control group

	Study group		Control group		Both groups		
	Number	%	Number	%	Number	%	
Gender	Male	79	80.6%	80	79.2%	159	79.9%
	Female	19	19.4%	21	20.8%	40	20.1%
	Total	98		101		199	
Age (mean)		58.2		59.1		58.6	
Standard deviation		10.8		11.3		11.1	

TABLE 2. Child-Pugh stage and complications of liver cirrhosis in both groups

	Study group		Control group		Both groups		
	Number	%	Number	%	Number	%	
Child-Pugh classification	A	33	33.7%	51	50.5%	84	42.2%
	B	21	21.4%	23	22.8%	44	22.1%
	C	44	44.9%	27	26.7%	71	35.7%
	Total	98		101		199	
Varices	Without	21	21.4%	18	17.8%	39	19.6%
	I. Grade	27	27.6%	14	13.9%	41	20.6%
	II. Grade	20	20.4%	17	16.8%	37	18.6%
	III. Grade	25	25.5%	22	21.8%	47	23.6%
	IV. Grade	2	2.0%	3	3.0%	5	2.5%
	Unknown	3	3.1%	27	26.7%	30	15.1%
	Total	98		101		199	
Portal gastropathy	Yes	63	64.3%	39	38.6%	102	51.3%
	No	32	32.7%	23	22.8%	55	27.6%
	Unknown	3	3.1%	39	38.6%	42	21.1%
	Total	98		101		199	
Ascites	Yes	37	37.8%	46	46.0%	83	41.9%
	No	61	62.2%	54	54.0%	115	58.1%
	Total	98		100		198	
Peripheral oedema	No	45	46.4%	67	66.3%	112	56.6%
	Yes	52	53.6%	34	33.7%	86	43.4%
	Total	97		101		198	

Hospitalisation and outpatient examination rate in both groups

We compared the number of hospitalisations and outpatient examinations in both groups over 5 years. The hospitalisation rate caused by complications of liver cirrhosis (worsening of liver cirrhosis, worsening of renal function, alcoholic hepatitis, infection, gastrointestinal bleeding, hepatic encephalopathy) were measured in both groups.

TABLE 3. Concomitant diseases in both groups

		Study group		Control group		Total		p
		Nb.	%	Nb.	%	Nb.	%	
Stroke	Yes	96	98.0%	99	98.0%	195	98.0%	0.84
	No	2	2.0%	2	2.0%	4	2.0%	
	Total	98		101		199		
Atrial fibrillation	No	86	87.8%	90	89.1%	176	88.4%	0.78
	Yes	12	12.2%	11	10.9%	23	11.6%	
	Total	98		101		199		
Arterial hypertension	No	70	71.4%	86	85.1%	156	78.4%	0.21
	Yes	28	28.6%	15	14.9%	43	21.6%	
	Total	98		101		199		
Heart failure	No	87	88.8%	88	87.1%	175	87.9%	0.17
	Yes	11	11.2%	13	12.9%	24	12.1%	
	Total	98		101		199		
Diabetes	No	77	78.6%	78	77.2%	155	77.9%	0.77
	Yes	21	21.4%	23	22.8%	44	22.1%	
	Total	98		101		199		
Renal failure	No	74	75.5%	73	72.3%	147	73.9%	0.34
	Yes	24	24.5%	28	27.7%	52	26.1%	
	Total	98		101		199		

TABLE 4. The number of hospitalizations and outpatient examinations in study and control groups over 5 years

	Study group	Control group	p value
Total number of outpatient examinations over 5 years	543	229	0.00
Average number of outpatient examinations in 5 years (per patient)	5.54	2.27	
Total number of hospitalizations over 5 years	184	209	0.612
Average number of hospitalizations in 5 years (per patient)	1.88	2.07	

More outpatient controls were used in the study group than in the control group (5.54 examinations *vs.* 2.27 examinations, $p = 0.000$).

There were 10.2% of patients in the study group and 12.9% of patients in the control group admitted to hospital due to gastrointestinal bleeding ($p = 0.083$).

