Hepatocellular Carcinoma Size: Platelets, γ -Glutamyl Transpeptidase, and Alkaline Phosphatase

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Key Words

Hepatocellular carcinoma · Terciles · Thrombocytopenia · Portal vein thrombosis · α -Fetoprotein · γ -Glutamyl transpeptidase · Alkaline phosphatase

Abstract

Background: Thrombocytopenia is a cirrhosis surrogate which is associated with hepatocellular carcinoma (HCC) development. **Aims:** To compare the clinical characteristics of HCC in the presence and absence of thrombocytopenia. **Methods:** The baseline clinical data of a large cohort of randomly presenting, biopsy-proven HCC patients was examined for phenotypic patterns, after organizing the data by tumor size and subdivision into tumor size terciles. **Results:** Small tumor size tercile I patients had the lowest platelet counts. Patients with higher platelets within each size tercile had the lowest bilirubin and prothrombin time and higher γ -glutamyl transpeptidase (GGTP) and alkaline phosphatase (ALKP) levels. When patients with similar platelet and bilirubin levels were compared, α -fetoprotein, GGTP, and ALKP were significantly increased in patients with larger tumors and in the presence of portal vein thrombus. Large tumor size tercile III patients without thrombocytopenia had larger tumors, higher GGTP and ALKP, and lower bilirubin levels than did patients with thrombocytopenia. **Conclusions:**

Thrombocytopenia occurred in 40.7% of patients with smaller tumors but only in 11.3% of patients with larger tumors. Patients without thrombocytopenia had elevated GGTP and ALKP and lower bilirubin levels, regardless of tumor size, but they also had larger tumors within the large tumor tercile.

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Introduction

Hepatocellular carcinoma (HCC) is thought to arise typically on a background of chronic hepatic inflammation due to hepatitis B or C, chronic alcoholism, a combination of these, or various metabolic liver disorders, including those associated with obesity. Given that the choice of treatment, and thus the prognosis, depends on early diagnosis, many studies have identified HCC risk factors among patients with chronic liver injury to aid in screening for those at greatest risk [1–3]. These factors include: male gender, age, cirrhosis with portal hypertension, and its surrogate marker thrombocytopenia [4–6]. We recently found a relationship between thrombocytopenia and HCC size, with lower platelet levels associated with smaller tumors [7, 8]. The current study was undertaken to further explore this relationship.

Methods

Clinical Methods

The baseline clinical presentation data of 1,047 US patients presenting for treatment of biopsy-proven HCC in an unscreened population was examined. On initial clinical presentation for evaluation, all patients had the following assessments: baseline complete blood count and blood liver function tests, blood α -fetoprotein (AFP) levels and hepatitis serology, physical examination, liver and tumor biopsy, and a triphasic helical computed axial tomography (CAT 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 following a university Institutional Review Board-approved protocol for the retrospective analysis of de-identified HCC patient records.

Statistical Analysis

Means ($\pm$ SD) for continuous variables, and relative frequencies for categorical variables, were used as indices of the centrality and dispersion of parameter 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 the identification of terciles of maximum tumor sizes, since the tumor size distribution was not normal, the values were transformed into a natural logarithm scale from which the relative terciles were defined, and subsequent statistical evaluations were performed on them.

All statistical computations were made using Stata 10.0 statistical software (Stata Statistical Software, College Station, Tex., USA)

Results

Relation of Maximum Tumor Size to Plasma Platelet Levels

The relationship between plasma platelet levels and maximum tumor sizes in the whole cohort was examined (fig. 1a), together with the linear regression line of the plot. An approximate relationship between increasing tumor size and increasing platelet levels was discerned. To further clarify this relationship, we trichotomized our data set into size terciles to more clearly separate patients on the outside 'wings' of the tumor size distribution (fig. 1b). The tercile distributions showed a major density clustering of patients in the smallest tumor size tercile I at the lowest platelet levels (fig. 1b). By contrast, tercile III patients with the largest tumors had a broader range of platelet distribution and a higher mean. The platelet level means were (fig. 1b, bottom) 142, 158, and $239 \times 10^9/l$ for patients in terciles I, II, and III, respectively ($p = 0.0001$). Significant differences were also found when terciles I versus II, I versus III, and II versus III were compared. Tercile III patients (90%) had much less cirrhosis than did

tercile I patients (55%), as previously reported [7]. However, the terciles were similar with respect to alcoholism, hepatitis B and C, or no hepatitis, and there was a 70% male incidence.

