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Incidence, risk factors and consequences of portal vein and systemic thromboses in hepatocellular carcinoma

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Abstract

Introduction—Hemostatic activation may be important for tumor biology. Hepatocellular carcinoma (HCC) is commonly associated with portal vein thrombosis (PVT). Little is known about factors predictive for PVT in patients with HCC or its correlation with systemic venous thromboembolism (VTE).

Methods—We conducted a retrospective chart review of 194 consecutive patients diagnosed with HCC at the University of Rochester between 1998 and 2004 to identify the frequency and risk factors for PVT and its correlation with VTE and survival.

Results—Sixty patients (31%) had PVT with a higher rate in the non-transplant group compared to transplanted patients (34% vs. 24%; $p=0.15$). In multivariate analysis, Child Turcotte Pugh (CTP) class, stage, major vessel involvement, serum albumin, and serum AFP were independently associated with PVT ($p<0.05$ for each). The presence of PVT was associated with reduced survival (median survival 2.3 months for those with PVT versus 17.6 months for those without PVT, HR 2.05, $p=0.004$). The incidence of systemic VTE in the total population was 6.7%, and patients with PVT had a higher rate of systemic VTE compared to patients without PVT (11.5% vs. 4.4%; $p=0.04$).

Conclusion—PVT is common in patients with HCC, indicates advanced disease, is associated with worse survival and correlates with systemic VTE, suggesting a common mechanism of hemostatic activation. Advanced stage, higher CTP class, major vessel involvement, low serum albumin, and high AFP levels are predictive of PVT in patients with HCC.

VTE is the second leading cause of death in cancer patients, and is associated with significantly reduced survival rates (1,2). Large population-based case-control studies have reported a 4-7 fold increased risk of venous thrombosis in patients with malignancy (3,4), and the approximate

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annual incidence of VTE in cancer patients is 1/200 compared with 1/1000 in the general population (5-7).

HCC is the fifth most common neoplasm and the third most common cause of cancer-related death in the world (8). The burden of HCC in the United States is estimated to increase over the next two decades largely due to the increasing incidence of cirrhosis from hepatitis C infection (9,10). The incidence of hepatitis C infection in the United States peaked in the 1960's and 1970's due to increased rates of intravenous drug use (11). The latency period between hepatitis C infection and development of HCC from hepatitis C related cirrhosis is 30-35 years (12), so the incidence of hepatitis C related HCC should rise significantly over the next decade.

The prognosis of HCC has improved over the past two decades, especially in developed countries where 30-40% of cases are now being diagnosed at early stages when curative treatments can be initiated (13,14). Potentially curative treatments include surgical resection and liver transplantation with reported 5 year survival of 41-93% (15-19) and 49-75% respectively (16,20-23).

Like most cancers, HCC is also associated with hemostatic activation, with a reported incidence of PVT ranging from 20%-65% (24-27). As with other cancer-associated thromboses, the presence of PVT in patients with HCC is associated with reduced survival. (25,28-32) However, little is known about factors predictive for PVT in patients with HCC. In a single autopsy study of 72 patients with HCC PVT was found in 44%, and female sex and older age were identified as predictive factors (26).

The prevalence and impact of systemic VTE in many types of cancers has been well documented. PE and DVT are clearly a major source of morbidity and mortality in cancer patients. Although the incidence and significance of PVT has been studied in patients with HCC, to the best of our knowledge, the incidence of systemic thromboses in patients with HCC has not been studied. It is possible that a shared mechanism of hemostatic activation could lead to both local thrombotic events such as PVT as well as systemic VTE. In this context, it would be of interest to identify if patients with HCC associated PVT have a greater risk of developing systemic VTE as well. Furthermore, identifying and providing prophylaxis to patients at higher risk for systemic VTE may help reduce cancer-associated morbidity in patients with HCC.

We conducted this retrospective study to better characterize the incidence and risk factors for development of PVT in HCC, and to determine the overall impact of PVT on survival in patients with HCC. The group we studied consisted of both patients managed with potentially curative treatments such as liver transplantation and patients with more advanced inoperable disease. We also aimed to define the incidence of systemic thromboses (DVT and PE) in patients with HCC and define any correlation between PVT and systemic thrombosis.

