RESEARCH ARTICLE

Multicenter Epidemiologic Study on Hepatocellular Carcinoma in Turkey

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Abstract

Background: Hepatocellular cancer (HCC) is one of the important health problems in Turkey, being very common and highly lethal. The aim of this study was to determine clinical, demographic features and risk factors. Materials and Methods: Nine hundred and sixth-three patients with HCC from 13 cities in Turkey were included in this study. Results: Only 205 (21%) of the 963 patients were women, with a male:female predominance of 4.8:1 and a median age of 61 years. The etiologic risk factors for HCC were hepatitis B in 555 patients (57.6%), 453 (81%) in men, and 102 (19%) in women, again with male predominance, hepatitis C in 159 (16.5%), (14.9% and 22.4%, with a higher incidence in women), and chronic alcohol abuse (more than ten years) in 137 (14.2%) (16.8% and 4.9%, higher in males). The Child-Pugh score paralleled with advanced disease stage amd also a high level of AFP. Conclusions: According to our findings the viral etiology (hepatitis B and hepatitis C infections) in the Turkish population was the most important factor in HCC development, with alcohol abuse as the third risk factor. The Child-Pugh classification and AFP levels were determined to be important prognostic factors in HCC patients.

Keywords: Hepatocellular carcinoma - etiologic factors - alpha-fetoprotein - Turkey

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Introduction

Hepatocellular carcinoma (HCC) is one of the common tumors in the world. It is the 5th and 8th most common malignancy in men and woman respectively (Monto et al., 2001). HCC has various risk factors. Hepatitis B virus is frequently positive especially in Asia and Africa, whilst hepatitis C virus is positive in Europe and North America (Bosch et al., 1999, Bruix et al., 2005; Norsa'adah and Nurhazalini-Zayani, 2013; Su et al., 2013; Yeo et al., 2013). AASLD Practice Guidelines). Chronic liver disease and cirrhosis, is the most common cause of HCC. Hepatitis B and C viruses are the most common factors of chronic liver disease and cirrhosis (Monto et al., 2001;). Therefore, HCC incidence was parallel to hepatitis B and C incidences. Other risk factors of HCC are alcohol, aflatoxin exposure, hemochromatosis, and cryptogenic hepatitis, for example.

The rate of hepatitis B carriage (HBS ag+) is 4%; and the rate of hepatitis C carriage (Anti HVC+) is 0.95% in Turkey, according to TURKHEP's 2010 data on the hepatitis B and C incidences of in Turkey (TURKHEP, 2010). HCC incidence is 0.83/100000, according to 2003 data from the Ministry of Health of Turkey.

HCC prognosis is very poor. Classical chemotherapeutic agents are barely effective. Long time of life is possible only in cases containing surgically full-excision or liver transplantation. Therefore, early diagnosis and scanning are highly important. In China, semi-annual AFP and liver ultrasonography scan of 18,816 men and women has reduced the HCC related mortality by 37% (Zhang et al., 2004).

Our study is aimed at determining the epidemiological characteristics, etiological causes, tumor characteristics and AFP levels of HCC in Turkey; as well as emphasizing the fact that a full healing can be achieved through the early diagnosis of HCC that is a reasonably preventable type of cancer.

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Materials and Methods

Throughout Turkey, a total of 963 patients diagnosed with HCC were included in this study. The distribution of the patients by provinces is as follows: 181 from Ankara, 40 from Diyarbakir, 185 from Izmir, 103 from Van, 16 from Malatya, 100 from Antalya, 50 from Isparta, 13 from Sivas, 98 from Istanbul, 50 from Bolu, 83 from Kayseri, 25 from Elazig, and 20 from Gaziantep.

Their diagnoses of HCC were made histological, by means of Liver biopsy. Their demographic characteristics, tumor characteristics, tumor sizes, lymph node involvements, and existent distant metastases were identified. Tumor staging was made in accordance with version 2010 7th ed of the American Joint Committee on Cancer (AJCC).

