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Epidemiology and Survival of Hepatocellular Carcinoma in Turkey: Outcome of Multicenter Study

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Objective: Hepatocellular cancer (HCC) is one of the important health problems in Turkey. We aimed to determine the clinical and demographic features of HCC in the Turkish population and to evaluate the prognostic and survival features.
Method: Two hundred and twenty-one patients with HCC from five hospitals in Turkey are included in this study.
Results: In 44.4% of the 221 patients with hepatitis B virus and in 21.3% of the 221 patients with hepatitis C virus were found to be responsible for HCC etiology. It has been shown that HCC developed on cirrhosis basis in 74.2% of the patients. HCC was presented with single solitary nodule in 69.2% of the patients. Non-liver metastasis was present in 12.5% of the patients. In 21.7% of the patients, α-fetoprotein (AFP) levels were above the diagnostics level of 400 ng/ml. The median overall survival (OS) of 221 patients was 14 months. The median OS of the patients with Child-Pugh A class was significantly longer than that with Child-Pugh B and C classes. The OS of the individuals with normal AFP levels was also longer than that with high AFP levels. The OS of the patients with Stage I HCC according to tumor node metastasis (TNM) classification, the female patients and the treated patients group was found to be significantly good.
Conclusions: In conclusion, the viral etiology (hepatitis B and C infections) in Turkish population is found to be an important factor in HCC development. The Child-Pugh classification, AFP levels, TNM classification, being female and treatment were determined to be important prognostic factors in HCC patients.

Key words: hepatocellular cancer – HCC – prognosis – Turkey

INTRODUCTION

Hepatocellular cancer (HCC) is one of the most common cancers in the world. It is the fifth most common malignancy in men and the eighth most common malignancy in women worldwide (1). The incidence and the etiology of HCC vary according to the geographic region. Eastern Asia and Southeast Africa have high incidence for HCC (2).

The cirrhosis is the most important risk factor for HCC. The hepatitis B and C infections are the predominant causes of chronic liver disease and cirrhosis (1). Therefore, the incidence of HCC is parallel with the incidence of viral hepatitis B and C. The other risk factors are aflatoxin exposure and hereditary hemachromatosis.

Turkey is a hepatitis B endemic country with a hepatitis B carrier rate of 5–10%. The incidence of hepatitis C in the Turkish population is 1.5% (3). The HCC incidence was 0.83/100 000 according to 2003 Ministry of Health report in Turkey. The annual incidence of HCC in Turkey was similar between 2000 and 2003 (0.80/100 000 at 2000, 0.87/100 000 at 2001, 1.1/100 000 at 2002 and 0.87/100 000 at 2003).

The prognosis of HCC is very poor. The cure and long-term survival are possible only when tumors can be resected completely.

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In this multicenter study, we evaluated epidemiologic characteristics, prognostic factors and survival of HCC in Turkish patients.

PATIENTS AND METHODS

Two hundred and twenty-one patients with HCC were included in this study consecutively from five hospitals in Turkey (158 patients from Dokuz Eylul University in Izmir, 34 patients from Erciyes University in Kayseri, 10 patients from Firat University in Elazig, nine patients from Gaziantep University and 10 patients from Ankara Oncology Hospital). All centers reviewed the medical records of their HCC cases in the period of 1994–2007 retrospectively.

DATA COLLECTION

Medical records were included gender, age at diagnosis, symptoms, etiologic factors (hepatitis B or C virus, alcohol, cirrhosis, etc), laboratory data [hemoglobin, white blood cell counts, platelet counts, albumin, bilirubin, alanine-aminotransferases (ALT) and aspartate-aminotransferases (AST), prothrombin time (PT), alkaline phosphatase (ALP), gama-glutamyl transpeptidase (GGT)], degree of hepatic disease (Child-Pugh score), sizes of tumor, types of tumor (uninodular, multinodular or diffuse), α-fetoprotein (AFP) and the methods of HCC diagnosis, treatment of HCC [surgical resection, liver transplantation, arterial chemoembolization (ACE), percutaneous alcohol injection (PAI), radiofrequency ablation (RFA), chemotherapy (CT), hormonotherapy (HT) or no treatment].

