Published in final edited form as:

Semin Oncol. 2014 June ; 41(3): 415–421. doi:10.1053/j.seminoncol.2014.04.001.

Platelet-related phenotypic patterns in hepatocellular carcinoma patients

Brian I. Carr, M.D, F.R.C.P, Ph.D¹, Chih-Yun Lin, MS², and Sheng-Nan Lu, MD, MPH, PhD²

¹Dept. of Liver Tumor Biology, IRCCS S. de Bellis, Castellana Grotte, Italy

²Division of Hepatogastroenterology, Dept. of Internal Medicine, Chang Gung Memorial Hospital, Kaohsiung Medical Center and Chang Gung University, Kaohsiung, Taiwan

Abstract

Background—Small HCCs usually arise in cirrhosis, often with associated thrombocytopenia. Many large HCC patients have normal blood platelet counts.

Aims—To compare parameter and phenotype patterns of patients with small 3cm and larger HCCs.

Methods—Retrospective analysis was undertaken of a 4139 patient HCC database to compare patient demographics, liver and tumor characteristics associated with small and large size HCCs, especially with respect to platelet counts.

Results—Patients with larger HCCs had more tumor nodules and PVT positivity, and had higher blood AFP, bilirubin and platelet counts. In patients with larger tumors and normal platelets (43.7% of the cohort), tumors were larger and AFP levels were higher, with lower bilirubin and AST levels than in patients with larger tumors and thrombocytopenia (17.5%). A parsimonious multinomial regression model showed high Odds Ratio for AFP and platelets for tumors >3cm with PVT.

Conclusions—Platelet levels are associated with distinct large HCC phenotypes.

Keywords

HCC size; platelets; AFP; GGTP; surveillance

Introduction

Hepatocellular carcinoma (HCC) frequently arises in chronic hepatitis or any cause of cirrhosis (1–4). It occurs predominantly in the third world, but increasingly in western

© 2014 Elsevier Inc. All rights reserved.

Correspondence: Brian I. Carr MD, FRCP, PhD, IRCCS' de Bellis', via Turi 27, 70013 Castellana Grotte (BA), Italy, Tel. 39 080 4994603; Fax. 39 080 4994313, brianicarr@hotmail.com.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures: none; Grant support: none

countries (5, 6). Prognosis is limited when it presents at advanced stage, as is frequent. Thrombocytopenia associated with liver fibrosis has been suggested as a cirrhosis surrogate (7), to be potentially useful in screening for patients at risk of HCC (8) and for prognosis (9–11). In this study, we compared several clinical parameters of patients with small and larger HCCs and report that different parameter patterns could be discerned.

Methods

Data collection

Clinical practice data, recorded from a Taiwanese HCC screening program, was prospectively collected on over 4139 newly diagnosed HCC patients and entered into a database that was used for routine patient follow-up. Data included baseline CAT-scan characteristics of maximum tumor diameter (MTD) and number and presence or absence of portal vein thrombosis (PVT). Demographics (gender, age, alcohol history, presence of hepatitis B or C); Complete blood counts (hemoglobin, platelets, PT); blood AFP and routine blood liver function tests, (total bilirubin, AST,GGTP, albumin). This was a university IRB-approved analysis of de-identified HCC patients.

Statistical methodology

Median (inter-quartile range (IQR)) and standard deviation (SD) for continuous variables, and relative frequency for categorical variables, were used as indices of centrality and dispersion of the distribution. Chi-square test for categorical variables, and Mann-Whitney test or Kruskal-Wallis test for continuous variables was used to test associations between groups.

A multiple logistic regression model was used to evaluate associations between MTD or number or PVT, on single variables and was corrected for sex, age, and use of alcohol. A parsimonious multinomial multiple logistic regression, was also used to evaluate associations between MTD and PVT combined on AFP and platelets in the model, corrected for sex, age, and use of alcohol. Spearman correlation coefficient was calculated for the whole cohort, for MTD, AFP, PVT, AST and GGTP, with platelet values as a continuous variable.

