

SURVIVAL IN PATIENTS WITH LIVER CIRRHOSIS: A PROSPECTIVE STUDY

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ABSTRACT

Introduction: The differences in the survival time of cirrhotic patients reported by different studies are probably caused by the influence of many contributing factors. The aim of the study was to evaluate the survival over a one-year period, to register the occurrence of acute decompensation (AD) and to determine the most frequent causes of death.

Material and methods: Out of 71 patients enrolled in the study, 63 completed the prospective one-year follow-up. During the follow-up, we evaluated the occurrence of AD, the causes of death, and we registered three-month, six-month and one-year survival regarding the AD status at presentation.

Results: Of the 63 patients, 24 (38.09%) died before the end of the study (14 patients before the end of three months, 6 before the end of six months and 4 patients before the end of one year). The overall survival was 38.09% and the mean survival time was 108 ± 98.53 days. The most prevalent cause of death was bleeding from esophageal varices (5 patients, 20.83%). AD patients had a significantly shorter survival than patients without AD (97 ± 90.54 vs. 229 ± 138.59) and 78.57% of them died during the follow-up. The estimated six-month and one-year median survival time were 272.8 [95% CI (238.4–307.2)] and 267.1 [95% CI (232.9–301.2)] days, respectively. The six-month and one-year survival were significantly shorter in AD patients ($p < 0.0001$).

Conclusion: The etiology, stage of liver disease and the presence of AD are important factors that influence on the survival in cirrhotic patients.

Keywords: liver cirrhosis, death, survival

INTRODUCTION

The problem of survival in patients with liver cirrhosis is a much explored research topic. There are many factors that influence on the survival in these patients, but it is considered that it mainly depends on the stage of the liver disease

and on the presence of some manifestations and complications of portal hypertension (PH). Also, the presence of acute decompensation (AD) and acute-on-chronic liver failure (ACLF) are two entities related to chronic liver disease that since

recently have been recognized as two conditions that make a significant prognostic impact on the survival in these patients.

The natural course of liver cirrhosis is characterized by two phases. The first, compensated phase, is followed by a rapidly progressing, decompensated phase characterized by the presence of complications of PH and/or liver dysfunction [1]. As the disease progresses, portal pressure increases and liver function declines, leading to the development of ascites, portal hypertensive gastrointestinal bleeding, encephalopathy, and jaundice [1]. The appearance of any complication of PH marks the transition from compensated to decompensated phase [1]. The appearance of ascites is the most common initial complication in cirrhotic patients [2] and is usually considered a sign of the decompensated phase [1].

By combining the data from two large studies that included 1,649 patients and analyzed the natural course of the disease [2,3], four clinical stages of cirrhosis were defined, each with a different clinical presentation and significantly different prognosis [1]. Stage 1 is characterized by the absence of esophageal varices and ascites (mortality rate about 1% per year); stage 2 is characterized by the presence of esophageal varices, but without bleeding and without ascites (mortality rate 3.4% per year); stage 3 is characterized by the presence of ascites with or without the presence of varicosities in patients who have never bled (mortality rate 20% per year) and stage 4 is characterized by gastrointestinal bleeding with or without the presence of ascites (mortality rate 57% per year). Stage 1 and 2 correspond to compensated and stage 3 and 4 to decompensated cirrhosis [1]. The transition from compensated to decompensated phase occurs at a rate of 5-7% per year [4, 5], and with the appearance of the first episode of decompensation, the life expectancy of patients is significantly shortened [1].

The aim of this study was to evaluate the survival in patients with liver cirrhosis over a one-year period, to register the occurrence of AD during follow-up and to determine the most frequent causes of death in these patients.

MATERIALS AND METHODS

The study enrolled 71 patients with liver cirrhosis that were treated at the University

Clinic for Gastroenterohepatology in Skopje. At presentation, we performed clinical examination, abdominal ultrasound, complete blood count, blood biochemistry and urinalysis, and afterwards we determined the stage of liver disease and the presence of AD. After enrolment, patients were prospectively followed for one year. During the follow up, we collected data regarding the occurrence of AD and the causes of death in deceased patients. We also registered data regarding three-month, six-month and one-year survival and we analyzed the difference in the survival regarding AD status at presentation.