The use of alcohol was considered to be >60g per day in women, and >80g per day in men, for a period of decade. (HBS Ag+) and (Anti HCV+) were referred to for HBV positivity (+) and HVC positivity (+), respectively. Existence of albumin, total bilirubin, INR (prothrombin time), acid and encephalopathy in the patients were determined, and their Child-pugh scores were calculated. Child score was divided into 3 groups (A, B, C). They were classified as Child A with Child score 5-6, Child B with Child score 7-9, and Child C with Child score 10-15. The alpha fetoprotein (AFP) levels were measured in venous blood. The normal AFP limit was considered to be <5.8 ng/ml. The AFP levels were divided into three groups, as Group 1 with lower AFP: 5, 8-20 ng/ml, Group 2 with mean AFP: 20-400 ng/ml, Group 3 with high AFP: >400 ng/ml.

Statistical analysis

Descriptive statistics for studied variables (characteristics) were presented as count and percent. For determination the relationships among the categorical variables, Chi-square test was carried out. Statistical significance levels were considered as 5%. The SPSS (ver. 13) statistical program was used for all statistical computations

Results

In total, 963 patients were evaluated. Of the patients, 205 (21%) were female, and 758 (79%) were men. Mean age of the women was 60.05±13.8 (15-91), and that of the men was 61.42 ±11.1 (18-96). As one of the risk factors, HBV was positive in 555 (57.6%) patients. HBSag was found to be positive (+) in 453 (59.8%) of the men patients, and 102 of the women patients (49.8%). HBV rate was observed to be higher in men (p: 0.01). HCV was positive in 159 (16.5%) patients. Anti HCV was found to be positive (+) in 113 of the men (14.9%), and in 46 of the women (22.4%). When compared to the men, the women were observed to have higher levels of HCV (p: 0.01). On the other hand, HDV was could be analyzed in 582 patients. HDV was positive in 24 (4.1%) patients. The presence of alcohol use was ascertained in 137 (14.2) patients. In parallel to this, 127 of the men (16.2%), and 10 of the women (4.9%) had used alcohol. When compared to the women, the men had more history of alcohol (p: 0.001) Child-pugh scores of the patients were observed. Of the patients, 517 (53.7%) were Child A, 254 (26.4%) were Child B, and 192 (19.6%) were Child C. 104 (50.7%) of the women and 413 (54.5%) of the men were Child A, 59 (28.8%) of the women and 195 (25.7%) of the men were Child B, 42 (20.5%) of the women and 150 (19.8%) of the men were Child C. The Child scores in the both sexes were found to be similar (p: 0.596) (Table 1). AFP levels could be measured in 862 of the patients. Among those patients, 190 (22%) were women and 672 (78%) were men. Patients were classified in 3 groups, according to their AFP levels. There were 315 (36.5%) patients in Group I, 297 (34.5%) patients in Group II, and 250 (29%) patients in Group III. Of the women, 77 (40.5%) were in Group I, 64 (33.7%) were in Group II, and 49 (25.8%) were in Group III, according to AFP level. Of the men, 238 (35.4%) were in Group I, 233 (34.7%) were in Group II, and 201 (29.9%) were in Group III, according to AFP level. According to the AFP groups, there was no difference between the men and women (p.0.374) (Table 3). Tumor staging in the patients was made according to version 7 (AJCC, 2010). There were 193 (20%) patients at Stage II, 248 (25.8%) at Stage II, 261 (27.1%) at Stage III, and 261 (27.1%) at Stage IV. Of the women, 44 (21.5%) had Stage I disease, 54 (26.3%) had Stage II disease, 51 (24.9%) had Stage III disease, and 56 (27.3%) had Stage IV disease. Of the men, 149 (19.7%) had Stage I disease, 194 (25.6%) had Stage II disease, 210 (27.7%) had Stage III disease, and 205 (27%) had Stage IV disease. No difference was found between men and women, in terms of tumor stage classification (p: 0.855) (Table 2).