Comparisons within Terciles

We then examined the clinical characteristics of patients within tumor size terciles for patterns of heterogeneity after dichotomizing for platelet values $<100 \times 10^9/l$ or $\geq 100 \times 10^9/l$ (table 1a), since thrombocytopenia serves as a surrogate for cirrhosis and subsequent portal hypertension with associated splenomegaly [4]. The subsets of patients with higher platelet values in terciles I (59% of patients) and III (89% of patients) had more normal total bilirubin and prothrombin time (PT) and a slightly larger maximum tumor size, although this was significant only in tercile III. Patients with higher platelet levels also had significantly elevated γ -glutamyl transpeptidase (GGTP) and alkaline phosphatase (ALKP) levels compared to patients with lower platelet levels. These levels occurred in patients with significantly lower bilirubin levels. The AFP levels in each tercile were also elevated in the higher platelet subsets, but with large SD. The low platelet subset of tercile III (11.3% or 39/345 patients) also had large tumors despite thrombocytopenia and elevated bilirubin levels, although the mean tumor diameters were smaller than for patients with normal platelets in the same size tercile.

Comparisons between Tumors in Patients with Similar Platelet Levels

To minimize the confounding effects of differences in liver function, patients in different size terciles, i.e. I and III, but with similar platelet levels, and thus bilirubin levels, were examined (table 1b) after re-arranging table 1a to compare patients within the same platelet dichotomization. Within each platelet dichotomization, tercile III patients with larger tumors had significantly more portal vein thrombosis (PVT) and significantly higher AFP levels than did tercile I patients, as expected. Despite similarities in bilirubin and PT, tercile III patients had significantly higher GGTP and ALKP levels compared to tercile I patients, which is consistent with the idea that GGTP and ALKP levels might be related to tumor size and not just to liver damage. This is clearest for patients with platelets $\geq 100 \times 10^9/l$ with lower bilirubin levels.

Tercile Subsets and PVT

PVT is considered a poor prognostic factor [2, 3, 9] and often limits therapy choices. Terciles I and III were

Fig. 1. a Scatterplot of platelet counts and maximum tumor size in the overall sample ($r = 0.38$; $p < 0.0001$), together with a linear regression line of platelets on the maximum tumor size. **b** Distribution of platelets in each category of maximum tumor size tertiles and platelet comparisons between the tertiles.

	Maximum tumor size tertiles			p value ^a	Contrast ^b	p value
	tercile I (n = 336)	tercile II (n = 366)	tercile III (n = 345)			
Mean platelets $\pm$ SD, $\times 10^9/l$	142.0 $\pm$ 96.8	158.8 $\pm$ 95.0	239.9 $\pm$ 145.6	0.001	I vs. II	0.002
Range, $\times 10^9/l$	22–639	21–586	28–1,074		I vs. III	<0.0001
					II vs. III	<0.0001

^a Kruskal-Wallis rank test. ^b Mann-Whitney rank test.

Table 1. Characteristics of patients in different tumor size tertiles**a** Comparisons within tumor size tertiles

