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Original Research Article

Trends of etiology and treatment in hepatocellular carcinoma over the years

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ABSTRACT

Background: HCC has been the fastest-growing cause of cancer-related deaths. The aim of this study was to investigate the change trends in the etiology, treatment and mortality of HCC over the last 12 years.
Methods: The study included 523 patients who were admitted to our clinic with the diagnosis of primary malignancy of the liver between 2006-2018. Demographic data, HCC etiologies, alpha feto-protein (AFP) values and imaging characteristics were recorded. The patients were divided into two groups as diagnosed before 2013 and 2013 and later. Because the number of patients with alcohol and HBV was high, it was evaluated as a separate etiology group. HCC was accepted related to NASH in the patients with obesity and diabetes mellitus (DM) after exclusion of HBV, HCV, and autoimmune hepatitis. The patients without obesity and DM were accepted as cryptogenic HCC and added to other etiologies group.
Results: When the patients were evaluated, there was a significant increase in the rate of patients who were in compensated cirrhosis stage and in UCSF criteria in and 2013 and later ($p = 0.0001$, $p = 0.037$, respectively). A significant increase was observed in the ratio of NASH-related HCC 2013 and later ($p = 0.032$). Transplantation, resection and RFA / PEI rates were 14.9% before 2013 and 22.2% 2013 and later ($p = 0.047$).
Conclusions: The rates of NAFLD related HCC due to diabetes and obesity are increasing. Knowing the change of HCC causes over the years is necessary for the effective treatment for these reasons in the future.

Keywords: Hepatocellular carcinoma, Hepatitis B, Hepatitis C, Mortality, Non-alcoholic steatohepatitis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 6th most common type of cancer in the world.[1] It is the 3rd most common cause of cancer related death in the world and is the cause of 750,000 deaths in 2012.[2,3] The incidence of HCC in the United States (US) has tripled in the last 3 decades and has been the fastest-growing cause of cancer-related deaths.[4,5] The risk of HCC incidence in patients with cirrhosis is 1-8% for per year.[6] Modeling shows that the incidence of HCC will increase in 2020 and later.[7]

HCC causes may vary according to geographic regions. While hepatitis B virus (HBV) is the most common HCC cause worldwide, hepatitis C (HCV) is the most common HCC cause in the US. HBV is the most common cause of HCC in Turkey.[8]

Hepatitis C virus (HCV) and hepatitis B virus (HBV) were found to be major risk factors for HCC globally in studies before 2000.[9] One of the most important reason for this was the increase of people infected with HCV in the 1960s and 1970s.[10] As advances in antiviral therapy

in HCV, the HCV-associated HCC ratio has started to decrease. It has been reported that the rate of HCC related NASH increases in the world.[11-13] NASH is the most important cause of chronic liver disease in developed countries.[14] The obesity and diabetes epidemic is the most important cause of NASH related cirrhosis and HCC.[15-17] It was reported in a study that HCC risk in NASH is higher than HCV infection.[18]

The aim of this study was to investigate the change trends in the etiology, treatment and mortality of HCC over the last 12 years.

METHODS

The study included 523 patients who were admitted to authors' clinic with the diagnosis of primary malignancy of the liver between 2006-2018.

The diagnosis of HCC was made by radiologically with arterial premature contrast staining and venous washout in cross-sectional imaging methods in the patients. Liver biopsy was performed in patients without typical contrast staining pattern. The patients were enrolled in the study when they first applied to authors' clinic and they were followed-up prospectively. The data were evaluated retrospectively. Demographic data, HCC etiologies, alpha feto-protein (AFP) values and imaging characteristics were recorded. Each patient was questioned for additional diseases, drug use and medical history.

The patients were divided into two groups as diagnosed before 2013 and 2013 and later. Because the number of patients with alcohol and HBV was high, it was evaluated as a separate etiology group. HCC was accepted related to NASH in the patients with obesity and Diabetes Mellitus (DM) after exclusion of HBV, HCV, and autoimmune hepatitis. The patients without obesity and DM were accepted as cryptogenic HCC and added to other etiologies group (Figure 1).

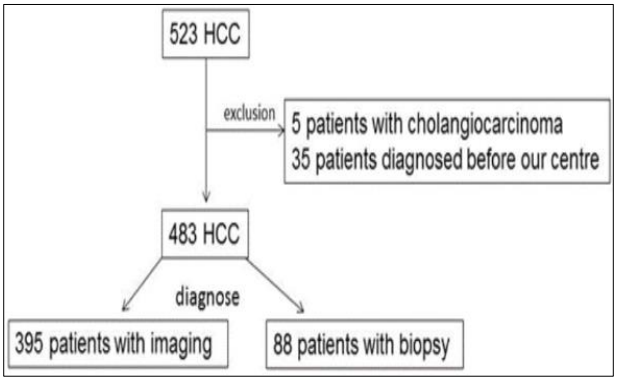

Figure 1: Flow charts of the patients.

