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Distinguishing Tumor From Bland Portal Vein Thrombus in Liver Transplant Candidates With Hepatocellular Carcinoma: the A-VENA Criteria

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Abstract

Differentiating tumor versus bland portal vein thrombosis (PVT) is essential in determining liver transplantation (LT) candidacy for patients with hepatocellular carcinoma (HCC). We aimed to evaluate radiographic and clinical features that could noninvasively distinguish tumor PVT from bland PVT in HCC patients. Of 467 patients with HCC listed for LT from 2004 to 2011, 59 (12.6%) had PVT and 12 of 59 (20.3%) were deemed malignant. When comparing tumor versus bland PVT, thrombus enhancement was seen in 100% versus 8.5%; venous expansion was seen in 91.7% versus 10.6%; neovascularity was seen in 58.3% versus 2.1%; and being adjacent to HCC or prior treatment site was seen in 100% versus 21.3% (all $P < 0.001$). Combining these 4 imaging characteristics with alpha-fetoprotein (AFP) >1000 ng/dL, the presence of ≥3 criteria best characterized tumor PVT with 100% sensitivity, 93.6% specificity, 80% positive predictive value, and 100% negative predictive value. No LT recipients with presumed bland PVT had macrovascular invasion on explant. There were no differences in post- LT survival or HCC recurrence with bland PVT versus no PVT. In conclusion, we proposed noninvasive criteria that could accurately differentiate tumor PVT from bland PVT called A-VENA, which is based on the presence of ≥3 of the following: AFP >1000 ng/dL; venous expansion; thrombus enhancement; neovascularity; and adjacent to HCC. Use of the A-VENA criteria can assist in standardizing the evaluation of PVT in patients with HCC being considered for LT.

Portal vein thrombosis (PVT) is often identified in patients with cirrhosis during liver transplantation (LT) evaluation or at the time of LT with a prevalence of 5%–26%.(1) In these patients, PVT may be associated with various underlying pathologies, such as altered portal venous blood flow due to portal hypertension, malignant tumor infiltration, or hypercoagulable states. In patients with hepatocellular carcinoma (HCC), PVT is a common complication and has been reported to occur in 10%–40% of patients.(2–4) The presence of tumor PVT in patients with HCC portends a poor prognosis.(2) Macroscopic tumor PVT is

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considered an absolute contraindication to LT due to high rates of tumor recurrence,[5–7] and these patients may be considered for systemic therapy,[8] radioembolization,[9] or supportive care only. It is therefore critical to exclude a malignant etiology of PVT given its profound implications on treatment.

Differentiation of tumor PVT from bland PVT may be challenging, and definitive diagnosis often relies on fine-needle biopsy of the thrombus.[10–13] However, fine-needle biopsy is an invasive procedure and may be contraindicated in the setting of coagulopathy and/or ascites. Noninvasive diagnostic strategies are preferred to determine the etiology of PVT, but specific criteria are not well established. A number of studies have evaluated imaging features that distinguish tumor PVT from bland PVT. Intrathrombus neovascularity, venous expansion, direct invasion of the portal vein (PV) by HCC, PVT continuity with HCC, and generalized PVT enhancement have been reported as characteristics suggestive of tumor PVT.[14,15]

Although various imaging characteristics of tumor PVT have been described, standardized noninvasive criteria for the differentiation of tumor PVT from bland PVT have not been firmly established. The Liver Imaging Reporting and Data System (LI-RADS) recently published an imaging definition for tumor in vein, which is the presence of unequivocal enhancing soft tissue in vein, regardless of visualization of parenchymal mass.[16] Additional imaging features that suggest tumor in vein but do not establish its presence include occluded vein with ill-defined walls, occluded vein with restricted diffusion, occluded or obscured vein in contiguity with malignant parenchymal mass, and heterogeneous vein enhancement not attributable to artifact.[16] Limitations in the imaging diagnosis of tumor in vein exist, such as early venous enhancement due to arterial portal shunting leading to a mistaken characterization as an enhancing tumor.[17] We therefore aimed to evaluate radiographic features as well as clinical characteristics to refine noninvasive criteria that could reliably distinguish tumor PVT from bland PVT in patients with HCC listed for LT.

Patients and Methods

STUDY DESIGN AND PATIENT POPULATION

This was a retrospective cohort study of consecutive patients aged 18 years and older with HCC listed for LT with Model for End-Stage Liver Disease (MELD) exception from January 2004 to February 2011 at our center. Of the 470 patients initially identified, 3 patients were ultimately excluded due to lack of available imaging for independent review. The final cohort consisted of the remaining 467 patients. Per institution protocol, all patients underwent cross-sectional imaging for HCC surveillance at a minimum of every 3 months after listing for LT with HCC MELD exception.

