Clinical Study

Oncology

Oncology 2018;94:116–124
DOI: 10.1159/000484564

Received: September 19, 2017
Accepted after revision: October 24, 2017
Published online: December 6, 2017

Characteristics of Hepatocellular Carcinoma Aggressiveness Factors in Turkish Patients

Hikmet Akkiz[a] Brian I. Carr[b] Kendal Yalçın K.[c] Vito Guerra[d] Sedef Kuran[a] Engin Altıntaş[e] Oğuz Üsküdar[a] Ümit Karaoğullarından[a] Ayşegül Özakyol[f] Salih Tokmak[a] Mehmet Yücesoy[g] Halil İbrahim Bahçeci[h] Abdulalh Ülkü[a] Tolga Akçam[a] Kamil Yalçın Polat[i] Nazım Ekinci[c] Halis Şimşek[j] Necati Örmeci[k] Abdulalh Sonsuz[l] Mehmet Demir[m] Murat Kılıç[n] Ahmet Uygun[o] Tuğsan Ballı[a] Ali Demir[p] Burcu Arslan[a] Figen Doran[a]

[a]Gastroenterology Department, Çukurova Üniversitesi, Adana, [b]Department of Experimental Therapeutics, Izmir Biomedicine and Genome Institute, Dokuz Eylul University, Izmir, and [c]Dicle Üniversitesi, Diyarbakır, Turkey; [d]IRCCS de Bellis Medical Center, Castellana Grotte, Italy; [e]Mersin Üniversitesi, Mersin, [f]Eskişehir Osmangazi Üniversitesi, Eskişehir, [g]Erciyes Üniversitesi, Kayseri, [h]Fırat Üniversitesi, Elazığ, [i]İstanbul Memorial Hastanesi, Istanbul, [j]Hacettepe Üniversitesi and [k]Ankara Üniversitesi, Ankara, [l]İstanbul Cerrahpaşa Üniversitesi, Istanbul, [m]Hatay Mustafa Kemal Üniversitesi, Antakya, [n]Izmir Kent Hastanesi, Izmir, [o]Haydarpaşa Sultan Abdülhamid Eğitim Araştırma Hastanesi, Istanbul, and [p]Konya Necmettin Erbakan Üniversitesi, Konya, Turkey

Keywords
Albumin · Hepatocellular carcinoma · Turkey · α-Fetoprotein · Tumor mass · Aggressiveness

Abstract
A large cohort of hepatocellular carcinoma (HCC) patients from several collaborating Turkish institutions were examined for the tumor parameters of maximum diameter (MTD), portal vein thrombosis (PVT), and α-fetoprotein (AFP) levels. A relationship was found between MTD and blood platelet levels. Patients with large ≥5 cm tumors who had normal platelet levels had significantly larger tumors, higher percent of PVT, and significantly lower blood total bilirubin and liver cirrhosis than similar ≥5 cm tumor patients having thrombocytopenia. A comparison of patients with and without PVT showed significantly larger tumors, greater multifocality, blood AFP, and C-reactive protein levels, and, interestingly, lower HDL levels in the patients with PVT. Fifty-eight percent of the total cohort had AFP levels ≤100 IU/mL (and 42.1% had values ≤20 IU/mL). These patients had significantly smaller tumors, less tumor multifocality and percent PVT, lower total bilirubin, and less cirrhosis. There was considerable geographic heterogeneity within Turkey in the patterns of HCC presentation, with areas of higher and lower hepatitis B virus, hepatitis D virus, cirrhosis, and tumor aggressiveness parameters. Turkish patients thus have distinct

H.A. and B.I.C. contributed equally to this work.

E-Mail karger@karger.com
www.karger.com/ocl

Prof. Brian I. Carr
Department of Experimental Therapeutics
Izmir Biomedicine and Genome Institute, Dokuz Eylul University
İnciraltı Yerleşkesi, TR–35340 Izmir (Turkey)
E-Mail brianicarr@hotmail.com

patterns of presentation, but the biological relationships between MTD and both platelets and bilirubin levels are similar to the relationships that have been reported in other ethnic patient groups.

Introduction

The classification of tumors and prognostication for patients with hepatocellular carcinoma (HCC) has generally been considered to be a reflection of 2 sets of separate factors since the first such report by Okuda et al. [1]. These are liver factors and tumor factors, which are separate yet likely related [2, 3]. All modern classification schemata incorporate parameters from both sets of factors [4, 5]. However, there are many characteristics that distinguish HCC patients in various parts of the world from each other. We report here, for the first time, on a large HCC database from several collaborating institutions in Turkey, which is a Mediterranean country that constitutes a land bridge between Europe and Asia, and we focus on 3 parameters of tumor behavior, namely maximum tumor diameter (MTD), portal vein thrombosis (PVT), and α-fetoprotein (AFP) levels, and the correlates of each parameter.

Methods

Patient Data

We analyzed a database of 1,332 prospectively accrued HCC patients who had full baseline tumor parameter data, including computed tomography scan information on HCC size, number of tumor nodules, presence or absence of PVT, and plasma AFP levels; complete blood count; routine blood liver function tests (total bilirubin, γ-glutamyl transpeptidase [GGTP], alkaline phosphatase [ALKP], albumin, and transaminases); and patient demographics. Diagnosis was made either via tumor biopsy or according to international guidelines [6, 7]. Database management conformed to legislation on privacy, and this study conforms to the ethical guidelines of the Declaration of Helsinki; approval for this retrospective study on de-identified HCC patients was obtained from the institutional review board.