Over 5 years there were fewer hospitalisations in the study group than in the control group (1.88 hospitalisations *vs.* 2.07). Patients in the study group had 25 fewer hospitalisations (10.2%, $p = 0.612$)

and 214 more outpatient examinations (23.7%, $p = 0.000$) than patients in the control group (Table 4).

Pharmacological treatment

The average number of medications that were taken was 2.7 ± 1.5 in the study group and 2.4 ± 1.4 in the control group. In the study group, furosemide was prescribed at a statistically higher percentage (59.2% *vs.* 41.6%, $p = 0.047$) and in higher doses than in the control group.

Spironolactone was prescribed at a higher percentage in the study group (55.1% *vs.* 46.5%; $p = 0.279$). More patients were treated with beta-blockers in the study group, but the difference was not statistically significant ($p = 0.279$). There were no other differences between uses of medications in both groups. We observed that laxatives were prescribed in less than one third of all patients in both groups.

Patient's survival in the study and control groups

Cumulative survival is a probability of survival. At the beginning of the hospitalisation (point 0), the probability of survival for all patients was the same (equals 1). Patients in the control group had decreased survival rates compared to the study group patients in the first year after hospitalisation. The median survival rate was 4.66 years in the study group and 2.9 years in the control group ($p = 0.021$).

We compared how many patients died at home and how many died in the hospital. In the study group, 39 (78%) patients died in the hospital and 49 (75.4%) patients in the control group died in the hospital ($p = 0.001$). All other patients died at home. We have analysed the causes of death of all 88 patients (in both groups) who died in the hospital. Data were collected from the hospital information system Birpis.

All patients died because of a complication or multiple complications of liver cirrhosis (hepatic encephalopathy, spontaneous bacterial peritonitis, other infections, gastrointestinal bleeding, hepatorenal syndrome, alcoholic hepatitis, heart failure). Patients who died in accidents were excluded from the study (Table 5).

We compared the distribution of patients' survival in both groups with the log-rank and Breslow tests. Survival probability at each time point during the observation interval was higher for the study group, irrespective of the number of cases that had been exposed to the risk ($p = 0.021$).

In general, the likelihood of survival depends on the degree of liver failure, which is defined by the Child-Pugh classification. Patients in the Child A stage had an average survival of one year longer ($p = 0.035$) in the study group compared to patients in the control group. Patients with Child B stage in the study group had 0.6 years of longer survival than patients in the control group, but the difference between groups was not statistically significant. Patients with Child C classification had longer survival by 1.6 years in the study group than patients in the control group ($p = 0.006$). Irrespective of the degree of severity of the disease (Child-Pugh classification), patients in the study group had a longer survival in the observed period (Table 6).

We monitored the average age at the time of death and found no difference between both groups. The average age at death of all patients independent of the Child-Pugh classification was 62.3 years.

Patients in both groups with Child A classification had on average 4.6 years longer survival than patients with Child C classification ($p = 0.06$). We tested the distribution of age at death in all Child-Pugh stages in both groups using the Breslow test. The difference between both groups was not statistically significant.

Alcohol consumption-comparison of both groups

We monitored the consumption of alcohol in both groups (Table 7). Data were collected with anamnesis, heteroanamnesis and from the hospital information system Birpis. We also monitored laboratory tests. The data were less reliable in patients who lived alone (39.8%). Consumption of alcohol was lower in the study group than in the control group. The difference between the groups was statistically significant ($p = 0.018$).

We collected data about alcohol addiction treatment at Ormož Psychiatric Hospital for all patients. In the study group seventeen patients were treated, and in the control group 15 patients were treated at the psychiatric hospital ($p = 0.158$).