The quantitative series were analyzed by using the measures of central tendency (average, median, minimum values, maximum values, interactive ranks) and dispersion measures (standard deviation, standard error). The survival was shown with Kaplan-Meier curves. The comparison of survival time between the two groups was tested with the Log Rank test. A level of $p < 0.05$ was considered to be statistically significant. All patients signed an informed consent for participation in the study. The study protocol was in line with the ethical principles of the Declaration of Helsinki and it was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje.

RESULTS

Out of 71 enrolled cirrhotic patients, 63 were followed until the end of the study, that is, until the occurrence of death. Of these, 24 (38.09%) patients died before the end of the study (14 patients before the end of three months, 6 patients before the end of six months and 4 patients before the end of one year). The mean survival of the entire study group was 108 ± 98.53 days. Moreover, the survival of patients with AD was significantly shorter than the survival of patients without AD (97 ± 90.54 vs. 229 ± 138.59). Of all 24 patients who died during the follow-up, only two patients did not have AD at presentation, while AD at presentation was registered in 10 of the 39 surviving patients. The overall survival in the study was 38.09%, and there was a significant difference in the average survival between the two groups (78.57 vs 5.71%). Moreover, 78.57% of AD patients died during the one-year follow-up. During the follow-up,

we registered the occurrence of AD in 38% of patients and the most common type of decompensation was the presence of variceal bleeding. Regarding the cause of death, the most prevalent was variceal bleeding (5 patients, 20.83%), followed by liver failure in 3 (12.5%), hepatorenal syndrome in 2 (8.33%), hepatic encephalopathy in 2 (8.33%), postoperative water and electrolyte imbalance in 2 (8.33%), infection in 1 (4.17%), and in 9 patients the cause of death remained unknown (37.5%). Onset of new episode of AD during the one-year follow up was registered in 26 patients (41.26 %). During the follow-up, we specifically analyzed three-month, six-month and one-year survival regarding the presence of AD at presentation.

1. Three-month survival

The analysis of the three-month survival in the whole sample of 63 (100%) patients showed that in 14 (22.2%) of them death occurred before the seventieth day of the follow-up and that 49 (77.8%) patients survived longer than three months (Figure 1). Regarding the analysis of the three-month survival according to AD status, of 35 (100%) patients in the group without AD no one died, while of 28 (100%) in the AD group 14 (50%) patients died (Figure 2). The analysis of the three-month survival in AD patients indicated that less than 50% survived 69 days and less than 75% survived 33 days from the beginning of the follow-up. Due to the fact that no deaths occurred, the test for significance of the difference between the two groups in terms of three-month survival was not performed (Table 1).

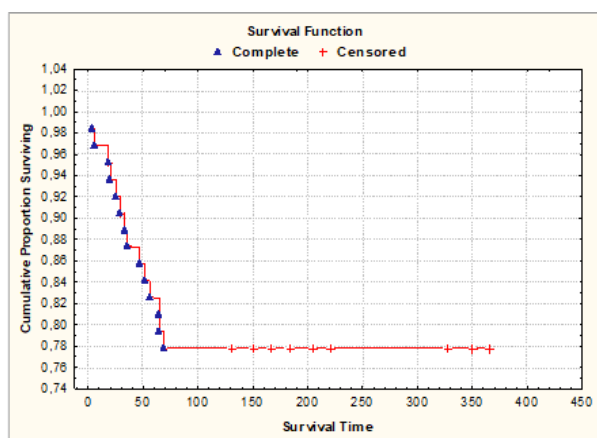


Figure 1. Kaplan-Maire curve for three-month survival in liver cirrhosis

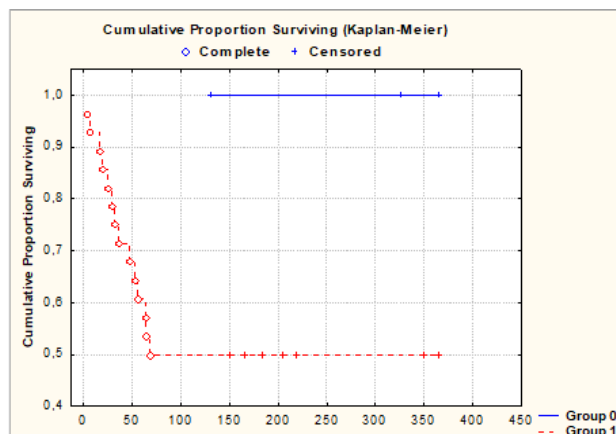


Figure 2. Kaplan-Meier curve of three-month survival according to AD status

Table 1. Descriptive analysis of the estimation of the average three-month survival time in AD patients