STATISTICAL ANALYSIS

All statistical analysis was performed using the SPSS 10.0 statistical package. Numerical variables were summarized by their median, mean and range. Categorical variables were described by counts and relative frequencies. Overall survival (OS) was defined as the time between diagnosis and death (due to any causes) or end of follow-up (censored observations). The univariate analysis to identify predictors of survival was performed using the Kaplan–Meier method and was compared with the Mantel log-rank test. $P < 0.05$ was considered as significant. Multivariate analysis was performed by Cox regression analysis.

RESULTS

A total of 221 patients with HCC were included this study. The characteristics of patients were presented in Table 1. The median age of HCC patients was 62 ± 11.3 (range: 15–84) years. There were 170 males (76.9%) and 51 females (22.3%).

Table 1. The characteristics of patients with HCC

Socio-demographic characteristics	HCC patient's *N* (%)
Sex	
Male	170 (76.9)
Female	51 (23.1)
Age (mean ± SD) (range)	62 ± 11.3 (15–84)
Etiology	
Hepatitis B	98 (44.4) (5 with alcohol abuse, 2 with hepatitis D)
Hepatitis C	47 (21.3) (5 with alcohol abuse)
Hepatitis B–C	11 (5)
Alcohol	13 (5.9)
Cryptogenic cirrhosis	9 (4.1)
Idiopathic	43 (19.5)
Cirrhosis	
Yes	164 (74.2)
No	57 (25.8)
Child-Pugh class	
A	49 (29.8)
B	41 (25)
C	74 (45.2)

HCC, hepatocellular cancer; SD, standard deviation.

Among the 221 HCC patients, 11 were asymptomatic at presentation. The other HCC patients had different symptoms, such as anorexia, malaise, abdominal pain, abdominal discomfort, nausea and vomiting, loss of weight, gastrointestinal bleeding and icterus.

The laboratory data of HCC patients were given in Table 2.

The etiologic risk factors for HCC were hepatitis B (98 patients; 44.4%) (five of them had alcohol abuse and two patients had hepatitis D also), hepatitis C (47 patients; 21.3%) (five of them also had alcohol abuse), hepatitis B and C (11 patients; 5%), chronic alcohol abuse (more than 10 years) (13 patients; 5.9%) and cryptogenic cirrhosis (nine patients; 4.1%). No etiologic cause could be identified in 43 patients (19.5%).

One hundred and sixty-four of 221 HCC patients (74.2%) were diagnosed as cirrhosis clinically and/or histologically. In 57 patients, there was no evidence of cirrhosis. Fourteen of the 57 patients had chronic hepatitis.

The distribution of the 164 patients with cirrhosis was as follows: Child A, 49 (29.8%) patients; Child B, 41 (25%) patients; Child C, 74 (45.2%) patients.

The biopsy (histologic or cytologic) in 141 (63.8%) patients and imaging (ultrasonography, computerized tomography, magnetic resonance imaging and angiography) in 80 (36.2%) patients were used for the diagnosis of HCC.

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Table 2. Laboratory data of HCC patients

	All HCC patients $N = 221$	HCC patients with HBV $N = 98$	HCC patients with HCV $N = 47$
Hemoglobin (g/dl)	12.5 ± 1.99	12.6 ± 2.1	13 ± 1.8
WBC $\times 10^9$/l	7.5 ± 2.4	7.1 ± 3.0	6.1 ± 3.1
Platelet $\times 10^9$/l	174 ± 65	177 ± 85	122 ± 143
AST (U/l)	76 ± 111	77 ± 115	83 ± 100
ALT (U/l)	57 ± 117	56.5 ± 130	60 ± 117
GGT (U/l)	129 ± 241	137 ± 155	78 ± 151
ALP (U/l)	293 ± 274	286 ± 210	270 ± 130
Total bilurubin (mg/dl)	1.4 ± 3.0	1.5 ± 3.9	1.3 ± 1.5
Albumin (g/dl)	3.4 ± 0.6	3.6 ± 0.6	3.4 ± 0.7
PT (sn)	14.1 ± 8.8	14.5 ± 6.8	14.9 ± 3.1

HBV, hepatitis B virus; WBC, white blood cell; AST, aspartate-aminotransferases; ALT, alanine-aminotransferases; GGT, gama-glutamyl transpeptidase; ALP, alkaline phosphatase; PT, prothrombin time.

