

Prognostic factors, treatment methods and survival time in hepatocellular carcinoma: A decade of experience at a single center

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Abstract

Background and Aim: The objective of this study was to investigate the etiology, prognostic factors, treatment methods, and effects of treatment on survival in cases of hepatocellular carcinoma (HCC).

Materials and Methods: This was a retrospective study of 158 patients diagnosed with HCC at a single hospital between the years 2000 and 2010.

Results: The etiological factor of HCC was the hepatitis B virus (HBV) in 53.2% of the cases, the hepatitis C virus (HCV) in 21.5%, alcohol use in 6.3%, HBV+alcohol in 5.7%, HCV+alcohol in 1.9%, HBV+HCV in 1.9%, and the cause was unknown in 9.5%. Of the 158 patients, 120 were treated at the study hospital, and complete follow-up data were available for 81. The mean length of follow-up was 17.9 months (range: 0.6–124 months). Multivariate analysis indicated that a lesion size >5 cm, Child-Pugh class C, a high creatinine level, and a distant metastasis were prognostic factors of reduced survival.

Conclusion: HBV was the most frequent cause of HCC in this study group, followed by HCV. The most effective treatment methods for survival were liver transplantation and hepatic resection. A lesion size >5 cm, Child-Pugh class C, a high creatinine level, and distant metastasis were independent poor prognostic factors for survival.

Keywords: Hepatitis B virus; hepatocellular carcinoma; liver transplantation.

Introduction

Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide. It is significantly more common in males than in females.^[1] More than 80% of presenting hepatocellular carcinoma (HCC) cases develop in the presence

of cirrhosis and HCC accounts for 75% to 85% of primary liver cancers.^[1–3] The most common cause of HCC cases worldwide is hepatitis B virus (HBV) infection (54%), followed by hepatitis C virus (HCV) infection (31%), and other causes account for 15%.^[4] The prevalence of HBV and HCV in HCC cases is greater than 60% in most countries.^[5]

Although hepatic resection and liver transplantation are still considered the gold standard in the treatment of hepatic tumors, most tumors are not surgically resectable at the time of diagnosis. Factors that may prevent resection include the number of lesions, proximity to large vascular and biliary structures, residual functional parenchymal insufficiency, and medical comorbidities.^[6]

Currently, curative HCC therapies include resection, liver transplantation, and ablative techniques. Non-curative treatments include transarterial chemoembolization (TACE), transarterial radioembolization, radiation therapy, and systemic chemotherapy.^[7]

This study was designed to examine the risk factors, tumor characteristics, and prognostic factors of HCC patients at a single hospital and to investigate the treatment methods applied and the effect of these treatments on survival time.

Materials and Methods

This was a retrospective study that included patients diagnosed with HCC between January 2000 and August 2010 at Baskent University Department of Gastroenterology and General Surgery based on laboratory, radiological, and pathological findings and the American Association for the Study of Liver Diseases guidelines. A total of 158 patients were included in the study. The diagnosis of HCC was made in 117 patients with a liver biopsy, and 41 patients were diagnosed according to radiological findings and alpha-fetoprotein (AFP) values. The presence of another malignant disease was considered an exclusion criterion. The patient data analyzed were extracted from patient records. In all, 120 of 158 patients diagnosed with HCC were treated at the hospital. Of these, 81 patients had sufficient follow-up and survival data for inclusion in the study.

The treatment methods used included resection, transplantation, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), TACE, systemic chemotherapy, palliative care, and combinations of these modalities. Due to the small number of patients in some treatment groups, the TACE+RFA, TACE+PEI, and TACE+PEI+RFA groups were classified as the combined treatment group, and RFA, PEI, RFA+PEI groups were accepted as the percutaneous ablation group in the evaluation of the effects of treatments on survival.

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Portal vein thrombosis was defined as the detection of a thrombus in the main portal vein, right portal vein, or left portal vein branch. Invasion of the main portal vein, hepatic vein, vena cava inferior, or main hepatic artery was considered macrovascular invasion. Follow-up time was defined as the time from diagnosis until the patient's death or the termination of follow-up. This study was approved by the Baskent University Institutional Review Board on May 4, 2010 (no: KA10/69).

