

**Effect of Smoking on Cirrhosis with Heavy Alcohol Consumption****Sezgin Vatanserver<sup>1</sup>, Zehra Betul Pakoz<sup>2\*</sup>, Sami Deniz<sup>3</sup>, Belkis Unsal<sup>4</sup>**<sup>1</sup>Ataturk Training and Research Hospital, Izmir, Turkey<sup>2</sup>Tepecik Training and Research Hospital, Izmir, Turkey<sup>3</sup>Suat Seren Research and Training Hospital, Izmir, Turkey<sup>4</sup>Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey**Original Research Article****\*Corresponding author***Zehra Betul Pakoz***Article History***Received: 12.09.2018**Accepted: 25.09.2018**Published: 30.09.2018***DOI:**

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**Abstract:** Term and quantity of alcohol consumption is one of the most significant factors in terms of occurrence of alcoholic liver disease. In some studies, it has been found out that due to prevalence of smoking-related morbidity, reason of death of alcoholics is more probably smoking related diseases more than alcohol-related disorders. In this study, we aimed to determine characteristics of smoking in cirrhosis with heavy alcohol consumption, its effect on mortality and risk factors. 401 cirrhotic patients with heavy alcohol consumption applying to gastroenterology clinic between the years of 2008-2018 successively were assessed retrospectively. Patients used to consume alcohol minimum 40 g/day a day and for more than 10 years. Term of alcohol abuse, type of alcohol and smoking condition were questioned for the patients. Patients with GIS malignancy and diseases other than liver were not included in the study. Patients were divided into 3 groups as smoker, ex-smokers and non-smokers. Rate of smoking was found as 90.3%. Age of starting alcohol and body mass index was found as significantly lower in patients who have still smoked. Quantity of daily alcohol use in smokers was significantly higher. In multi-variate analysis, age and quantity of smoking was significantly related to the mortality. Mortality was found less in persons abusing alcohol with strength of 15% above. In our study, smoking has been found as related to the mortality in cirrhosis patients with heavy alcohol consumption. For this reason, we suppose that quitting smoking will be beneficial for increasing rate of survival in cirrhosis patients with heavy alcohol consumption.

**Keywords:** smoking, Alcohol, cirrhosis, alcohol abuse.

**INTRODUCTION**

Alcohol is an addictive substance being one of the major reasons of liver disease and consumed widespread all around the world. Every year, it is the reason of 85.000 [1] deaths in the United States of America and 2.5 million of death all over the world [2]. It is predicted that 6.5% of deaths in Europe and 5.9% in the world are related to the alcohol [3]. Half of cirrhosis induced deaths are related to the alcohol [2]. 16.6% of deaths related to the global alcohol are the deaths originating from cirrhosis [4].

Term and quantity of alcohol consumption is one of the most significant factors in terms of occurrence of alcoholic liver disease [5]. It is indicated that comorbid liver diseases, obesity and smoking increases the risk [6]. It is seen that rate of a number of addictive substance abuse mainly smoking with alcohol abuse is high. Tendency of addiction to more than one substance has been demonstrated for the addicted in the studies [7, 8].

Alcoholism is a physical and psychological addiction and alcohol affects a number of neurotransmitters mainly dopamine and also gamma aminobutyric acid, glutamate, serotonin, norepinephrine in brain [9]. It has been shown that nicotine addiction causes increase of alcohol use in the studies [10,11].

Rate of smoking has reduced in the world [12]. However, rate of smoking of alcoholics is quite high and it has been reported as rates above 80% [13, 14]. At the same time, risk of alcohol use disorder in smokers has been found as 10 times more compared to the non-smokers [15]. Nicotine addiction of alcoholic smokers is more severe and it is more difficult for them to quit smoking [14]. Synergic effects of co-use of cigarette and alcohol on occurrence of diseases such as colorectal cancer [16], esophageal cancer [17], pancreatitis [18], and hepatocellular cancer [19], cardiovascular diseases have been determined. In some studies, it has been found out that due to prevalence of smoking-related morbidity, reason of death of alcoholics is more

probably smoking related diseases more than alcohol-related disorders [21, 22]. It was determined that smoking addiction treatment in alcoholic patients reduced the mortality rates [23]. In previous studies, effect of smoking on alcoholic patients was assessed however, effect of smoking on mortality in cirrhotic patients has not been clear yet. In this study, it was aimed to determine characteristics of smoking in cirrhosis with heavy alcohol consumption, its effect on mortality and risk factors.

