Marmara Medical Journal 2019; 32: 44-49
DOI: 10.5472/marumj.476330

ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

The evaluation of complications and mortality in non-alcoholic steatohepatitis-related cirrhosis

Non-alkolik steatohepatite bağlı sirozda komplikasyonların ve mortalitenin değerlendirilmesi

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ABSTRACT

Objectives: Cirrhosis is seen in 4-8% of patients with non-alcoholic fatty liver disease (NAFLD), and death occurs in 1-5% of them due to hepatocellular carcinoma (HCC). The aim of this study was to determine the factors associated with complications and mortality in patients with cirrhosis secondary to non-alcoholic steatohepatitis (NASH).

Materials and Methods: The patients with cirrhosis due to NASH diagnosed between 2008 and 2018 in our clinic formed the study population. Patients with diabetes, obesity, or insulin resistance and those with cirrhosis due to other causes were excluded. The patients were enrolled and followed up prospectively.

Results: A total of 185 patients were included in the study. The survival was 94.6% at the 1st year and 57.0% at the 5th year. Median survival duration was 5.83 years. The rate of HCC development was 0.7% at the 1st year and 9.7% at the 5th year. In the multivariate Cox analysis, age (OR: 1.12, 95% CI: 1.04-1.21; P = 0.003), creatinine (OR: 24.4, 95% CI: 2.32-257.8; P= 0.008) and encephalopathy (OR: 24.49, 95% CI: 1.06-19.6; p = 0.042) were found as independent predictors of mortality. Development of ascites occurred in 46.9%, variceal bleeding in 21.9% and encephalopathy in 18% of patients at the 5th year.

Conclusion: Patients with NASH-related cirrhosis should be carefully monitored for HCC development, variceal bleeding, ascites, and encephalopathy.

Keywords: Non-alcoholic Steatohepatitis, Cirrhosis, Mortality

ÖZ

Amaç: Non-alkolik yağlı karaciğer hastalığı (NAYKH) saptanan hastaların %4-8'inde siroz ve %1-5'inde hepatoselüler karsinom (HCC) nedeni ile ölüm görülmektedir. Bu çalışmada amaç, non-alkolik steatohepatit (NASH)'e sekonder siroz gelişen hastalarda, siroza ait komplikasyonlar ve mortalite ile ilişkili faktörlerin belirlenmesidir.

Gereçler ve Yöntemler: Çalışmaya, 2008-2018 yılları arasında kliniğimizde NASH'e bağlı siroz tanısı alan hastalar alındı. Diyabeti, obezitesi ya da insülin direnci olan ve diğer siroz nedenleri dışlanan hastalar NASH'e bağlı siroz olarak kabul edildi. Hastalar prospektif olarak kayıt altına alınıp takip edildi, analizler retrospektif olarak yapıldı.

Bulgular: Çalışmaya toplam 185 hasta dahil edildi. Sağkalım 1. yılda %94,6 ve 5. yılda %57,0 bulundu. Median sağkalım 5,83 yıl saptandı. HCC'un ortaya çıkması 1. yılda %0,7 ve 5. yılda %9,7 bulundu. Çok değişkenli Cox analizinde yaş (OR 1,12, 95% CI 1,04-1,21; P=0.003), kreatinin (OR 24,4, %95 CI 2,32-257,8; P=0.008) ve ensefalopati (OR 24,49, %95 CI 1.06-19.6; p=0.042) bağımsız prediktörler olarak saptandı. Hastalarda 5. yılda assit gelişimi %46,9, varis kanaması gelişimi %21,9 ve ensefalopati gelişimi %18 saptandı.

Sonuç: Non-alkolik steatohepatite sekonder siroz gelişen hastalar HCC, varis kanaması, assit ve ensefalopati gelişimi açısından dikkatli takip edilmelidir.