Statistical Analyses

The analysis of the data was performed with SPSS for Windows, Version 11.5 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed as mean±SD or median (minimum–maximum) for continuous variables, and the number of cases or percentage for categorical variables.

The impact of categorical variables on survival rate and life expectancy was determined using Kaplan-Meier survival analysis and the log-rank test. The 1-, 3-, and 5-year survival rate, mean survival time, and 95% confidence interval (CI) were calculated for each variable. The effect of continuous variables on survival rate was assessed for significance using the Cox proportional hazards model. The hazard ratio and 95% CI for each variable were calculated.

Multivariate Cox proportional hazards regression analysis was used to examine the effects of variables found to have an effect on survival in univariate analysis and risk factors thought to be clinically significant. Variables with a result of $p < 0.25$ in univariate analysis were included in the multivariate model as candidate risk factors. A p value of < 0.05 was considered statistically significant.

Results

A total of 158 patients were enrolled in the study. The mean age of the patients was 59.9 ± 11.3 years; 84.8% were male and 15.2% were female. Classification according to etiology revealed that the cause was HBV in 53.2% of the cases, HCV in 21.5%, excessive alcohol consumption in 6.3%, HBV+alcohol in 5.7%, HCV+alcohol in 1.9%, HBV+HCV in 1.9%, and in 9.5% the etiology was unknown. The median follow-up time of the 81 patients with sufficient data was 17.9 months. The patient with the shortest follow-up period, 0.6 months, was in the palliative care group. The patient with the longest follow-up, 124 months, was in the resection group (Table 1).

In all, 43.9% of the patients were classified as Child-Pugh class A, 31.2% were class B, and 24.8% were evaluated as class C. Portal venous thrombosis was detected in 30 patients, macrovascular invasion in 20 patients, and distant metastasis in 11 patients. Since computed tomography and magnetic resonance imaging results of 1 patient were not available, 157 patients were included in the assessments. Twenty of the 81 patients with follow-up data died during the follow-up period. Additional patient data are provided in Table 1.

Of the 158 patients, 120 were treated; however, adequate follow-up data were present for only 81 cases. Liver transplantation was performed in 35 patients, resection in 9 patients, TACE in 25 patients, TACE+RFA in 7 patients, TACE+PEI in 12 patients, TACE+PEI+RFA in 1 patient, RFA alone in 7 patients, PEI in 4 patients, RFA+PEI in 1 patient, chemotherapy in 2 patients, and palliative care was provided for 17 patients. One patient in the systemic chemotherapy group received 5-fluorouracil (5-FU), and doxorubicin followed by sorafenib were administered to the other.

Table 1. Baseline characteristics of the patients

Variables	n=158
Age (years), Mean±SD (Min–Max)	59.9±11.3 (17–90)
Gender, n (%)	
Male	134 (84.8%)
Female	24 (15.2%)
Etiology, n (%)	
HBV	84 (53.2%)
HCV	34 (21.5%)
Alcohol	10 (6.3%)
HBV+Alcohol	9 (5.7%)
HCV+Alcohol	3 (1.9%)
HBV+HCV	3 (1.9%)
Unknown etiology	15 (9.5%)
Number of lesions, Median (Min–Max)	2 (1–5)
1 nodule, n (%)	73 (46.5%)
2 nodules, n (%)	23 (14.6%)
3 nodules, n (%)	18 (11.5%)
>3 nodules, n (%)	39 (24.8%)
Diffuse, n (%)	4 (2.5%)
Largest lesion size (cm), Median (Min–Max)	3.75 (1.2–29)
Largest lesion size (cm), n (%)	
≤3 cm	57 (36.1%)
3.1–5.0 cm	41 (25.9%)
>5.0 cm	54 (34.2%)
Child-Pugh classification, n (%)	
A	69 (43.9%)
B	49 (31.2%)
C	39 (24.8%)
Albumin (g/dL), Median (Min–Max)	3.4 (2.1–4.8)
PT (second), Median (Min–Max)	15.8 (12.0–33.0)
Total bilirubin (mg/dL), Median (Min–Max)	1.5 (0.2–32.9)
ALT (u/L), Median (Min–Max)	43.0 (6.0–962.0)
Creatinine (mg/dL), Median (Min–Max)	0.8 (0.4–3.3)
Platelet ($\times 10^3/\mu\text{L}$), Median (Min–Max)	111.5 (27.0–451.0)
AFP (ng/mL), Median (Min–Max)	26.7 (1.85–1168789.0)
AFP level (ng/mL), n (%)	
≤20.0	64 (46.7%)
20.1–200.0	33 (24.1%)
>200.0	40 (29.2%)
Portal venous thrombosis*	30 (19.1%)
Macrovascular invasion*	20 (12.7%)
Distant metastasis*	11 (7.0%)
Exitus#	20 (24.7%)
Follow-up time (months), Median (Min–Max)	17.9 (0.6–124)