Methods

We conducted a retrospective chart review to determine the frequency and significance of portal vein thrombosis and systemic venous thromboembolism in patients with hepatocellular carcinoma. All patients diagnosed with hepatocellular carcinoma at the James P. Wilmot Cancer Center of the University of Rochester between January 1998 and December 2004 were identified through the institution's cancer tumor registry (n=224). Of these, 30 were excluded from the study because of incomplete records. The University of Rochester is a tertiary care referral center, and some of the patients (n=29) in our study returned to community physicians for follow-up after the initial diagnosis and work-up was completed.

Data extracted included patient demographics, comorbidities, date of diagnosis, survival and outcome, treatment modalities, radiographic staging, pathological analysis, and laboratory

values (platelet count, International Normalized Ratio (INR), serum albumin, serum creatinine, total bilirubin level, serum alpha-fetoprotein (AFP) level, and hepatitis serology). Data extraction was conducted by a single author (GCC).

Patients undergoing liver transplant (n=66) and tumor resection (n=20) were staged using the AJCC staging system (33) based on pathology reports of surgical specimens and radiographic work-up for metastasis which for some patients included bone scan, chest CT, and head CT. The American Joint Committee on Cancer (AJCC) staging system is based on a combination of factors including nodule size, number of nodules, invasion of major vasculature, and distant metastasis. Seventeen of 66 transplant patients were discovered to have HCC after surgical resection and pathological analysis of the explants. Two-thirds (n=42, 65%) of the remaining surgically staged patients had a pre-surgical radiographic stage which correlated with the post-surgical stage. The non-surgical patients were staged clinically based on a combination of computed tomography (CT) (n=105), magnetic resonance imaging (MRI) (n=23), and ultrasound (n=58). Metastatic work-up in the total population included bone scan (n=83), chest CT (n=115), and head CT (n=41). Definitive diagnosis of HCC was made by biopsy in 71 out of 121 non-surgical patients (64%), and the remainder of these patients were diagnosed with HCC based on European Association for the Study of the Liver (EASL) criteria (34) and other clinical factors suggesting HCC such as liver nodules and elevated AFP.

The primary endpoints of this study were presence of PVT at or before diagnosis of HCC and any systemic thrombosis. The secondary endpoint was overall survival calculated from time of diagnosis. Data were summarized in terms of their median, mean, and standard deviation. Proportions were compared using the paired t-test. Univariate and multivariate logistic regression analyses were conducted to assess the association of PVT with a set of clinical covariates. The survival curve was estimated using the method of Kaplan-Meier. PVT and transplant status were used as stratification factors, and difference in survival across groups was assessed using the log-rank test. Patients who developed PVT greater than 30 days after diagnosis with HCC were excluded from the survival analysis. P-values < 0.05 were considered statistically significant.

Results

Patient characteristics

We analyzed 194 patients with hepatocellular carcinoma diagnosed between 1998 and 2004. The clinical features of the study population at time of diagnosis are presented in Table 1. The mean age of the total population was 60.4 ± 11.9 years. One-third of the patients underwent liver transplant. Transplanted patients were younger (mean age of transplanted patients 56.3 versus 62.4 in non-transplanted patients, p-value=0.0007) and had less advanced disease (24% of transplanted patients were stage III/IV versus 56% of non-transplanted patients, p value<0.0001) than the non-transplant patients. Sixteen percent of the study population (n=30) had distant metastases with the most common sites being bone (n=12, 6.2%) and lung (n=20, 10.3%).

PVT

Sixty patients (31%) were found to have PVT. The incidence was higher in the non-transplant group compared to transplanted patients (34% vs. 24%; p= 0.15). The majority of PVT were diagnosed radiographically by computed tomography (n=41, 68.3%), MRI (n=5, 8.3%), and ultrasound (n=8, 13.3%). The remaining were diagnosed at the time of liver transplant (n=6, 10.0%). One-half of all PVT's (n=31, 51.7%) were located in the main portal vein, while 35% and 15% were in the right portal vein and left portal vein respectively. Twenty-five patients with PVT (41.6%) also had associated tumor invasion of a major vessel.