Anahtar kelimeler: Non-alkolik steatohepatit, Siroz, Mortalite

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common disease of the liver in recent years and affected about 25% of adults globally [1]. Cirrhosis develops in 4-8% of patients with NAFLD and the mortality rate due to NAFLD-induced HCC is 1-5%. NAFLD is one of the most common causes of liver transplantation and HCC in the United States (US) [2,3]. Among all causes of transplantation in the US, non-alcoholic steatohepatitis (NASH) takes place in 1.2% of all causes in 2001, which

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Submitted / Gönderilme: 02.09.2018 **Accepted/Kabul:** 19.10.2018

has risen to 9.7% in 2009 [4]. In the US, it is estimated that there are 64 million cases in 2017 that yielded an economic cost of 103 billion $ [5].

There is a close association between NASH and type 2 diabetes mellitus (DM), central obesity, dyslipidemia, the metabolic syndrome. The prevalence of NAFLD has been reported to be 40-70% in type 2 DM patients and up to 90% in obese individuals [6,7]. In parallel with the increased prevalence of obesity, the prevalence of NASH increased from 15% in 2005 to 25% in 2010 [4]. As the prevalence of obesity and type 2 DM has increased in society, NASH-related liver disease is estimated to increase by 178% in the year 2030 [8]. Although, cardiovascular diseases are the most common cause of mortality in NASH patients, the presence of hepatic fibrosis is a significant prognostic predictor [9]. The hazard ratio was found 1.9 in F0 fibrosis stage and 104.9 in F4 for the development of the severe liver disease. The advanced fibrosis stage is the most critical parameter in predicting overall mortality [10].

Risk factors for advanced liver disease include age, increased body mass index and the presence of DM [11]. The progression of fibrosis in NASH is slower than other chronic liver disease causes. The mean duration to develop a severe hepatic disease is 22-26 years in patients with stage F0, 9.3 years in stage F2 and 0.9 years in stage F4 [9]. In the presence of NASH in NAFLD, 7 years are required for each fibrosis stage, whereas the period is 14 years unless NASH exists.

In NAFLD, fibrosis begins in the pericellular space around the central vein and the peri-sinusoidal region. Therefore, portal hypertension in patients with NAFLD begins before cirrhosis. Portal hypertension complications such as esophageal variceal bleeding are the most common cause of first referral to hospital in these patients [13].

NASH-related HCC usually develops in elderly patients with advanced fibrosis stage which is less aggressive than HCC due to viral hepatitis. Therefore, it can mistakenly be overlooked during routine imaging studies [14].

The aim of this study was to determine cirrhosis-induced complications and independent factors associated with mortality in patients with NAFLD-induced cirrhosis.

Materials and Methods

The patients who were diagnosed as NAFLD-induced cirrhosis between 2008 and 2018 in our clinic were enrolled to the study. The patients with DM, or insulin resistance, obese patients and those who had cirrhosis due to other causes were excluded. Viral hepatitis, autoimmune hepatitis and Wilson's disease had been excluded during the diagnostic process in every patient. The patients were enrolled and followed up prospectively. Statistical analysis was performed at the end of enrollment retrospectively.

The patients were diagnosed as cirrhosis by clinical and biochemical examinations together with imaging modalities. Cirrhosis, jaundice, ascites, hepatic encephalopathy, prothrombin time (PT) prolongation, the presence of low serum albumin and presence of nodular liver and splenomegaly on radiological examinations were considered as signs of chronic liver disease.

In addition, patients who were diagnosed two years before or longer, and presented with a mass in the liver were not included in the study.

The patients who had ascites were offered a salt-free diet, and spironolactone or spironolactone plus furosemide were also given orally. Propranolol 40-80 mg/day was started in patients with varices on endoscopy. Band ligation was performed to patients who had variceal bleeding or patients with grade 2-3 varices on endoscopy. Patients who had encephalopathy were given low protein diet and lactulose and rifaximine 600 mg/day was added to treatment when encephalopathy recurred. Obese patients were advised to lose weight and diabetic patients were advised for blood glucose regulation. Patients with cirrhosis-related complications were referred to liver transplantation. The patients were followed-up at 6-12 months intervals. The study was approved by Izmir Katip Celebi University Ethics Committee (No:2018-394).