Results

Tumor size and blood platelet levels

Patient data were ordered according to maximum tumor diameter (MTD) and then trichotomized, resulting in 3 tumor size terciles. The MTD tercile analysis in relation to platelet counts (Fig. 1) shows that median platelet counts were significantly different when tercile I was compared to terciles II or III, $p < 0.0001$, with larger tumors being associated with higher platelet counts than smaller tumors. Tumor and patient characteristics changed with increasing tercile in a significant manner (Table 1), with tercile III patients being associated with increased percent of tumor multifocality and percent of patients with portal vein thrombosis (PVT) compared to tercile I patients. Blood alpha-fetoprotein (AFP) levels were also significantly increased in tercile I vs. tercile III, as did gamma glutamyl

transpeptidase (GGTP) levels. Bilirubin levels were increased with increases in tercile, as were prothrombin times (PT) and glutamic oxaloacetic transaminase (SGOT) levels.

Tumor size groups dichotomized by platelets

Thrombocytopenia is a risk for HCC in predisposed patients (3, 12–15), and associated with small HCC size (16, 17). We combined terciles II and III to create a manageable large tumor category for this analysis. Small and large tumor groups were dichotomized according to blood platelet levels (Table 2). Large tumor size patients with higher platelet levels (Table 2, column d) were 43.7 % of the total cohort and had significantly larger size tumors, significantly higher AFP levels and slightly more PVT, compared to large tumor patients with lower platelets who comprised 17.5 % of the total cohort (Table 2, column c). Despite having larger tumors, the normal platelet sub-group (column d) had significantly lower blood bilirubin, AST and prothrombin values, and higher albumin levels, all consistent with better liver function. Thus, higher platelet counts were associated with larger size tumors, but not with increased tumor numbers or PVT.

Comparison of platelet sub-groups for small tumors (Table 2, columns a and b), respectively 20.8 and 18% of the total cohort), also showed several differences. Patients with higher platelets (column b) had lower bilirubin, AST, GGTP and prothrombin time, consistent with less liver fibrosis. Neither tumor size, tumor number, nor PVT was different between these 2 groups. However, AFP levels were significantly higher for the low compared to high platelet sub-group (columns a and b), opposite to the pattern of larger tumor patients, although all were at comparatively low AFP levels.

Given the findings of patients with larger tumors having higher platelet counts (Fig. 1 and Table 1), we performed a Spearman correlation analysis (Table 3). Platelet counts significantly correlated with tumor size ($\rho=0.411$, $p<0.001$), but weakly with tumor numbers, PVT or AFP levels.

Multiple logistic regression model of tumor diameter, tumor number and PVT

A multiple logistic regression analysis was performed to relate maximum tumor diameter (MTD), tumor number or presence of PVT to baseline clinical parameters (Table 4). We found significance within the MTD group for tumor number, presence of PVT, AFP and platelet counts. In the tumor number analysis, there was significance for MTD, presence of PVT, bilirubin, AST but not for AFP. Within the PVT analysis, there was significance for MTD, tumor number, AFP and platelets, but not for bilirubin. We then devised a most parsimonious multinomial multiple logistic regression model for MTD and PVT combined (Table 5), as being amongst the most important prognostic features. We found that tumors >3cm MTD plus presence of PVT were significantly correlated with AFP and platelet values, OR 5.41 and 3.11, respectively, each $p<0.001$.

Discussion

Factors influencing HCC prognosis include tumor size and number, PVT and AFP levels (18, 19) and liver factors: bilirubin, ascites and encephalopathy, as reflected in the Okuda classification and others (20, 21). Thrombocytopenia is a cirrhosis surrogate, an HCC risk

factor, prognostic factor, and is associated with small HCCs (7–13, 16, 17). Non-cirrhotic HCCs can be large (22, 23, 24), and associated with thrombocytosis (25), which is a general sign of early malignancy (26). We found that small tumors (38.8% of the total cohort) were significantly associated with higher blood albumin and lower bilirubin, AST and GGTP levels, all consistent with better liver function, despite the liver fibrosis that thrombocytopenia likely reflects (Table 1). Presence of fibrosis in absence of cirrhosis has been noted previously (27, 28). The smaller tumor patients had lower numbers of tumor nodules, less PVT and AFP levels, than patients with larger tumors.