The characteristics of tumors were presented in Table 3. The single nodule was the dominant tumor pattern (in 153 patients, 69.2%). The most common tumor diameter was <5 cm in 100 (45.2%) patients. Extra hepatic metastasis (lung, bone and adrenal gland) was present in 12 (5%) patients. Stage IV tumor according to TNM classification was present in 58 patients. The HCC patients with HBV had mostly Stage 3 and 4 disease (41.8 and 26.5%, respectively), whereas HCC patients with HCV had shown mostly similar distributions according to disease stage (Stage 1, 12.8%; Stage 2, 29.8%; Stage 3, 27%; Stage 4, 29.7%). The AFP levels were >400 ng/dl in 48 (21.7%) patients, which was considered as diagnostic for HCC.

Only 31 (14%) patients received surgical therapy (resection, liver transplatation). One hundred and ninety (86%) patients received palliative (PAI, RFA, ACE, CT and HT) therapy or no therapy (Table 3).

The OS was 14 months (Fig. 1). Patients aged <60 and female patients had longer survival compared with those aged >60 and male patients (median OS: 15 versus 12.6 months, $P = 0.619$ and 17.6 versus 11.7 months, $P = 0.057$, respectively). The OS of patients with cirrhosis and non-viral hepatitis was shorter survival with respect to these with no cirrhosis and non-viral hepatitis (median OS: 13.9 versus 19.1 months, $P = 0.286$ and 10.7 versus 15.3 months, $P = 0.797$) although it did not show any statistical significance.

Child-Pugh class had a significant effect on survival. Child-Pugh A class had a longer survival with respect to Child-Pugh B and C (median OS: 26.8 versus 15.3 and 8 months, $P = 0.045$) (Fig. 2). TNM classification systems were found to be significantly predictive for OS. The median OS of patients with AFP level ≤ 20 ng/ml was better than that of patients with AFP level >20 ng/ml significantly (median OS: 23.8 versus 8.5 months, $P = 0.003$) (Fig. 3).

There were significant differences in prognosis between subgroups ($P = 0.025$) (Fig. 4). Stages I and II patients showed the best prognosis in TNM classification (Table 4).

Table 3. The characteristics of tumors and treatment in HCC patients

Tumor characteristics	HCC patient's N (%)
Tumor extension	
Single nodule	153 (69.2)
Multiple nodule	55 (29.8)
Diffuse	2 (1)
Tumor size (cm)	
<5	100 (45.2)
5–<9	75 (33.9)
≥ 9	46 (20.9)
TNM class	
Stage I	23 (10.4)
Stage II	44 (19.9)
Stage III	96 (43.4)
Stage IV	58 (26.2)
AFP levels (ng/ml)	
<20	85 (38.9)
21–400	68 (30.3)
>400	48 (21.7)
Unknown	20 (9)
Treatment	
None	79 (35.7)
Surgery (resection, liver transplantation)	31 (14)
Palliative (ACE, RFA, PAI, chemo/hormonotherapy)	111 (50.2)

AFP, α-fetoprotein; ACE, arterial chemoembolization; RFA, radiofrequency ablation; PAI, percutaneous alcohol injection.

The effect of treatment on OS was studied in HCC patients. The patients received some treatment were a longer survival with respect to patients received no treatment (median OS: 23.8 versus 3.3 months, $P < 0.0001$) (Fig. 5). The OS