Patients with metastasis or invasion for treatment were referred to medical oncology. Patients under the age of 70 with an AFP of less than 1000, without a serious co-morbid disease were referred to the liver transplant center. In cirrhotic patients with computed synapses, the masses smaller than 3cm were directed for RFA / PEI and those larger than 3cm were directed for TACE / TARE. Patients with non-cirrhosis, non-portal hypertension and non-metastatic HCC were directed for resection.

The treatment status of the patients was evaluated according to the most effective treatment.

Statistical analysis

Statistical analysis of the study was done by SPSS 22 package program. 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. Survival was assessed by Kaplan-Meier Log Rank graph analysis. P value <0.05 was considered significant.

RESULTS

A total of 483 newly diagnosed HCC patients were evaluated. The mean age was 64.4 years.

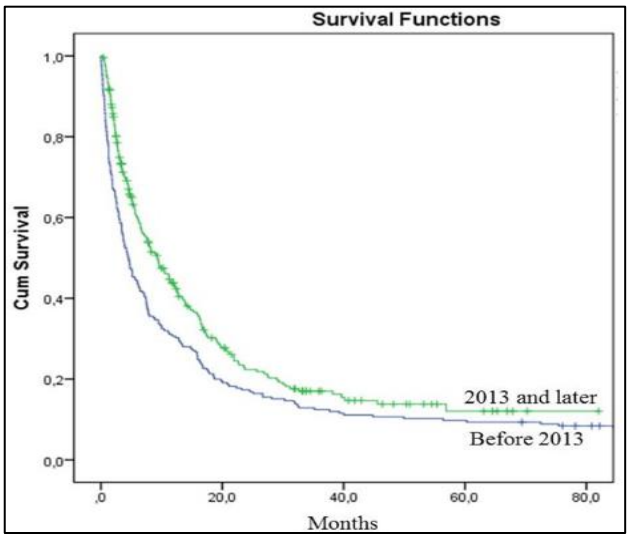

Figure 2: Survival before (green) 2013 and later (p = 0.001).

The number of women was 78. The initial AFP was normal (cut-off value: 9ng/ml) in 20%, was between 9-400 in 42.9% and was over 400 in 37% of the patients. Alcohol history was present in 5 patients with HCV. Therefore, it was not evaluated as a separate group. Multiple mass was detected in 47.7% of patients.

When the patients were evaluated, there was a significant increase in the rate of patients who were in compensated cirrhosis stage and in UCSF criteria in and 2013 and later (p = 0.0001, p = 0.037, respectively). A significant increase was observed in the ratio of NASH-related HCC

2013 and later (p = 0.032). Transplantation, resection and RFA / PEI rates were 14.9% before 2013 and 22.2% 2013 and later (p = 0.047). No significant difference was found in alcohol and alcohol + HBV groups between 38 (17.7%) patients before 2013 and 59 (22.6%) patients 2013 and later (p = 0.140). Table 1 summarizes the initial characteristics of patients.

Median survival was evaluated according to years. Survival was found 0.42 years before 2013 and 0.93 years in 2013 and later. Survival was found better in 2013 and later than before significantly (p = 0.001) (Figure 2).

Authors evaluated mortality rate according to etiology. Mortality rate was higher in HCV related HCC. Mortality rate in HBV related HCC were better than HCV and NASH related HCC mortality, but the difference between the groups was not statistically significant (p = 0.117) (Figure 3).

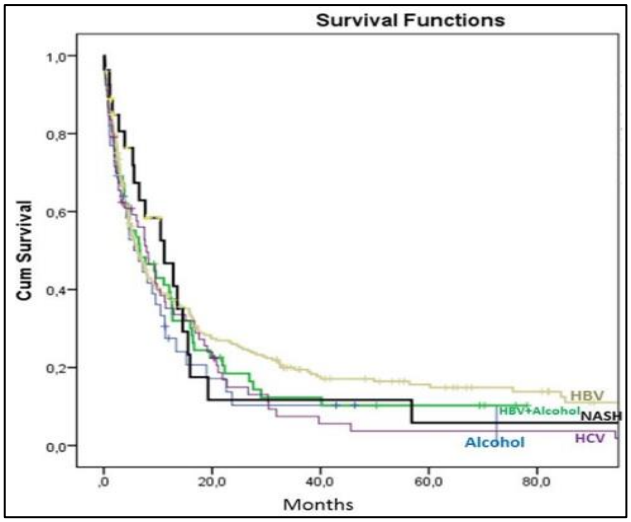

Figure 3: Survival according to etiology (p = 0.117).