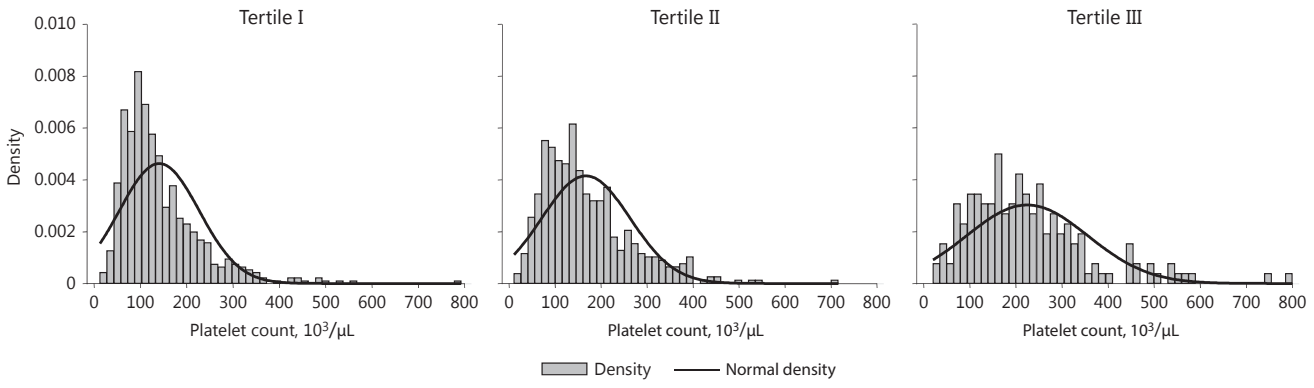
Statistical Analysis

Means and standard deviations for continuous variables and relative frequencies for categorical variables were used as indices of centrality and dispersion of the distribution. For categorical variables, the χ^2 test and z test for proportions were used. The Pearson correlation was used to measure the association between 2 continuous variables, the Wilcoxon rank-sum (Mann-Whitney) test to test the difference between 2 categories, and the Kruskal-Wallis rank test to test the difference among categories.

Table 1. Characteristics of HCC patients in the total cohort (n = 1,332)

Gender	
Females	18.89
Males	81.11
Age, years	62.16±11.36
Cirrhosis	81.42
Cigarettes	51.02
Alcohol	15.37
HbsAg positive	60.86
HCV positive	20.72
MTD, cm	5.89±4.03
MTD	
<3.5 cm	31.78
≥3.5/≤6.5 cm	34.79
>6.5 cm	33.43
PVT	28.55
AFP, IU/mL	5,686.54±36,413.94
LDL, mg/dL	99.57±91.84
Triglycerides, mg/dL	105.73±62.18
HDL, mg/dL	36.55±18.29
Creatinine, mg/dL	1.10±2.18
HbA1c, mmol/mol	5.96±2.01
Total protein, g/dL	6.90±7.77
Albumin, g/dL	3.09±0.75
INR	1.43±3.52
CRP, mg/L	17.52±31.75
ALKP, U/L	216.68±270.10
GGTP, U/L	162.32±179.42
AST, U/L	141.04±449.32
ALT, U/L	79.89±171.85
Total bilirubin, mg/dL	2.96±4.69
Platelet count	
<125 10^3/μL	30.95
≥125 10^3/μL	69.05
AFP	
≤20 IU/mL	42.13
>20/≤100 IU/mL	15.91
>100/≤1,000 IU/mL	20.42
>1,000 IU/mL	21.55
CRP	
>10 mg/L	35.84
≤10 mg/L	64.16

All values are means ± standard deviations or % of patients. HCC, hepatocellular carcinoma; HbsAg, HBV surface antigen; HCV, hepatitis C virus; MTD, maximum tumor diameter; PVT, portal vein thrombosis; AFP, α-fetoprotein; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; INR, international normalized ratio; CRP, C-reactive protein; ALKP, alkaline phosphatase; GGTP, γ-glutamyl transpeptidase; AST, aspartate aminotransaminase; ALT, alanine aminotransaminase.



	MTD				Tertile comparisons,[b] *p* value
	tertile I (MTD <5.0 cm) (47.8%)	tertile II (MTD 5.0 – 10.0 cm) (39.1%)	tertile III (MTD >10.0 cm) (13%)	*p* value[a]	
Platelet count, $\times 10^3/\mu L$					
Mean ± SD	140.91 ± 86.36	167.15 ± 96.13	224.36 ± 131.90	0.0001	I vs. II, $p < 0.0001$
Min.–max.	13 – 791	11 – 714	20 – 795		I vs. III, $p < 0.0001$
Median (IQR)	118 (84 – 175)	145 (95 – 213)	205 (133 – 278)		II vs. III, $p < 0.0001$

MTD, maximum tumor diameter; SD, standard deviation; IQR, interquartile range. [a] Kruskal-Wallis rank test. [b] Mann-Whitney rank test.

