ORIGINAL ARTICLE

ETIOLOGY AND DEMOGRAPHIC FEATURES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Hepatosellüler Karsinoma Tanılı Hastalarda Etiyoloji ve Demografik Özellikleri

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ABSTRACT

Objective: Hepatocellular cancer (HCC) is an aggressive tumor that often develops on the basis of chronic liver disease and cirrhosis. It was aimed to examine the demographic, clinical and tumor characteristics of hepatocellular cancer due to different etiologies.

Material and Methods: Patients aged 18 years and older who applied to the gastroenterology department of Ege University Medical Faculty Hospital between 2006 and 2012 with the diagnosis of HCC were included in the study.

Results: Eighty-two and one tenths percent of the patients were male, 17.9% were female, and there was a significant difference between the genders. It was observed that 58% of HCC developed due to hepatitis B infection (HBV). While 54% of the patients had a known diagnosis of chronic liver disease (CHD) before the diagnosis of HCC, 46% had no known history of CHD. The serum alpha-fetoprotein (AFP) level used in the diagnosis of HCC was ≥400 ng/ml in 30.6% of the patients. When patients were evaluated according to MELD scoring, it was found to be significantly associated with prognosis. During the follow-up, 47 of the patients died due to HCC recurrence, liver failure, and coma. The mean follow-up period of patients who ended in death was 8.48 months.

Conclusion: Hepatocellular carcinoma is usually seen in older male patients. While viral hepatitis is more common in HCC etiology than other diseases, it is seen that HBV infection is the most common in this group. The MELD score is a valuable predictor of HCC prognosis.

Keywords: *Hepatocellular Carcinoma; Etiology; Chronic Viral Hepatitis.*

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ÖZET

Amaç: Hepatoselüler kanser (HCC), sıklıkla kronik karaciğer hastalığı ve siroz temelinde gelişen agresif bir tümördür. Çalışmamızda farklı etiyolojilere bağlı hepatoselüler kanserin demografik, klinik ve tümör özelliklerinin incelenmesi amaçlandı.

Gereç ve Yöntemler: Çalışmaya 2006-2012 yılları arasında Ege Üniversitesi Tıp Fakültesi Hastanesi gastroenteroloji kliniğine başvuran 18 yaş üstü HCC tanılı hastalar alındı.

Bulgular: Hastaların %82'si erkek, %17,9'u kadındı ve cinsiyetler arasında anlamlı fark vardı. HCC'nin %58'inin hepatit B enfeksiyonuna (HBV) bağlı geliştiği gözlendi. Hastaların %54'ünün HCC tanısından önce bilinen bir kronik karaciğer hastalığı (KKH) tanısı varken, %46'sının bilinen bir KKH öyküsü yoktu. HCC tanısında kullanılan serum alfa-Fetoprotein (AFP) düzeyi hastaların %30,6'sında ≥400 ng/ml idi. Hastalar MELD skorlamasına göre değerlendirildiğinde prognoz ile anlamlı olarak ilişkili bulundu. Takiplerde 47 hasta HCC nüksü, karaciğer yetmezliği ve koma nedeniyle öldü. Ölümle sonuçlanan hastaların ortalama takip süresi 8.48 aydı.

Sonuç: HCC genellikle ileri yaşta ve erkek hastalarda görülür. En sık neden viral hepatitlerdir ve en sık HBV enfeksiyonları görülmektedir. MELD skoru hastalığın prognozunu gösteren değerleri bir belirteçtir.

Anahtar Kelimeler: *Hepatoselüler Karsinoma; Etiyoloji; Kronik Viral Hepatitler*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver, and is the fifth most common solid tumor in the world, and the third in cancer-related deaths (1, 2). The most important known risk factor for the development of HCC is cirrhosis, and more than 80% develop on the basis of cirrhotic liver. The incidence of HCC in cirrhosis is 1-6% (3, 4). Viral infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV) are the main causes of cirrhosis (5). In countries with moderate endemicity, including Turkey, the prevalence of hepatitis B infection varies between 2% and 8% (6). HCV seropositivity has been reported as 0.5% in our country (7). Eighty percent of the etiology of HCC is due to chronic HBV and chronic HCV infections (8). Additional factors such as age, gender, alcohol use, and concomitant diseases may contribute to the development of HCC or may occur in patients with no risk factors (9).