Table 1: Characteristics of patients diagnosed with HCC.

	No. of patients	Before 2013	2013 ve later	
	n=483	**n=222**	**n=261**	**p**
Age	64.4±10.5	63.5±11.1	64.8±10.2	0.181
Sex (F/M)	78/405	35/186	43/221	0.893
AFP	132 (1-769149)	175 (1-55191)	107 (1-769149)	0.572
In Milan criteria	141 (29.2%)	56 (25.2%)	86 (33%)	0.099
In UCSF criteria	189 (39.1%)	75 (33.8%)	112 (42.9%)	0.037
Compansated cirrhosis	301 (62.3%)	107 (48.2%)	193 (73.9%)	<0.0001
Etiology				
Alcohol	39 (8.1%)	16 (7.2%)	23 (8.8%)	0.616
Alcohol+HBV	58 (12%)	22 (9.9%)	36 (13.8%)	0.261
HBV	255 (52.8%)	120 (54.1%)	134 (51.3%)	0.525
HCV	67 (13.9%)	36 (16.2%)	31 (11.9%)	0.186
NASH	27 (5.6%)	7 (3.2%)	20 (7.7%)	0.032
Other	38 (7.9%)	21 (9.5%)	17 (6.5%)	0.238
Treatment				
Transplantation	40 (8.3%)	20 (9%)	18 (6.9%)	0.422
Resection	14 (2.9%)	8 (3.6%)	7 (2.7%)	0.632
RFA/PEİ	29 (6%)	5 (2.3%)	23 (8.8%)	0.009
TACE/TARE	108 (22.4%)	35 (15.8%)	74 (28.4%)	0.004
CT/Supportive treatment	271 (56.1%)	149 (67.1%)	124 (47.5%)	0.0001
Operable (with no treatment)	20 (4.1%)	5 (2.3%)	15 (5.7%)	0.132
Diagnosed by follow up	198 (41%)	92 (41.4%)	105 (40.2%)	0.826

HCC: hepatocellular carcinoma, F: female, M: male, AFP: alpha feto-protein, UCSF: University of California, San Francisco, HBV: hepatitis B virus, HCV: hepatitis C virüs, NASH: non alcoholic steatohepatitis, RFA: radio frequency ablation, PEİ: percutaneous ethanol injection, TACE: transarterial chemoembolization, TARE: transarterial radioembolization, CT: chemotherapy

DISCUSSION

Chronic HBV infection is the most common cause of HCC worldwide. Approximately it is responsible for 50% of all HCCs.[19] There are 240 million people (3.2%) infected with HBV worldwide. However, while the infection is endemic in Asia and Africa, the prevalence in western Europe and North America is less than 1%.[20] In present study authors found that the most common cause of HCC in Turkey is HBV infection. Authors found that

HBV infection rate was similar in HCC etiology before and 2013 and later. This may be due to the low awareness of HBV infection in our country.[21] The fact that 59.0% of studied patients was diagnosed as HCC without the diagnosis of cirrhosis were also supportive of this argument.

HCC rates associated with chronic HCV infection also vary across the world. The rates of HCV infection in patients with HCC were 30-50% in the USA, 44-75% in Europe and 80-90% in Japan. Male gender, advanced age, co-infection with HBV and HIV, intense alcohol consumption, diabetes mellitus and obesity are risk factors for the development of HCC in HCV infection.[19,22] In a European study, HCV-induced cirrhosis death rates were found to be decreased with the effective treatment of HCV infection.[23] In present study, the rate of HCV infection was found to be less in the etiology of HCC 2013 and later, but no significant difference was found between before 2013 and 2013 and later. As known, development of cirrhosis due to HCV takes 20 years.[24] In addition, the rate of treated patients with HCV can be very low in the community can.[25] It is thought that HCV infection rate decreases with antiviral treatments, but more time is required for decreasing HCC rates.[26]