Fig. 1. Peripheral blood platelet count ($10^3/\mu L$) in maximum tumor diameter (cm) tertiles.

A linear regression model was used to evaluate the associations between MTD and single variables examined. The final multiple linear regression was obtained with the backward stepwise method, and the variables that showed associations with $p < 0.10$ were left in the models.

When testing the null hypothesis of no association, the probability level of α error, 2 tailed, was 0.05. All the statistical computations were made using STATA 10.0 Statistical Software (StataCorp, 2007, Stata Statistical Software, release 10, College Station, TX, USA).

Results

Patient Characteristics of the Total Cohort

Table 1 shows the descriptive characteristics of the total patient cohort: 81.11% were male, and 81.42% had cirrhosis. The predominant etiological factor was hepatitis B virus (HBV) in 60.86%, followed by hepatitis C virus (HCV) in 20.72% of patients. The mean MTD was 5.89 cm, with approximately one-third of patients having tumors <3.5, 3.5–6.5, and >6.5 cm. The mean AFP level was 5,686.54 IU/mL; 42.13% of patients had normal AFP laboratory values, and 41.97% of patients had AFP values >100 IU/mL. The mean albumin was low at 3.09 g/dL, and the mean total bilirubin was elevated at 2.96 mg/dL.

Maximum Tumor Diameter

The MTD was then further examined. Patients were divided into 3 size tertiles, and the means and distributions of the associated peripheral blood platelet counts were then calculated. Figure 1 shows that the mean platelet count increased with an increase in MTD tertile, as has been reported in other cohorts [8, 9]. Patients with the largest MTD tumors had normal platelet counts and, thus, lesser degrees of fibrosis, as noted previously [10]. Characteristics of HCC patients with small and large MTD tumors were then further characterized after merging tertiles II and III, due to the small patient number in tertile III. Patient groups with either MTD <5 or ≥5 cm tumors were then each dichotomized according to blood platelet counts of <125 or $\geq 125 \times 10^3/\mu L$ (Table 2), as low blood platelets are a cirrhosis surrogate [11]. In the small-tumor group, there was little difference in tumor characteristics between the platelet subgroups, although

Table 2. Comparisons between HCC patients in tumor diameter groups dichotomized by platelet levels

Parameter	MTD					
	MTD <5.0 cm		*p* value[a]	MTD ≥5.0 cm		*p* value[a]
	platelets <125 10^3/μL (24.7%)	platelets ≥125 10^3/μL (23.1%)		platelets <125 10^3/μL (16.9%)	platelets ≥125 10^3/μL (35.2%)	
Platelet count, 10^3/μL	83.74±24.36	201.98±87.02	<0.0001	83.07±25.51	228.89±101.83	<0.0001
Hemoglobin, g/dL	12.00±2.27	12.75±2.25	0.0001	12.03±2.10	12.57±2.19	0.004
GGTP, U/L	131.30±168.25	166.40±192.89	0.17	123.29±114.89	200.31±191.84	<0.0001
ALKP, U/L	162.73±137.63	216.78±256.68	0.23	185.69±136.80	251.02±243.25	0.009
Total bilirubin, mg/dL	2.76±3.22	2.21±3.90	<0.0001	3.32±3.99	2.56±4.48	<0.0001
Albumin, g/dL	3.00±0.75	3.29±0.76	<0.0001	2.89±0.67	3.12±0.74	0.0002
AFP, IU/mL	1,384.09±7,792.46	2,441.81±14,956.60	0.12	5,058.27±19,926.07	10,152.25±45,830.54	0.02
MTD, cm	3.01±1.00	3.03±0.97	0.81	8.30±3.69	9.28±3.88	0.0002
Nodules			0.72[b]			0.13[b]
1	237 (72.70)	220 (71.43)		149 (68.04)	283 (61.26)	
2–3	89 (27.30)	88 (28.57)		70 (31.96)	176 (38.10)	
>3	0 (0.00)	0 (0.00)		0 (0.00)	3 (0.65)	
PVT	45 (13.89)	49 (17.56)	0.21[b]	77 (35.32)	194 (44.29)	0.03[b]
Cirrhosis	307 (93.31)	207 (68.09)	<0.001[b]	216 (96.43)	345 (74.03)	<0.001[b]
Etiology						
HBV	132 (43.71)	124 (45.42)	0.68[b]	100 (52.08)	193 (46.17)	0.17[b]
HCV	69 (21.70)	53 (17.91)	0.24[b]	47 (21.46)	67 (14.92)	0.03[b]
HDV	43 (13.61)	16 (5.52)	0.001[b]	20 (9.22)	35 (7.97)	0.59[b]

All values are means ± standard deviations for continuous variables and *n* (%) for categorical variables. HCC; hepatocellular carcinoma; MTD, maximum tumor diameter; GGTP, γ-glutamyl transpeptidase; ALKP, alkaline phosphatase; AFP, α-fetoprotein; PVT, portal vein thrombosis; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus. [a] Wilcoxon rank-sum (Mann-Whitney) test. [b] χ^2 test.