Statistical Analysis

Statistical analysis of the data was done with the help of SPSS version 22.0 package program. Normally distributed numerical data were expressed as mean and standard deviation. The chi-square test was used for categorical variables. The normality and homogeneity of the groups were evaluated. Mann Whitney U test was used for data not consistent with normal distribution, while Student T was used for data fitting normal distribution. The emergence of complications of cirrhosis was demonstrated by Kaplan-Meier graph. Cox regression univariate analysis was performed to evaluate the mortality and the variables having a P-value of less than 0.1 were included in the model to

identify independent variables by multivariate analysis. A P value of <0.05 was considered as statistically significant.

Results

A total of 185 patients were included in the study. The median follow-up period was 3.1 years. The characteristics of the patients are summarized in Table I. In terms of the development of cirrhosis complications, the 1st year, 3rd year and the 5th year follow-up examinations were performed (Table II). Ascites, variceal bleeding, hepatic encephalopathy and HCC development are summarized in Figure 1.The median duration of ascites development was 8.99 years. Survival rate was 94.6% at the 1st year, 71.9% at the 3rd year and 57.0% at the 5th year. Median survival duration was 5.83 years (Figure 2). In multivariate Cox analysis, age and serum creatinine level were found to be independently associated with mortality. Table III and Table IV show the univariate and multivariate parameters associated with mortality.

Table I. Characteristics of patients diagnosed with NASH-related cirrhosis

Characteristics of patients	N=185
Age	63.9±8.9
Sex (F/M)	116/69
Total bilirubin (mg/dl)	1.4±0.9
Albumin (gr/dl)	3.6±0.6
INR	1.3±0.4
Platelet (/mm^3)	135±68
Ferritin (mg/dl)	38 (3-674)
HbA1c*	7.5±1.8
Weight	84±18
Height	161±9
BMI (kg/m^2)	32.4±7.0
Triglyceride (mg/dl)	133±93
Ascites **	29 (15.7%)
Variceal bleeding **	28 (15.2%)
Encephalopathy **	12 (6.5%)

*In patients with diabetes,**Rate at admission
INR:International normalized ratio

Table II. The complication rate of NASH-related cirrhosis.

	1. year	3. year	5. year
Ascites (%)	26.0	40.2	46.3
Variceal bleeding (%)	19.3	21.9	21.9
Encephalopathy (%)	10.4	13.2	18.0
Hepatocellular carcinoma (%)	0.7	5.4	9.7

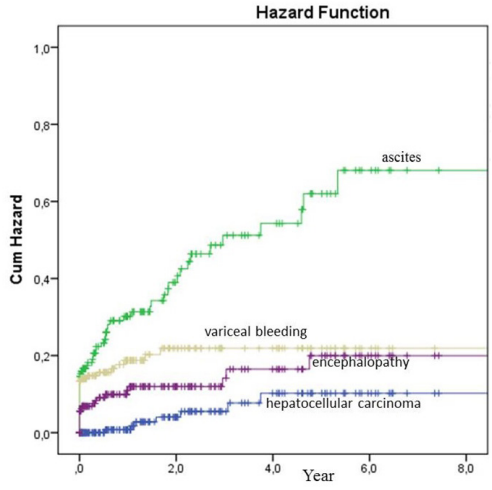

Figure 1. Complications of NASH – related cirrhosis; ascites, variceal bleeding, encephalopathy and development of hepatocellular carcinoma after diagnosis.