A majority of the non-transplanted patients (n=31, 70.5%) were diagnosed with PVT at the time of HCC diagnosis. Two patients (2.5%) were diagnosed with PVT before HCC (4.4 months and 4.7 months), and a further 11 (25%) developed PVT after diagnosis with HCC. For the patients found to have PVT after diagnosis with HCC the median time from diagnosis of HCC to diagnosis of PVT was 4.4 months (range, 1.5-13.2 months).

For the transplanted patients, 6 (37.5%) were diagnosed with PVT at the same time they were diagnosed with HCC. Four patients (25%) were found to have PVT before diagnosis of HCC was made with the median time between diagnoses of 4.8 months (range, 1.1-9.1 months). Six patients (37.5%) were found to have PVT after diagnosis of HCC with a median time between diagnoses of 3.9 months (range, 1.1-32.9 months).

Risk factors for PVT

Univariate logistic regression analysis identified several factors that were significantly associated with the development of PVT in this population (Table 2). These included advanced stage, major vessel involvement, higher MELD score, higher Child Turcotte Pugh classification, lower serum albumin, higher serum bilirubin, elevated serum alpha-fetoprotein level, and elevated INR ($p<0.05$ for each). The presence of multinodular disease and largest nodule size trended toward higher incidence of PVT, but these values were not significant.

We constructed two complementary multivariate models using either individual variables or commonly used composite scores such as the MELD score and the CTP classification (Table 3). Advanced stage, higher CTP classification, elevated serum AFP, higher serum bilirubin, and major vessel invasion continued to be independently associated with PVT in multivariate analyses ($p<0.05$ for each).

Systemic VTE

The incidence of systemic VTE in patients for whom follow-up data was available (n=165) was 6.7%. The majority of systemic VTE's were lower extremity deep vein thromboses (DVT) (n=7, 63.6%). There were also two IVC thromboses and two upper extremity DVT's. The median time from diagnosis with HCC to diagnosis with systemic VTE was 4.2 months (range, 0-30.6 months). Among the patients with long-term follow-up (n=165), those with PVT had a higher rate of systemic VTE compared to patients without PVT (11.5% vs. 4.4%; $p=0.04$).

PVT and survival

The presence of PVT at or before diagnosis of HCC was associated with significantly reduced survival in the total population (HR=2.06, $p=0.0004$) (Figure 1). The median survival in patients with PVT was 2.3 months compared to 17.4 months in patients without PVT. In transplanted patients the median survival in those with PVT was 22.7 months as compared to 36.3 months in those without PVT (HR=2.06, $p=0.21$). In non-transplanted patients the median survival in those with PVT was 1.0 month compared to 6.2 months in those without PVT (HR=1.91, $p=0.003$).

Transplanted patients had significantly improved survival compared to non-transplanted patients whether or not PVT was present. In transplanted patients with PVT the median survival was 22.7 months compared to 1.0 month in non-transplanted patients with PVT (HR=5.3, $p=0.002$). In transplanted patients without PVT the median survival was 36.3 months compared to 6.2 months in non-transplanted patients without PVT (HR=6.56, $p<0.001$).

In bivariate analyses, the presence of PVT was found to be an independent negative survival predictor when combined with transplant status (HR 1.910, $p=0.0015$), stage (HR 1.597, $p=0.027$), CTP class (HR 1.753, $p=0.0087$), and serum AFP level (HR 1.628, $p=0.0336$).

(Figure 2). Non-transplant status (HR 6.131, $p<0.0001$), advanced stage (HR 2.383, $p<0.0001$), higher CTP class (HR 1.56, $p=0.0351$), and elevated serum AFP level (HR 2.125, $p=0.004$) were also associated with reduced survival in these bivariate analyses (Figure 2).