Table 3. Linear regression model of MTD and single variables (**a**) and final multiple linear regression model, in a stepwise method, of MTD and all variables included together in the model (**b**)

Parameter	β	SE (β)	*p* value	95% CI
a *MTD and single variables*				
Platelet count (10^3/μL)	0.012	0.001	<0.001	0.010 to 0.05
Hemoglobin (g/dL)	–0.076	0.068	0.265	–0.209 to 0.057
GGTP (U/L)	0.002	0.001	0.010	0.0005 to 0.0038
ALKP (U/L)	0.002	0.001	0.013	0.0004 to 0.0030
Total bilirubin (mg/dL)	0.011	0.038	0.776	–0.065 to 0.086
Albumin (g/dL)	–0.068	0.198	0.731	–0.458 to 0.321
AFP (IU/mL)	0.00002	0.000005	0.001	0.000006 to 0.000025
Nodules number (%)	0.335	0.297	0.259	–0.248 to 0.917
PVT (%)	2.516	0.309	<0.001	1.909 to 3.123
Cirrhosis (%)	–0.763	0.375	0.042	–1.498 to –0.028
b *MTD and all variables included together*				
Platelet count (10^3/μL)	0.011	0.001	<0.001	0.009 to 0.014
PVT (%)	2.210	0.296	<0.001	1.630 to 2.790

MTD, maximum tumor diameter; β, coefficient; SE (β), standard error of coefficient; CI, confidence interval; GGTP, γ-glutamyl transpeptidase; ALKP, alkaline phosphatase; AFP, α-fetoprotein; PVT, portal vein thrombosis.

Table 4. Characteristics of HCC patients according to PVT categories

Variables	PVT		*p* value[a]
	negative	positive	
Male sex	959 (80.86)	393 (82.91)	0.33[b]
Age, years	62.46±11.15	61.18±11.98	0.03
Cigarettes	316 (50.32)	160 (54.42)	0.24[b]
Alcohol	97 (16.39)	47 (16.43)	0.99[b]
Cirrhosis	917 (78.71)	383 (84.36)	0.01[b]
HbsAg positive	691 (60.14)	293 (65.99)	0.03[b]
HCV positive	229 (19.93)	85 (19.14)	0.72[b]
Glucose, mg/dL	121.62±56.36	115.55±44.31	0.35
Total cholesterol, mg/dL	151.31±50.08	152.61±52.60	0.67
LDL, mg/dL	95.25±41.90	101.43±44.76	0.11
HDL, mg/dL	37.27±16.67	34.14±20.67	0.003
Triglycerides, mg/dL	105.94±61.41	105.09±59.17	0.96
MTD, cm	5.08±3.55	8.07±4.55	<0.0001
Nodules			<0.001
1	845 (72.28)	215 (49.77)	
2–3	322 (27.54)	216 (50.00)	
>3	2 (0.17)	1 (0.23)	
Hemoglobin, g/dL	12.48±2.25	12.07±2.24	0.001
Hct, %	37.29±6.75	36.05±6.67	0.0005
Platelet count, $10^3/\mu L$	153.74±95.34	176.71±110.25	0.0002
Ferritin, ng/mL	262.90±510.74	282.80±366.39	0.002
Creatinine, mg/dL	1.01±0.73	1.20±4.02	0.31
HbA1c, mmol/mol	6.21±1.70	6.18±1.80	0.73
Total protein, g/dL	6.94±9.41	6.83±4.69	0.03
Albumin, g/dL	3.12±0.75	2.97±0.69	0.0003
PT, %	14.63±4.47	14.82±5.60	0.81
INR	1.47±4.58	1.35±0.53	0.23
CRP, mg/L	12.32±22.85	21.17±34.01	<0.0001
AFP, IU/mL	2,910.73±16,801.27	9,890.79±44,862.11	<0.0001
ALKP, U/L	194.60±186.56	248.68±262.28	0.002
GGTP, U/L	150.33±172.01	188.37±181.97	<0.0001
AST, U/L	113.59±216.89	113.24±106.04	0.005
ALT, U/L	81.69±183.25	62.15±53.90	0.71
Total bilirubin, mg/dL	2.33±3.49	3.07±4.50	0.01

All values are means ± standard deviations for continuous variables and *n* (%) for categorical variables. HCC, hepatocellular carcinoma; PVT, portal vein thrombosis; HbsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; MTD, maximum tumor diameter; Hct, hematocrit; HbA1c, glycated hemoglobin; PT, prothrombin time; INR, international normalized ratio; CRP, C-reactive protein; AFP, α-fetoprotein; ALKP, alkaline phosphatase; GGTP, γ-glutamyl transpeptidase; AST, aspartate transaminase; ALT, alanine transaminase. [a] Wilcoxon rank-sum (Mann-Whitney) test. [b] χ^2 test.

albumin and bilirubin levels were significantly worse in the low-platelet subgroup, as expected. In contrast, in the larger-tumor group, AFP was significantly higher and PVT percent of patients was significantly higher in the high-platelet subgroup compared to the low-platelet subgroup. In the large-MTD subgroup with higher platelets and larger tumors, cirrhosis was significantly less, as was total bilirubin. Thus, platelet dichotomization selects for a patient phenotype with better liver function but more advanced HCC. A linear regression model of MTD showed several significant single variables (Table 3). However, in the final multiple linear regression model, only platelet count and presence of PVT were significant.