Only 0-10% of patients survive for 5 years after symptoms related to cancer appear (10). The Model for End-stage Liver Disease (MELD), Barcelona Clinic Liver Cancer Staging System (BCLC), Cancer of the Liver Italian Program (CLIP) and Okuda staging criteria have been revealed through various studies in patients with HCC (11). Treatment might be curative options such as surgical resection and transplantation when the disease is diagnosed at an early stage when symptoms do not occur (9). However, there are also non-curative treatments such as transarterial embolization (TAE), transarterial chemoembolization (TACE) and sorafenib (9). There are many studies in the literature that include demographic and laboratory data of HCC patients. In our study, we aimed to evaluate the data of our own centre. We aimed to determine the demographic characteristics of our patients with HCC and the prognostic factors affecting survival.

MATERIAL and METHODS

In our study, 357 HCC patients followed up in Ege University, Faculty of Medicine Gastroenterology Clinic between January 2006 and January 2012 were retrospectively analysed. Thirty-three patients were excluded from the study due to insufficient data. Age, gender, comorbidity, drug and alcohol usage history of all patients included in the study were recorded. The study was approved by the Ege University Clinical Research Ethics Committee (Decision no:12-6/10, 18.07.2012)

All patients' aspartate aminotransferase (AST 0-35 u/L), alanine aminotransferase (ALT 0-35 u/L), gamma-Glutamyltransferase (GGT 0-38 u/L), alkaline phosphatase (ALP 30-120 u/L), albumin (3.5-5.5 g/dL), prothrombin time (PT), total and direct bilirubin (total bilirubin:0.2-1.2 mg/dl, direct bilirubin: 0-0.3 mg/dl), α-fetoprotein (AFP) levels and hemogram results were recorded. Anti-HCV, as well as diagnosis hepatitis B surface antigen (HBsAg), anti-HBs, and anti-delta values (Anti-HDV) were studied with the enzyme linked immunosorbent assay (ELISA) method and recorded. The presence of accompanying portal vein thrombosis (PVT), ascites, esophageal variceal bleeding (EVB), and hepatic encephalopathy were evaluated. From all these results, the patients' MELD score ((9.6 x Cre mg/dL) + (3.8 x Bilirubin mg/dL) + (11.2 x INR)) and Child Turcotte Pugh (CTP) scores were calculated.

The number, size and localization of tumours were recorded by liver ultrasonography and magnetic resonance imaging of the patients.

The treatment of the patients was determined according to the Milan criteria and BCLC staging.

The time from the time of diagnosis to the last outpatient admission or death was taken as survival.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) program version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY). The relationship between clinical data and etiology was calculated by Kaplan-Meier method, Fisher's Exact Test and Chi-Square tests. p value <0.05 was considered significant.

RESULTS

Three hundred twenty-four patients were included in the study. Of these patients, 82.1% were male and 17.9% were female, and there was a significant difference between the genders (p<0.001). The mean age was 61.73 ± 10.173 in men and 62.71 ± 11.335 in women. There was no significant difference between the genders in terms of mean age (Table 1).

It was observed that HCC was due to HBV 48.3% and HCV 18.3%. HBV and HDV association was 5.1%,

Bozok Tıp Derg 2022;12(2):57-62
Bozok Med J 2022;12(2):57-62

Table 1. Demographic data in hepatocellular carcinomas.

	Number of patients (n, %)
Age (mean)	61.9
Sex	
Female	58 (17.9)
Male	266 (82.1)
Etiology	
HBV	161 (48.3)
HCV	61 (18.3)
HBV+HDV	17 (5.1)
HBV+HCV	4 (1.2)
Ethanol	37 (11,1)
Cryptogenic	34 (10.2)
NASH	2 (0.6)
Noncirrhotic	5 (1.5)
Autoimmune hepatitis	1 (0.3)
PSC	1 (0.3)
PBC	1 (0.3)
CHD	
Present	175 (54)
Absent	149 (46)
DM	
Present	70 (21.6)
Absent	254 (78.4)

NASH: Non-alcoholic steatohepatitis,
PSC: Primary sclerosing cholangitis, **PBC:** Primary biliary cirrhosis,
CHD: Chronic liver disease, **DM:** Diabetes mellitus,
HBV: Hepatitis B virus, **HCV:** Hepatitis C virus, **HDV:** Hepatitis D virus

HBV and HCV association was 1.2%. Of the patients with HBV infection, 87.5% were male and 12.5% were female. There was a significant difference between the genders (p<0.001). While male gender was detected in 62.3% of patients with HCV infection, female gender was 37.7%. When evaluated in terms of HCC etiology, HBV (53%) in men and HCV (39.6%) in women were predominant (Table 1).