When considering the HCC etiologic factors, 555 patients were distributed according to their Child score classification. Of the HBV patients, 287 (51.7%) were Child A, 151 (27.2%) were Child B, and 117 (21.1%) were Child C patients. 408 HBV (HBSag-) negative patients were distributed according to Child score classification. Of the HBV patients, 230 (56.4%) were Child A, 103 (25.2%) were Child B, and 75 (18.4%) were Child C patients. No difference was found between the HBV+ patients and HBV– patients, in terms of Child score classification (p: 0.341) (Table 1). The correlation between the existence of HBV and AFP levels were analyzed. AFP levels of 862 patients were analyzed. Accordingly; Of the 492 HBV (HBSag+) positive patients, 159 (32.3%) were in Group I, 173 (35.2%) were in Group II, and 160 (32.5%) were Group III. Of the 370 HBV (HBSag-) negative patients, 156 (42.2%) were in Group I, 124 (33.5%) were in Group II, and 90 (24.3%) were Group III. The HBSag+ patients were seen to be associated with higher AFP levels (p: 0.005) (Table 3). The correlation between the existence of HBV and tumor stage was analyzed. Accordingly; Of the 555 HBV (HBSag+) positive patients, 118 (21.3%) were at Stage I, 142 (25.6%) were at Stage II, 139 (25%) were at Stage III, and 156 (28.1%) were at Stage IV. Of the 408 HBV (HBSag-) negative patients, 75 (18.4%) were at Stage I, 106 (26%) were at Stage II, 122 (29.9%) were at Stage III, and 105 (25, 7%) were at Stage IV. These results do not show us a significant difference between the existence of HBV and the tumor stage (p:

0.318) (Table 2). 159 HCV (anti HCV+) patients were distributed according to Child score classification: Of the anti HCV (+) positive patients, 77 (48.4%) were Child A, 40 (25.2%) were Child B, and 42 (26.4%) were Child C patients. 804 Anti HCV (-) negative patients were distributed according to Child score classification. Of the HCV (-) patients, 440 (54.7%) were Child A, 216 (26.6%) were Child B, and 150 (18.4%) were Child C patients. No difference was found between the HCV (+) patients and HCV (–) patients, in terms of Child score classification (p: 0.078) (Table 1). The correlation between the existence of HCV and AFP levels were analyzed. AFP levels of 862 patients were analyzed. Of the 156 anti HCV (+) positive patients, 48 (30.8%) were in Group I, 77 (49.4%) were in Group II, and 31 (19.9%) were in Group III. Of the 706 anti HCV (-) negative patients, 267 (37.8%) were in Group, 220 (31.2%) were in Group II, and 219 (31%) were in Group III. The anti HCV+ patients were seen to be associated with higher AFP levels (p: 0.001) (Table 3). The correlation between the existence of HCV and tumor stage was analyzed. Of the 159 HCV (+) positive patients, 30 (18.9%) were at Stage I, 36 (22.6%) were at Stage II, 30 (18.9%) were at Stage III, and 63 (%39.6) were at Stage IV. Of the 804 Anti HCV (-) negative patients, 163 (20.3%) were at Stage I, 212 (26.4%) were at Stage II, 231 (28.7%) were at Stage III, and 198 (24.6%) were at Stage IV. As one of the etiologic factors of HCC, HCV positivity were seen to be associated with advanced-stage tumor (p: 0.001) (Table 2).

The patients were classified in Groups A, B, and C, according to the Child scores. The correlation between Child score and tumor stage was analyzed. Of the 517 patients in Child score Group A, 122 (23.6%) had Stage I, 151 (29.2%) had Stage II, 110 (21.3%) had Stage III, and 134 (25.9%) had Stage IV diseases. Of the 254 patients in Child score Group B, 41 (16.1%) had Stage I, 61 (24%) had Stage II, 74 (29.1%) had Stage III, and 78 (30.7%) had Stage IV disease. Of the 254 patients in Child score Group C, 30 (15.6%) had Stage I, 36 (18.8%) had Stage II, 77 (40.1%) had Stage III, and 49 (25.5 %) had Stage IV diseases. High Child score and advanced-stage disease were seen to be associated with each other (p: 0.001) (Table 2).

