Thrombocytopenia in Relation to Tumor Size in Patients with Hepatocellular Carcinoma

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Key Words

Hepatocellular carcinoma • Diameter • Thrombocytopenia • Portal vein thrombosis • α -Fetoprotein • γ -Glutamyl transpeptidase

Abstract

Background: Hepatocellular carcinoma (HCC) size at diagnosis is important in management. Without screening programs, tumor size at diagnosis is heterogeneous. **Aims:** To examine the clinical parameters related to tumor size. **Methods:** Using prospectively collected data from a 1,100-patient biopsy-proven HCC cohort presenting in the absence of screening, tumor sizes were ordered and trichotomized and the resulting terciles were compared for tumor and blood parameters. **Results:** The terciles were significantly different with respect to portal hypertension and thrombocytopenia, which were present in a higher percent of tercile I patients with smaller tumors. Tercile III patients with larger HCCs had the highest serum α -fetoprotein (AFP), γ -glutamyl transpeptidase (GGTP), and alkaline phosphatase (ALKP) levels and the most portal vein (PV) thrombosis. Subclassification of tercile I patients by AFP showed that patients with high serum AFP had increased numbers of tumor nodules, more PV thrombosis, higher bilirubin, ALKP, and GGTP levels, and shorter survival. **Conclusions:** Smaller-tumor tercile I pa-

tients had more advanced portal hypertension with thrombocytopenia than did larger-tumor patients. Tercile I patients with higher AFP levels had more frequent PV thrombosis and worse survival than those with lower AFP levels. Elevated serum GGTP and ALKP levels appear to be associated with a more aggressive HCC phenotype. These differing patterns suggest more than one HCC pathway.

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Introduction

Primary hepatocellular carcinoma (HCC) is frequently associated with cirrhosis and has been attributed to a variety of risk factors including chronic hepatitis B (HBV) and C virus (HCV), environmental carcinogen exposure, and chronic alcohol consumption [1]. However, it is not known whether disease progression represents a single entity or a heterogeneous group of diseases, each with a different etiology and natural history as well as geographic variation [2]. A difficulty in the assessment of variations in the natural history is the arbitrary time at which the diagnosis is made in each patient's tumor development. Diagnosis can involve early identification due to screening, or coincidental discovery on computed axial tomography scan prior to the disease being symptomatic, or diagnosis later in the

disease progression due to complications from tumor growth or from hepatic failure due to loss of functioning hepatic parenchyma. The serum tumor marker α -fetoprotein (AFP) is included in several HCC classification systems, as higher levels have been shown to represent worse prognoses [3–8]. However, in the USA, where there is no national screening program, the majority of HCC patients present at an advanced and incurable phase of their disease. The difficulty of analysis in HCC is further compounded by the fact that tumor growth can cause a variety of different complications due to direct tumor extension as well as to a reduction in hepatic function resulting from either the associated cirrhosis or from tumor extension and destruction of liver parenchyma. There are few studies of large HCC databases from patients in the USA. The recent availability of information obtained at baseline assessment from an exceptionally large case cohort of 1,100 patients [6, 7] provides an opportunity to examine various clinical subsets. All patients were referred to a single physician at one institution over 19 years for management of HCC and follow-up. We used this experience to address the hypothesis that HCC may represent a heterogeneous group of diseases. If valid, then patients with differing identifiable profiles at disease presentation could be anticipated to have differences in treatment outcomes and prognosis. As a first step in this process, we showed in this study that patients with smaller tumors seem to have clinical profiles different from those with larger tumors. Furthermore, when the patients with smaller tumors were dichotomized according to serum AFP levels, 2 different disease patterns emerged at diagnosis in this small-tumor tercile.

Methods

Clinical Methods

On initial clinical presentation for evaluation, all 1,100 HCC patients had: baseline complete blood count, blood liver function tests, bloods AFP levels and hepatitis serology, physical examination, liver and tumor biopsy, and a triphasic helical computed axial tomography scan of the chest, abdomen, and pelvis. The data and CT descriptors were prospectively recorded and entered into an HCC database intended for follow-up and analysis. This analysis was done under a university IRB-approved protocol for the retrospective analysis of de-identified HCC patient records.