SD: Standard deviation; Min: Minimum; Max: Maximum; AFP: Alpha-fetoprotein; ALT: Alanine transferase; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PT: Prothrombin time; *: The calculation was made based on 157 subjects; #: The calculation was made based on 81 subjects.

Survival rate and mean survival time analysis were performed for 81 patients. Univariate analysis indicated that a large lesion, macrovascular

Table 2. Results of univariate analysis

Variables	Survival rate (%)			Mean survival time (months) (95% CI)	p*
	1 year	3 years	5 years		
Gender					0.656
Male (n=68)	83.1	69.3	65.9	83.8 (68.0–99.6)	
Female (n=13)	83.3	83.3	83.3	60.0 (45.9–74.2)	
Etiology					0.513
HBV (n=44)	80.9	73.8	73.8	94.0 (77.5–110.4)	
HCV (n=19)	82.4	54.1	36.1	43.2 (27.7–58.7)	
Alcohol (n=2)	50.0	NA	NA	10.5 (0.0–23.1)	
HBV+Alcohol (n=6)	83.3	83.3	83.3	53.1 (35.0–71.3)	
HCV+Alcohol (n=2)	100.0	–	–	29.5 (29.5–29.5)	
Unknown etiology (n=8)	100.0	100.0	100.0	70.5 (64.5–76.5)	
Child-Pugh classification					0.253
A (n=41)	88.1	71.7	71.7	88.2 (66.8–109.6)	
B (n=22)	85.4	85.4	56.9	49.9 (36.1–63.8)	
C (n=18)	61.1	54.3	54.3	43.8 (27.8–59.8)	
Number of lesions					0.722
1 nodule (n=40)	84.3	60.2	45.2	52.0 (40.3–63.7)	
2 nodules (n=10)	88.9	88.9	88.9	111.2 (86.7–135.4)	
3 nodules (n=11)	81.8	81.8	81.8	58.7 (43.0–74.3)	
>3 nodules (n=18)	80.5	71.6	61.3	54.1 (37.8–70.4)	
Diffuse (n=2)	50.0	50.0	50.0	38.6 (0.0–88.8)	
Largest lesion					<0.001
≤3.0 cm (n=36)	94.2	85.6	85.6	102.3 (84.5–120.0)	
3.1–5.0 cm (n=18)	88.9	67.7	67.7	56.6 (41.9–71.3)	
>5.0 cm (n=25)	63.7	31.9	–	25.5 (17.0–33.9)	
Portal venous thrombosis					0.197
No (n=69)	85.1	74.5	70.8	88.6 (73.1–104.0)	
Yes (n=12)	70.1	35.1	35.1	38.1 (15.3–61.0)	
Macrovascular invasion					<0.001
No (n=76)	86.6	73.5	70.0	88.7 (73.8–103.6)	
Yes (n=5)	0.0	–	–	4.7 (2.1–7.3)	
Distant metastasis					<0.001
No (n=76)	85.1	72.2	68.8	87.4 (72.5–102.3)	
Yes (n=5)	NA	NA	NA	3.5 (2.0–5.0)	
AFP					0.520
≤20.0 (n=39)	92.3	78.2	78.2	62.0 (53.4–70.5)	
20.1–200.0 (n=13)	90.9	75.8	75.8	61.4 (42.3–80.5)	
>200 (n=19)	81.4	69.8	55.8	79.2 (47.4–110.9)	
Albumin					0.379
≤3.5 (n=44)	81.3	66.5	59.1	51.9 (41.1–62.6)	
>3.5 (n=37)	85.4	75.5	75.5	91.0 (70.9–111.1)	
General	83.1	70.5	67.2	85.4 (70.6–100.2)	–