The variables collected included demographic data (age, sex, and ethnicity), laboratory data at the time of listing (alpha-fetoprotein [AFP] and MELD score), tumor size and number at time of listing, and liver-related factors (etiology of liver disease and Child-Turcotte-Pugh [CTP] score). The presence of PVT was determined by review of cross-sectional imaging reports. Clinical characteristics at the time of PVT diagnosis were collected, including AFP,

tumor size, and tumor number. In patients found to have PVT, contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI) images were independently reviewed by a radiologist with over 10 years of experience in abdominal imaging who was blinded to the original diagnosis and patient outcome. Tumor PVT versus bland PVT was determined after blinded review. On the basis of literature review of previously described radiographic features of bland and tumor PVT, the following imaging characteristics of PVT were collected: thrombus enhancement (defined as a difference in Hounsfield units >20), venous expansion, neovascularity, and continuity with HCC lesion or prior treatment site. Data regarding the use of locoregional therapy (LRT) were collected for patients with PVT, specifically timing, type, and number of procedures.

Among patients who underwent LT, explant pathology was reviewed to determine histologic grade based on the modified Edmondson criteria (grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated),[18] tumor stage, and presence of vascular invasion. Explant tumor staging was determined based on size and number of only viable tumors.

OUTCOMES

We evaluated whether noninvasive criteria with radiographic and biochemical characteristics could reliably distinguish tumor PVT from bland PVT in patients with HCC listed for LT. Among LT recipients with and without PVT, post-LT survival and HCC recurrence were secondary outcomes. Intention-to-treat survival of patients with tumor PVT, bland PVT, and no PVT was an additional secondary outcome. Date of death was obtained from our institution transplant database and confirmed using the Social Security Death Index.

STATISTICAL ANALYSIS

Patient, tumor, and PVT characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables, and differences were assessed using the Wilcoxon, chi-square, and Fisher's exact tests, as appropriate. The ability of PVT characteristics and number of risk factors to identify tumor versus bland PVT was assessed by calculating sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) with exact binomial 95% confidence intervals (CIs). The area under the receiver operating characteristic curve (AUROC) was calculated for the presence of 2–5 risk factors and compared with the AUROC for 3 or more factors.

Kaplan-Meier intention-to-treat survival and 95% CI were estimated from time of LT listing to death or last follow-up. Post-LT outcomes, patient survival (event defined as post-LT death) and HCC recurrence-free survival (event defined as the first of HCC recurrence or death), were evaluated using the Kaplan-Meier method. Patients were followed from LT to the first event of interest or last follow-up. Survival was compared between patients with bland PVT and those without PVT using the log-rank test.

Two-sided P values < 0.05 were considered statistically significant. Data analysis was completed using SAS, version 9.4 (SAS Institute Inc., Cary, NC). This study was approved by the Committee for Human Research, institutional review board number 12–09018.

Results

PATIENT CHARACTERISTICS

Baseline demographic and clinical characteristics of the 467 patients composing the study population are summarized in Table 1. Within the cohort, 59 (12.6%) patients were found to have PVT (Fig. 1). The median age at the time of LT listing was 57 years, and 77.3% were men. Caucasians (43.9%) and Asians (31.1%) made up the majority of the study population. Hepatitis C virus was the most common etiology of liver disease (60.4%), followed by hepatitis B virus (24.8%). At the time of listing with HCC MELD exception, the median calculated MELD score was 11 and median CTP score was 7. The median AFP level was 13 ng/dL at the time of listing. AFP level was <20 ng/dL in 269 patients (58.0%) and >1000 ng/dL in 32 patients (6.9%). In total, 71.1% of the cohort had a single HCC lesion. The median size of the largest HCC lesion was 2.7 cm (IQR, 2.2–3.5 cm).

PVT CHARACTERISTICS

Of the 59 patients within the cohort found to have PVT, 12 (20.3%) were determined to have tumor PVT (Fig. 1). Concordance with independent radiologic review was 100% in the diagnosis of tumor PVT versus bland PVT. CT was the most frequent imaging modality (88.1%) used in the identification of PVT, compared with MRI (11.9%). Enhancement and venous expansion were both identified in 27.1%, neovascularity in 13.6%, and continuity with either an HCC lesion or a prior HCC treatment site was demonstrated in 37.3% of all PVT.