## METHODS

401 cirrhotic patients with heavy alcohol consumption applying to gastroenterology clinic between the years of 2008-2018 successively were assessed retrospectively. Patients having the diagnosis of chronic liver disease within the last one year were included in the study. Diagnosis was established by clinic, biochemical and imaging methods. Patients used to consume alcohol minimum 40 g/day a day and for more than 10 years. Term of alcohol abuse, type of alcohol and smoking condition were questioned for the patients. Patients with GIS malignity and diseases other than liver were not included in the study. Patients were divided into 3 groups as smoker, ex-smokers and non-smokers.

Total quantity of alcohol abuse was determined as the amount of total absolute alcohol throughout the use of alcohol (daily alcohol quantity \*365\* term of alcohol abuse (year).

Type of alcohol was divided into two groups as drinks with low alcoholic strength (<15%) (Beer and wine) and high alcoholic strength (>15%) (Gin, vodka, whiskey, raki).

## RESULTS

Total 401 cirrhotic patients were included in the study. Rate of smoking was found as 90.3%. Average age of the group who quit smoking was determined as significantly high. Age of starting alcohol and body mass index was found as significantly lower in patients who have still smoked. Quantity of daily alcohol use in smokers was significantly higher. A significant relationship between smoking and type of alcohol abused was not found in terms of evaluating the patients for mortality. Term of smoking, frequency (package/day) total quantity of alcohol, term of abusing alcohol, strength of alcohol being above 15% and age were found as related with mortality significantly. In multi-variate analysis, age and quantity of smoking was significantly related to the mortality. Mortality was found less in persons abusing alcohol with strength of 15% above.

Smoking (package.year) and total quantity of alcohol use ( $r=0.228$ ,  $p<0.000$ ) and starting age of alcohol abuse ( $r=0.365$ ,  $p<0.0001$ ) was found as moderately correlated.

Cut off value for smoking.package year was found as 25.5 years by ROC curve.

**Table-1: Comparison of demographical data in smoker, ex-smoker and non-smoker cirrhosis patients with heavy alcohol consumption**