Table 5. Comparisons between AFP groups in HCC patients

Parameter	AFP						
	a AFP <100 IU/mL (n = 1,027)	**b** AFP 100–1,000 IU/mL (n = 364)	**c** AFP >1,000 IU/mL (n = 382)	p value[a]	Comparisons, p value[b]		
					b vs. **a**	**c** vs. **a**	**c** vs. **b**
Platelet counts, 10^3/μL	148.96±96.31	157.14±91.55	182.82±106.50	0.0001	0.06	<0.0001	0.0009
Hemoglobin, g/dL	12.36±2.31	12.26±2.19	12.02±2.33	0.04	0.70	0.02	0.06
GGTP, U/L	135.73±165.25	175.91±162.20	203.10±193.38	0.0001	<0.0001	<0.0001	0.17
ALKP, U/L	201.94±302.30	222.41±213.92	240.38±239.29	0.0001	0.003	0.0001	0.58
Total bilirubin, mg/dL	2.52±3.76	3.68±6.09	3.21±4.91	0.002	0.002	0.007	0.70
Albumin, g/dL	3.17±0.76	3.02±0.74	2.95±0.71	0.0001	0.005	<0.0001	0.20
AFP, IU/mL	18.10±22.08	433.71±296.65	25,931.36±75,120.01	0.0001	<0.0001	<0.0001	<0.0001
MTD, cm	5.30±3.71	6.29±4.09	7.54±4.35	0.0001	<0.0001	<0.0001	0.0001
Nodules				0.04[c]			
1	633 (70.65)	212 (66.04)	202 (61.77)		0.13[d]	0.004[d]	0.26[d]
2–3	262 (29.24)	109 (33.96)	124 (37.92)		0.12[d]	0.005[d]	0.29[d]
>3	1 (0.11)	0 (0.00)	1 (0.31)		0.32[d]	0.55[d]	0.32[d]
PVT	184 (21.03)	105 (34.09)	145 (44.48)	<0.001[c]	<0.0001[d]	<0.0001[d]	0.007[d]
Cirrhosis	803 (79.11)	304 (83.98)	325 (85.08)	0.01[c]	0.04[d]	0.007[d]	0.68[d]

All values are means ± standard deviations for continuous variables and n (%) for categorical variables. AFP, α-fetoprotein; HCC, hepatocellular carcinoma; GGTP, γ-glutamyl transpeptidase; ALKP, alkaline phosphatase; MTD, maximum tumor diameter; PVT, portal vein thrombosis. [a] Kruskal-Wallis rank test. [b] Wilcoxon rank-sum (Mann-Whitney) test. [c] χ^2 test. [d] z test for proportions.

PVT and AFP Levels

Patients were next examined according to presence or absence of PVT (Table 4). Patients who were PVT positive had significantly larger tumors (in terms of MTD) and higher platelet levels, significantly higher AFP and C-reactive protein levels, and higher total bilirubin, ALKP, and GGTP levels. Interestingly, levels of "good" HDL cholesterol were significantly lower in the PVT-positive group. To our knowledge, this has not been previously reported.

Patients were next divided into 3 groups according to blood AFP levels of <100, 100–1,000, and >1,000 IU/mL (Table 5), and their tumor and nontumor parameters were examined. As expected, MTD and PVT percent significantly increased with an increase in AFP. There was also a trend to tumor multifocality with an increase in AFP. There were also increases in ALKP, GGTP, and total bilirubin levels with an increase in AFP as well as a statistically significant increase in platelet counts, likely reflective of the increase in MTD.

We then examined the associations for MTD and platelets (Fig. 2a) and for MTD and PVT (Fig. 2b). We found a significant correlation for MTD and platelets (r = 0.3348; p < 0.0001). Box plots were then created for MTD and PVT categories. There were significant differences in the MTD between PVT-positive and -negative patients (p < 0.0001).

Turkish Geography and HCC

As this database was composed of patients from several geographic sites throughout Turkey, we were curious as to whether there might be any regional differences in the patterns of HCC presentation or the patients. Table 6 shows patient groups from the locations that contributed most patients, and several marked differences were observed. MTD differed by locale, with the highest mean MTD of 7.0 cm being found in Mersin and the lowest mean MTDs of 5.03 and 5.33 cm being found in Ankara and Hatay, respectively. There were also large differences in PVT percent, with 40.74% in Mersin (where there was also the highest MTD) and the lowest PVT percent in Hatay with 20.69% (where there was also the smallest MTD). Multifocality with >1 tumor nodule was highest in Diyarbakır (53.49% of patients) and lowest in Mersin (17.02% of patients). Mean AFP levels were highest in Mersin (10,109 ng/mL) and lowest in Mardin and Ankara (2,885 and 3,254 ng/mL, respectively). There were also large regional differences in underlying liver disease. Cirrhosis was present in 88.29% of patients in Diyarbakır but only in 62.92% of