Table 1. Child-pugh Score Distribution According to Gender, Child-pugh Score Relationship with HBV and HCV

	Child A N (%)	Child B N (%)	Child C N (%)	Total N (%)
Child-pugh score distribution according to gender*				
Female	104 (50.7)	59 (28.8)	42 (20.5)	205 (100)
Male	413 (54.5)	195 (25.7)	150 (19.8)	758 (100)
Total	517 (53.7)	254 (26.4)	192 (19.9)	963 (100)
Child-pugh score relationship with HBV**				
HBV-negatif	230 (56.4)	103 (25.2)	75 (20.5)	408 (100)
HBV+pozitif	287 (51.7)	151 (27.2)	117 (21.1)	555 (100)
Total	517 (53.7)	254 (26.4)	192 (19.9)	963 (100)
Child-pugh score relationship with HCV***				
HCV-negatif	440 (54.7)	214 (26.6)	150 (18.7)	804 (100)
HCV+pozitif	77 (48.4)	40 (25.2)	42 (26.4)	159 (100)
Total	517 (53.7)	254 (26.4)	192 (19.9)	963 (100)

*x^2: 1.03, p: 0.596; **x^2: 2.15, p: 0.341; ***x^2: 5, p: 0.078, HCV-: Anti HCV negative, HCV+: Anti HCV positive

Table 2. Tumor Stage

	I N (%)	II N (%)	III N (%)	IV N (%)	Total N (%)
Tumor stage according to gender[a]					
Female	44 (21.5)	54 (26.3)	51 (24.9)	56 (27.3)	205 (100)
Male	149 (19.7)	194 (25.6)	210 (27.7)	205 (27)	758 (100)
Total	193 (20)	248 (25.8)	261 (27.1)	261 (27.1)	963 (100)
Tumor stage relationship with HBV[b]					
HBV-	75 (18.4)	106 (26)	122 (29.9)	105 (25.7)	408 (100)
HBV+	118 (21.3)	142 (25.6)	139 (25)	156 (28.1)	555 (100)
Total	193 (20)	248 (25.8)	261 (27.1)	261 (27.1)	963 (100)
Tumor stage relationship with HCV[c]					
HCV-	163 (20.3)	212 (26.4)	231 (28.7)	198 (24.6)	804 (100)
HCV+	30 (18.9)	36 (22.6)	30 (18.9)	63 (39.6)	159 (100)
Total	193 (20)	248 (25.8)	261 (27.1)	261 (27.1)	963 (100)
Child-pugh score and tumor stage relationship[d]					
A	122 (23.6)	151 (29.2)	110 (21.3)	134 (25.9)	517 (100)
B	41 (16.1)	61 (24)	74 (29.1)	78 (30.7)	254 (100)
C	30 (15.6)	36 (18.8)	77 (40.1)	49 (25.5)	192 (100)
Total	193 (20)	248 (25.8)	261 (27.1)	261 (27.1)	963 (100)
AFP score and tumor stage relationship[e]					
Grup I	82 (26)	87 (27.6)	79 (25.1)	67 (21.3)	315 (100)
Grup II	60 (20.2)	67 (22.6)	79 (26.6)	91 (30.6)	297 (100)
Grup III	45 (18)	59 (23.6)	77 (30.8)	69 (27.6)	250 (100)
Total	187 (21.7)	213 (24.7)	235 (27.3)	227 (26.3)	962 (100)

[a]x^2: 0.77, p: 0.855; [b]x^2: 3.5, p: 0.318; HBV-: HBSag negative, HBV+: HBSag positive; [c]x^2: 16.6, p: 0.001; HCV-: Anti HCV negative, HCV+: Anti HCV positive; [d]x^2: 33.9, p: 0.001; [e]x^2:13.4, p: 0.037; Group I: AFP: 5.8-20 ng/ml, Group II AFP 20-≤400 ng/ml, Group III AFP: >400 ng/ml

Table 3. AFP Level

	Group I N (%)	Group II N (%)	Group III N (%)	Total N (%)
AFP level distribution according to gender*,***				
Female	77 (40.5)	64 (33.7)	49 (25.8)	190 (100)
Male	238 (35.4)	233 (34.7)	201 (29.9)	672 (100)
Total	315 (36.5)	297 (34.5)	250 (29)	862 (100)
AFP level relationship with HBV**,***				
HBV-	156 (42.2)	124 (33.5)	90 (24.3)	370 (100)
HBV+	159 (32.3)	173 (35.2)	160 (32.5)	492 (100)
Total	315 (36.5)	297 (34.5)	250 (29)	862 (100)
AFP level relationship with HCV***,****				
HCV-	267 (37.8)	220 (31.2)	219 (31)	709 (100)
HCV+	48 (30.8)	77 (49.4)	31 (19.9)	156 (100)
Total	315 (36.5)	297 (34.5)	250 (29)	862 (100)