Before the diagnosis of HCC, 175 patients (54%) had a known diagnosis of chronic liver disease (CHD), while 149 patients (46%) had no known history of CHD and were diagnosed with HCC at the first admission. The mean time between the diagnosis of CHD and the diagnosis of HCC was 72.25 months. While this period was 77.5 months in patients with HBV diagnosis, it was 70.2 months in patients with HCV diagnosis. There was no significant relationship between the time to HCC development and etiology.

Three hundred and twenty-three patients were evaluated for tumor characteristics. Single lesion in 50.6% patients (n= 164), two lesions in 11.4% patients (n= 37), three lesions in 6.2% patients (n= 20), four or more lesions (multiple tumours) in 31.5% patients (n= 102) were seen. In the patient group that ended in death, a single tumor was found in 53.2%, two tumours in 14.9%, three tumours in 4.3%, and four or more tumours in 14.4%. No significant correlation was found between the prognosis and the number of tumours (p>0.05).

The serum AFP level used in the diagnosis of HCC was <20 ng/ml in 137 patients (42.3%), 20-200 ng/ml in 63 patients (19.4%), and 201-399 ng/ml in 25 patients (7.7%). AFP level was found above ≥400 ng/ml in 99 of the cases (30.6%) (Table 2). When we evaluated the relationship between AFP level and prognosis in patients with ended death, 10.2% of the patients had AFP <20ng/ml, 20.2% had AFP ≥400ng/ml, and a significant difference was found between the two groups. (p<0.05). It was observed that the death rate increased as the AFP level increased. When the number of tumours and AFP values were compared, the mean AFP was 30.50 in those with a single tumor, while it was 138.00 in those with multiple tumours, and a significant difference was observed between these two values (p<0.005).

Of the 324 patients in the study, 317 were evaluated for PVT and it was present in 30% (n= 97). PVT was seen in 25.5% of patients with HBV and in 33.9% of patients with HCV. Hepatic encephalopathy was present in 9.9% (n= 32) and EBV was present in 12.7% (n= 41) of patients (Table 2).

In our study, patients were evaluated according to various staging systems (Table 2). CTP staging of 308 patients was calculated. Accordingly, Child-A was 52.6% (n= 162), Child-B was 33.8% (n= 104) and Child-C was 13.6% (n= 42). Of the 47 patients who died, 28.8%

Bozok Tıp Derg 2022;12(2):57-62
Bozok Med J 2022;12(2):57-62

Table 2. Complications and tumor characteristics in hepatocellular carcinomas

	Number of patients (n, %)
AFP level	
<20 ng/ml	137 (42.3)
20-200 ng/ml	63 (19.4)
201-399 ng/ml	25 (7.7)
>400 ng/ml	99 (30.6)
Portal Vein Thrombosis	
Present	97 (30)
absent	227 (70)
Hepatic Encephalopathy	
Present	32 (9.9)
Pbsent	292 (90.1)
Esophageal Varicose Bleeding	
Present	41 (12.7)
Absent	283 (87.3)
Number of Tumours	
1	164 (50.8)
2	37 (11.5)
3	20 (6.2)
≥4	103 (31.5)
CTP stage	
Child-A	162 (52.6)
Child-B	104 (33.8)
Child-C	42 (13.6)
BCLC Staging	
BCLC-A	94 (30.4)
BCLC-B	76 (24.6)
BCLC-C	88 (28.5)
BCLC-D	51 (16.5)
Distant Metastasis	
Present	30 (9.3)
Absent	294 (90.7)

AFP: Alpha-Fetoprotein,
CTP: Child Turcotte Pugh,
BCLC: Barcelona Clinic Liver Cancer Staging

were Child A, 44.4% Child B, 26.8% Child C (This group does not include end-stage patients with Child C who are out of follow-up for some reason). When the MELD Score was calculated, while it was 10% in the living group, it was 15.89% in the group that ended in death, and a significant difference was found between the two groups ($p<0.001$).

Table 3. Treatment options for hepatocellular carcinomas

Treatment option	Number of patients (n, %)
Transplantation	14 (4.3)
Surgical resection	16 (4.9)
Radiofrequency ablation	52 (16)
Percutaneous ethanol injection	14 (4.3)
Transarterial embolization or chemoembolization	136 (42)
Systemic chemotherapy	31 (11.7)

Liver transplantation was performed in 14 of 324 patients (4.3%) in our centre, and 22 patients (6.8%) were referred to another centre for liver transplantation. Liver transplantation was performed from a cadaveric donor in 3 patients and from a living donor in 10 patients, and the information of 1 patient could not be reached. Resection was performed in 16 patients (4.9%), radiofrequency ablation (RFA) in 52 patients (16%), percutaneous ethanol injection (PEE) in 14 patients (4.3%), and chemoembolization (TAE/TACE) in 136 patients (42%). Systemic chemotherapy was given to 37 patients (11.7%) (Patients in the study may have been treated with more than one method, and patients with recurrence after transplantation were recalculated in this group) (Table 3).