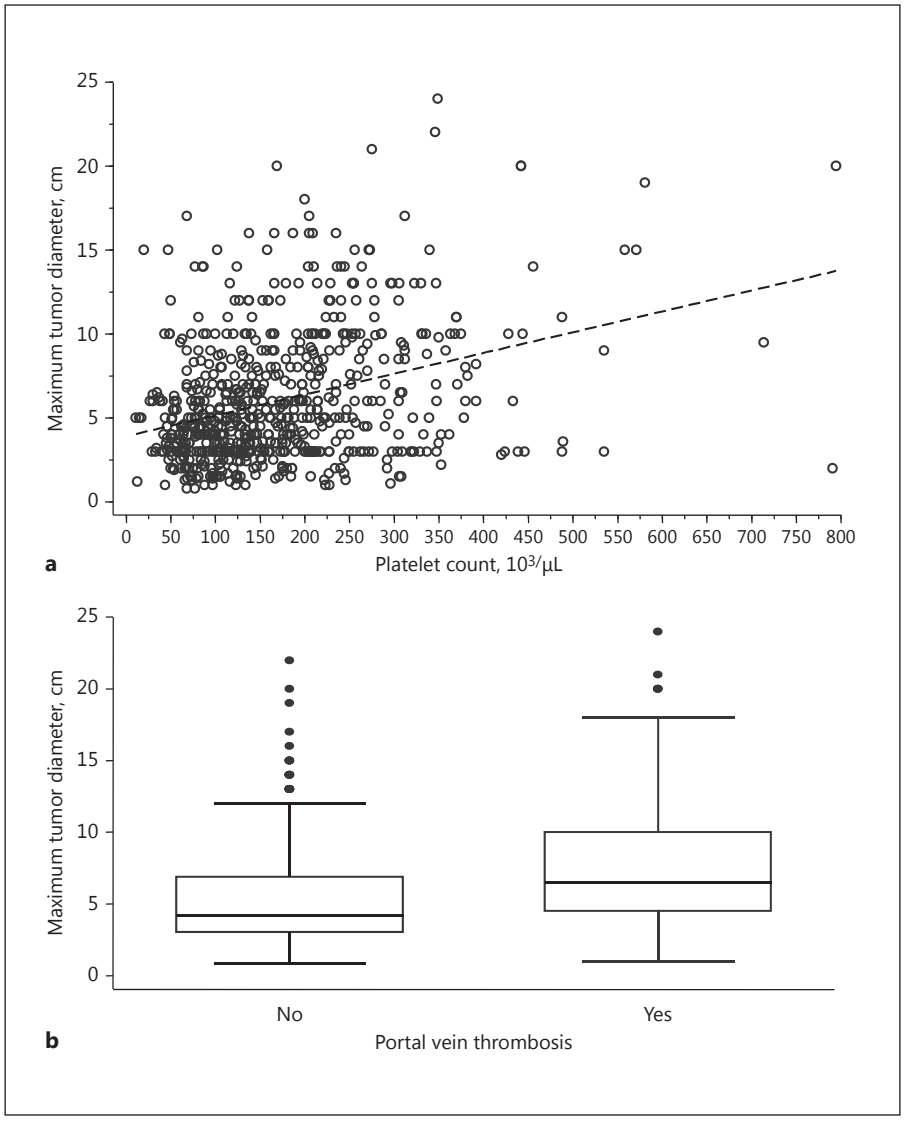


Fig. 2. a Scatter plot of maximum tumor diameter (cm) and platelet count (10^3/μL). Pearson correlation: $r = 0.3348$; $p < 0.0001$. **b** Box plot of maximum tumor diameter (cm) and portal vein thrombosis categories. Wilcoxon rank-sum (Mann-Whitney) test: $p < 0.0001$.

patients in Hatay. Furthermore, there were big regional differences in HBV, HCV, and hepatitis D virus (HDV). HBV was 73.95% in Diyarbakır but only 40.24% in Hatay. Conversely, HCV incidence in these HCC patients was highest in Hatay (30.49%) and lowest in Diyarbakır and Mardin (8.37 and 7.81%, respectively). In contrast, HDV was 17.13% in Diyarbakır but <10% elsewhere. Thus, Mersin patients had the largest tumors, highest incidence of PVT, and highest AFP levels. HBV was highest in Diyarbakır (Mardin a close second), and HCV was highest in Hatay. Mersin patients not only had the largest MTD, but also the highest total bilirubin levels (4.63 mg/dL), and the lowest bilirubin levels were found in Adana (2.20 mg/dL).

Discussion

Tumor characteristics that are generally considered for HCC patients are predominantly maximum tumor size or MTD and PVT and, to a lesser extent, AFP (due to its variability). Larger tumors have a worse prognosis in cancer in general as well as in HCC [12]. However, 40% of this cohort of HCC patients had AFP levels <20 IU/mL. This is similar to findings elsewhere [13] and doubtless contributes to the uncertainty concerning the use of blood AFP levels as a screening tool [14]. Platelets have been previously found to be both a harbinger of HCC in patients that are predisposed as well as a cirrhosis surrogate and to be associated with tumor size [9, 11, 15]. In