However, both small (< 3cm) and larger HCC groups could be divided into patients with thrombocytopenia or without it (1:1 for small tumors, 1:2.4 for larger tumors). The larger tumor sub-group with normal platelets had significantly larger tumors and significantly higher AFP levels (Table 2) than larger tumor patients with thrombocytopenia. Larger tumor patients without thrombocytopenia had significantly lower bilirubin, PT, AST and higher albumin levels, than larger tumor patients with thrombocytopenia, showing that the association of platelets with tumor size, is likely one amongst several factors in HCC biology. The small tumor patients showed no significant differences in tumor size, number or PVT, between platelet sub-groups, although low platelet patients had significantly higher bilirubin, AST, GGTP and PT values. They also had higher AFP levels than small tumor patients without thrombocytopenia. The reason for this is not clear, although both groups had low AFP values compared to most larger tumor patients. High AST levels are also reported as a poor prognostic factor (29) as have GGTP levels (30, 31); however survival data was not available for this cohort. The correlation matrix showed a significant correlation for platelets with tumor size, but less of a correlation with tumor number or presence of PVT. Thus, there seem to be 2 sets of liver factors involved with small HCCs. One is fibrosis as reflected by thrombocytopenia, which is associated with smaller tumors. Another is liver damage caused by infiltrating tumor, possibly a reflection of the high AST and AFP levels in small tumor patients with thrombocytopenia.

A multiple logistic regression model showed that AFP and platelets, tumor number and PVT were significant factors for tumor size. Since fibrosis and thrombocytopenia are usually irreversible, pathways for large HCC development with normal platelets are likely different from pathways for small HCCs and thrombocytopenia. Although larger tumors might be able to grow when there is less liver damage and thus less likelihood of liver failure, this can only be a partial explanation. This is because the patients with larger tumors and thrombocytopenia (Table 2, column c) had elevated bilirubin and lower albumin levels than patients without thrombocytopenia (Table 2, column d), yet they had a similar range of larger tumor sizes. Recent evidence suggests that platelets themselves may be involved with tumors in general and with HCC development and growth in particular, since they can produce multiple inflammatory and tumor growth factors (32–36) which are potentially ‘druggable’ HCC targets for tumor growth control (35, 36).

Abbreviations

HCC hepatocellular carcinoma

AFP	alpha-fetoprotein
GGTP	gamma glutamyl transpeptidase
CT	computerized axial tomography scan
Hb	hemoglobin
WBC	white blood cells
AST	aspartate aminotransferase
PT	prothrombin time
PVT	portal vein thrombosis
MTD	maximum tumor diameter

References

1. Vernook AP, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist*. 2010; 15(suppl 4):5–13.
2. Nagoaki Y, Hyogo H, Tanaka M, et al. Recent trend of clinical features in patients with hepatocellular carcinoma. *Hepatol. Res.* 2012; 42:368–375. [PubMed: 22151896]
3. Sherman, m. Hepatocellular carcinoma: New and emerging risks. *Dig and Liver Dis.* 2010; 425:S215–S222.
4. Sherman M, Llovet J. Smoking, hepatitis B virus infection, and development of hepatocellular carcinoma. *J. Nat Cancer Inst.* 2011; 103:1642–1643. [PubMed: 22021668]
5. Shebl FM, Capo-Ramos DE, et al. Socioeconomic status and hepatocellular carcinoma in the United States. *Cancer Epidemiol Biomarkers Prev.* 2012; 21:1330–1335. [PubMed: 22669949]
6. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012; 142:1264–1273. [PubMed: 22537432]
7. Lu SN, Wang JH, Liu SL, 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. [PubMed: 17019738]
8. Huang YC, Huang CF, Chang KC, et al. Community-based screening for hepatocellular carcinoma in elderly residents in a hepatitis B- and C-endemic area. *J. Gastroenterol. Hepatol.* 2011; 26:129–134. [PubMed: 21175806]
9. Pompili M, Rapaccini GL, Covino M, et al. Prognostic factors for survival in patients with compensated cirrhosis and small hepatocellular carcinoma after percutaneous ethanol injection therapy. *Cancer*. 2001; 92:126–135. [PubMed: 11443618]
10. Yamanaka, y; Shiraki, K.; Miyashita, K., et al. Risk factors for the recurrence of hepatocellular carcinoma after radiofrequency ablation of hepatocellular carcinoma in patients with hepatitis C. *World J. Gastroenterol.* 2005; 11:2174–2178. [PubMed: 15810088]
11. Amano T, Tashiro H, Oshita A, et al. Significance of platelet counts in the outcomes of hepatectomized patients with hepatocellular carcinoma exceeding the Milan criteria. *J. Gastrointest. Surgery*. 2011; 15:1173–1181.
12. Fattovich G, Giustina G, Schalm SW, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and Cirrhosis. *Hepatology*. 1995; 21:77–82. [PubMed: 7806171]
13. Lok AS, Seeff LB, Morgan TR, et al. HALT-C Trial Group. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology*. 2009; 136:138–148. [PubMed: 18848939]