Clinical characteristics at the time of PVT diagnosis are described in Table 2. Both bland PVT and tumor PVT cohorts had a median of 1 HCC lesion at the time of PVT diagnosis. The median diameter of the largest HCC lesion was significantly larger in the tumor PVT cohort (4.3 cm) compared with the bland PVT cohort (2.6 cm; $P = 0.01$). Among those with tumor PVT, the median AFP was 3597 ng/dL, which was significantly higher than the median AFP in the bland PVT cohort (8 ng/dL; $P < 0.001$). With regard to PVT location, the majority of bland PVTs were found in the main PV (59.6%), whereas the majority of tumor PVTs were identified in the right or left PV (58.3%). Significantly more patients in the tumor PVT cohort underwent LRT prior to PVT diagnosis (91.7% versus 53.2% in the bland PVT cohort; $P = 0.02$), but the median time from LRT to PVT diagnosis was not significantly different among the groups.

Given the lack of pathologic confirmation in the 12 patients deemed to have tumor PVT, further clinical and radiographic characteristics for these patients were evaluated (Table 3). In this cohort, 9 patients had AFP >1000 ng/dL during their clinical course. Only 1 patient (patient 6) had normal AFP, and this patient underwent PVT biopsy, which confirmed HCC. Of the 12 patients categorized as tumor PVT, 50% developed extrahepatic metastatic disease during follow-up. The median time from diagnosis of PVT to diagnosis of extrahepatic metastatic disease was 6.8 months (range, 0–17.2 months). Autopsy data were not available for any patient in this cohort. The cause of death was varied and confirmed to be metastatic HCC in 4 patients. The median time from diagnosis of PVT to death for the 11 patients who died was 3.5 months (range, 0.8–24.2 months).

Presence of the 4 imaging criteria and the clinical criterion of AFP >1000 ng/dL at diagnosis of PVT were compared between the bland PVT and tumor PVT groups (Table 4). When comparing tumor PVT versus bland PVT, venous expansion was seen in 91.7% versus 10.6%, thrombus enhancement in 100% versus 8.5%, neovascularity in 58.3% versus 2.1%, and being adjacent to HCC lesion or prior treatment site in 100% versus 21.3%, respectively (all $P < 0.001$). AFP >1000 ng/dL was seen in 77.8% of the tumor PVT cohort compared with 7.5% of the bland PVT cohort. Of these 5 criteria, neovascularity had the highest PPV of 87.5%, whereas all 5 criteria had NPV of >90%. When combining these 5 noninvasive characteristics, the presence of ≥3 criteria best characterized tumor PVT with 100% sensitivity, 93.6% specificity, 80% PPV, and 100% NPV (Table 5). The AUROC was 0.97 for ≥3 criteria, which was significantly improved compared with that for ≥4 criteria (0.82; $P = 0.04$) and 5 criteria (0.71; $P = 0.001$; Fig. 2). We proposed our noninvasive criteria called A-VENA that is based on the presence of ≥3 of the following to differentiate tumor PVT from bland PVT: AFP >1000 ng/dL; venous expansion; thrombus enhancement; neovascularity; and adjacent to HCC.

INTENTION-TO-TREAT SURVIVAL AND POSTTRANSPLANT OUTCOMES

Of the 467 patients in the cohort, 326 (69.8%) underwent LT at last follow-up. Of the 326 patients who received LT, 32 had bland PVT (68.1% of the 47 patients with bland PVT), and 294 patients had no PVT. No patient with tumor PVT received LT. For the entire cohort of 467 patients, overall median follow-up time from the date of listing with MELD exception to death or last follow-up was 4 years (IQR, 1.6–6.3 years). Overall survival from the date of listing for the entire cohort was 85.6% at 1 year (95% CI, 82%–88%) and 61.1% at 5 years (95% CI, 56%–66%). When comparing patients without PVT to those with any PVT, overall survival from date of listing was 86.5% at 1 year (95% CI, 83%−90%) and 62.6% at 5 years (95% CI, 57%–67%) versus 79.7% at 1 year (95% CI, 67%–88%) and 51.6% at 5 years (95% CI, 38%–64%), respectively ($P = 0.06$). Survival at 1 year from listing was significantly worse for patients with tumor PVT compared with those with bland PVT: 41.7% (95% CI, 15%–66%) versus 89.4% (95% CI, 76%–95%), respectively ($P < 0.001$). The median intention-to-treat survival for the 12 patients with tumor PVT was 0.8 years (95% CI, 0.40–2.20). For patients with bland PVT, the overall 1- and 5-year survival rates were 89.4% (95% CI, 76%–95%) and 62.9% (95% CI, 47%–75%), respectively, versus 86.5% (95% CI, 83%–90%) and 62.6% (95% CI, 57%–67%), respectively, for those without PVT. The difference was not statistically significant (Fig. 3). Among patients with bland PVT who underwent LT, none had macrovascular tumor invasion on explant. The presence of bland PVT was not associated with microvascular tumor invasion on explant; microvascular tumor invasion was identified in 6.2% of bland PVT compared with 5.4% without PVT ($P = 0.69$).