Parameters	Tercile I (≤ 4.4 cm) platelet counts		p value ^a	Tercile III (≥ 9.7 cm) platelet counts		p value ^a
	<100 ($\times 10^9/l$) (n = 137)	≥ 100 ($\times 10^9/l$) (n = 199)		<100 ($\times 10^9/l$) (n = 39)	≥ 100 ($\times 10^9/l$) (n = 306)	
AFP, ng/ml	2,634.7 $\pm$ 1,293.9	28,538.5 $\pm$ 19,469.6	0.14	11,892.0 $\pm$ 3,406.2	66,864.5 $\pm$ 21,611.4	0.56
GGTP, U/100 ml	177.7 $\pm$ 131.2	278.6 $\pm$ 249.0	0.002	238.7 $\pm$ 146.2	362.1 $\pm$ 317.3	0.04
ALKP, U/100 ml	154.9 $\pm$ 103.9	197.4 $\pm$ 147.0	0.04	211.4 $\pm$ 132.5	303.0 $\pm$ 292.8	0.04
Total bilirubin, mg/dl	1.9 $\pm$ 2.3	1.7 $\pm$ 3.0	<0.0001	2.9 $\pm$ 5.1	1.6 $\pm$ 2.5	0.0003
PT, s	14.3 $\pm$ 3.1	13.3 $\pm$ 2.9	<0.0001	14.0 $\pm$ 2.2	13.2 $\pm$ 2.1	0.006
Albumin, g/l	3.0 $\pm$ 0.5	3.3 $\pm$ 0.7	<0.0001	3.1 $\pm$ 0.6	3.3 $\pm$ 0.6	0.16
WBC, $\times 10^9/l$	6.6 $\pm$ 3.7	8.1 $\pm$ 4.2	0.0002	6.7 $\pm$ 6.3	9.3 $\pm$ 5.2	<0.0001
Maximum tumor size, cm	2.8 $\pm$ 0.9	2.9 $\pm$ 1.0	0.30	11.8 $\pm$ 3.3	14.3 $\pm$ 4.0	0.02
Tumor nodules, n	2.8 $\pm$ 1.9	3.4 $\pm$ 2.2	0.03	3.0 $\pm$ 2.2	3.5 $\pm$ 2.2	0.26
PVT, % patients	16.1	23.0	0.14 ^b	54.5	59.3	0.44 ^b

b Comparisons between tertiles with similar liver function

Parameters	Platelet counts <100 ($\times 10^9/l$)		p value ^a	Platelet counts ≥ 100 ($\times 10^9/l$)		p value ^a
	tercile I (≤ 4.4 cm) (n = 137)	tercile III (≥ 9.7 cm) (n = 39)		tercile I (≤ 4.4 cm) (n = 199)	tercile III (≥ 9.7 cm) (n = 306)	
AFP, ng/ml	2,634.7 $\pm$ 1,293.9	11,982.0 $\pm$ 3,406.2	<0.0001	28,538.5 $\pm$ 19,469.6	66,864.5 $\pm$ 21,611.4	<0.0001
GGTP, U/100 ml	177.7 $\pm$ 131.2	238.7 $\pm$ 146.2	0.002	278.6 $\pm$ 249.0	362.1 $\pm$ 317.3	<0.0001
ALKP, U/100 ml	154.9 $\pm$ 103.9	211.4 $\pm$ 132.5	0.005	197.4 $\pm$ 147.0	303.0 $\pm$ 292.8	<0.0001
Total bilirubin, mg/dl	2.9 $\pm$ 2.3	2.6 $\pm$ 5.1	0.63	1.7 $\pm$ 3.0	1.6 $\pm$ 2.5	0.81
PT, s	14.3 $\pm$ 3.1	14.0 $\pm$ 2.2	0.28	13.3 $\pm$ 2.9	13.2 $\pm$ 2.1	0.42
Albumin, g/l	3.0 $\pm$ 0.5	3.1 $\pm$ 0.6	0.23	3.3 $\pm$ 0.7	3.3 $\pm$ 0.6	0.89
WBC, $\times 10^9/l$	6.6 $\pm$ 3.7	6.7 $\pm$ 6.3	0.16	8.1 $\pm$ 4.2	9.3 $\pm$ 5.2	0.004
Maximum tumor size, cm	2.8 $\pm$ 0.9	11.8 $\pm$ 3.3	<0.0001	2.9 $\pm$ 1.0	14.3 $\pm$ 4.0	<0.0001
Tumor nodules, n	2.8 $\pm$ 1.9	3.0 $\pm$ 2.2	0.70	3.4 $\pm$ 2.2	3.5 $\pm$ 2.2	0.63
PVT, % patients	16.1	54.5	<0.001 ^b	23.0	59.3	<0.001 ^b