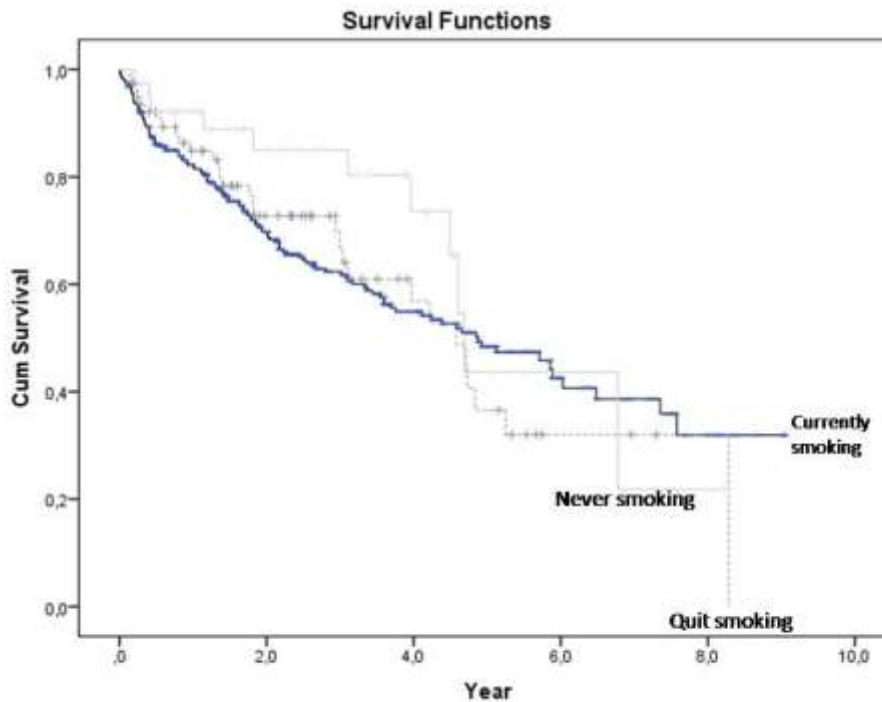
	Smokers n=285	Ex-smokers n=77	Non-smokers n=39	p
Age	54.0±8.8	60.9±9.3	58.5±9.8	<0.0001
Age of starting alcohol consumption	26.8±8.6	29.9±9.7	30.9±7.5	0.002
Age of starting smoking	21.6±8.2	22.0±8.6		0.678
Sex (W/M)	4/281	0/77	0/39	0.439
Weight	80.9±17.4	89.8±19.8	85.5±13.5	0.009
BMI (kg/m <sup>2</sup> )	27.2±5.4	29.8±6.2	28.1±4.1	0.021
Duration of smoking (year)	32.6±10.2	26.1±11.4	-	<0.0001
Smoking (package.year)	36.8±19.5	29.1±17.9	-	0.002
Duration of alcohol consumption	27.3±9.5	31.4±9.9	27.9±8.2	0.004
Amount of alcohol (gr/day)	151±59	129±58	133±58	0.008
Alcohol consumption of last 10 years (gr/day)	168±81	140±70	148±79	0.014
Total quantity of alcohol consumption (lt)	1517±837	1492±920	1387±775	0.670
HBs Ag (%)	14.4	11.7	10.2	0.684
Anti HBc IgG (%)	49.4	38.6	47.1	0.284
Anti HCV (%)	3.2	2.6	2.6	0.951
Strenght of alcohol (%)	69.5	75.3	69.2	0.595
Type of alcohol				0.453
Beer (%)	22.1	19.5	28.2	
Wine (%)	8.8	5.2	2.6	
Raki /whiskey /vodka (%)	69.2	75.3	70.3	

**Table-2: Relation of smoking with mortality in cirrhosis patients with heavy alcohol consumption**

	B	SE	Wald	p	OR	95,0% CI for Exp(B)	
						Lower	Upper
Smoking	,412	,328	1,579	,209	1,510	,794	2,871
Duration of smoking (year)	,020	,007	8,447	,004	1,021	1,007	1,035
Smoking (package.year)	,014	,004	12,661	,000	1,014	1,006	1,022
Total quantity of alcohol (lt)	,000	,000	4,287	,038	1,000	1,000	1,000
Duration of alcohol consumption (year)	,026	,009	8,670	,003	1,026	1,009	1,044
Strenght of alcohol (>% 15)	-,347	,172	4,065	,044	,707	,504	,990
Type of alcohol	-,179	,094	3,635	,057	,837	,696	1,005
Age	,032	,009	13,491	,000	1,033	1,015	1,051

**Table-3: Cox regression multivariate analysis**

	B	p	OR	95.0% CI for Exp(B)	
				Lower	Upper
Age	.030	.003	1.030	1.010	1.051
Duration of alcohol consumption	.007	.499	1.007	.987	1.027
Strenght of alcohol (>% 15)	-.361	.036	.697	.497	.977
Smoking (package.year)	.013	.001	1.013	1.005	1.021



**Fig-1: Relation between time and survival in smoker cirrhosis patients with heavy alcohol consumption (p=0.406)**

**DISCUSSION**

It was shown in the literature that rate of smoking of persons abusing alcohol increased. For instance, while rate of smoking in the society in the United States of America was 23%, it was 75% for alcohol addict [24-26]. In the study performed by Batel *et al.* rate of smoking addiction was found as 88% in

alcohol addict [27]. The reason of it was suggested as genotypes causing nicotine and alcohol addiction [28]. In our study, rate of smoking in alcoholic patients were found as 90.1%. In a study carried out in Turkey, rate of smoking in general population was determined as 60.3% [29].