*: Kaplan-Meier survival analysis using the log-rank test; AFP: Alpha-fetoprotein; ALT: Alanine transferase; CI: Confidence interval; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NA: Not analyzed; PT: Prothrombin time.

invasion, and distant metastasis had significant effects on overall survival ($p<0.001$, $p<0.001$, and $p<0.001$, respectively, Table 2). The mean survival time of the group with a lesion ≥ 5 cm in size was significantly

lower than groups with a lesion size of ≤ 3 cm and 3.1–5.0 cm ($p<0.001$, $p=0.027$, respectively). There was no significant difference in the survival rate between groups with a lesion size of ≤ 3 cm and 3.1–5.0 cm ($p=0.422$).

Table 3. Evaluation of univariate analysis results

Variables	HR	95% CI	p*
Age	1.003	0.961–1.047	0.883
PT	0.977	0.855–1.117	0.737
Total bilirubin	0.982	0.829–1.162	0.830
ALT	1.000	0.991–1.010	0.959
Creatinine	27.702	5.857–131.018	<0.001
Platelet	1.004	0.999–1.009	0.083

*: Cox proportional hazards regression analysis; ALT: Alanine transferase; CI: Confidence interval; HR: Hazard ratio; PT: Prothrombin time.

Analysis of the effect of age, prothrombin time, and levels of total bilirubin, alanine transaminase, creatinine, and platelet count on overall survival revealed a statistically significant relationship only between the creatinine level and survival (95% CI: 5.857–131.018; p<0.001) (Table 3).

Among the 81 follow-up patients, there were 20 in the liver transplantation group, 6 in the resection group, 16 in the TACE group, 18 in the combined treatment group, 9 in the percutaneous ablation group, 2 in the chemotherapy group, and 10 in the palliative care group. The distribution of these patients according to the Child-Pugh classification is shown in Table 4.

The 1-, 3-, and 5-year survival rate of patients with a liver transplantation was 95.0%, 85.0%, 79.7%, respectively, and the mean length of survival was 65.8 months. The 1-, 3-, and 5-year survival rate of patients who underwent a resection was 100% at all time intervals; therefore, the mean survival time was not calculated for the resection group. The 1- and 3-year survival rate of patients who were treated with TACE was 61.8% and 0%, respectively, and the mean survival time was 22.3 months. The 1-, 3-, and 5-year survival rate of the combined treatment group was 100%, 66.7%, and 66.7%, respectively, and the mean survival time was 54 months. The 1-year survival rate of the percutaneous ablation group was 66.7% and the mean survival time was 19.6 months. The 1-year survival rate of the palliative care group was 65.6%, and the mean survival time was 17.2 months (Table 4).

Univariate statistical analysis indicated that large lesion size, macrovascular invasion, distant metastasis, and a high creatinine level had a significant effect on overall survival. Portal venous thrombosis and

Table 5. Multivariate analysis of risk factors

Variables	HR	95% CI	p
Child-Pugh B	1.973	0.376–10.363	0.422
Child-Pugh C	7.054	1.647–30.215	0.008
Lesion size 3.1–5.0 cm	3.682	0.736–18.418	0.113
Lesion size >5.0 cm	13.707	2.680–70.118	0.002
Portal venous thrombosis	1.670	0.409–6.830	0.475
Macrovascular invasion	1.445	0.191–10.938	0.722
Distant metastasis	12.237	1.177–127.208	0.036
Creatinine	19.477	1.840–206.129	0.014
Platelet	1.004	0.997–1.011	0.265

CI: Confidence interval; HR: Hazard ratio.

the platelet count had p values of <0.25, and the Child-Pugh classification p value was 0.253, signifying borderline probability, so they were considered candidate risk factors for multivariate analysis. Multivariate Cox proportional hazards regression analysis revealed that the factors that had the greatest impact on overall survival were, in order of importance, lesion size >5 cm, Child-Pugh class C, high creatinine level, and distant metastasis (p=0.002, p=0.008, p=0.014, and p=0.036, respectively) (Table 5).