*x^2: 1.96, p: 0.374; **x^2: 10.6, p: 0.005; ***x^2: 19, p: 0.001; HCV-: Anti HCV negative, HCV+: Anti HCV positive; ****Group I: AFP: 5,8-20 ng/ml, Group II AFP 20-≤400 ng/ml, Group III AFP: >400 ng/ml

The patients were classified in 3 groups, according to their AFP levels. (I, II, III). The correlation between AFP levels and tumor stage was analyzed. Accordingly, of the 315 patients in AFP Group I, 82 (26%) had Stage I, 87 (27.6%) had Stage II, 79 (25.1%) had Stage III, and 67 (21.3%) had Stage IV diseases. Of the 297 patients in AFP Group II, 60 (20.2%) had Stage I, 67 (22.6%) had Stage II, 79 (26.6%) had Stage III, and 91 (30.6%) had Stage IV diseases. Of the 250 patients in AFP Group III, 45 (18%) had Stage I, 59 (23.6%) had Stage II, 77 (30.8%) had Stage III, and 69 (27.9%) had Stage IV diseases. High AFP level and advanced-stage disease were seen to be associated with each other (p: 0.037) (Table 3).

Discussion

HCC is a malignant epithelial liver tumor. HCC is the fifth most common type of cancer in the world. It is ranked 3rd among the cancer-related deaths (Kamangar et al., 2006) Our study is aimed at determining the

epidemiological characteristics, etiological causes, tumor characteristics and AFP levels of HCC in Turkey.

According to our findings, HCC is a disease of the elderly population in particular. HBV and HCV viruses as well as the use of alcohol are the major risk factors of HCC. In our study, HBV virus, HCV virus, and alcohol use were ascertained to be the 1st, 2nd and 3rd most common risk factors of HCC, with the ratios of 57.6 %, 16.5%, and 14.2%, respectively.

Hepatitis B virus is the most known factor of HCC. According to a study carried out by TURKHEP in 2010, hepatitis B virus carriage (HBSag+) is 4% in Turkey (TURKHEP, 2010). HCC development risk for HBV carriers throughout their lives is 1%. The risk of HCC development has 100-fold increased in those infected with HBV, when compared with that in those not infected with HBV. (Beasley et al., 1981). HBV virus is the most common cause of HCC, particularly in Asian, the Middle Eastern and Far Eastern countries (Ozer et al., 2003; Marrero et al., 2007; Lehman et al., 2009). In 5 separate studies in Turkey, the HBV incidence in HCC etiology was different (Uzunalimoglu et al., 2001; Alacacioglu et al., 2008; Dogan et al., 2012; Yaprak et al., 2012; Yalcin et al., 2013). In the study carried out by Uzunalimoglu. et al. (2001), the HBV incidence in HCC patients was 56% . In the study carried out by Alacaci et al in 2008, the HBV incidence in HCC patients was 44.4%. In the study carried out by Dogan et al. (2012), the HBV incidence in HCC patients was 60.2%. In the study carried out by Yaprak et al. (2012), the HBV incidence in HCC patients was 53.3%. In the study carried out by Zidan et al. (2012), the HBV incidence in HCC patients was 67% in China. In the study carried out by Lee et al. (2013), the HBV incidence in HCC patients was 61.6% in Taiwan. In the study carried out by Lim et al. (2013), the HBV incidence in HCC patients was 76.1% in Korea. In the study carried out by Yalcin et al. (2013), the HBV incidence in HCC patients was 45%. In the study carried out by Geramizadeh et al. (2012) the HBV incidence in HCC patients was 87%. And in our study, the HBV incidence in HCC patients was 57.6%. According to the findings in our study, the men had higher HBSag+ than the women (p: 0.01).