Table 6. Comparisons of HCC patients according to birth place

Parameter	Birth place						*p* value[a]
	Adana (*n* = 213)	Ankara (*n* = 45)	Diyarbakır (*n* = 222)	Hatay (*n* = 90)	Mardin (*n* = 65)	Mersin (*n* = 105)	
Male sex	173 (81.22)	36 (80.00)	188 (84.68)	68 (75.56)	55 (84.62)	84 (80.00)	0.51
Age, years	63.33±11.28	62.96±9.02	58.57±11.94	64.31±12.62	59.35±12.72	62.87±9.27	0.0001
Cirrhosis	160 (76.19)	37 (82.22)	196 (88.29)	56 (62.92)	53 (81.54)	88 (85.44)	<0.001
Etiology							<0.001[b]
HBV(–) & HCV(–)	40 (20.51)	11 (25.58)	38 (17.67)	24 (29.27)	13 (20.31)	25 (26.60)	
HBV(+) & HCV(–)	120 (61.54)	25 (58.14)	159 (73.95)	33 (40.24)	46 (71.88)	50 (53.19)	
HBV(–) & HCV(+)	35 (17.95)	7 (16.28)	18 (8.37)	25 (30.49)	5 (7.81)	19 (20.21)	
HDV(+)	10 (5.08)	0 (0.00)	37 (17.13)	4 (4.88)	6 (9.68)	5 (5.00)	<0.001
Platelet count, 10^3/μL	175.33±111.09	133.09±72.95	161.07±95.23	164.34±110.62	187.41±129.35	157.67±101.54	0.21
Hemoglobin, g/dL	12.14±2.15	11.95±2.65	12.26±2.30	11.31±2.07	12.10±2.27	11.45±2.28	0.002
GGTP, U/L	121.03±155.33	295.00±130.11	185.87±162.03	121.28±113.40	216.14±261.51	138.66±181.97	0.0001
AST, U/L	85.57±182.56	160.00±104.65	128.59±142.77	85.90±65.42	119.74±122.60	413.13±1420.63	0.0001
ALKP, U/L	160.97±119.41	223.00±97.58	205.33±164.69	216.04±237.91	269.09±269.01	271.43±640.20	0.01
Total bilirubin, mg/dL	2.20±2.91	2.99±16.56	2.58±3.61	2.41±3.88	3.47±5.86	4.63±6.95	0.32
AFP, IU/mL	5,857.67±23,424.97	3,253.74±15,819.15	8,508.09±53,108.07	9,469.25±39,870.72	2,884.87±8,652.05	10,108.97±46,954.41	0.08
MTD, cm	6.39±4.29	5.03±3.27	6.19±3.89	5.33±3.66	5.78±3.42	7.0±3.65	0.03
Nodules							<0.001[b]
1	117 (60.00)	28 (66.67)	99 (46.05)	66 (77.65)	33 (52.38)	39 (82.98)	
2–3	78 (40.00)	14 (33.33)	115 (53.49)	19 (22.35)	30 (47.62)	8 (17.02)	
>3	0 (0.00)	0 (0.00)	1 (0.47)	0 (0.00)	0 (0.00)	0 (0.00)	
PVT	61 (29.61)	17 (41.46)	73 (33.80)	18 (20.69)	22 (35.48)	11 (40.74)	0.11[b]

All values are means ± standard deviations for continuous variables and *n* (%) for categorical variables. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; (–), negative; (+), positive; GGTP, γ-glutamyl transpeptidase; AST, aspartate aminotransaminase; ALKP, alkaline phosphatase; AFP, α-fetoprotein; MTD, maximum tumor diameter; PVT, portal vein thrombosis. [a] Kruskal-Wallis rank test. [b] χ^2 test.

this cohort, 80.4% of patients had cirrhosis and 30.9% had thrombocytopenia (Table 1). Furthermore, there was a significant difference in platelet levels between patients having smaller versus larger MTD tumors (p = 0.0001; Fig. 1), and this was also confirmed by the significant Pearson correlation (Fig. 2). In a regression analysis, both platelets and presence of PVT were significant for MTD (Table 3).

PVT positivity was present in 28.55% of the total cohort (Table 1). When PVT-positive and -negative patients were compared (Table 4), the PVT-positive patients were found to have significantly larger tumors (in terms of MTD), as also seen in Figure 2, as well as tumor multifocality, higher AFP levels, and higher total bilirubin levels. Whether this is due to more aggressive tumors causing parenchymal destruction, or due to an increased PVT in patients with worse cirrhosis, is not addressed here, except that there was less cirrhosis in the PVT-positive group. Remarkably, however, there were significantly higher cardioprotective HDL levels in the PVT-negative group. We think this is the first report of this association, as we are not aware of this having been reported elsewhere.

Patients were trichotomized into 3 groups based on their AFP levels of <100, 100–1,000, and >1,000 IU/mL (Table 5). The majority of patients had levels <100 IU/mL (Table 1, 5). Patients in the high AFP group also had significantly larger tumors (in terms of MTD), tumor multifocality, and high PVT percent as well as platelet numbers. Patients with higher AFP also had worse liver function, as judged by total bilirubin, GGT, and ALKP levels, and lower albumin and higher cirrhosis percent, but the differences were not significant between the 2 elevated AFP groups.