Discussion

HBV was the cause of HCC in 53.2% of our patients. HBV positivity in HCC patients has been reported to range from 44.4% to 65.7% in studies conducted in Turkey.^[8–10] The rate of HCV positivity was 21.5% in our patients. In research from our country, the incidence of HCV in HCC has been reported to vary between 21.3% and 28.6%.^[8–11] Aside from Russia and Greece, where HBV is more prevalent, HCV is more common than HBV in European countries. The same predominance of HCV can be seen in most South American countries and in the United States, where HBV is observed at a very low rate (8%). However, HBV is predominant in East Asian countries. In Western Asia, HBV and HCV rates are similar in Saudi Arabia and Yemen, while HBV infection is more prevalent in Turkey.^[5]

The etiological agent was alcohol abuse in 6.3% of our patients. Other studies from Turkey have reported an alcohol-related HCC rate of

Table 4. Evaluation of survival rate and mean survival time by treatment group

	Child-Pugh class A	Child-Pugh class B	Child-Pugh class C	Survival rate (%)			Mean survival time* (months) (95% CI)
				1 year	3 years	5 years	
Liver transplantation (n=20)	6	4	10	95.0	85.0	79.7	65.8 (55.8–75.7)
Resection (n=6)	5	1	0	100.0	100.0	100.0	NA
TACE (n=16)	12	1	3	61.8	0.0	–	22.3 (14.5–30.0)
Combined treatment (n=18)	12	6	0	100.0	66.7	66.7	54.0 (26.3–81.6)
Percutaneous ablation (n=9)	2	3	4	66.7	–	–	19.6 (12.8–26.3)
Chemotherapy (n=2)	1	1	0	–	–	–	–
Palliative care (n=10)	3	6	1	65.6	–	–	17.2 (8.7–25.7)

*: Kaplan-Meier survival analysis; CI: Confidence interval; NA: Not analyzed; TACE: Transarterial chemoembolization.

5.1%, 5.9%, and 7.2%, which are similar to our findings.^[8,10,11] The HBV+alcohol ratio was 5.7% in our study. HBV+alcohol has been evaluated within the HBV group, and the HCV+alcohol within the HCV group in other research.^[8] Among our patients, the HCV+alcohol ratio was 1.9%. HBV+HCV coinfection was detected in 1.9%. In other studies from Turkey, the HBV+HCV coinfection rate ranged between 2% and 5%.^[8-10] We observed HCC of unknown etiology in 9.5% of the study group. In other research from our country, the rate of patients with HCC of unknown etiology has ranged from 5.1% to 19.5%.^[8,10] The results of our study were consistent with the literature in terms of etiology. HBV is the most common cause of HCC in Turkey, followed by HCV. The incidence of HBV has decreased from 8.26 per 100,000 people in 2002 to 4.26 per 100,000 people in 2010, due to the HBV vaccination given to newborns since 1998.^[12] The HBV 3-shot vaccination rate in Turkey has increased from 72% in 2002 to 98% in 2016.^[13]

The male-to-female ratio in our study was 5.5/1. HCC is reported 2 to 3 times more in men than women in most regions of the world, and the ratio of male to female occurrence in published articles has ranged from 2/1 to 8/1.^[1,14] Gender differences in HBV and HCV may explain the higher prevalence of HCC in males. However, environmental differences, geographic differences, hormonal variation, behavioral risk factors (alcohol, smoking), and compliance with antiviral treatments may also influence these differences.^[15] In other studies performed in Turkey, a male/female ratio of 3.3/1, 3.7/1, 4/1, and 7/1 have been reported.^[8-11]

According to the univariate analysis performed in our study, the survival rate in patients with macrovascular invasion was significantly lower than that of those without macrovascular invasion. Most studies in the literature have identified macrovascular invasion as an independent prognostic factor in terms of survival.^[16-18]