The median post-LT follow-up was 4.5 years (IQR, 2.6–6.3 years). The overall post-LT survival was 93.8% at 1 year (95% CI, 91%–96%) and 78.3% at 5 years (95% CI, 73%–83%). There was no statistically significant difference in post-LT survival for patients with bland PVT (n = 32) compared with those without PVT (n = 294). The 1- and 5-year post-LT survival rates were 100% and 77% (95% CI, 50%), respectively, in patients with PVT versus 93.1% (95% CI, 90%–96%) and 78.2% (95% CI, 72%–83%; $P = 0.61$), respectively, in

those without PVT. There was also no significant difference in recurrence-free probabilities when comparing those with bland PVT and those without PVT. The 1- and 5-year recurrence-free probabilities for those with bland PVT were 93.8% (95% CI, 77%–98%) and 87.2% (95% CI, 69%–95%), respectively, versus 96.1% (95% CI, 93%–98%; $P = 0.55$) and 85.0% (95% CI, 80%–89%; $P = 0.92$), respectively, in those without PVT.

Discussion

Patients with tumor PVT have poor outcome after LT[5–7] and thus accurate pre-LT diagnosis of tumor PVT is critically important to exclude these patients from LT. Nevertheless, distinguishing bland PVT from tumor PVT can be difficult with current imaging modalities alone, and standardized noninvasive criteria for tumor PVT have not been firmly established. Sotiropoulos et al.[19] have reported that pre-transplant imaging studies had an accuracy of only 58% with corresponding sensitivity and specificity of 50% and 80%, respectively, when evaluating the origin of PVT in HCC patients who underwent LT. Several studies have attempted to develop radiographic criteria for tumor PVT.[14,20] Tublin et al.[14] retrospectively reviewed CT scans of 58 patients with cirrhosis with PVT and demonstrated that when venous expansion (specifically main portal vein diameter ≥23 mm) or PVT neovascularity was present, CT had a sensitivity of 86% and specificity of 100% for revealing tumor PVT. In a study of 35 patients with PVT and HCC, the presence of at least 2 of the 3 following MRI findings had a sensitivity of 100% and specificity of 90% for the diagnosis of tumor PVT: distance from tumor to PVT of <2 cm, HCC size >5 cm, and PVT arterial enhancement.[20] LI-RADS recently defined tumor in vein as unequivocal enhancing soft tissue in vein regardless of visualization of the parenchymal mass, which can be observed in HCC and non-HCC malignancies.[16] Additional imaging features suggestive of tumor in vein but not definitive were also described.

In the present study, we built upon previously suggested radiographic features for tumor PVT and proposed our noninvasive diagnostic criteria, A-VENA, which combines AFP >1000 ng/dL with 4 imaging characteristics (venous expansion, thrombus enhancement, neovascularity, and adjacent to HCC or prior treatment site) for the differentiation of bland PVT from tumor PVT in patients with HCC being considered for LT. We have found that the presence of ≥3 criteria best characterized tumor PVT with sensitivity of 100%, specificity of 94%, PPV of 80%, NPV of 100%, and AUROC of 0.97. Adding AFP >1000 ng/dL to imaging characteristics represents a novel aspect of our criteria that clearly improves over radiographic features alone in our ability to differentiate between tumor PVT and bland PVT. In our cohort, no patient with bland PVT by these criteria had macrovascular invasion on explant. All imaging studies were independently reviewed by an experienced radiologist who was blinded to the original diagnosis and patient outcome to minimize bias.