AD	50% Percentiles		75% Percentiles	
	Estimate (day)	Std. Error	Estimate (day)	Std. Error
Yes	69.000	.	33.000	12.602

2. Six-months survival

The analysis of the six-month survival in patients with liver cirrhosis showed that death occurred in 20 (31.75%) patients. Between the third and sixth month, death occurred in 5 (8.1%) patients and in all of them between 130–185 days of the follow-up. In 43 (68.2%) patients, the survival was longer than six months (Figure 3). According to AD status on admission, we observed that in the six-month period, of 35 (100%) patients in the group without AD, only 1 (2.9%) patient died, while of 28 (100%) AD patients, 19 (67.9%) patients died (Figure 4). The estimated six-month median survival time of patients in the whole sample was 272.8 [95% CI (238.4 – 307.2)] days. The estimated six-month overall survival according to AD status on admission was 358.3 [95% CI (345.4 – 371.2)] vs. 165.9 [95% CI (111.9 – 219.9)]. For $p < 0.05$, the comparison between the median six-month survival time between the two groups was significantly different (Log Rank - Mantel-Cox: Chi-Square = 33.209; $df=1$; $p < 0.0001$), i.e., the six-month survival was significantly longer in the non-AD group (Table 2).

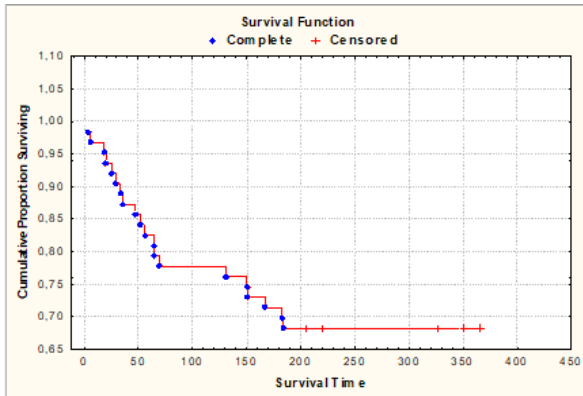


Figure 3. *Kaplan-Meier curve of six-month survival in liver cirrhosis*

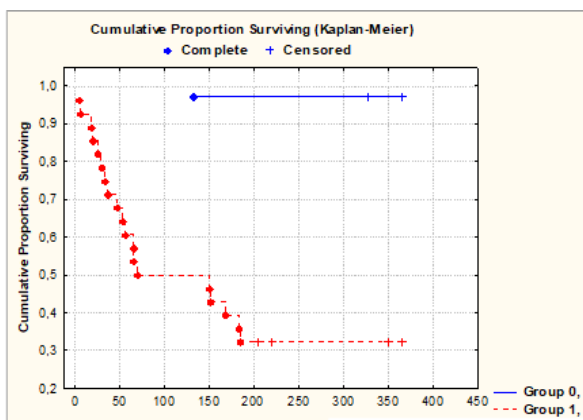


Figure 4. *Kaplan-Meier curve of six-month survival according to AD status*

3. One-year survival

The analysis of the one-year survival in patients with liver cirrhosis indicated that death occurred in 24 (38.1%) patients. Between the sixth and twelfth months, death occurred in 4 (6.4%) patients, all between 220–350 days of the follow-up. For 25% of patients, the survival was shorter than 145.2 days, and 39 (61.9%) patients survived longer than one year (Figure 5). According to AD status on admission, we observed that over the one-year period, 2 (5.7%) of 35 (100%) non-AD patients died, and 22 (78.6%) of 28 (100%) AD patients died (Figure 6). The estimated one-year

median survival time of the entire patient sample was 267.1 [95% CI (232.9 – 301.2)] days (Table 3). The one-year overall survival estimated according to AD status was 357.2 [95% CI (34.2 – 370.2)] vs. 154.5 [95% CI (104.4 – 204.5)]. For $p < 0.05$, the comparison between the median one-year survival time between the two groups was significantly different (Log Rank - Mantel-Cox: Chi-Square = 41.087; $df=1$; $p < 0.0001$), i.e., the one-year survival was significantly longer in the non-AD group.