14. Kumada T, Toyoda H, Kiriya S, et al. Predictive value of tumor markers for hepatocarcinogenesis in patients with hepatitis C virus. *J. Gastroenterol.* 2011; 46:536–544. [PubMed: 21132575]
15. Colombo M, Sangiovanni A. Etiology, natural history and treatment of hepatocellular carcinoma. *Antiviral Res.* 2003; 60:145–150. [PubMed: 14638411]
16. Carr BI, Guerra V, De Giorgio M, Fagioli S, Pancoska P. Small hepatocellular carcinomas and thrombocytopenia. *Oncology.* 2012; 83:331–338. [PubMed: 23006906]
17. Carr BI, Guerra V, Pancoska P. Thrombocytopenia in relation to tumor size in patients with hepatocellular carcinoma. *Oncology.* 2012; 83:339–345. [PubMed: 23006937]
18. Personeni N, Bozzarelli S, Pressiani T, et al. Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. *J. Hepatol.* 2012; 57:101–107. [PubMed: 22414760]
19. Memon K, Kulik L, Lewandowski RJ, et al. Alpha-fetoprotein response correlates with EASL response and survival in solitary hepatocellular carcinoma treated with transarterial therapies: a subgroup analysis. *J. Hepatol.* 2012; 56:112–120.
20. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. *Cancer.* 1985; 56:918–928. [PubMed: 2990661]
21. Grieco A, Pompili M, Caminiti G, et al. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. *Gut.* 2005; 54:411–418. [PubMed: 15710992]
22. Nzeako UC, Goodman ZD, Ishak KG. Hepatocellular carcinoma in cirrhotic and noncirrhotic livers. A clinic-histopathologic study of 804 North American patients. *Am. J. Clin. Path.* 1996; 105:65–75. [PubMed: 8561091]
23. Okuda K, Nakashima T, Kojiro M, et al. Hepatocellular carcinoma without cirrhosis in Japanese patients. *Gastroenterology.* 1989; 97:140–146. [PubMed: 2542116]
24. Trevisani F, D'Intino PE, Caraceni P, et al. Etiologic factors and clinical presentation of hepatocellular carcinoma. Differences between cirrhotic and noncirrhotic Italian patients. *Cancer.* 1995; 75:2220–2232. [PubMed: 7536121]
25. Carr BI, Guerra V. Thrombocytosis and hepatocellular carcinoma. *Dig. Dis, Sci.* 2013 Jan 12. Epub.
26. Levin J, Conley CL. Thrombocytosis associated with malignant disease. *Arch. Int. Med.* 1964; 114:497–500. [PubMed: 14184638]
27. Ripoll C, Groszmann RJ, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J. Hepatol.* 2009; 50:923–928. [PubMed: 19303163]
28. Jackson BD, Doyle JS, Hoy JF, et al. Non-cirrhotic portal hypertension in HIV mono-infected patients. *J. Gastroenterol. Hepatol.* 2012; 27:1512–1519. [PubMed: 22497527]
29. Changchien CS, Chen CL, Yen YH, et al. Analysis of 6381 hepatocellular carcinoma patients in southern Taiwan: prognostic features, treatment outcome, and survival. *J. Gastroenterol.* 2008; 43:159–170. [PubMed: 18306990]
30. Wang NY, Zhang D, Zhao W, et al. Clinical application of an enzyme-linked immunosorbent assay detecting hepatoma-specific gamma-glutamyltransferase. *Hepatol Res.* 2009; 39:979–987. [PubMed: 19624768]
31. Xu K, Meng XY, Wu JW, et al. Diagnostic value of serum gamma-glutamyl transferase isoenzyme for hepatocellular carcinoma: a 10-year study. *Am J Gastroenterol.* 1992; 87:991–995. [PubMed: 1353662]
32. Buergy D, Wenz F, Groden C, Brockmann MA. Tumor-platelet interaction in tumors. *Int. J. Cancer.* 2012; 130:2747–2760. [PubMed: 22261860]
33. Ripoche J. Blood platelets and inflammation: their relationship with liver and digestive diseases. *Clin. Res. Hepatol. Gastroenterol.* 2011; 131:2747–2760.
34. Zhu H, Shao Q, Sun X, et al. Bone marrow cells: Important role in neovascularization of hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 2012; 27:1241–1251. [PubMed: 22142567]