Statistical Analysis

Means and standard deviations (SD) for continuous variables, and relative frequencies for categorical variables, were used as indices of centrality and dispersion of the distributions.

The χ^2 test for categorical variables, the Kruskal-Wallis rank test, and the Wilcoxon rank-sum (Mann-Whitney) test for continuous variables were used to test associations.

For correlation, because the variables were not normally distributed, Spearman's rho was used to evaluate the magnitude and direction of the association between two variables.

For the identification of terciles of the maximum diameter of the tumor, since its distribution was not normal, the values were transformed into the natural logarithm scale; this was then used to identify relative terciles, on which we then performed the statistical evaluations.

When testing the null hypothesis of no association, the probability level of α error, two-tailed, was 0.05. In addition to tumor diameter, we assessed the total tumor mass (maximum diameter $\times$ number of tumor nodules) as previously described [9, 10]. Survival for tercile I subsets was determined by the Mann-Whitney rank-sum test.

All statistical computations were done using STATA 10.0 statistical software (StataCorp, College Station, Tex., USA).

Results

Patient Characteristics

In order to clearly separate patients with the smallest-diameter tumors from those with the largest-diameter tumors, this 1,100-patient biopsy-proven HCC data set was ordered according to maximum tumor diameter and then divided into terciles, with each tercile representing equivalent thirds of the data set. Tercile I represented patients with the smallest tumor size and tercile III represented the patient cohort with the largest tumor size. Table 1 shows the descriptive characteristics of patients in the three terciles, who were similar with respect to age, gender, hepatitis B and C positivity, and alcohol consumption. A greater percent of patients in tercile I had cirrhosis compared to tercile III patients (88 vs. 62%). There were also more smokers in tercile III than in tercile I or II.

Tercile Analysis of Tumor and Liver Characteristics

The tumor and liver characteristics of the patients in the three terciles are shown in table 2. There was no significant difference between the terciles with respect to the number of tumor nodules. However, there was a significant increase in portal vein (PV) thrombus (both main and branch PV), with the largest percent being in the larger-tumor tercile III patients ($p < 0.001$). Conversely, there was a significant increase in the percent of patients with cirrhosis in small-tumor tercile I patients, as well as the sequelae of cirrhosis, varices, and splenomegaly ($p < 0.001$), but not ascites.

Tercile Analysis of Hematologic and Biochemical Parameters

Thrombocytopenia was most evident in the small-tumor patients of tercile I (means $\pm$ SD) and the mean

platelet values increased in terciles II and III. Comparison between the tercile groups showed overall significance ($p = 0.0001$) and significant differences between the groups, especially tercile I versus tercile III ($p < 0.0001$). Significant overall differences in the white blood cell (WBC) count were also found ($p < 0.0001$), consistent with portal hypertension. The AFP values also showed significance for overall values between groups ($p = 0.0001$), with patients with larger tumors of tercile III having the highest AFP values. However, the range of AFP values in each tercile was wide. Total bilirubin values were highest in tercile I patients with the smaller tumors, and the values trended to decrease with the larger tumors in tercile III, but the differences were not statistically significant. However, both γ -glutamyl transpeptidase (GGTP) and alkaline phosphatase (ALKP) values increased with increases in terciles, which was significant in the overall comparison ($p < 0.000$), as well as between terciles I and III and between terciles II and III. There were no significant differences in terciles with respect to albumin or prothrombin time.

Tercile I Subset Analysis

Early stage HCC, as with most other tumors, has the best potential for long survival after treatment. We therefore focused on the data for tercile I patients, which were analyzed after dichotomization into low (<100 ng/ml) and high (≥ 100 ng/ml) AFP levels (tables 4, 5). The tumors with high AFP levels were significantly different from those with low AFP levels with respect to the number of tumor nodules, but not maximum tumor size, and with respect to the presence of PV thrombus (table 4). However, there were no significant differences between the 2 subsets with respect to cirrhosis and portal hypertension. The data was also analyzed using AFP cutoffs of 200 and 300 ng/ml, with identical results (data not shown). GGTP and ALKP values in the 2 subsets were highly significantly different, with higher values in the patients with elevated-AFP small HCCs, compared to the lower-AFP patients (table 5). There were significant differences in survival between the subsets despite being within the same small-tumor size group.