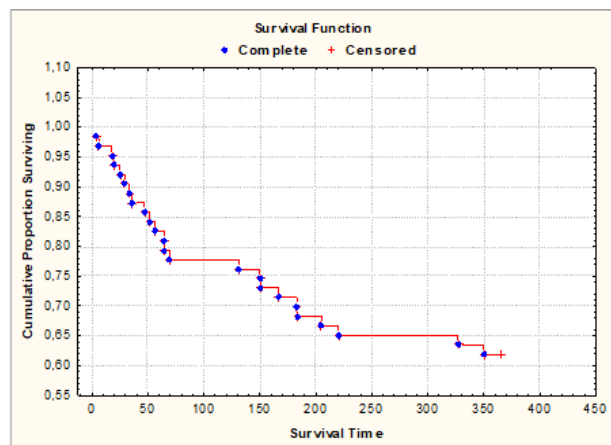


Figure 5. *Kaplan-Meier curve of one-year survival in liver cirrhosis*

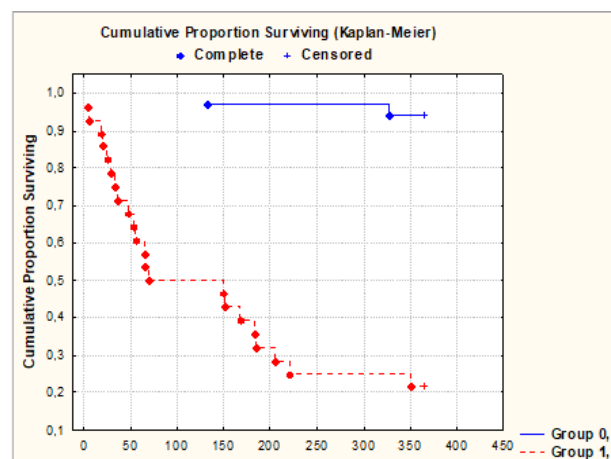


Figure 6. *Kaplan-Meier curve of one-year survival according to AD status*

Table 2. *Mean and median of the six-month survival*

AD	Mean				Median			
	(day) Estimate	Std. Error	95% Confidence Interval		(day) Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
No	358,314	6,590	345,399	371,230	69,000	50,269	,000	167,528

Table 3. Mean and median of the one-year survival

AD	Mean				Median			
	(day) Estimate	Std. Error	95% Confidence Interval		(day) Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
No	357,229	6,645	344,205	370,252	69,000	50,269	,000	167,528
Yes	154,464	25,521	104,443	204,486				
Total	267,111	17,419	232,970	301,252				

DISCUSSION

Our study provided data regarding the survival time of patients with liver cirrhosis and pointed out the most common forms of decompensation and causes of death in cirrhotic patients. Also, we analyzed the largest and most reliable related studies in order to compare our results with the relevant literature data.

Many studies have investigated the survival time, causes of death and predictors of survival and their relevance in different stages of liver cirrhosis. D'Amico et al. performed a systematic review of 118 studies that analyzed the natural course of liver cirrhosis. The review reported a wide range of survival between the analyzed studies. Also, there was a significant difference in the survival between patients with compensated and decompensated disease, i.e., the median survival was significantly shorter in patients with decompensated than in patients with compensated disease (2 vs. 12 years). They confirmed that the most significant predictors of mortality in compensated cirrhosis were those associated with PH, while variables related to renal failure or hepatocellular carcinoma were more significant predictors in decompensated patients [1]. Samonakis et al. evaluated the clinical outcomes in compensated and decompensated cirrhosis in a long-term study comprising 522 patients [5]. Patients were extensively followed for 9 years and 10 months until the occurrence of decompensation, death (or liver transplantation), or hepatocellular carcinoma. The survival in this study was similar to the survival in the systematic review by D'Amico et al. in the compensated and somewhat better in decompensated patients (115 vs. 55 months, respectively). Also, they confirmed that the etiology of the liver disease and the presence of decompensation

were the most significant predictors of survival [5]. According to another study, the mortality rate of patients on the waiting list for liver transplantation was 25.7%, with a median time spent on the waiting list until death of 265.5 days (26–1092 days) [6].