Discussion

We conducted a retrospective analysis to identify the incidence, risk factors and outcomes associated with PVT in patients with HCC, and to study the correlation between PVT and systemic VTE. We found that nearly one third of patients with HCC had PVT, with the majority identified at the same time as diagnosis of HCC. Our reported rate of PVT in this population is similar to previously reported incidence of 20%-65% in patients treated with surgical resection and non-surgical modalities (24-27). We found a 24% rate of PVT in patients with HCC treated with liver transplant in this study, but we were unable to find published rates of PVT in transplant patients for comparison. In this analysis, advanced stage, higher CTP classification, elevated serum AFP, higher serum bilirubin, and major vessel invasion were predictive for PVT. The presence of PVT was associated with significantly reduced survival in non-transplanted patients, and this survival difference was significant when accounting for stage and CTP classification. Patients with PVT also suffered from a higher incidence of systemic VTE, and we are not aware of any other studies describing the incidence of cancer-associated systemic thrombosis in HCC.

VTE is a common complication of malignancy (1,3,4) with varying rates among different cancers (35-40) and especially high rates in GI malignancies (39,41). The development of VTE in patients with active cancer has several clinical implications including increased mortality (1,2,42). Death in cancer patients with VTE may be directly attributable to the thromboembolic event itself, particularly pulmonary embolism. However, cancer patients who develop VTE also have increased mortality that cannot be directly attributed to thromboembolism. In an analysis of the Danish Cancer Registry, the one-year survival rate was 12 percent in cancer patients with VTE, as compared with 36 percent in a matched group without VTE ($P<0.001$), and these findings could not be explained by the type or extent of cancer, age, or mortality directly attributable to VTE (2).

HCC poses a unique situation with regards to cancer-associated thrombosis. A significant percentage of patients with cirrhosis, even in the absence of HCC, develop PVT (43-46). Cirrhosis and liver failure often precede the development of HCC, and thrombocytopenia and abnormalities in coagulation assays associated with liver failure are commonly perceived to decrease the risk of thrombosis. However, the incidence of DVT and PE in patients with cirrhosis has been reported to be 0.5%-1.0% (47), and studies have shown that an elevation of conventional coagulation parameters in patients with liver failure does not protect against thrombotic events. Indeed, a deficiency in the natural anticoagulant system in liver failure may actually contribute to a prothrombotic state (48). Other factors such as platelet dysfunction, endothelial dysfunction, increased levels of von-willebrand factor, and hemodynamic changes related to portal hypertension all factor into the net coagulation status of patients with liver disease (49). In patients with HCC, mechanical obstruction of blood flow by compression from HCC may further add to the prothrombotic state at the local level and subsequent development of PVT.

However, the correlation of PVT with systemic VTE observed in our study strongly suggests an underlying hemostatic activation that predisposes to both local and systemic thrombotic events. Two recent studies have shown that tissue factor (TF) expression by tumor cells may be predictive of systemic VTE in patients with pancreatic and ovarian cancer (50,51). Tumor cells in HCC also have been shown to express TF (52,53). TF expression by HCC has been shown to correlate with venous invasion and tumor thrombus in the portal vein (52,53). It is

possible, therefore, that TF expression by tumor cells may be responsible, in part, for both the local and systemic hypercoagulable state of HCC. This issue is deserving of further study.

Several studies in patients with advanced HCC managed with non-surgical modalities have demonstrated that PVT is associated with reduced survival (25,28,29). One study in HCC patients treated with ablation, percutaneous ethanol injection, and RFA (30) used a multivariate survival analysis to demonstrate that PVT was a significant and independent negative predictor of survival. The impact of portal vein tumor thrombosis (PVTT) has been studied extensively in patients undergoing surgical resection for HCC, and these studies have clearly shown that PVTT is one of the most predictive negative prognostic indicators (31,32). The incidence and clinical significance of PVT in patients receiving liver transplant for HCC has not previously been reported to the best of our knowledge, but findings from our study suggest a non-significant association with worsened survival. The presence of PVT should not preclude liver transplantation in patients with HCC.