Forty-seven of the patients diagnosed with hepatocellular carcinoma died during follow-up due to relapse, liver failure, and coma. The mean follow-up period of the patients who ended in death was calculated as 8.48 months.

DISCUSSION

HCC is the most common (75%) primary tumor of the liver and its other name is hepatoma (12). While this rate was reported as 3.7/1 in our country, it was found as 4.4/1 in our study (13, 14).

The age of occurrence of HCC may vary according to

Bozok Tıp Derg 2022;12(2):57-62
Bozok Med J 2022;12(2):57-62

gender and possible etiology. It is seen in low-risk populations aged 75 and over, while in high-risk populations, it peaks between the ages of 60-65 in men and 65-70 in women (15). In our study, the mean age was 61.73 (SD= ±10.173) in men and 62.71 (SD= ±62.71) in women.

The incidence of HCC is related to HBV and 54% of the etiology of HCC is related to HBV (16). The most important factor increasing the risk of HCC in Turkey is HBV (17). In the study of Özer et al., the frequency of HBV was reported as 65.7%, and the frequency of HCV was 28.6% in patients with HCC (14). In the study of Uzunalimoğlu et al., the presence of HBV alone in the etiology of HCC was found to be 40% (13). In our study, HBV alone was observed in 48.3% of the patients and HCV alone was observed in 18.3% of the patients. HBV infection is still the most important cause of HCC.

In our study, 87.5% of the patients diagnosed with HBV were male and 12.5% were female, a statistically significant difference was found between the genders ($p<0.001$). On the other hand, 62.3% of the patients with HCV were male and 37.7% were female. It was observed that HBV and HCV infections were more common in males.

It is known that HCC often develops in the background of underlying CHD. In our study, 54% of the cases had a previous history of CHD. The mean time to HCC development in patients with known CHD was 72.25 months. This period was determined as 3.2 years in the study of Arhan et al. (7). The fact that this period was long in our study may be attributed to the regular follow-up of the patients and the increase in treatment modalities.

Tumor size and number are important in terms of treatment approach in HCC. Although a single nodular tumor is usually seen in CHD, more than one tumor can be seen in 1/3 of the patients (7, 18). In our study group, 50.6% single tumor and 31.5% multiple tumours were detected, no statistically significant correlation was found between the prognosis and the number of tumours.

Studies have shown that hypoalbuminemia, elevated bilirubin and AFP affect the prognosis of HCC (19). AFP levels between 10-20 ng/mL are known to have 60% sensitivity and 90% specificity, but AFP alone has low diagnostic value (20). AFP values of >400 ng/mL are known to indicate a poor prognosis (9). In our study, AFP level was also found to be an important marker in prognosis ($p<0.05$).

The MELD scoring system has been developed to evaluate patients according to bilirubin, prothrombin activity and creatinine levels. This system is used to identify patients awaiting transplantation (21). It is a reliable scoring system to show short-term mortality in patients with end-stage liver failure (22). In our study, the mean MELD score of the patients in the living group was 10%, while it was 15.89% in the death group. The MELD score successfully was shown mortality due to HCC.

The efficacy of treatments in hepatocellular carcinoma patients was compared, and the five-year survival rate was found to be 89% with surgical resection, 70% with RFA, 70% with PEE for tumours between 2-3 cm, 50% for tumours larger than 3 cm, and 44% with TACE (23). When the treatment methods in our study were evaluated, it was seen that surgical resection was performed in 4.9% of the patients, RFA in 16%, PEE in 4%, and chemoembolization (TAE/TACE) in 42%. Systemic chemotherapy was given to 37 patients (11.7%) (Here, a patient may have been treated with more than one method, patients with recurrence after transplantation were also recalculated in this group). These results show that there are many factors affecting treatment. HCC's BLCL and CTP staging, tumor number, tumor burden and disease complications are determinative in the treatment. Early diagnosis of the disease is important for curative treatment.

Our study has limitations such as being retrospective and inaccessibility of all patient data. Our study results are important because the number of patients in the study is high and the demographic and laboratory characteristics of HCC are shown in detail.

CONCLUSION

Hepatocellular cancers are a common carcinoma with a high mortality. Viral hepatitis is still the most important factor. Early diagnosis is the most important factor in determining the treatment of the disease and curative treatment is possible. Therefore, patients with viral hepatitis or risk factors for HCC should be followed with care. After the development of HCC, the MELD score is an important score for predicting prognosis.

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