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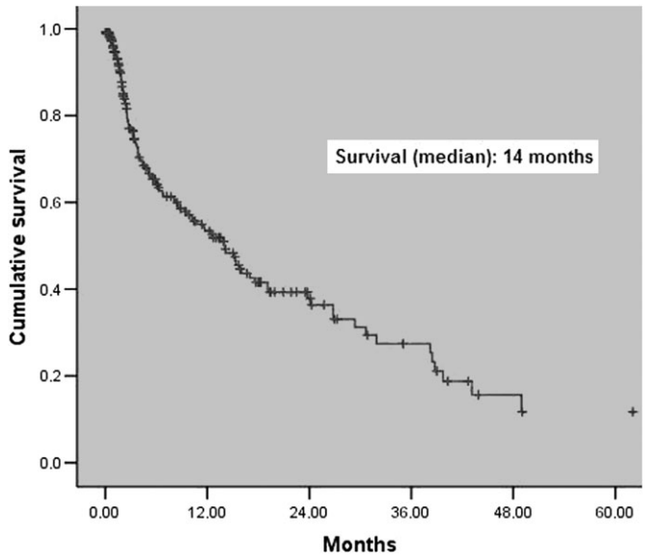


Figure 1. Overall survival of hepatocellular cancer (HCC) patients.

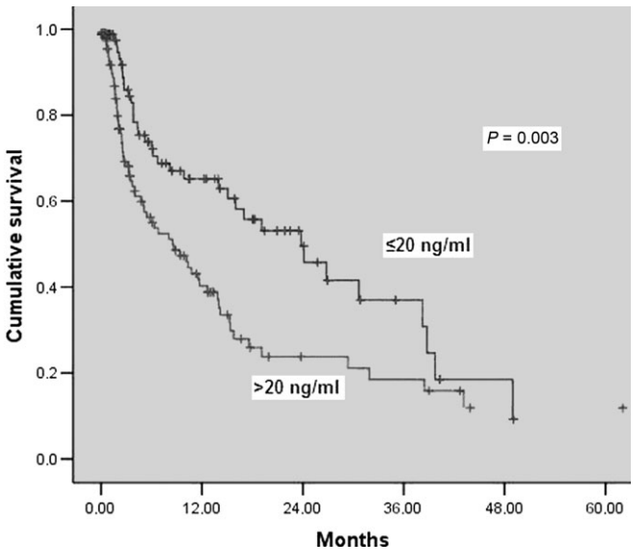


Figure 3. Survival of HCC patients according to α-fetoprotein levels.

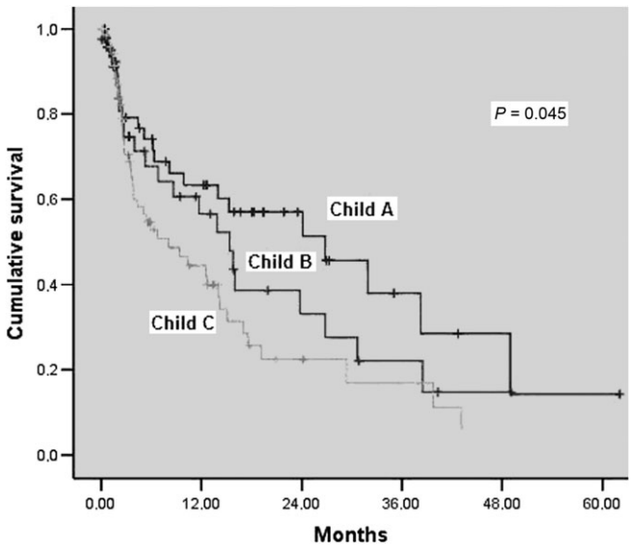


Figure 2. Survival of HCC patients according to Child-Pugh class.

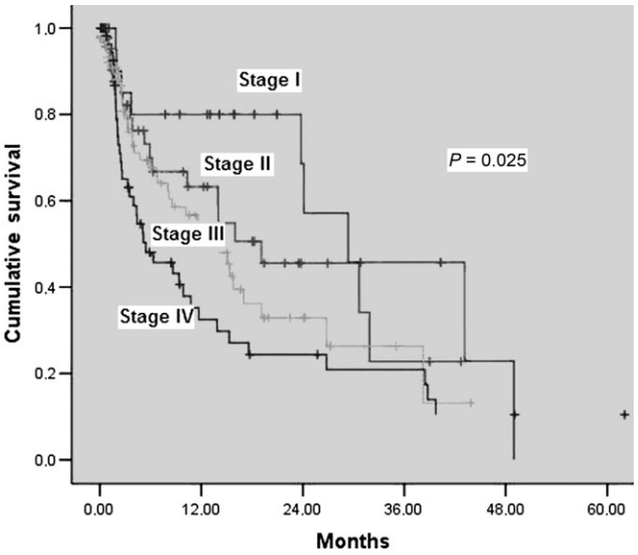


Figure 4. Survival of HCC patients according to TNM classification.

of the patients who underwent surgery were longer compared with patients who underwent other treatment options ($P < 0.0001$) (Fig. 6).