In the study conducted by Paavola *et al.* a strong relationship was found between abusing alcohol in early-adolescent period and prevalence of smoking in adult age [30]. It was seen that age of starting to abuse alcohol in smokers was earlier in our study. Moreover, age of starting to smoke was found as earlier than age of starting to abuse alcohol in smokers. We suppose that the reason of it is that smoking encourages abusing alcohol due to common genotypes.

In the study conducted by Hurt *et al.* they analyzed the reasons of mortality in alcoholic cirrhosis patients and found reasons of mortality related to the smoking in 50.9% and they also determined reasons of mortality related to the alcohol in 34.1%. Mortality rate expected within 20 years was found as 48.1% in smokers and as 18.5% in non-smokers. It was indicated that nicotine addiction increased the risk in terms of mortality in alcoholic patient group [21]. In another study published by Hunt *et al.*, in 2003, they expressed those treatments for quitting smoking was necessary for alcoholics smoking due to high mortality and morbidity rates [22].

Finney *et al.* followed patients for 10 years after they had received alcohol treatment in their study and mortality was found as related to the quantity of alcohol [31]. In another study conducted by Dawson, reasons of mortality in alcohol addicts were investigated and mortality was found as higher in persons abusing alcohol for longer time and more, having heavy drinking episodes and having additional disease [32]. In the study performed by Yuan *et al.* with 18,244 Chinese males, mortality was found as related to the quantity of alcohol [33]. Similar studies were carried out with 12,321 British males and 13,285 Danish females and males and in these studies, mortality was found as related to the alcohol quantity however, a relationship between smoking and mortality was not found [34, 35]. Littleton *et al.* expressed that smoking-based mortality increased in persons abusing alcohol in the review they published in [36]. Bullock *et al.* followed 234 males quitting alcohol and they found mortality more in persons having relapse. They did not find the relationship between smoking and mortality in Cox analysis [37]. There are studies in the literature showing the relationship between age and mortality in alcohol abusers [31, 38, 39].

John *et al.* evaluated mortality due to liver cirrhosis for 62 years in a study they performed in 2013 and found out that mortality due to cirrhosis reduced. They suggested that reduction of alcohol use and smoking were the main factors reducing the mortality in cirrhosis patients [40].

As it is seen, there are various studies in the literature investigating the effect of smoking on mortality in alcoholic patients. In these studies, alcohol addicted patients were evaluated. The property of our

study is that we have investigated patients having liver dysfunction and organic symptoms together with alcohol abuse. According to our study, it was seen that mortality was related to the age and frequency of smoking in alcoholic patients. Effect of smoking on mortality was found in cirrhosis patients with heavy alcohol consumption ( $p < 0.001$ ).

Limitations of our study include being retrospective, not evaluating the patients in terms of addiction scores and number of non-smokers is low.

## CONCLUSION

Rate of smoking is quite high in alcohol abusers. While there are studies showing the effect of alcohol and smoking on morbidity and mortality, there are also contrary studies. In our study, smoking has been found as related to the mortality in cirrhosis patients with heavy alcohol consumption. For this reason, we suppose that quitting smoking will be beneficial for increasing rate of survival in cirrhosis patients with heavy alcohol consumption. Alcoholic cirrhosis patients should be encouraged to quit smoking.