Our study was based entirely on CT or MRI imaging of HCC and PVT. As the vast majority of patients in our study were evaluated with CT (88.1% CT versus 11.9% MRI), test characteristics of CT versus MRI in the differentiation of tumor from bland PVT were not evaluated. Contrast-enhanced ultrasound (CEUS) has been studied in the context of differentiating tumor PVT from bland PVT. In a study of 54 patients with cirrhosis with HCC and PVT, Tarantino et al.[21] reported sensitivity of 88%, specificity of 100%, PPV of

100%, and NPV of 83.3% with an accuracy of 92.5% for the diagnosis of tumor PVT. In a more recent study evaluating CEUS, Raza et al.[22] demonstrated sensitivity of 100%, specificity of 83%−92%, PPV of 95%−97%, and NPV of 100% in differentiating malignant from benign venous thrombosis in 50 patients with HCC. Criteria for the diagnosis of bland PVT have also been described. In a study of patients with HCC and PVT being evaluated for LT, the simultaneous presence of the following features predicted bland PVT: lack of vascularization of PVT on CEUS and CT or MRI, absence of mass-forming features of PVT, and absence of disruption of vein walls.[23] Although CEUS may be a promising tool for differentiating tumor versus bland PVT, it is not readily available in clinical practice in the United States.

The presence of bland PVT did not affect post-LT survival or recurrence-free probabilities in the present study. Although a number of other single-center studies[24–26] also showed no significant differences in post-LT survival with or without PVT, a systematic review of the literature[27] found a significantly increased 1-year post-LT mortality in patients with PVT when compared with those without PVT (18.8% versus 15.4%). Only complete PVT (versus partial PVT) accounted for this increase in mortality. Additionally, in a recent analysis of the Organ Procurement and Transplant Network national database from 2002 to 2013 including patients with HCC,[28] PVT was independently associated with an increased 90-day post-LT mortality (odds ratio, 1.7; $P < 0.001$) and graft failure (odds ratio, 1.7; $P < 0.001$). However, there was no significant difference in these outcomes for patients surviving longer than 180 days.

Our study has several limitations, most notably the retrospective study design and the lack of histologic confirmation of PVT etiology in patients who did not undergo LT. Current clinical practice patterns limit the ability to perform a study with pathologic confirmation of tumor PVT because risks associated with PVT biopsy often preclude pursuing this procedure and autopsy is infrequently used in the context of known malignancy.[29] In our study, the diagnosis of tumor PVT was supported by significantly worse survival compared with patients with bland PVT as well as the clinical impression determined at the time of clinical care. Detailed clinical and radiographic review of the 12 patients deemed to have tumor PVT provides additional evidence to justify their categorization as having tumor PVT. In particular, this is supported by the development of extrahepatic metastatic disease in 50% of this cohort with very short median time from PVT to diagnosis of metastatic disease and the relatively rapid median time to death after PVT diagnosis. Additionally, the absence of vascular invasion in the explant for patients in the bland PVT group provided further support that patients with PVT had been assigned to the correct groups based on our proposed criteria.

In summary, making the important distinction between tumor and bland PVT in LT candidates with HCC can be accomplished by a combination of noninvasive radiographic and clinical characteristics. Specifically, we proposed noninvasive criteria, A-VENA, for tumor PVT, which is based on AFP >1000 ng/dL, venous expansion, thrombus enhancement, neovascularity, and adjacent to HCC. The presence of ≥3 of these criteria could accurately differentiate tumor PVT from bland PVT, and use of these criteria may assist in standardizing the evaluation of LT candidates with HCC and PVT. Independent

validation of the proposed criteria is still needed. Future application of the A-VENA criteria to a cohort of patients with pathologically confirmed tumor PVT would be useful to validate these noninvasive criteria.

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Abbreviations:

AFP	alpha-fetoprotein
AUROC	area under the receiver operating characteristic curve
CEUS	contrast-enhanced ultrasound
CI	confidence interval
CT	computed tomography
CTP	Child-Turcotte-Pugh
HCC	hepatocellular carcinoma
IQR	interquartile range
LI-RADS	Liver Imaging Reporting and Data System
LRT	locoregional therapy
LT	liver transplantation
MELD	Model for End-Stage Liver Disease
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
NPV	negative predictive value
PPV	positive predictive value
PV	portal vein
PVT	portal vein thrombosis