All values are presented as means $\pm$ SD, except for PVT. Hgb = Hemoglobin; WBC = white blood cell count. ^a Wilcoxon rank-sum (Mann-Whitney) test. ^b χ^2 test.

each dichotomized according to PVT (right, left, both or main portal vein). The PVT subsets did not have significant differences in tumor size (table 2a), although PVT-positive tercile I patients (78/299 = 26%) had more tumor nodules ($p = 0.0006$), but PVT-positive tercile III patients (193/312 = 62%) had significantly more clinical evidence of portal hypertension (varices, splenomegaly, and ascites). Bilirubin and AFP levels were significantly higher in PVT-positive patients compared to PVT-negative patients within each tercile (table 2b), likely reflecting tumor aggressiveness.

Discussion

Analysis of the clinical practice data is complicated by the heterogeneity of the tumor subsets and the influence of the tumor milieu (underlying liver). Most HCC arise on a background of chronic hepatitis or cirrhosis or both, and prognosis is considered to be related to tumor factors such as serum AFP levels, tumor size and number, and presence of PVT, as well as liver factors, such as portal hypertension and bilirubin levels [9–11]. There is likely an interaction between them, and both influences were recognized in the classification system of Okuda et al. [12] and subsequently by others, in which greater phenotypic

Table 2. PVT in the different tumor size terciles**a** Maximum tumor size terciles compared by PVT status

Characteristics	Tercile I (≤ 4.4 cm) PVT		p value ^a	Tercile III (≥ 9.7 cm) PVT		p value ^a
	no (n = 258)	yes (n = 78)		no (n = 152)	yes (n = 193)	
Maximum tumor size, cm	2.7 $\pm$ 0.9	2.8 $\pm$ 1.0	0.68 ^b	12.9 $\pm$ 3.7	14.4 $\pm$ 4.15	0.32 ^b
Tumor nodules, n	2.9 $\pm$ 2.0	3.9 $\pm$ 2.1	0.0006 ^b	3.3 $\pm$ 2.2	3.5 $\pm$ 2.2	0.61 ^b
Varices, % patients	49.1	45.0	0.57	21.9	32.9	0.04
Splenomegaly, % patients	60.6	53.3	0.31	23.5	40.6	0.002
Ascites, % patients	36.0	43.1	0.32	29.3	44.0	0.008
Cirrhosis, % patients	88.3	89.7	0.78	57.6	63.1	0.14

^a χ^2 test. ^b Wilcoxon rank-sum (Mann-Whitney) test.**b** PVT status of maximum tumor size terciles

Parameters ^a	Tercile I (≤ 4.4 cm) PVT		p value ^b	Tercile III (≥ 9.7 cm) PVT		p value ^b
	no (n = 258)	yes (n = 78)		no (n = 152)	yes (n = 193)	
AFP, ng/ml	8,351.3 $\pm$ 65,693.5	65,196.8 $\pm$ 325,043.9	<0.0001	45,895.0 $\pm$ 161,475.7	65,123.6 $\pm$ 207,957.9	0.003
GGTP, U/100 ml	211.1 $\pm$ 271.1	297.7 $\pm$ 348.2	0.0007	322.6 $\pm$ 324.4	387.7 $\pm$ 300.5	0.003
ALKP, U/100 ml	162.2 $\pm$ 111.8	222.6 $\pm$ 156.1	0.001	254.6 $\pm$ 232.5	331.7 $\pm$ 327.7	<0.0001
Total bilirubin, mg/dl	1.5 $\pm$ 1.9	3.0 $\pm$ 4.8	0.002	1.2 $\pm$ 1.1	2.0 $\pm$ 3.0	0.0007
PT, s	13.5 $\pm$ 2.5	14.2 $\pm$ 2.6	0.006	13.1 $\pm$ 2.1	13.4 $\pm$ 2.2	0.29
Albumin, g/l	3.2 $\pm$ 0.6	3.1 $\pm$ 0.6	0.08	3.4 $\pm$ 0.6	3.3 $\pm$ 0.5	0.23
WBC, $\times 10^9$ /l	7.1 $\pm$ 4.0	9.1 $\pm$ 4.3	0.0001	8.9 $\pm$ 4.9	9.0 $\pm$ 5.6	0.60
Platelets, $\times 10^9$ /l	132.2 $\pm$ 92.6	161.4 $\pm$ 116.2	0.08	201.7 $\pm$ 132.5	252.3 $\pm$ 143.7	0.06