Multivariate analysis showed that being female, TNM Stage I disease and low titer AFP were independent risk factors for better survival (Table 5).

DISCUSSION

We determined in this multicenter study that the hepatitis B infection is the primary risk factor (44.4%) for HCC development in the Turkish population. In the epidemiologic studies of Uzunalimoğlu et al. (3), it has been shown that the hepatitis B infection is the most important risk factor in Turkey. In both studies, hepatitis C infection has been found to be the secondary risk factor. In Europe and the other countries of the Mediterranean, it has been reported that viral etiology, especially the hepatitis C virus infection, is the most important risk factor responsible for HCC development (4–6).

In our study, the median survival of the patients was 14 months. Sakar et al. (7) reported that the median OS in Turkish patients with cirrhosis was 16.9 months, whereas Borzio et al. (4) reported that the median survival rate was 19.7 months in the Italian population.

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Table 4. Prognostic factors affecting survival (univariate analysis)

Variable	*N*	Median survival (months)	95% CI	*P* value*
Sex				
Female	51	17.6	1.2–33.9	0.057
Male	170	11.7	5.5–17.8	
Age (years)				
≤60	98	15	8.3–21.7	0.619
>60	123	12.6	7.7–17.5	
Etiology				
Viral	156	15.3	11.6–18.9	0.797
Non-viral	65	10.7	4.1–17.3	
Cirrhosis				
Yes	164	13.9	0–10.3	0.286
No	57	19.1	9.2–18.6	
Child-Pugh class				
A	49	26.8	10.2–43	0.045
B	41	15.3	9.5–21.1	
C	74	8	2.3–13.7	
Tumor size (cm)				
<5	100	15.3	12.1–18.4	0.695
≥5	121	10.7	4.8–16.7	
TNM class				
Stage I	23	29.3	12.1–46.5	0.025
Stage II	44	19.1	6.3–31.8	
Stage III	96	14.1	9.3–19.9	
Stage IV	58	5.4	1–9.8	
AFP (ng/ml)				
≤20	85	23.8	13.9–33.6	0.003
>20	116	8.5	4.1–12.8	
Treatment				
No	79	3.3	0.3–6.6	<0.0001
Yes	142	23.8	11.5–36.0	

CI, confidential interval. *Log-rank test.

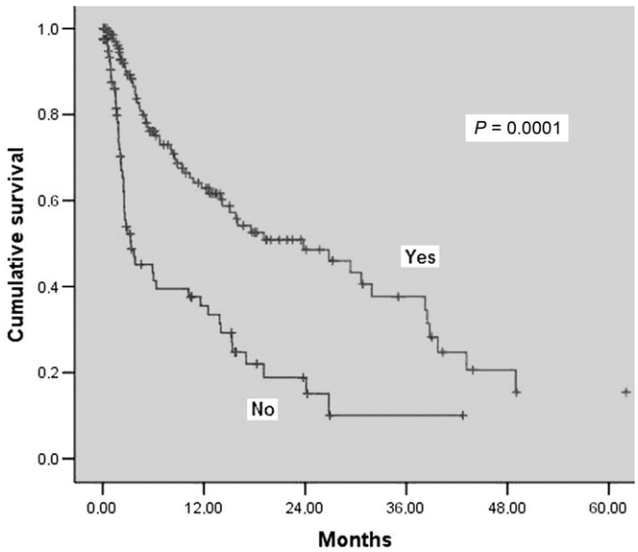


Figure 5. Survival of HCC patients according to treatment.