The survival rate at 1, 3, and 5 years was 95%, 85%, and 79.7%, respectively, in our liver transplantation patients. Liver transplantation was performed in 10 patients according to the Milan criteria, and in other 10 patients based on the expanded criteria.^[19] Regardless of the number and size of the tumors, patients without macrovascular invasion or extrahepatic metastasis were included in the expanded group.^[19,20] The mean survival time was 68.6 months in our patients who met the Milan criteria, and 60.3 months in the expanded criteria group. Univariate analysis comparison of these 2 groups yielded no significant difference in the mean survival time. Poon et al.^[21] conducted 43 liver transplantations based on the Milan criteria and found that the 1-, 3-, and 5-year survival rate was 98%, 92%, and 81%, respectively. Yao et al.^[22] reported on 70 patients and observed a 1- and 5-year survival rate in patients with small primary solitary HCC tumors (pT1 or pT2 classification) was 91.3% and 72.4%, respectively, while it was 82.4% and 74.1% in pT3 tumors. Our survival rates were similar to the results of these earlier studies.

The 5-year survival rate in our resection group was 100%. Literature reports have noted survival rates after resection of 58% to 100% for 1-year survival, 28% to 88% for 3-year survival, 11% to 75% for 5-year survival, and 19% to 26% for 10-year survival.^[23] The higher 5-year survival rate observed in our study may be due to the small number of patients.

TACE, RFA, PEI, a combination of these treatments, or chemotherapy was administered to patients for whom resection was not possible and those for whom liver transplantation was contraindicated or not convenient. The benefit of a TACE+PEI combined treatment was first demonstrated by Tanaka et al.^[24] The rationale of combined treatment is to reduce the tumor density and to dissolve intratumoral septa, thus increasing ethanol diffusion into the tumor.^[25] The addition of PEI after

TACE is expected to achieve complete tumor necrosis.^[26] Subsequent studies found that this was also valid for RFA.

Multivariate analysis of our data indicated that independent poor prognostic factors of survival included a tumor size >5 cm, Child-Pugh class C, high creatinine level, and distant metastasis. In their study of 1569 HCC patients, Shi et al.^[18] reported that the Child-Pugh classification, macrovascular invasion, and large tumor size were independent prognostic factors. Schwarz et al.^[17] also observed that distant metastasis, large tumor size, and macrovascular invasion were independent prognostic factors in HCC. These 2 studies did not assess creatinine level. Other research has determined that the creatinine level was a prognostic factor of survival.^[27-29]

In conclusion, our study results demonstrated that HBV was the most common causative agent of HCC, followed by HCV infection. The policy of HBV vaccination of newborns should be maintained, and the overall vaccination rate should be improved. Vaccination of high-risk groups should be a focus. The most effective treatment methods to prolong survival in patients with HCC were liver transplantation and hepatic resection in eligible patients. A tumor size >5 cm, Child-Pugh class C, high creatinine level, and distant metastasis were found to be independent prognostic factors of reduced survival.

Ethics Committee Approval: The Baskent University Clinical Research Ethics Committee granted approval for this study (date: 04.05.2010, number: KA10/69).

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–424 doi: 10.3322/caac.21492
2. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020-1022
3. Collier J, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998;27(1):273-278.
4. Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. *JAMA Oncol* 2017;3:1683–1691.
5. de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. *Hepatology* 2015;62(4):1190–1200.
6. Curley SA. Radiofrequency ablation of malignant liver tumors. *Oncologist* 2001;6(1):14-23.
7. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68:734.
8. Alacacioglu A, Somali I, Simsek I, Astarcioglu I, Ozkan M, Camci C. Epidemiology and survival of hepatocellular carcinoma in Turkey: outcome of multicenter study. *Jpn J Clin Oncol* 2008;38(10):683-688.