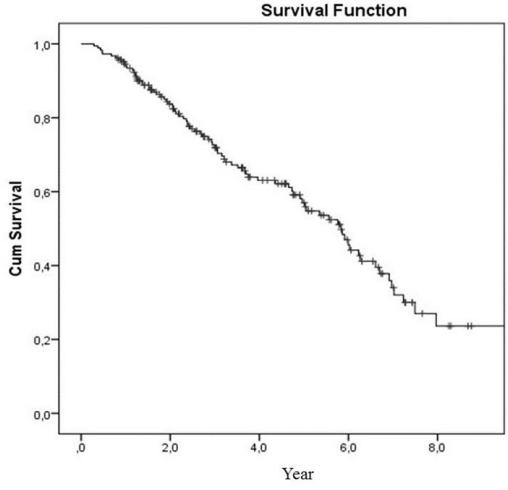

Figure 2. Mortality chart in NASH-related cirrhotic patients

Table III. Univariate Cox regression analysis for predicting mortality.

	B	Wald	P	OR	95.0% CI OR	
					Lower limit	Upper limit
Variceal bleeding*	0.162	0.36	0.549	1.176	0.692	2.000
Ascites*	0.960	12.542	<0.001	2.611	1.535	4.442
Encephalopathy*	0.979	8.841	0.003	2.662	1.396	5.076
Age	0.067	26.078	<0.001	1.07	1.042	1.097
Total bilirubin	0.214	3.536	0.06	1.239	0.991	1.549
Presence of DM	-0.044	0.007	0.932	0.957	0.347	2.637
Platelet	-0.005	5.813	0.016	0.995	0.991	0.999
Albumin	-0.918	42.081	<0.001	0.399	0.303	0.527
INR	0.700	10.056	0.002	2.014	1.307	3.104
Creatinine	2.821	7.536	0.006	16.799	2.241	125.918

*Rate at admission CI: confidence interval, OR:odds ratio

Table IV. Independent variables for predicting mortality in multivariate Cox regression analysis

	B	Wald	P	OR	95.0% CI OR	
					Lower limit	Upper limit
Age	0.116	8.564	0.003	1.123	1.039	1.214
Creatinine	3.198	7.082	0.008	24.471	2.322	257.855
Encephalopathy*	1.502	4.149	0.042	4.491	1.058	19.056

*at admission CI: confidence interval, OR:odds ratio

Discussion

The prevalence of NASH has been increasing rapidly all over the world because of sedentary life, excessive nutrition intake (primarily glucose and fructose), genetic factors, age, type 2 DM, and obesity [15]. Approximately, 11% of NASH cases progress to cirrhosis in 15 years, 7% of those who have cirrhosis progress to develop HCC in 6.5 years and 31% of cirrhotic patients proceed to decompensation in 8 years [16].

The mean age of the patients was 63.9±8.9 in this study. In a previous study, patients with NASH-related cirrhosis were reported to be elder and having more co-morbidities than those with HCV cirrhosis who were on the transplantation list [17]. This difference seems to be related to the slow progression of cirrhosis due to NASH than other cirrhosis causes.

In our study, the most common complication at the end of the 5th year was ascites. The survival rate was 57.0% at the 5th year. In a study in which NASH-related cirrhotic patients were followed up for 29 months, 20% of patients had ascites, 20.8% had variceal bleeding, 20.8% had encephalopathy, and 4.2% died [18]. In our study, the data at the end of the 3rd year was similar to the results of this study.

In a study including 256 patients with NASH-related cirrhosis, any hepatic complication was observed in 19% of the patients during a mean follow-up period of 26.7 months. Survival was 92% at the 24th month, and independent predictive factors of mortality were low serum albumin level and high baseline hepatic portal venous gas (HPVG) pressure [19]. In the follow-up of 30 patients diagnosed with NASH-related cirrhosis, ascites and variceal bleeding were found to be the most common cirrhotic complications [20]. In another study, ascites was observed in 70% of patients, variceal bleeding in 24% and HCC in 9% during the 10-year follow-up period. Age, bilirubin, albumin, international normalized ratio (INR), and platelet count parameters of the patients were reported to associate with survival independently [21]. Ascites was also the most common decompensation finding in our study.