35. Sitia G, Aiolfi R, Di Lucia P, et al. Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. *Proc Natl Acad Sci U S A*. 2012; 109(32):E2165–E2172. [PubMed: 22753481]
36. Stock P, Monga D, Tan X, et al. Platelet-derived growth factor receptor-alpha: a novel therapeutic target in human hepatocellular cancer. *Mol. Cancer Ther*. 2007; 6:1932–1941. [PubMed: 17604334]

	Tumor Size Tertiles (I, II, III)			p-value [‡]	Tercile comparisons [¥] (p-value)	
	I: ≤3.0 (n=1360)	II: 3.0-6.5 (n=1382)	III: ≥6.5 (n=1397)			
Platelet (M±SD)	116.39±66.58	140.21±77.60	213.40±105.83	0.0001	I° vs II°	p<0.0001
(min-max)	(7.1-557)	(19-780)	(21-873)		I° vs III°	p<0.0001
(median (IQR))	116 (75-167)	140 (95-190)	200 (137-267)		II° vs III°	p<0.0001

[‡] Kruskal-Wallis rank test [¥] Mann-Whitney rank test

Fig. 1.
Tumor size tertiles in relation to peripheral blood platelet counts

Table 1

Patient clinical parameters according to tumor size terciles.

\$Parameter	Tumor Size Terciles (I, II and III)			P
	I: <3.0 cm n=1360 (32.9%)	II: 3.8–6.5 cm n=1382 (33.4%)	III: 6.5 cm n=1397 (33.8%)	
Sex (F)	459 (33.8)	327 (23.7)	247 (17.7)	<0.001
Age (years)	61 (53–68)	62 (54–70)	58 (49–69)	0.001
Tumor number				<0.001
1–3	1175 (86.4)	1078 (78.0)	647 (46.3)	
>3	185 (13.6)	304 (22.0)	750 (53.7)	
PVT (yes)	36 (2.6)	172 (12.4)	744 (53.3)	<0.001
Child Pugh				<0.001
A	1021 (75.1)	1003 (72.6)	725 (51.9)	
B	281 (20.7)	312 (22.6)	518 (37.1)	
C	58 (4.3)	67 (4.8)	154 (11.0)	
AFP	16.4 (6.6–94.0)	25.9 (6.5–339.8)	701.0 (20.3–23035.2)	<0.001
PT	10.8 (10.3–11.7)	10.7 (10.2–11.4)	11.1 (10.5–12.0)	<0.001
Albumin	3.6 (3.1–4.0)	3.6 (3.1–4.0)	3.3 (2.8–3.8)	<0.001
Total bilirubin	0.9 (0.7–1.4)	0.9 (0.7–1.5)	1.2 (0.8–2.0)	<0.001
AST	53 (35–85)	52 (35–81)	92 (54–152)	<0.001
GGTP	27 (16–55)	35 (19–71)	90 (47–171)	<0.001
WBC	5.0 (3.8–6.2)	5.5 (4.3–7.0)	7.1 (5.5–9.1)	<0.001
Hb	12.9 (11.3–14.3)	13.1 (11.4–14.4)	12.4 (10.8–14.2)	0.001
Platelets	116 (75–167)	140 (95–190)	200 (137–267)	<0.001