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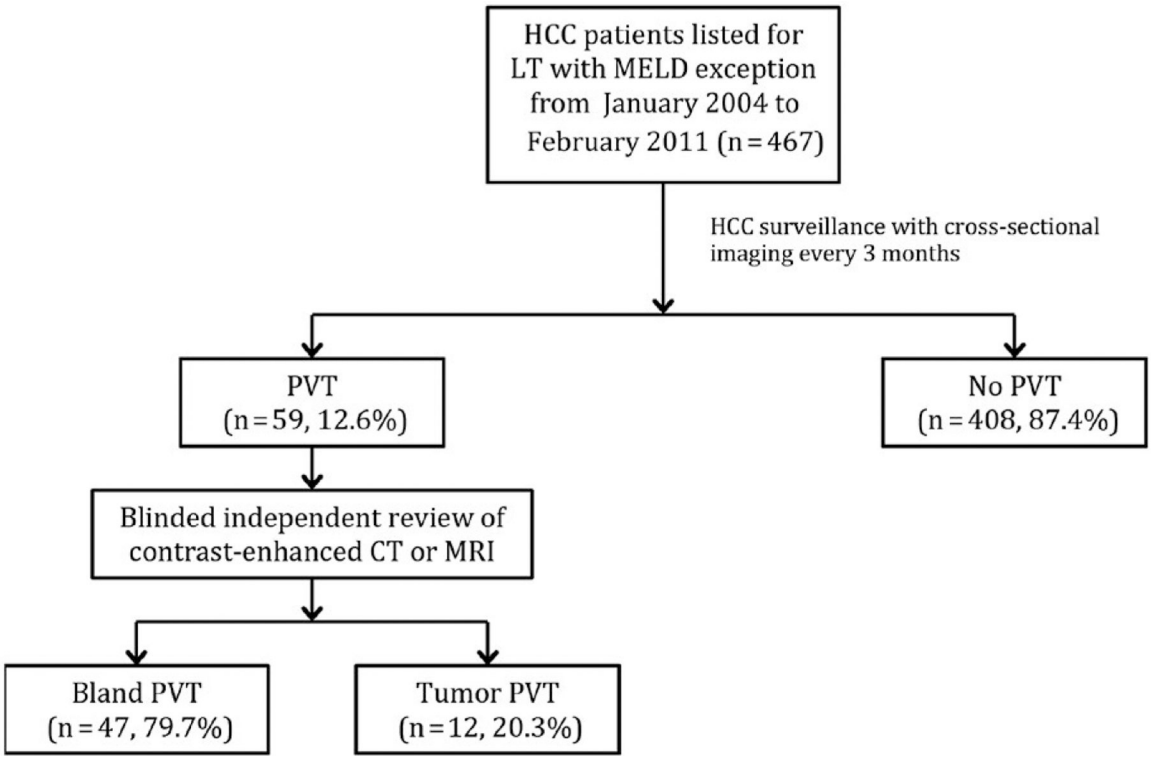

FIG. 1.
Flow diagram of study patients.

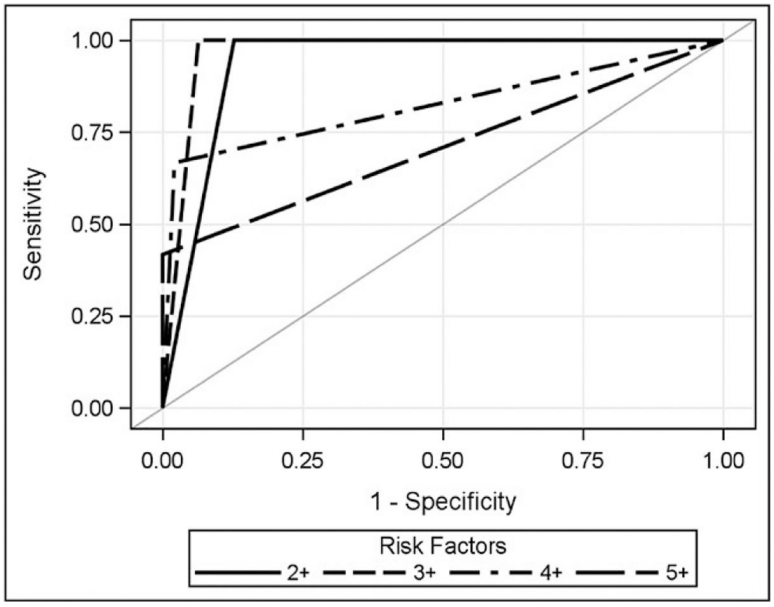

FIG. 2.

ROC curve for combinations of radiographic and biochemical characteristics in distinguishing tumor PVT from bland PVT.