At the time of diagnosis, 15.7% of our patients had ascites, 15.3% had hemorrhage, and 6.3% had hepatic encephalopathy. In a study evaluating patients who underwent transplantation due to NASH-related cirrhosis, 61% of the patients had ascites, 25% had encephalopathy, and 18% had variceal bleeding at the time of diagnosis [22]. In another study evaluating 354 patients diagnosed with NAFLD, 28% of the patients had portal hypertension, 33% had experienced variceal bleeding, 12% had ascites, and 7% had encephalopathy findings at the time of diagnosis [13]. Similar to these studies, the rate of decompensated cirrhosis at the time of admission was quite high in our patients.

According to our results, variceal bleeding was not independently associated with mortality which might be due to the fact that we frequently used endoscopic band ligation as a primary prophylactic measure, so other complications became more dominant on death. Besides, there was no variceal hemorrhage after the 3rd year among the patients who had no previous bleeding experience.

The cause of HCC development in NASH-related cirrhosis is the changes in apoptosis, necroptosis, and autophagy mechanisms in cells, together with increased fibrogenesis, inflammation and cellular proliferation [23]. Obesity, DM, advanced age and hepatic iron accumulation are associated with HCC development in patients with cirrhosis secondary to NASH [2, 24-26]. NAFLD is still the third most common HCC cause in the US. Considering that NASH is believed to be the most common cause of HCC in the future, NASH-related HCC has begun to attract particular attention [27]. In a United Kingdom study, there was a 10-fold increase in NAFLD-associated HCC between 2000 and 2010, and the NASH-related HCC rate was 34.8% among all HCC cases [27]. In our study, the rate of HCC at the end of the 5th year was 9.7%. In the literature, results are ranging from 9%-to-22.5% [21, 28, 29]. Previous publications have reported that NASH-associated HCC is less aggressive than HCC due to other causes [14]. In a study by Piscaglia et al., in patients with NASH-related HCC, the malignant mass was larger, more infiltrative in histological behavior and the survival was shorter than those in HCV-related HCC cases [30]. A careful and thorough examination is critical because HCC may be missed during radiological studies in these patients [14].

Cardiovascular diseases are the most common cause of death in patients with NAFLD [31]. In NASH patients with advanced fibrosis, hepatic causes are the leading cause of death [10]. Fibrosis is the most important predictor of mortality [32], while variceal bleeding due to portal hypertension is the most catastrophic complication in these patients. Variceal bleeding is responsible for 20% of NASH-related mortality [33]. In our study, the survival rate was 94.9% at the 1st year, 71.9% at the 3rd year and 57% at the 5th year. Age, serum creatinine level and presence of encephalopathy were independent predictive factors of mortality. In similar studies, mortality rates were reported as 4.2% at the end of 29 months, 8% after 24 months and 11% after 60 months [18, 19]. In these studies, low serum albumin level, high baseline HPVG pressure, patient age, bilirubin, albumin, INR, and platelet count parameters were reported to be independently associate with survival [19, 21].

The main limitations of our study were its retrospective design and the fact that some of our patients had advanced cirrhosis. In addition, we could not assess other causes of mortality such as cardiovascular mortality; we analyzed total mortality alone. Data of patient who underwent liver transplantation was not precise, too.

In conclusion, NAFLD is a complex condition associated with cardio-metabolic risk and hepatic disease. Its prevalence is increasing rapidly all over the world. In parallel, rates of cirrhosis and liver transplantation due to NASH are rapidly growing as well. NAFLD will be the most common cause of cirrhosis and liver transplantation in the near future. The development of HCC in these patients is another critical condition. Patients with cirrhosis secondary to NASH should be carefully monitored for developing HCC, varices, ascites, and hepatic encephalopathy. Patients with decompensation, such as ascites, variceal bleeding, hepatic encephalopathy, should be followed up at a transplantation capable center. Treatment aims to reduce cirrhosis progression. Lifestyle changes, such as changing the nutritional habit and doing exercise, are essential in the management. Concomitant conditions such as DM, dyslipidemia, and obesity should be managed appropriately [34]. Appropriate control of NASH would decrease the rate of development of cirrhosis and cirrhosis-related complications such as ascites, varices, HCC, and death.

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