[§]Parameter values are expressed as Median (IQR) or n (%); P, p value for tercile I versus tercile III; n = number of patients. I,II,III, patient trichotomization according to maximum tumor diameter(MTD) terciles.

Units: size=max tumor diameter(cm); AFP, ng/ml; albumin g/l; bilirubin, mg/100ml; AST, GGTP IU/l; WBC $\times 10^3$ /ml, Hb g/dl; Plt $\times 10^9$ /l.

Table 2

Small and large size tumor patient groups dichotomized by blood platelet counts

Parameter	a.		b.		c.		d.		P1	P2
	#Platelets <125 *size 3cm (20.8% of cohort)	Platelets 125 Size 3cm (18.0% of cohort)	Platelets <125 Size >3cm (17.5% of cohort)	Platelets 125 Size >3cm (43.7% of cohort)						
Median (IQR) or n (%)	2.1 (1.7–2.5)	2.1 (1.7– 2.6)	5.3 (4.0–8.6)	8.2 (5.0–11.0)	0.008	<0.001				
Maximum tumor diameter (cm)									0.565	0.731
Tumor number										
1–3	737 (85.6)	646 (86.6)	437 (60.4)	1080 (59.7)						
>3	124 (14.4)	100 (13.4)	286 (39.6)	729 (40.3)						
PVT	35 (4.1)	24 (3.2)	236 (32.6)	657 (36.3)	0.367	0.080				
Child Pugh					<0.001	<0.001				
A	546 (63.4)	662 (88.7)	377 (52.1)	1164 (64.3)						
B	251 (29.2)	79 (10.6)	265 (36.7)	516 (28.5)						
C	64 (7.4)	5 (0.7)	81 (11.2)	129 (7.1)						
AFP	22.4 (8.1–119.2)	12.3 (5.3–86.0)	87.0 (11.0–2006.1)	161.0 (8.9–7403.9)	<0.001	0.033				
PT	11.4 (10.7–12.3)	10.5 (10.1–10.8)	11.4 (10.7–12.4)	10.7 (10.2–11.5)	<0.001	<0.001				
Albumin	3.4 (2.9–3.8)	3.8 (3.4–4.2)	3.3 (2.8–3.8)	3.5 (3.0–4.0)	<0.001	<0.001				
Total bilirubin	1.2 (0.8–1.7)	0.8 (0.6–1.1)	1.3 (0.9–2.1)	1.0 (0.7–1.5)	<0.001	<0.001				
AST	62 (43–100)	42 (29–66)	74 (48–118)	67 (40–126)	<0.001	0.006				
GGTP	30.5 (17.8–55.3)	23.0 (14.0–55.0)	56.0 (29.5–108.8)	55.0 (24.0–132.5)	0.031	0.750				
WBC	4.1 (3.1–5.1)	6.0 (5.0–7.0)	4.8 (3.7–6.1)	7.0 (5.5–8.9)	<0.001	<0.001				
Hb	12.3 (10.7–13.8)	13.5 (12.0–14.7)	12.5 (10.6–14.0)	12.9 (11.2–14.4)	<0.001	<0.001				
Platelets	79 (58–102)	174 (146–209)	93 (69–109)	205 (161–260)	<0.001	<0.001				

P1: p value for column a versus b. P2: p value for column c versus d;

* size = max tumor diameter (cm).

platelet # $\times 10^9/L$. All lab value units as per Table 1.