## REFERENCES

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States. *Jama* 2000;2004(291):1238-45.
2. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol*. 2013;59:160-168.
3. World HealthOrganization. Global statusreport on alcohol and health. 2014 ed. 2014.
4. World HealthOrganization. Global status report on alcohol and health. 2011 ed. 2011.
5. Kamper-Jorgensen M, Gronbaek M, Tolstrup J, Becker U. Alcohol and cirrhosis: Dose—response or threshold effect? *J Hepatol*. 2004;41:25-30.
6. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology*. 2011 Nov 1;141(5):1572-85.
7. Zhao X, Harris M. Demand for marijuana, alcohol and tobacco: participation, levels of consumption and cross equation correlations. *Econ Rec* 2004;80(251):394-410.
8. Manrique J, Jensen H. Consumption of tobacco and alcoholic beverages among Spanish consumers. *Southwest Econ Rev*. 2004;31:41-56.
9. Koob GF. Alcoholism: allostasis and beyond. *Alcohol Clin Exp Res*. 2003 Feb; 27(2):232-43.
10. Le AD, Wang A, Harding S, Juzysch W, Shaham Y. Nicotine increases alcohol self-administration and reinstates alcohol seeking in rats. *Psychopharmacology (Berl)*. 2003 Jul;168(1-2):216-221.
11. Le AD, Li Z, Funk D, Shram M, Li TK, Shaham Y. Increased vulnerability to nicotine self-administration and relapse in alcohol-naive off

- spring of rats selectively bred for high alcohol intake. *J Neurosci.* 2006 Feb 8;26(6): 1872-9.
12. Meyerhoff DJ, Tizabi Y, Staley JK, Durazzo TC, Glass JM, Nixon SJ. Smoking comorbidity in alcoholism: neurobiological and neurocognitive consequences. *Alcohol Clin Exp Res.* 2006 Feb;30(2):253-64
  13. Bobo JK. Nicotine dependence and alcoholism epidemiology and treatment. *J Psychoactive Drugs.* 1992 Apr-Jun; 24(2): 123-9.
  14. Romberger DJ, Grant K. Alcohol consumption and smoking status: the role of smoking cessation. *Biomed Pharmacother.* 2004 Mar;58(2):77-83
  15. DiFranza JR, Guerrera MP. Alcoholism and smoking. *Journal of studies on alcohol.* 1990 Mar;51(2):130-5.
  16. Otani T, Iwasaki M, Yamamoto S, Sobue T, Hanaoka T, Inoue M, Tsugane S. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. *Cancer Epidemiology and Prevention Biomarkers.* 2003 Dec 1;12(12):1492-500.
  17. Wu M, Zhao JK, Zhang ZF, Han RQ, Yang J, Zhou JY, Wang XS, Zhang XF, Liu AM, van't Veer P, Kok FJ. Smoking and alcohol drinking increased the risk of esophageal cancer among Chinese men but not women in a high-risk population. *Cancer Causes & Control.* 2011 Apr 1;22(4):649-57.
  18. Setiawan VW, Pandol SJ, Porcel J, Wilkens LR, Le Marchand L, Pike MC, Monroe KR. Prospective study of alcohol drinking, smoking and pancreatitis: the multiethnic cohort. *Pancreas.* 2016 Jul;45(6):819.
  19. Mukaiya M, Nishi M, Miyake H, Hirata K. Chronic liver diseases for the risk of hepatocellular carcinoma: a case-control study in Japan. Etiologic association of alcohol consumption, cigarette smoking and the development of chronic liver diseases. *Hepatogastroenterology.* 1998 Nov-Dec;45(24):2328-32.
  20. Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. *Prog Cardiovasc Dis.* 2003 Jul-Aug;46(1):91-111.
  21. Hurt RD, Offord KP, Croghan IT, Gomez-Dahl L, Kottke TE, Morse RM, Melton LJ 3rd. Mortality following inpatient addictions treatment. Role of tobacco use in a community-based cohort. *JAMA.* 1996 Apr 10;275(14):1097-103.
  22. Hurt RD, Patten CA. Treatment of tobacco dependence in alcoholics. *Recent Dev Alcohol.* 2003;16:335-59.
  23. Miller NS, Gold MS. Comorbid cigarette and alcohol addiction: epidemiology and treatment. *J Addict Dis.* 1998;17(1):55-66.
  24. CDC. Cigarette smoking among adults in the United States. *MMWR (Morb Mortal Wkly)* 2002;51:300-303
  25. Gulliver SB, Rohsenow DJ, Colby SM, Dey AN, Abrams DB, Niaura RS, Monti PM. Interrelationship of smoking and alcohol dependence, use and urges to use. *Journal of studies on Alcohol.* 1995 Mar;56(2):202-6.
  26. Gulliver SB, Kalman D, Rohsenow DJ, Colby SM, Eaton CA, Monti PM. Smoking and drinking among alcoholics in treatment: cross-sectional and longitudinal relationships. *Journal of Studies on Alcohol.* 2000 Jan;61(1):157-63.
  27. Batel P, Pessione F, Maitre C, Rueff B. Relationship between alcohol and tobacco dependencies among alcoholics who smoke. *Addiction.* 1995 Jul;90(7):977-80.
  28. Daepfen JB, Smith TL, Danko GP, Gordon L, Landi NA, Nurnberger JI Jr, Bucholz KK, Raimo E, Schuckit MA. Clinical correlates of cigarette smoking and nicotine dependence in alcohol-dependent men and women. The Collaborative Study Group on the Genetics of Alcoholism. *Alcohol Alcohol.* 2000 Mar-Apr;35(2):171-5.
  29. Dr. Kültegin Ögel, Dr. Defne Tamar, Dr. Erol Özmen, Dr. Tamer Aker, Dr. Afşin Sağduyu, Dr. Cumhuriyet Boratav, Psk. Olcay Liman. Prevalence of Cigarette Use in Istanbul. *Journal of Dependence* 2003; 4: 105-108
  30. Paavola M, Vartiainen E, Haukka A. Smoking, alcohol use, and physical activity: a 13-year longitudinal study ranging from adolescence into adulthood. *J Adolesc Health.* 2004 Sep;35(3):238-44.
  31. Finney JW, Moos RH. The long term course of treated alcoholism: II. Predictors and correlates of 10 year functioning and mortality. *J Stud Alcohol.* 1992 Mar; 53(2): 142-53.
  32. Dawson DA. Alcohol consumption, alcohol dependence, and all-cause mortality. *Alcohol Clin Exp Res.* 2000 Jan;24(1):72-81
  33. Juan J-M, Ross RK, Gao Y-T, Henderson BE, Yu MC. Follow up study of moderate alcohol intake and mortality among middle-age men in Shanghai, China. *Br Med J.* 1997 314:18-23
  34. Doll R, Peto R, Hall E, Wheatley K, Gray R. Mortality in relation to consumption of alcohol: 13 years observation on male British doctors. *Br Med J.* 1994 309: 911-918.