This study has some limitations. It was confined to a single institution, but the University of Rochester is the largest tertiary referral center for liver transplantation in Upstate New York. Since complete follow-up was not available for all patients, the rate of PVT could have been underestimated if it developed at a later date. However, this would be unlikely to alter the PVT incidence significantly given that the majority of PVT's were diagnosed at the same time as HCC. We were unable to distinguish between PVT and PVTT in the non-surgical patients in this study.

In summary, PVT is common in patients with HCC and is associated with worsened survival, particularly in patients not undergoing liver transplant. The correlation between PVT and systemic VTE suggests a common mechanism of hemostatic activation. Stage, CTP class, major vessel involvement, serum albumin, and serum AFP levels are predictive of PVT. Identifying patients at high-risk for PVT and instituting prophylaxis may affect HCC outcomes, and such an approach warrants further study.

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Figure 1. Kaplan-Meier Survival Analysis for patients with portal vein thrombosis versus patients without portal vein thrombosis

Figure 1 shows the Kaplan-Meier Survival Analysis for patients with portal vein thrombosis versus patients without portal vein thrombosis. The presence of PVT at or before diagnosis of HCC was associated with significantly reduced survival in the total population (HR=2.06, $p=0.0004$). The median survival in patients with PVT was 2.3 months compared to 17.4 months in patients without PVT.

Figure 2. Kaplan-Meier survival analysis by transplant status

Figure 2 shows the Kaplan-Meier survival analysis for subgroups of patients based on both transplant status and presence portal vein thrombosis. Patients with portal vein thrombosis had decreased survival in both the transplanted ($HR=2.06$, $p=0.21$) and non-transplanted ($HR=1.91$, $p=0.003$) subgroups, but this difference was significant in only the non-transplanted patients. Transplanted patients had significantly improved survival compared to non-transplanted patients whether or not PVT was present.

Table 1

Patient Characteristics

Characteristic	Total (n=194)(%)	Transplanted (n=66) (%)	Non-transplanted (n=128) (%)
Age >65	73 (37.6)	10/66 (15.2)	65/128 (50.8)
Male	156 (80.4)	53 (80.3)	103 (80.5)
Female	38 (19.6)	13 (19.7)	25 (19.5)
Hypertension	81 (41.8)	30 (45.5)	51 (39.8)
Diabetes	66 (34.0)	27 (40.9)	39 (30.5)
Coronary Artery Disease	25 (12.9)	4 (6.1)	21 (16.4)
Tobacco Abuse	100 (51.5)	37 (56.1)	63 (49.2)
Hepatitis B	7 (4.3) [*]	1 (1.5) [*]	6 (6.2) [*]
Hepatitis C	79 (48.5) [*]	36 (54.5) [*]	43 (44.3) [*]
Alcohol Abuse	34 (17.5)	8 (12.1)	26 (20.3)
Autoimmune Hepatitis	3 (1.5)	1 (1.5)	2 (1.6)
Hemochromatosis	3 (1.5)	3 (4.5)	1 (0.8)
Non-alcoholic steatohepatitis	10 (5.2)	7 (10.6)	2 (1.6)
CTP Class			
A	60 (30.9)	19 (28.8)	41 (32.0)
B	87 (44.8)	29 (43.9)	58 (45.3)
C	46 (23.7)	18 (27.3)	28 (21.9)
Laboratory Values			
Mean Platelet (StDev) ^{**}	152 (116.5)	114 (112)	171 (112)
Median Platelet (range) ^{**}	116.5 (26-769)	87 (26-536)	151.5 (32-769)
Mean Albumin (StDev) ^{**}	3.16 (0.74)	3.16 (0.74)	3.18 (0.74)
Median Albumin (range) ^{**}	3.2 (1.5-5.2)	3.15 (1.5-5.2)	3.15 (1.6-5.0)
Mean INR (StDev)	1.37 (0.33)	1.4 (0.32)	1.36 (0.33)
Median INR (range)	1.3 (0.9-2.7)	1.4 (0.9-2.3)	1.3 (1.0-2.7)
Mean Bilirubin (StDev) ^{**}	2.83 (3.88)	2.92 (4.37)	2.79 (3.62)
Median Bilirubin (range) ^{**}	1.6 (0.2-27)	1.8 (0.3-27)	1.5 (0.2-19)
Mean AFP (StDev) ^{**}	8531 (36587)	919 (38382)	13139 (45730)
Median AFP (range) ^{**}	53 (1-334785)	13.5 (1-23602)	359 (2-334785)
Tumor Characteristics			
Stage I	64 (33.0)	28/66 (42.4)	36/128 (28.2)
Stage II	41 (21.1)	22/66 (33.3)	19/128 (14.8)
Stage III	56 (28.9)	14/66 (21.2)	42/128 (32.8)
Stage IV	33 (17.0)	2/66 (3.0)	31/128 (24.2)
Multinodular	101 (52.1)	35/66 (53.0)	66/128 (51.6)
Major Vessel Involvement	35 (18.0)	10/66 (15.2)	25/128 (19.5)
Treatments			
Transplant	66 (34.0)		
Chemotherapy	13 (6.7)	0/66 (0)	13 (10.2)
Radiation	8 (4.1)	1 (1.5)	7 (5.4)
Resection	20 (10.3)	4 (6.1)	16 (12.5)
Radiofrequency Ablation	19 (9.8)	7 (10.6)	12 (9.4)
Alcohol Ablation	5 (2.6)	2 (3.0)	3 (2.3)
Chemoembolization	6 (3.1)	2 (3.0)	4 (3.1)