9. Ozer B, Serin E, Yilmaz U, Gumurdulu Y, Saygili OB, Kayaselcuk F. Clinicopathologic features and risk factors for hepatocellular carcinoma: results from a single center in southern Turkey. *Turk J Gastroenterol* 2003;14(2):85-90.
10. Arhan M, Akdoğan M, İbiş M, Yalın Kılıç ZM, Kaçar S, Tunç B. Tek Merkeze Ait Hepatosellüler Karsinom Verileri; Retrospektif Çalışma. *Akademik Gastroenteroloji Dergisi* 2009;8:18-23.
11. Uzunalimoglu O, Yurdaydin C, Cetinkaya H, Bozkaya H, Sahin T, Colakoglu S. Risk factors for hepatocellular carcinoma in Turkey. *Dig Dis Sci* 2001;46(5):1022-1028.
12. The Ministry of Health of Turkey. Health Statistics Yearbook 2010. Ed. No:832, Ankara, 2011 Available at: <http://www.saglik.gov.tr/TR/dosya/1-72577/h/saglikistatistikleriyilligi2010.pdf>.
13. The Ministry of Health of Turkey. Health Statistics Yearbook 2016. Ed. No:1084, Ankara, 2017.
14. Tangkijvanich P, Mahachai V, Suwangool P, Poovorawan Y. Gender difference in clinicopathologic features and survival of patients with hepatocellular carcinoma. *World J Gastroenterol*. 2004;10(11):1547-50.
15. Wu EM, Wong LL, Hernandez BY, Ji JF, Jia W, Kwee SA, et al. Gender differences in hepatocellular cancer: disparities in nonalcoholic fatty liver disease/steatohepatitis and liver transplantation. *Hepatoma Res* 2018;4:66
16. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology* 2006;131(2):461-469.
17. Schwarz RE, Smith DD. Trends in local therapy for hepatocellular carcinoma and survival outcomes in the US population. *Am J Surg* 2008;195(6):829-836.
18. Shi M, Chen JA, Lin XJ, Guo RP, Yuan YF, Chen MS. Transarterial chemoembolization as initial treatment for unresectable hepatocellular carcinoma in southern China. *World J Gastroenterol* 2010;16(2):264-269.
19. Karakayali H, Moray G, Sozen H, Dalgic A, Emiroglu R, Haberal M. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. *Tranplant Proc* 2006;38(2):575-578.
20. Haberal M, Emiroglu R, Karakayali H, et al. Expanded criteria for hepatocellular carcinoma and liver transplantation. *Int Surg* 2007;92:110-115.
21. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation: impact on long-term survival. *Ann Surg* 2007;245(1):51-58.
22. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33(6):1394-1403.
23. D'Angelica M, Fong Y. The Liver. *Sabiston Textbook of Surgery The biological basis of modern surgical practice*. (Courtney M, Townsend Jr, ed). 17th edition. Philadelphia: Saunders Elsevier 2004;1513-1573.
24. Tanaka K, Okazaki H, Nakamura S, Endo O, Inoue S, Takamura Y, et al. Hepatocellular carcinoma: treatment with a combination therapy of transcatheter arterial embolization and percutaneous ethanol injection. *Radiology* 1991;179:713-717.
25. Becker G, Soezgen T, Olschewski M, et al. Combined TACE and PEI for palliative treatment of unresectable hepatocellular carcinoma. *World J Gastroenterol* 2005;11:6104-6109.
26. Yamamoto K, Masuzawa M, Kato M, Kurosawa K, Kaneko A, Ishida H, et al. Evaluation of combined therapy with chemoembolization and ethanol injection for advanced hepatocellular carcinoma. *Sem Oncol* 1997;24(2 Suppl 6):50-55.
27. Huo TI, Huang YH, Wu JC, Lee PC, Chang FY, Lee SD. Percutaneous injection therapy for hepatocellular carcinoma in patients with chronic renal insufficiency. *Eur J Gastroenterol Hepatol* 2004;16(3):325-331.
28. Chiang JK, Koo M, Kuo TB, Fu CH. Association between cardiovascular autonomic functions and time to death in patients with terminal hepatocellular carcinoma. *J Pain Symptom Manage* 2010;39(4):673-679.
29. Kim SU, Han KH, Nam CM, Park JY, Kim do Y, Chon CY. Natural history of hepatitis B virus-related cirrhotic patients hospitalized to control ascites. *J Gastroenterol Hepatol* 2008;23(11):1722-1727.