Alexopoulou et al. evaluated the survival of patients with liver cirrhosis and AD/ACLF. In cirrhotic patients with AD, the study registered 28-day mortality of 28.1%, three-month mortality of 49.05%, six-month mortality of 59.36% and one-year mortality of 64.83% [7]. In comparison to this study, the one-year mortality rate in AD patients in our study was relatively high (78.87% vs 64.83%), but we also registered a higher mortality rate for the other analyzed periods (50% for three months and 67% for six months), which was probably due to the fact that liver transplantation was not an available therapeutic option in these patients at that time. In contrast to the high mortality in the AD group, the one-year mortality in the group of patients without AD was very low (5.71%), which was expected given that most patients were in a stable stage of the disease. Hence, the presence of AD significantly affected the risk of death in patients with cirrhosis, especially in patients in an advanced stage of the disease.

Regarding the causes of death in patients with liver cirrhosis, different causes have been related to different stage or the presence of a specific complication of PH. In the majority of deceased patients in our study, the cause of death remained unknown (37.5%), which was a relatively high percentage compared to most studies (Samonakis et al. referred unknown cause of death in only 9%) [5]. Liver failure (including hepatorenal syndrome and sepsis) was the most common cause of death in both, the systematic review by D'amico et al. (followed by variceal bleeding and hepatocellu-

lar carcinoma) and in the study by Samonakis et al. (23.8%, followed by hepatorenal syndrome in 21.6%, sepsis in 10.8% and massive portal hypertensive bleeding in 6.5%). In contrast to these studies, the most common cause of death associated with liver disease in our study was bleeding from esophageal varices (5 patients, 20.83%). Among patients without AD at presentation, we registered the occurrence of AD during the follow-up in 38% of them, and the most common type of decompensation was again the presence of variceal bleeding. Regarding the onset of AD, Samonakis et al. recorded a median time to onset of AD of 65 months, and the most common type of decompensation was the presentation of ascites (73%, 256 patients), while 6% (22 patients) had more than one complication at the same time. Moreover, patients who decompensated with variceal bleeding had a better survival compared to other presentations of decompensation [5], which was not the case in our study where variceal bleeding was the most common cause of death. This discrepancy related to variceal bleeding outcomes could at least partially be explained by the differences in the applied principles of management of gastrointestinal hypertensive bleeding.

In conclusion, many factors influence on the survival in patients with liver cirrhosis. The etiology, the stage of liver disease, the complication of PH and also the presence of AD are important factors that make a significant contribution in the overall survival in cirrhotic patients.

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Conflict-of-interest statement

The author declares that there is no conflict of interest regarding the publication of this paper.

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Резиме

ПРЕЖИВУВАЊЕ КАЈ ПАЦИЕНТИ СО ЦРНОДРОБНА ЦИРОЗА: ПРОСПЕКТИВНА СТУДИЈА

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Вовед: Разликите во преживувањето на пациентите со црнодробна цироза, кои произлегуваат од различни студии, веројатно се должат на влијанието на многу различни фактори. Целта на студијата беше да се одреди преживувањето во период од една година, да се регистрира појавата на акутна декомпензација (АД) и да се утврдат најчестите причини за смрт кај пациентите со црнодробна цироза.

Материјал и методи: Од 71 пациент што беа вклучени во студијата, 63 го завршија проспективното едногодишно следење. За време на следењето ја регистриравме појавата на АД, причините за смрт и го регистриравме тримесечното, шестмесечното и едногодишното преживување во однос на АД статусот при презентацијата.

Резултати: Од 63 пациенти, смртен исход пред крајот на студијата беше регистриран кај 24 (38,09 %) од нив (кај 14 пациенти пред крајот на три, кај 6 пред крајот на шест и кај 4 пациенти пред крајот на една година). Вкупното преживување беше 38,09 %, а просечното време на преживување изнесуваше $108 \pm 98,53$ дена. Најзастапена причина за смрт беше крвање од езофагеални варикси (5 пациенти, 20,83 %). Пациентите со АД имаа значително пократко преживување во споредба со пациентите без АД ($97 \pm 90,54$ наспроти $229 \pm 138,59$) и смртен исход беше регистриран кај 78,57 % од нив. Проценетото шестмесечно и едногодишно средно време на преживување изнесуваше 272,8 [95 % CI (238,4-307,2)] и 267,1 [95 % CI (232,9-301,2)] дена, соодветно. Шестмесечното и едногодишното преживување беа сигнификантно пократки кај пациентите со АД ($p < 0,0001$).

Заклучок: Етиологијата, стадиумот на црнодробната болест, како и присуството на АД се важни фактори што влијаат на преживувањето кај пациентите со црнодробна цироза.

Клучни зборови: црнодробна цироза, смрт, преживување