Table 3

Correlation matrix for selected patient parameters

	Platelet	Tumor size	Tumor number	PVT	AST
Tumor size	0.411 (<0.001)				
Tumor number	0.067 (<0.001)	0.306 (<0.001)			
PVT	0.174 (<0.001)	0.502 (<0.001)	0.330 (<0.001)		
AST	-0.048 (0.002)	0.296 (<0.001)	0.323 (<0.001)	0.331 (<0.001)	
AFP	0.092 (<0.001)	0.351 (<0.001)	0.263 (<0.001)	0.320 (<0.001)	0.345 (<0.001)

Table 4

Multiple logistic regression model of maximum tumor diameter (≥ 3 cm vs. <3 cm), tumor number (≥ 3 vs. <3) or portal vein thrombosis (No vs. Yes) on single variables, corrected for sex, age, and use of alcohol.

	Maximum Tumor Diameter (≥ 3 cm)			Tumor Number (≥ 3)			Portal Vein Thrombosis, PVT (Yes)		
	OR	p value	95% C.I.	OR(se)	p value	95% C.I.	OR(se)	p value	95% C.I.
Maximum Tumor Diameter(≥ 3 cm)	--	--	--	2.19	<0.001	1.82–2.64	8.24	<0.001	6.15–11.03
Tumor number (≥ 3)	2.00	<0.001	1.65–2.42	--	--	--	3.47	<0.001	2.90–4.17
PVT (Yes)	6.90	<0.001	5.13–9.29	3.53	<0.001	2.95–4.23	--	--	--
Child Pugh B vs. A	1.42	0.006	1.11–1.83	1.14	0.261	0.91–1.44	2.49	<0.001	1.92–3.23
C vs. A	1.24	0.424	0.73–2.12	1.27	0.283	0.82–1.98	4.01	<0.001	2.48–6.49
AFP (per 1 unit increase)	1.00003	<0.001	1.00002–1.00004	0.99999996	0.629	0.9999978–1.00000013	1.00000197	<0.001	1.00000095–1.00000298
PT (per 1 unit increase)	1.100	0.766	0.588–2.059	0.99	0.960	0.62–1.58	1.12	0.663	0.68–1.83
Albumin (per 1 unit increase)	1.03	0.707	0.87–1.22	0.72	<0.001	0.61–0.85	1.05	0.607	0.87–1.27
Bilirubin (per 1 unit increase)	0.97	0.115	0.93–1.01	1.05	0.006	1.01–1.09	1.01	0.420	0.98–1.05
WBC (per 1 unit increase)	1.05	0.002	1.02–1.09	1.03	0.019	1.00–1.05	1.01	0.285	0.99–1.04
AST (per 1 unit increase)	1.001	0.043	1.000–1.002	1.003	<0.001	1.002–1.004	1.001	0.015	1.000–1.002
Hb (per 1 unit increase)	1.00	0.875	0.96–1.04	0.98	0.240	0.94–1.02	0.97	0.149	0.93–1.01
Plt (per 1 unit increase)	1.007	<0.001	1.006–1.008	1.001	0.196	1.000–1.002	1.002	0.001	1.001–1.003

All lab units as per Table 1.

Table 5

Most parsimonious multinomial multiple logistic regression model of MTD and PVT combined with AFP and Platelets, corrected for sex, age, and use of alcohol.

	OR	p value	95% C.I.
MTD>3cm and PVT negative			
Alpha fetoprotein (>30)	1.87	<0.001	1.62–2.17
Platelets (>125)	2.70	<0.001	2.32–3.13
MTD ≤3cm and PVT positive			
Alpha fetoprotein (>30)	1.86	0.021	1.10–3.14
Platelets (>125)	0.77	0.344	0.45–1.32
MTD>3cm and PVT positive			
Alpha fetoprotein (>30)	5.41	<0.001	4.46–6.56
Platelets (>125)	3.11	<0.001	2.58–3.76

Reference group was: MTD ≤3cm and PVT negative. AFP and platelet units as per Table 1.

MTD, maximum tumor diameter; PVT, portal vein thrombosis