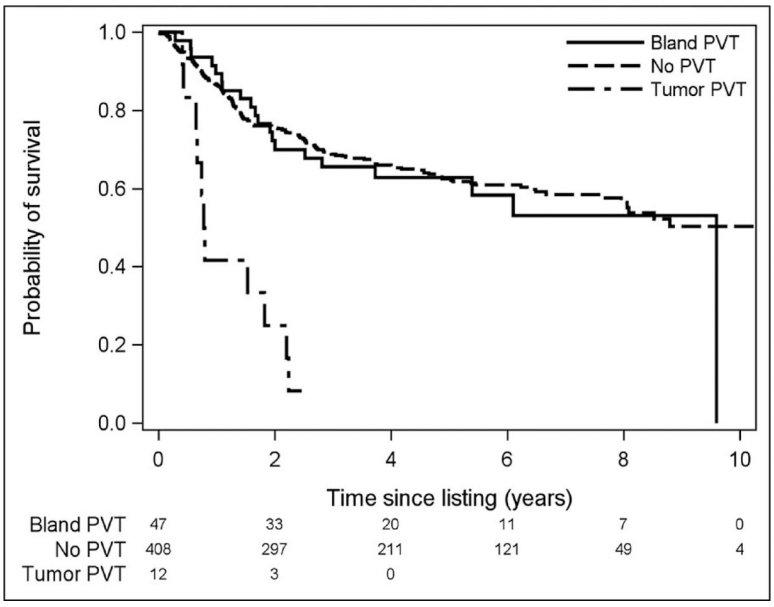

FIG. 3.

Kaplan-Meier plot of overall survival of patients with bland PVT, tumor PVT, and without PVT (n = 467).

TABLE 1.

Baseline Characteristics of the Study Population at Listing

	Overall (n = 467)	No PVT (n = 408)	PVT (n = 59)	PValue
Age, years	57 (53–62)	57 (53–62)	58 (53–63)	0.46
Sex, male	361 (77.3)	317 (77.7)	44 (74.6)	0.59
Race/ethnicity				0.36
Caucasian	205 (43.9)	176 (43.1)	29 (49.2)	
Asian	145 (31.1)	131 (32.1)	14 (23.7)	
Hispanic	77 (16.5)	64 (15.7)	13 (22)	
African American	24 (5.1)	23 (5.6)	1 (1.7)	
Other	16 (3.4)	14 (3.4)	2 (3.4)	
Etiology of liver disease				0.006
Hepatitis C	282 (60.4)	250 (61.3)	32 (54.2)	
Hepatitis B	116 (24.8)	107 (26.2)	9 (15.3)	
NAFLD	35 (7.5)	26 (6.4)	9 (15.3)	
Alcoholic liver disease	24 (5.1)	18 (4.4)	6 (10.2)	
Other	10(2.1)	7 (1.7)	3 (5.1)	
MELD score	11 (8–14)	11 (8–14)	11 (9–16)	0.13
CTP score	7 (5–9)	7 (5–8.5)	7 (9–16)	0.06
AFP, ng/dL *	13 (5–78.5)	13 (5–73)	13 (6–117)	0.50
<20 ng/dL	269 (58.0)	233 (57.5)	36 (61.0)	0.53
20–100 ng/dL	94 (20.3)	86 (21.2)	8 (13.6)	
101–1000 ng/dL	69 (14.9)	59 (14.6)	10 (16.9)	
>1000 ng/dL	32 (6.9)	27 (6.7)	5 (8.5)	
Tumor number				
1	332 (71.1)	292 (71.6)	40 (67.8)	0.14
2	96 (20.6)	86 (21.1)	10 (17)	
3	39 (8.4)	30 (7.4)	9 (15.2)	
Largest tumor diameter (cm)	2.7 (2.2–3.5)	2.7 (2.2–3.5)	2.9 (2.2–3.5)	0.56

NOTE: Data are given as n (%) and median (IQR).

*AFP values were available for 405 patients within the no PVT cohort and 59 patients within the PVT cohort.

TABLE 2.

Clinical Characteristics at the Time of PVT Diagnosis (n = 59)

	Bland PVT (n = 47)	Tumor PVT (n = 12)	*P* Value
Tumor number	1 (0–1)	1 (1–2)	0.19
Diameter of largest tumor, cm *	2.6 (1.9–4.1)	4.3 (2.7–6.5)	0.01
AFP, ng/dL †	8 (5–31)	3597 (1484–16691)	<0.001
PVT location			0.003
Main PV	28 (59.6)	1 (8.3)	
Right or left PV	12 (25.5)	7 (58.3)	
PV segmental branches	7 (14.9)	4 (33.3)	
LRT prior to PVT	25 (53.2)	11 (91.7)	0.02
Time from LRT to PVT, months ‡	3.6 (1.1–5.8)	1.5 (1.3–4.4)	0.72

NOTE: Data are given as n (%) and median (IQR).

* The median diameter of the largest tumor available for 29 patients within the bland PVT cohort and 11 patients within the tumor PVT cohort.

† AFP values were available for 40 patients within the bland PVT cohort and 9 patients within the tumor PVT cohort.