Discussion

Studies have shown a relationship between diabetes and the occurrence of liver cirrhosis. Sixty percent of patients with liver cirrhosis have intolerance to glucose, and approximately 20% of patients have diabetes.^{8,9} In our study, 21.4% of patients in the study group and 22.8% of patients in the con-

TABLE 5. Comparison of all patients who died in the hospital because of a complication or multiple complications of liver cirrhosis (one patient may have more than one complication)

	Study group (n)	Control group (n)	p
Hepatic encephalopathy	12	13	0.320
Spontaneous bacterial peritonitis	5	5	
Hepatorenal syndrome	12	14	0.158
Bleeding	4	4	
Infections	14	13	0.320
Heart failure	3	8	0.025
Alcoholic hepatitis	4	6	0.158
Total number of patient deaths	39	49	

TABLE 6. Five-year survival of patients according to the Child-Pugh classification

CHILD	Group	All	Number of deaths	Survivors		p value
				Number	Percent	
A	Study	32	13	19	59.4%	0.035
	Control	51	29	22	43.1%	
	Both	83	42	41	49.4%	
B	Study	21	11	10	47.6%	0.083
	Control	23	14	9	39.1%	
	Both	44	25	19	43.2%	
C	Study	43	25	18	41.9%	0.006
	Control	27	22	5	18.5%	
	Both	70	47	23	32.9%	
Total		197	114	83	42.1%	

TABLE 7. Alcohol consumption and treatment in the Ormož Psychiatric Hospital for both groups

	Study group %	Control group %	p value
No alcohol consumption	56.12	35.64	0.000
Alcohol consumption	43.88	64.36	0.018
Ormož Psychiatry	14.85	15.30	0.158

trol group had diabetes. This result is comparable with the results of other studies. Diabetes most often occurs due to a decreased secretion of insulin.¹⁰

Arterial hypertension is rare in patients with hepatic impairment. Studies have shown that arterial hypertension is present in 3–7% of the patients. Blood pressure often reduces to normal upon the occurrence of liver cirrhosis.^{11,12,13,14,15} Arterial hy-

pertension was more common in both groups as indicated in the literature. Heart failure was present in 12.1% of patients.

Renal failure represents a frequent and serious complication of advanced liver cirrhosis.¹⁶ The prevalence of hepatorenal syndrome in patients affected by liver cirrhosis with ascites is equal to 18% after 1 year, increasing to 39% at 5 years. Hepatorenal syndrome occurs almost exclusively in patients with ascites.¹⁷

At the time of death, 12 patients (30.8%) in the study group and 14 patients (29.6%) in the control group had hepatorenal syndrome (NS). Hepatorenal syndrome was common and was a poor prognostic indicator in both groups.

We compared the number of hospitalisations and outpatient examinations of both groups. Patients in the study group had 25 fewer hospitalisations (10.2%) and 214 outpatient examinations more (237%) than patients in the control group. The difference in outpatient examinations was statistically significantly higher in the study group ($p = 0.000$). The difference in hospitalisation was lower in the study group (10.2%), but did not reach statistical significance ($p = 0.612$). Our study confirmed that patients who had undergone an increased number of outpatient examinations had fewer complications of liver cirrhosis.

We monitored pharmacological treatment and compared both groups. More medications were prescribed in the study group than in the control group. The diuretic of choice in liver cirrhosis is spironolactone. A combination treatment with furosemide might be necessary in patients who do not respond to spironolactone alone.¹⁸ If necessary, the spironolactone dose is increased stepwise up to 400 mg/d and the furosemide dose is increased up to 160 mg/d.^{19,20,21} In the study group, furosemide was prescribed at a statistically higher percentage and in higher doses than in the control group. Spironolactone was prescribed at a higher percentage in the study group, but the difference was not statistically significant. Furosemide and spironolactone were prescribed in combination in the majority of patients. Higher doses of diuretic therapy in the study group can be explained by the higher Child-Pugh classification class. All patients in the study group were hospitalised at the Department of Gastroenterology, where higher doses of diuretic therapy were prescribed.

At each time point during the observation interval, the probability of survival was higher in the study group than in the control group. Patients in the study group had longer expected survival;

however, they were classified into a higher Child-Pugh classification class and had more severe hepatic failure.

We achieved decreased alcohol consumption in the study group, which may be one reason for improvement in the survival rate.