The most striking feature of present study was the significant increase in NASH among the causes of HCC 2013 and later. This increase is more pronounced in developed countries, especially in the US. NAFLD affects 20-30% of general adult population, 70% of type 2 diabetes mellitus patients and 90% of obese patients in the US.[27] Diabetes and obesity which are epidemic are risk factors in NAFLD related HCC (22). HCC risk is reported to be from 12.8% in 3 years to 2.4% in 7 years in patients with NASH-related cirrhosis.[28] Although HCV infection is the most common cause of HCC in Japan, it is predicted that this ratio will decrease with the success of antiviral treatments and NASH will be the most common cause of HCC in the future.[29]

In another study, while the rate of NAFLD increased, HCV and alcoholic liver disease were decreased in HCC causes between 2003 and 2015.[26]

In a study in which 1042 patients with a new diagnosis of HCC were followed for an average of 4.3 years, it was shown that patients diagnosed with HCC between the years of 2008 and 2014 were 1.6 times higher than those diagnosed between 2001 and 2007. The most common HCC etiology was HCV in 45%, alcoholic liver disease in 31% and NAFLD in 15%. In addition, 51% of HCV-infected patients had additional alcohol use. NAFLD has been identified as the most increased cause of HCC in time.[30]

Alcohol-induced HCC increased 2013 and later, but there was no significant difference. Alcoholic liver disease is an important cause of HCC in developed countries.[11] At the same time, alcohol, HBV infection, HCV infection and diabetes increases the risk of HCC.[31]

The mean age of the patients was 64.4 years. Male patients were in the majority. There was no difference between the mean age and gender before and 2013 and later. It is known that advanced age and male gender increase the risk of HCC in cirrhosis due to different etiologies.[6,11,19,32] HCC is rarely seen before 40-50 years of age.[19] The incidence of HCC in men is 2-4 times higher than in women worldwide.[28]

When the patients were evaluated, there was a significant increase in the rate of patients who were in compensated cirrhosis stage and in UCSF criteria in and 2013 and later. Thus, the rates of curative treatment were significantly higher 2013 and later. In a meta-analysis of 15158 patients with HCC, it was shown that HCC follow-up in patients with cirrhosis increased the rate of determined the mass at an earlier stage, curative treatment and survival.[33] With early detection of HCC and curative treatment, the 5-year survival rate in HCC increases to 70%.[34] In this case, the higher proportion of patients detected in early stage in 2013 and later may be the application of an earlier stage when the tumor size is still small. The reason for no change in transplantation rates may be due to problems in finding donors in our country.

In present study, a significant difference was found in the mortality rates related to HCC before and 2013 and later. It was thought that the reason for this was a higher rate of compensated cirrhosis at the time of diagnosis and the detection of the masses when it was still small. Mortality data in HBV-associated HCC were better than NAFLD and HCV-related mortality, but the difference was not statistically significant ($p = 0.117$).

In a US study, HCV was found to be the most common cause of HCC induced deaths with a rate of 67% between 2001 and 2013. 61.3% of patients with HCV infection had accompanying alcohol use. HCC mortality increased for 3 folds from 13 to 37 in every hundred thousand patient-years. The other most common causes of HCC mortality were NAFLD with 15% and alcoholic liver disease with 12%. It was estimated that NAFLD will be the main cause of HCC in the future due to the increasing rates of obesity and diabetes.[11]

In another study, the risk of HCC related mortality increased by 2% between 2007 and 2016. Although HBV associated HCC mortality was found to be decreased by effective antiviral therapy, the same decrease was not found in HCC related mortality rates due to HCV infection. HCC mortality rates related to HCV, NAFLD and alcoholic liver disease were similar in 10 years period.[35] In a similar study, there was a significant decrease in HBV-associated HCC mortality rates with effective antiviral treatment.[36] The results of these studies are similar to the causes of HCC-related mortality in present study.

One of the limitations of present study was that the diagnosis of NAFLD related cirrhosis was based on the presence of obesity and diabetes in patients excluded from viral hepatitis. In addition, the total mortality of the patients was investigated and the rate of deaths other than the liver is unknown. Another limitation of present study may be the follow up of the patients for 12 years. Changes in other groups may also be noticed during longer follow-up periods.

CONCLUSION

In conclusion, there have been significant changes in the etiology and mortality of HCC over the years. Worldwide, HCC rates associated with HBV and HCV infection, which are effectively treated with antiviral agents, are observed to be decreasing, while the rates of NAFLD related HCC due to diabetes and obesity are increasing. There is also an increase in alcohol-induced HCC rates and mortality, especially in developed countries. Most HCC related diseases are treatable diseases. Knowing the change of HCC causes over the years is necessary for the effective treatment for these reasons in the future.

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