An advantage of this multi-institutional study was the unusual possibility to compare HCC presentation in differing parts of a large country. Table 6 only includes the groups that contributed the largest patient numbers, predominantly in the center and east of Turkey. However, there were some remarkable differences. Firstly, the incidence of HDV was mainly found in patients from Diyarbakır and Mardin. Secondly, there was a considerable range of presence of cirrhosis, from 85.4% in Mersin to 62.9% in Hatay. Thirdly, tumor characteristics showed considerable heterogeneity. Thus, mean MTD was 7 cm in Mersin but 5 cm in Ankara; PVT was over 40% in Mersin and Ankara, yet only 20% in Hatay; tumor multifocality was 53% in Diyarbakır, yet only 17% in Mersin.

In Turkey, the prevalence of inactive HBV carrier patients is higher than in many countries, and these patients are usually ignored in terms of treatment. However, some of them may have severe fibrosis or cirrhosis. These patients may develop HCC over time. This could explain why HBV-related HCC patients more commonly have cirrhosis than other etiology-associated HCC patients in our cohort. In the Diyarbakır region, HDV infection is extremely prevalent (Table 6). Dual infection may cause cirrhosis more commonly.

In the Hatay region, HCV infection is more common than in other regions of Turkey. The high prevalence may be related to inappropriate dental treatments. It seems that this problem is being solved by dental awareness and added hygiene. However, it is difficult to explain why HCV-related HCC patients in Hatay had less cirrhosis. The average MTD of Hatay patients was the second lowest (above Ankara), possibly because of the mix of HBV-plus HCV-etiology patients in Hatay.

The relationship between cirrhosis and platelet count is an interesting and complex issue. HBV and HCV can replicate in the platelets and decrease platelet survival. This replication is more commonly seen in HCV infection than in connection with other causes and is related to cirrhosis. Furthermore, there is likely a relationship of thrombocytopenia to the degree of cirrhotic fibrosis, and measures of cirrhotic fibrosis severity were not available for this cohort. Platelet counts may also be related to the Child-Pugh score which indicates liver functional capacity. Patients with high Child-Pugh score may have lower platelet counts because thrombopoietin, which promotes bone marrow, is synthesized in the liver.

This study of a large HCC population at presentation shows certain unusual features, such as a high incidence of HBV, presence of HDV, and a large range of cirrhosis and tumor characteristics. Yet, the underlying biology, such as the relationship of MTD to platelets and to PVT, is similar to other reports. A drawback is the absence of survival data, in part due to many patients being from far-flung and rural areas. However, we show the fascinating variability in HCC presentation in a large country and how biological principles in the relationship between parameters can be reproduced here.

Disclosure Statement

The authors declare no conflicts of interest.

Funding Sources

This work was supported in part by NIH grant CA 82723 (B.I.C.).

References

1 Okuda K, Ohtsuki T, Obata H, et al: Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Cancer 1985; 56:918–928.
2 Carr BI, Guerra V: A hepatocellular carcinoma aggressiveness index and its relationship to liver enzyme levels. Oncology 2016;90: 215–220.
3 Carr BI, Guerra V, Giannini EG, Farinati F, et al: A liver index and its relationship to indices of HCC aggressiveness. J Integr Oncol 2016; 5.pii:178.
4 Sirivatanauksorn Y, Tovikkai C: Comparison of staging systems of hepatocellular carcinoma. HPB Surg 2011;2011:818217.
5 Chen ZH, Hong YF, Lin J, Li X, et al: Validation and ranking of seven staging systems of hepatocellular carcinoma. Oncol Lett 2017; 14:705–714.
6 Kudo M, Matsui O, Izumi N, Iijima H, et al; Liver Cancer Study Group of Japan: Surveillance and diagnostic algorithm for hepatocellular carcinoma proposed by the Liver Cancer Study Group of Japan: 2014 update. Oncology 2014;87(suppl 1):7–21.
7 Terzi E, Salvatore V, Negrini G, Piscaglia F: Ongoing challenges in the diagnosis of hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 2016;10:451–463.
8 Carr BI, Guerra V: HCC and its microenvironment. Hepatogastroenterology 2013;60: 1433–1437.
9 Carr BI, Guerra V, Pancoska P: Thrombocytopenia in relation to tumor size in patients with hepatocellular carcinoma. Oncology 2012;83:339–345.
10 Yamashita Y, Takahashi M, Baba Y, Kanazawa S: Hepatocellular carcinoma with or without cirrhosis: a comparison of CT and angiographic presentations in the United States and Japan. Abdom Imaging 1993;18:168–175.
11 Lu SN, Wang JH, Liu SL, Hung CH, et al: Thrombocytopenia as a surrogate for cirrhosis and a marker for the identification of patients at high-risk for hepatocellular carcinoma. Cancer 2006;107:2212–2222.
12 Huang WJ, Jeng YM, Lai HS, Sheu FY, et al: Tumor size is a major determinant of prognosis of resected stage I hepatocellular carcinoma. Langenbecks Arch Surg 2015;400:725–734.
13 Silva JP, Gorman RA, Berger NG, Tsai S, et al: The prognostic utility of baseline alpha-fetoprotein for hepatocellular carcinoma patients. J Surg Oncol 2017, DOI: 10.1002/jso.24742.
14 Cabibbo G, Craxì A: Epidemiology, risk factors and surveillance of hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2010;14: 352–355.
15 Colombo M, Sangiovanni A: Etiology, natural history and treatment of hepatocellular carcinoma. Antiviral Res 2003;60:145–150.