Correlations

The above data showed an association between tumor size (terciles) and both platelet numbers and AFP levels. Because the platelets and AFP variables were not normally distributed, Spearman's rho correlation was used to evaluate the magnitude and direction of the association between two variables (table 6). We found that

Table 1. Patient characteristics

	Terciles		
	I (≤ 4.4 cm)	II (4.5–9.6 cm)	III (≥ 9.7 cm)
Sex			
Male	71.6%	77.9%	71.2%
Female	28.4%	22.1%	28.8%
Mean age $\pm$ SD, years	64.0 $\pm$ 11.0	63.5 $\pm$ 12.1	60.7 $\pm$ 14.4
Hepatitis			
Negative	40.7%	41.3%	49.0%
HBV	9.3%	14.6%	12.4%
HCV	38.4%	34.8%	32.4%
HBV plus HCV	11.6%	9.3%	5.8%
Cirrhosis			
Negative	9.6%	24.9%	44.4%
Positive	90.4%	75.4%	55.6%
Mean smoking $\pm$ SD pack-years	4.0 $\pm$ 1.0	7.5 $\pm$ 2.0	15.0 $\pm$ 4.0
Alcohol			
Never	30.4%	23.7%	33.1%
Occasionally	26.4%	29.8%	23.4%
1–3 drinks/week	5.0%	11.4%	9.0%
Heavy >80 g/day (>10 yr)	38.1%	35.1%	34.4%

Table 2. Tercile analysis: radiologic characteristics

	Terciles of maximum tumor diameter			p^a
	I (≤ 4.4 cm) (n = 352)	II (4.5–9.6 cm) (n = 379)	III (≥ 9.7 cm) (n = 369)	
Number of tumors				0.95
1	107 (31.29)	112 (30.27)	110 (30.56)	
>1	235 (68.71)	258 (69.73)	250 (69.44)	
PV thrombosis (main)				<0.001
No	279 (86.92)	288 (83.00)	242 (72.67)	
Yes	42 (13.08)	59 (17.00)	91 (27.33)	
PV thrombosis (branch)				<0.001
No	257 (83.17)	239 (70.50)	149 (45.15)	
Left and/or right	52 (16.8)	100 (29.50)	181 (54.85)	
Varices				<0.001
No	161 (50.47)	191 (56.18)	230 (70.34)	
Yes	158 (49.53)	149 (43.82)	97 (29.66)	
Splenomegaly				<0.001
No	142 (42.64)	190 (53.67)	227 (65.61)	
Yes	191 (57.36)	164 (46.33)	119 (34.39)	
Ascites				0.61
No	202 (61.21)	222 (63.43)	205 (59.77)	
Yes	128 (38.79)	128 (36.57)	138 (40.23)	
Cirrhosis				<0.001
No	40 (11.66)	75 (20.49)	130 (38.12)	
Yes	303 (88.34)	291 (79.51)	211 (61.88)	

Values are presented as n (%). ^a χ^2 test.

the increase in tumor size correlated with increased platelet values ($\rho = 0.37$, $p < 0.0001$). The increase in total tumor mass (tumor maximum diameter $\times$ number of tumor nodules) also correlated with platelets counts ($\rho = 0.32$, $p < 0.0001$). However, there was little correlation between AFP levels and platelet values ($\rho = 0.05$, $p = 0.09$).

Discussion

The presence of thrombocytopenia in HCC patients probably reflects the severity of the portal hypertension which is secondary to the cirrhosis in which HCC usually develops, as has been noted previously [11–15]. To our

knowledge, an association between thrombocytopenia and HCC size has not previously been reported. The WBC was also decreased, together with platelets, in tertile I patients with smaller tumors, and this is likely also a reflection of portal hypertension. In patients diagnosed through a screening program (unlike most of this cohort), most would be expected to have smaller tumors, which is the hope for screening. Our patients presented randomly, as reflected in the tumor size range. In principle, a small tumor could be a slowly growing tumor, or a more aggressive tumor that is diagnosed early in its growth path. Conversely, a large tumor could be aggressive or could simply be a slowly growing mass that was detected late, possibly because its slow initial growth did not lead to symptoms. At diagnosis, the growth charac-