* The normal range for the laboratory values included in this table are as follows: platelets (150-400 thousand/ul), albumin (3.2-4.8 g/dl), bilirubin (0.3-1.5 mg/dl), and AFP (0-7 IU/ml)

** data on hepatitis status was available for only 163 of the 194 patients.

Table 2

Factors Predictive of PVT in Hepatocellular Carcinoma in Univariate Analysis

Category	Portal Vein Thrombosis	
	OR (95% Confidence Interval)	P value
Sex	0.99 (0.46-2.12)	0.98
Age	1.00 (0.97-1.02)	0.95
stage I	1.00	
stage II	1.72 (0.61-4.77)	0.30
stage III	7.13 (2.93-17.38)	<.0001
stage IV	3.97 (1.47-10.71)	0.006
CTP A	1.00	
CTP B	6.06 (2.35-15.60)	0.0002
CTP C	5.79 (2.06-16.22)	0.0008
MELD Score	1.07 (1.02-1.12)	0.005
Major Vessel Involvement	8.86 (3.89-20.19)	<.0001
Largest Nodule (cm)	1.33 (0.82-2.16)	0.25
Multinodular	1.71 (0.92-3.18)	0.09
Hepatitis B	0.85 (0.16-4.52)	0.85
Hepatitis C	0.70 (0.36-1.35)	0.28
INR $\geq$ 1.4	1.56 (0.84-2.90)	0.16
Albumin $<$ 3.5	2.22 (1.13-4.37)	0.02
Bilirubin $\geq$ 1.0	3.51 (1.54-8.01)	0.003
AFP $\geq$ 400	3.98 (2.03-7.79)	<.0001

Table 3
Factors Predictive of PVT in Hepatocellular Carcinoma in Multivariate Analysis

Factor	OR (95%confidence interval)	p value
Model 1		
Stage 3/4 vs. Stage 1/2	4.31 (2.03-9.13)	0.0001
Albumin <3.5 vs. > 3.5	2.43 (1.02-5.81)	0.04
INR >1.4 vs. <1.4	0.90 (0.41-1.95)	0.78
Bilirubin 1.0 vs. <1.0	2.48 (0.92-6.66)	0.072
AFP>400 vs. <400	2.87 (1.36-6.07)	0.006
Model 2		
Multinodular vs. Uninodular	0.80 (0.35-1.80)	0.58
Largest nodule >5cm vs. <5cm	0.93 (0.39-2.21)	0.87
Major vessel involvement	6.58 (2.35-18.41)	0.0003
CTP B/C vs. CTP A	7.284 (2.279-23.284)	0.0008
AFP >400 vs. <400	2.784 (1.199-6.466)	0.0172