Some trials have shown that lower alcohol consumption or abstinence may improve survival in patients with alcoholic liver disease. Heavy drinkers and abstainers have higher mortality rates than moderate drinkers.²² Thirty-four studies on men and women shows that higher doses of alcohol were associated with increased mortality.²³ While there is no question regarding the benefit of abstinence, motivating patients to follow this treatment regimen, monitoring their compliance and preventing relapse remain major obstacles to the treatment of alcoholic liver disease. Pharmacotherapy in combination with psychosocial interventions can aid patients in maintaining abstinence from alcohol.²³ The same conclusions were reached in our study. In the study group, patients had longer survival than patients in the control group. This was attributed to decreasing alcohol consumption, increased number of outpatient examinations, pharmacotherapy, better compliance and early detection of complications.

Survival data for patients with liver cirrhosis varied in different studies. When clinical signs of decompensation are present, prognosis is poor. Sixty percent of patients who stop drinking survive for 5 years. According to the literature, patients with liver cirrhosis survive 5 years in 15 to 42% of cases. Patients with portosystemic encephalopathy survive 1 year in 36% of cases.^{24,25,26,27,28}

Abstinence from alcohol leads to the resolution of alcoholic fatty liver disease (benign steatosis), and abstinence improves survival in alcoholic cirrhotic patients, even those with decompensated liver function. Furthermore, reducing alcohol consumption, but not completely stopping it, has been shown to improve survival in patients with alcoholic liver disease.²⁹

In the study group, consumption of alcohol was lower than in the control group, and the difference between the groups was statistically significant. Our study confirmed that abstinence remains the basis of the cure and improves overall survival. Survival of patients in our study is comparable to the rates reported by other published studies. Results for survival in the study group are comparable with the best results of published studies.^{30,31}

A prospective study on the treatment of patients with liver cirrhosis was published in 2013

in Clinical Gastroenterology and Hepatology by Wigg *et al.* The primary outcome was the number of days spent in a hospital bed for liver-related reasons. Sixty consecutive patients with cirrhosis and complications (ascites, variceal bleeding, portosystemic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, protein malnutrition, alcoholic hepatitis, sepsis and hepatocellular carcinoma) from chronic liver failure were assigned randomly to groups given intervention (n = 40) or usual care (n = 20), from 2009 to 2010.

Support was provided through the following: enhanced patient education during contact with the nurses concerning diet, medications, and need for investigation. Patients in the intervention group had a 30% higher rate of attendance at outpatient care (incidence rate ratio, 1.3; 95% confidence interval, 1.1–1.5; P = 0.004) and significant increase in quality of care. There was no difference in hospitalisations between both groups (18.8 vs. 11.0 the day per person/year). The authors found no difference in the number of admissions due to liver cirrhosis, the number of admissions due to other causes or the median length of hospitalisation and survival. The population in this study was composed predominantly of patients with decompensated Child–Pugh class C (48%) or B (33%) liver disease with an associated very poor predicted 2-year survival (25% and 60%, respectively). They concluded that larger trials with longer follow-up periods are needed.³²

We include more patients than Wigg *et al.* and implemented a longer follow-up period. The survival of patients in our study was longer. This could be partly attributed to more frequent systematic outpatient visits, reduced alcohol consumption and better medical treatment.

Weaknesses of our study

The diagnosis of alcoholic liver failure in the control group was made retrospectively on the basis of discharge diagnoses, data for history of alcohol consumption, laboratory tests, clinical status and abdominal ultrasound findings. Child-Pugh class was determined based on the collected data. The results of the control group were gathered from hospital discharges and the computer system Birpis.

In the control group, we used only discharge data from the hospital and did not follow any change of treatment in the course of research. Data about alcohol consumption may differ from actual consumption, because patients often conceal the truth

about alcohol consumption. There may be also a difference between the groups due to the random selection of data.

Conclusions

Our study confirmed that patients who were treated in outpatient clinics for liver cirrhosis were hospitalised less frequently and had a significantly longer survival. To date, there have been no other studies with five-year follow-up of such a large patient sample. Our data suggested that patients who were monitored for liver cirrhosis in the outpatient clinic were better treated than other patients. Such management significantly improves survival, reduces hospitalisation rates and decreases alcohol consumption. Our results speak for the need for regular outpatient controls in patients with alcohol liver cirrhosis.

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