Table 3. Tertile analysis: hematologic and biochemical characteristics

	Terciles of maximum tumor diameter			p^a	Comparisons	p^b
	I (≤ 4.4 cm) (n = 352)	II (4.5–9.6 cm) (n = 379)	III (≥ 9.7 cm) (n = 369)			
Platelets, $\times 10^9/l$	141.98 $\pm$ 96.85	158.81 $\pm$ 95.01	239.90 $\pm$ 145.65	0.0001	I vs. II I vs. III II vs. III	0.002 <0.0001 <0.0001
WBC, $\times 10^9/l$	7.49 $\pm$ 4.08	8.55 $\pm$ 4.90	8.98 $\pm$ 5.41	0.0001	I vs. II I vs. III II vs. III	0.006 <0.0001 0.45
AFP, ng/ml	8,132.0 $\pm$ 56,924.8	13,917.9 $\pm$ 50,626.6	44,591.4 $\pm$ 134,049	0.0001	I vs. II I vs. III II vs. III	0.0001 0.0001 0.008
Bilirubin, mg/dl	1.81 $\pm$ 2.81	1.75 $\pm$ 3.42	1.72 $\pm$ 2.89	0.09	I vs. II I vs. III II vs. III	0.07 0.05 0.87
GGTP, U/100 ml	237.07 $\pm$ 295.73	244.39 $\pm$ 219.72	348.71 $\pm$ 304.21	0.0001	I vs. II I vs. III II vs. III	0.03 <0.0001 <0.0001
ALKP, U/100 ml	179.82 $\pm$ 132.39	210.12 $\pm$ 212.01	293.78 $\pm$ 280.69	0.0001	I vs. II I vs. III II vs. III	0.08 <0.0001 <0.0001
Albumin, g/l	3.18 $\pm$ 0.61	3.25 $\pm$ 0.60	3.30 $\pm$ 0.56	0.05	I vs. II I vs. III II vs. III	0.10 0.02 0.49
Prothrombin time, s	13.72 $\pm$ 3.03	13.37 $\pm$ 2.35	13.31 $\pm$ 2.14	0.04	I vs. II I vs. III II vs. III	0.04 0.02 0.72

Values are presented as means $\pm$ SD.

^a Kruskal-Wallis rank test. ^b Wilcoxon rank-sum (Mann-Whitney) test.

teristics of an HCC are often not evident. It might be expected that, as the HCCs grow in size, the portal hypertension and hence the thrombocytopenia get worse, as the increasing tumor size destroys hepatic parenchyma. Worsening liver function could thus be due either to progression of cirrhosis or to increasing tumor mass destroying liver parenchyma. However, the opposite was found in this study: the larger tumors in tercile III were associated with higher blood platelet and WBC values. This was possibly because the underlying livers of these patients with larger tumors were less damaged, with less portal hypertension, as judged by the higher platelet and WBC values, higher albumin levels, and (slightly) lower bilirubin levels. The tumors in tercile III might have grown to their larger size before the consequences of their growth led to diagnostic evaluation. Conversely, HCCs that developed in livers with significant damage could probably not grow too large without causing liver failure and patient death. An alternative interpretation of the data is that there might be 2 HCC phenotypes, one developing in more normal liver and leading to larger tumors and the other developing in more damaged livers with associated portal hypertension and forming smaller tumors. Molecular HCC analysis might clarify this.

This HCC experience was not primarily associated with screening and patients were diagnosed as a result of multiple factors, including annual physical exams, new symptoms, or evaluation for unrelated problems. Many of the patients did not know they were hepatitis carriers since that testing was often only done as part of the HCC work-up. The serum total bilirubin levels were not sig-

Table 4. Tercile I: tumor and liver characteristics

	Maximum tumor diameter (≤4.4 cm)		p ^a
	AFP(−) (<100 ng/ml) (n = 198)	AFP(+) (≥100 ng/ml) (n = 154)	
Number of tumors			0.02
1	70 (38.04)	33 (25.58)	
>1	114 (61.96)	96 (74.42)	
Number of tumors	2.78 ± 1.96	3.46 ± 2.14	0.005 ^b
Maximum tumor size, cm	2.73 ± 0.94	2.76 ± 1.00	0.61 ^b
PV thrombosis (main)			<0.001
No	165 (93.75)	91 (76.47)	
Yes	11 (6.25)	28 (23.53)	
PV thrombosis (branch)			<0.001
No	157 (92.35)	77 (68.75)	
Left and/or right	13 (7.65)	35 (31.25)	
Varices			0.86
No	88 (51.46)	62 (50.41)	
Yes	83 (48.54)	61 (49.59)	
Splenomegaly			0.61
No	72 (40.22)	56 (43.08)	
Yes	107 (59.78)	74 (56.92)	
Ascites			0.48
No	112 (63.64)	77 (59.69)	
Yes	64 (36.36)	52 (40.31)	
Cirrhosis			0.87
No	20 (10.87)	15 (11.45)	
Yes	164 (89.13)	116 (88.55)	