35. Gronbaek M, Deis A, Sorensen TI, Becker U, Borch-Johnsen K, Müller C, Schnohr P, Jensen G. Influence of sex, age, body mass index, and smoking on alcohol intake and mortality. *BMJ*. 1994 Jan 29;308(6924):302-6.
36. Littleton J, Barron S, Predergast M, Nixon SJ. Smoking kills (alcoholics)! Shouldn't we do something about it? *Alcohol* 2007 May-Jun;42(3):167-73.
37. Bullock KD, Reed RJ, Grant I. Reduced mortality risk in alcoholic who achieve long-term abstinence. *JAMA* 1992 Feb 5;267(5):668-72.
38. Moos RH, Brennan PL, Mertens JR. Mortality rates and predictors of mortality among late-middle-aged and older substance abuse patients. *Alcohol Clin Exp Res*. 1994 Feb;18 (1):187-95.
39. Lewis CE, Smith E, Kercher C, Spitznagel E. Predictors of mortality in alcoholic men: a 20 year follow up study. *Alcohol Clin Exp Res*. 1995 Aug;19(4):984-91.
40. John U, Hanke M. Liver cirrhosis mortality, alcohol consumption and tobacco consumption over a 62 year period in a high alcohol consumption country: a trend analysis. *BMC research notes*. 2015 Dec;8(1):822.