WBC = White blood cell count. ^a All values are presented as means $\pm$ SD. ^b Wilcoxon rank-sum (Mann-Whitney) test.

complexity was taken into account. In addition, the non-tumoral liver may actually influence HCC biology and have characteristic ‘molecular signatures’ [13, 14].

Thrombocytopenia, a surrogate marker for cirrhosis, is associated with subsequent HCC development [2, 15–18] and smaller HCC [7, 8]. In noncirrhotic livers, HCC tend to be larger [19–22], probably since they can grow with less liver damage, whereas HCC growth in cirrhosis is often associated with parenchymal damage. Our larger HCC were associated with higher mean platelet counts, yet patients likely had some degree of fibrosis, as previously shown even in noncirrhotic HCC [20].

The smaller tumor sizes with thrombocytopenia could reflect cirrhotic liver limiting tumor growth (fig. 1). However, a tercile III subset of 11.3% of patients (39/345) with thrombocytopenia (table 1) showed that this is an insufficient explanation. In tercile I, 59% (199/336) had higher platelet levels, associated with lower bilirubin and higher AFP with more PVT (table 1a). They also had higher

GGTP and ALKP levels. Tercile III patients with higher platelet levels (306/345 or 88.6%) had significantly larger tumors, more PVT, higher AFP values (but not significantly), and more normal bilirubin, PT, and albumin values compared to patients with thrombocytopenia. GGTP and ALKP values were higher in both tercile I and III subsets with higher platelet levels and significantly lower bilirubin.

Since the liver milieu is important in HCC biology [13, 14, 19], we compared size terciles having equivalent platelet levels and thus bilirubin levels (table 1b). Tercile III patients had significantly larger tumors, more PVT, and higher AFP, as expected. Despite similar bilirubin, PT, and albumin values, the GGTP and ALKP levels were significantly higher in patients with larger tumors, as previously noted [23–25], and this is clearest in tercile III, with high platelet levels and large tumors, although the bilirubin and PT were relatively normal.

PVT had no relation to tumor size but was associated with portal hypertension in tercile III. Despite similar tumor sizes, PVT-positive patients in each tercile had significantly higher AFP, GGTP, ALKP, and bilirubin (table 2b). The elevated bilirubin levels associated with PVT likely reflect tumor invasion into liver parenchyma.

Two possibilities were considered to explain differences in tumor size in relation to platelets (fig. 1). Firstly, normal platelets associated with larger tumors may reflect that tumors can grow larger without causing failure in normal livers, but not with portal hypertension [26], without causing further parenchymal destruction. Thrombocytopenia thus only reflects hepatic fibrosis and portal hypertension and is not directly related to HCC growth. Secondly, platelets have several HCC growth and angiogenesis factors, such as platelet-derived growth factor, vascular endothelial growth factor, fibroblast growth factor, and serotonin [27–35], and also facilitate immune-mediated liver injury in hepatitis B virus mice, with anti-platelet therapy preventing HCC [36]. Platelets can also produce GGTP and ALKP [37, 38]. Thrombocytosis was reported in 2.7% of a large HCC series in association with large tumors, with platelets $>400 \times 10^9/l$ [39, 40]. There could thus be different pathways for HCC development in the presence or absence of thrombocytopenia. In addition

to their role in blood coagulation, platelets might also be involved in HCC growth and could be a novel target for HCC therapies in patients without thrombocytopenia. Thus, platelet-derived blood growth factors might be future markers or predictors of large size.

Conclusions

We previously focused on small HCC size and thrombocytopenia. We have now shown the usefulness of a tercile approach to identifying HCC subsets in a heterogeneous tumor population and also highlight the importance of elevated GGTP levels associated with larger tumors in the absence of increased bilirubin levels.

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Disclosure Statement

None.

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