Hepatitis C virus is the second most well-known factor of HCC. In TURKHEP's studies carried out in 2010, the hepatitis C virus carriage in Turkey (anti HCV+) was 0.95%. HCV viruses the primary cause of HCC, particularly in European and other Mediterranean countries (Markovic et al., 1998; Stroffolini et al., 1998; Borzio et al., 2007). In 5 separate studies in Turkey, the HCV incidence in HCC etiology was different. The HCV incidence in HCC patients was 23.2% in the study carried out by Uzunalimoglu et al. (2001). The HCV incidence in HCC patients was 21.3% in the study carried out by Alacaci et al. (2008). The HCV incidence in HCC patients was 15% in the study carried out by Dogan et al. (2012). The HCV incidence in HCC patients was 16.3% in the study carried out by Yaprak et al. (2012). In the study carried out by Geramizadeh et al. (2012) the HCV incidence in HCC patients was 13%. In the study carried out by Zidan et al. (2012) the HCV incidence in HCC patients was 14% in China. In the study carried out by Lee et al. (2013) the HCV incidence in HCC patients was 45.7% in Taiwan. The HCV incidence in HCC patients was 15%. in the study carried out by Yalcin et al. (2013). And in our study, the HCV incidence in HCC patients was 16.5%. According to the findings in our study, the women had higher HCV+ than the men (p: 0.01).

Alcohol use is another important cause of HCC. In the study carried out by Lee et al. (1966) the risk of annual HCC development in patients with alcohol-related cirrhosis was 1-4% of (Lee et al., 1966). In another study, the alcohol-related HCC development was 32% (Hassan et al., 2002). Alcohol-related HCC development is higher in western countries (Schoniger-Hekele et al., 2001). Alcohol use, as a cause of HCC, ranges from from 5 to 15.9%, according to the studies in Turkey (Uzunalimoglu et al., 2001; Alacacioglu et al., 2008; Dogan et al., 2012; Yaprak et al., 2012; Yalcin et al., 2013). And in our study, the alcohol-related HCC development was 14.2%. According to studies in Turkey, alcohol-related HCC development lower than that in western countries is caused by the Islamic societies in Turkey.

High Child-pugh score is an independent risk factor in chronic liver disease and HCC. The study carried out by Sakar et al. (1998), and the study carried out by Borzio et al. (2007) show that Child-pugh classification is an independent risk factor for HCC. In our study, it is seen that the high Cild-pugh score is parallel to advanced stage HCC disease (p: 0.001).

Tumor indicators are important indicators in cancer diagnosis, staging, prognosis determination, recurrence detection, evaluation of the response to follow-up and treatment for patient population and normal population. Despite this, the AFP (alpha feto protein) is an important tumor indicator in the diagnosis of HCC. AFP's sensitivity and specificity in HCC is 39-65% and 79-97% respectively. In many studies, it is stated that AFP is an important prognostic factor in HCC (Purtilo et al., 1973; Stuart et al., 1996; Fong et al., 1999; Wang et al., 2002; Yaprak et al., 2012; Chang et al., 2013). In the study carried out by Xu et al. (2012), the high AFP value (AFP >20 ng/dl) indicated that HCC had a poor prognosis. And in the study carried out by Sakar et al. (2004), high AFP levels in HCC patients in Turkey had a correlation with poor prognosis. In our study, 67.3% of the patients had high AFP levels (>20 ng/dL). At the same time, high AFP level was parallel to advanced-stage disease (p: 0.037).

As a result, HCC is a deadly tumor, to a considerable extent. Especially in Turkey, diagnosis is made at advanced-stages (stage III-IV). Therefore, it is very important in terms of making HCC diagnosis at an early stage. The high frequency of risk factors such as HBV and HCV in Turkey, and their follow-up through serial liver ultrasonography and as well as their AFP levels would enable HCC to be diagnosed at earlier stages. In our multicenter and retrospective study, it was emphasized that especially HBV and HCV viruses were among the most important factors of HCC in Turkey. At the same time, Child-pugh score and AFP level were emphasized to be prognostic for HCC.

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