Values are presented as means ± SD or n (%). ^a χ^2 test. ^b Wilcoxon rank-sum (Mann-Whitney) test.

Table 5. Tercile I: hematologic and biochemical characteristics

	Maximum tumor diameter (≤4.4 cm)		p ^a
	AFP(−) (<100 ng/ml) (n = 198)	AFP(+) (≥100 ng/ml) (n = 154)	
Platelets, × 10 ⁹ /l	137.75 ± 98.24	140.24 ± 82.21	0.32
WBC, × 10 ⁹ /l	7.66 ± 4.30	7.52 ± 3.91	0.98
Bilirubin, mg/dl	1.29 ± 1.56	2.33 ± 3.65	0.0001
GGTP, U/100 ml	193.17 ± 250.55	281.12 ± 281.74	<0.0001
ALKP, U/100 ml	157.49 ± 122.10	209.55 ± 135.93	<0.0001
Albumin, g/l	3.26 ± 0.63	3.09 ± 0.59	0.01
PT, s	13.70 ± 3.49	13.80 ± 2.42	0.08
Median survival, days	421	181	<0.001

Values are presented as means ± SD unless otherwise stated. ^a Wilcoxon rank-sum (Mann-Whitney) test.

Table 6. Correlations

	Platelets (rho ^a)	p value
Maximum tumor diameter	0.3688	<0.0001
Total tumor mass (size × number)	0.3234	<0.0001
AFP	0.0529	0.0882

^a Spearman's rank correlation.

nificantly different overall, although there was a significant difference between terciles I and III. By contrast, the levels of both serum GGTP and ALKP increased with increasing terciles and were significantly different overall as well as between terciles I and III. Both GGTP and ALKP were also significantly different in the dichotomized tercile I subsets (table 5) of high- and low-AFP patients ($p < 0.0001$). GGTP [16–19] and ALKP levels [20–24] have previously been reported to have prognostic significance in HCC patients. Thus, for the same size grouping (tercile I), the patients with higher AFP had increased levels of GGTP, ALKP, and total bilirubin, and lower serum albumin levels, showing worse liver function with high AFP and thus putatively a more aggressive HCC phenotype, reflected in their worse survival. However, there was no significant difference in the mean platelet or WBC counts between the two tercile I subsets. There has also been recent molecular profiling evidence for a relationship between HCC biology and the underlying

ing liver [25, 26], providing potential mechanistic support for the idea of the liver disease influencing HCC behavior. Comparison of changes in ALKP and GGTP between terciles in table 3 (whole cohort) and between subsets in table 5 revealed a similar trend. In table 3, higher levels were associated with larger tumors (tercile III), while in table 5 higher levels were associated with higher AFP and shorter survival. Thus, ALKP and GGTP in HCC patients may reflect tumor aggressiveness [16, 19, 21, 27], in addition to their role as markers of liver function.

A main finding in this report was a decrease in platelet and WBC counts in association with a smaller tumor size and more normal platelet levels in patients with larger tumors (table 3). We therefore used the Spearman rank correlation test to examine whether there was a relationship between tumor size and platelet levels in the whole cohort. We found that increased tumor diameter correlated with increased blood platelet values ($\rho = 0.37$, $p < 0.0001$) and an increase in total tumor mass (tumor maximum diameter × number of tumor nodules) also correlated with increased platelets ($\rho = 0.32$, $p < 0.0001$). This most likely reflects the decreased platelet number being a surrogate for the degree of cirrhosis-induced portal hypertension [11], but the mechanisms relating smaller tumor size to portal hypertension remain to be identified.

Disclosure Statement

None of the authors have a conflict of interest to declare.

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