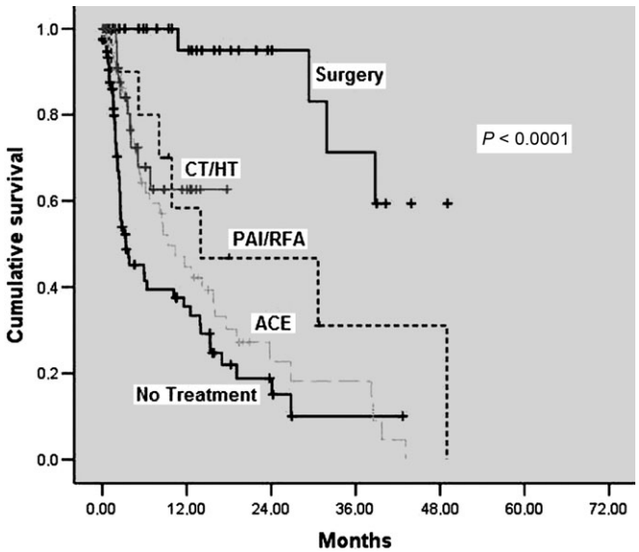


Figure 6. Survival of HCC patients according to treatment options. CT, chemotherapy; HT, hormonotherapy; PAI, percutaneous alcohol injection; RFA, radiofrequency ablation; ACE, arterial chemoembolization.

Table 5. Prognostic factors affecting survival (multivariate analysis)

Variable	Relative risk	95% CI	*P* value*
Sex	1.65	1.04–2.61	0.03
TNM stage	1.86	1.20–2.88	0.005
AFP	1.79	1.06–3.03	0.02

*Cox regression.

Median survival was longer in female patients (6) than in males (17.6 versus 11.6 months, $P = 0.05$). In the studies of Dohmen et al. (8), the longer survival rate of female patients has been emphasized.

In our patients, the presence or absence of cirrhosis (13.9 versus 19.1 months, $P = 0.28$) had no significant impact on median survival. In the patient group with cirrhosis, the Child-Pugh classification has been determined to be an important prognostic factor. The median survival of the Child-Pugh A class patients has been statistically determined to be longer than that of the Child-Pugh B and C classes (26.8 versus 15.8 versus 8 months, $P = 0.04$). Also in the studies of Sakar et al. (7) and Borzio et al. (4), it is reported that the Child-Pugh classification is an independent prognostic factor and that the survival of Child-Pugh A class patients is significantly longer.

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Serum AFP levels being >400 ng/ml is considered to be diagnostic for HCC diagnosis (6). Only 21.7% (48) of our patients have been determined to have an increase above the AFP diagnostic value. In the Italian study (6) in 18% of the patients and in 20% of the Far East study, a value above the AFP diagnostic value was determined. Our study, just like the other studies, shows a low sensitivity of the AFP diagnostic value in the Turkish population. However, high AFP value has been determined to be a prognostic factor. The median survival of patients with an AFP of ≤20 ng/ml is significantly higher than that of patients with an AFP of >20 ng/ml (23.8 and 8.5 months, $P = 0.003$).

In various studies in the literature, AFP is stated as an important prognostic factor (9–12). In the studies of Sakar et al. (7), in the Turkish population, they have reported that the AFP level is a prognostic factor.

In our study, it has been determined that the TNM classification is also an important prognostic factor. The median survival of stage I patients was high. While the stage of the disease was increasing, the median survival of patients significantly decreased (29.3, 19.1, 14.1 and 5.4 months, $P = 0.025$).

Median survival has been found to be significantly higher in the treated patient group compared with that in untreated patients (23.8 versus 3.3 months, $P < 0.0001$). In the other studies, it has been emphasized that the treatment has a significant contribution to median survival (4,7). Especially in patients with a surgical treatment, survival difference was more evident. There is still no any screening program for HCC in Turkey. Owing to this, our patients had been caught mostly at advanced or inoperable stage. So, the median survival was poor in our patients.

As a conclusion, in this multicenter retrospective study, it has been determined that the viral etiology (hepatitis B and C infection) in the Turkish population is an important factor in HCC development. In HCC patients, Child-Pugh classification, AFP level, TNM classification, being female and treatments were shown as important prognostic factors.

Conflict of interest statement

None declared.

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