‡ The median time from LRT to PVT was available in 25 patients within the bland PVT cohort and 11 patients within the tumor PVT cohort.

TABLE 3.

Characteristics of Patients With Tumor PVT (n = 12)

Patient	Tumor at Listing	MELD at Listing*	AFP at Listing (ng/dL)	Tumor at PVT	AFP at PVT (ng/dL)	Peak AFP (ng/dL)	Extrahepatic Disease	Cause of Death	PVT to Death (months)
l	1 lesion, 3.3 cm	10	16	1 lesion, 6 cm	414	5352	No, progressive intrahepatic disease	Unknown	15.7
2	3 lesions, up to 2.3 cm	10	191	0	3596.6	170,756.8	Yes, biopsy-proven retroperitoneal, supraclavicular lymph nodes	Metastatic HCC, decompensated cirrhosis	18.2
3	1 lesion, 5.1 cm	6	1022	1 lesion, 4.3 cm	None	32,836.5	Yes, pulmonary	Metastatic HCC, pulmonary embolism	24.2
4	1 lesion, 4.9 cm	10	34	1 lesion, 3.7 cm	34.4	209.5	Yes, celiac lymph node	Metastatic HCC	9.4
5	3 lesions, up to 2.2 cm	11	783	2 lesions, up to 5.5 cm	58,000	58,095.6	Yes, peritoneal implants	Unknown	2.5
6	1 lesion, 4.3 cm	7	14	2 lesions, up to 7.5 cm	None	5.3	PVT biopsy positive for HCC	Unknown	3.2
7	1 lesion, 3 cm	9	157	1 lesion, 2.2 cm	16,690.5	19,770.8	No	Not applicable (alive at end of follow-up)	N/A
8	1 lesion, 3.9 cm	8	63	1 lesion, 4 cm	None	81.4	Yes, chest wall	Gastrointestinal bleed	9.8
9	3 lesions, up to 2.7 cm	10	5106	1 lesion, 2.7 cm	>35,350	>35,350	Yes, brain	Metastatic HCC	3
10	3 lesions, up to 1.5 cm	8	1315	1 lesion, 2.7 cm	2009	2009	No	Spontaneous bacterial peritonitis, hepatorenal syndrome	3.5
11	2 lesions, up to 3 cm	7	255	2 lesions, up to 6.5 cm	4273	4273	No	Unknown	0.8
12	2 lesions, up to 2.8 cm	11	1137	1 lesion, 8 cm	1484	1484	No	Unknown	0.8

*At listing, 9/12 patients were CTP 5–6 and 3/12 patients were CTP 7–8.

TABLE 4.

Noninvasive Criteria at the Time of PVT (n = 59)

	Bland PVT (n = 47)	Tumor PVT (n = 12)	*P* Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95%CI)
Enhancement			<0.001	100% (73.5%−100%)	91.5% (79.6%−97.6%)	75% (47.6%−92.7%)	100%(91.8%−100%)
Yes	4 (8.5)	12 (100)					
No	43 (91.5)	0 (0)					
Expansion			<0.001	91.7% (61.5%−99.8%)	89.4% (76.9%−96.4%)	68.8% (41.3%−89%)	97.7% (87.7%−99.9%)
Yes	5 (10.6)	11 (91.7)					
No	42 (89.4)	1 (8.3)					
Neovascularity			<0.001	58.3% (27.7%−84.8%)	97.9% (88.7%−100%)	87.5% (47.4% −99.7%)	90.2% (78.6%−96.7%)
Yes	1 (2.1)	7 (58.3)					
No	46 (97.9)	5 (41.7)					
Continuous with HCC lesion or treatment site			<0.001	100% (73.5%−100%)	78.7% (64.3%−89.3%)	54.6% (32.2% −75.6%)	100% (90.5%−100%)
Yes	10 (21.3)	12 (100)					
No	37 (78.7)	0 (0)					
AFP >1OOO ng/dL at PVT diagnosis *			<0.001	77.8% (40.0%−97.2%)	92.5% (79.6%−98.4%)	70% (34.8%−93.3%)	94.9% (82.7%−99.4%)
Yes	3 (7.5)	7 (77.8)					
No	37 (92.5)	2 (22.2)					

NOTE: Data are given as n (%) and median (IQR).

* AFP values were available for 40 patients within the bland PVT cohort and 9 patients within the tumor PVT cohort.

TABLE 5.

Test Characteristics of Noninvasive Criteria

	Bland PVT (n = 47)	Tumor PVT (n = 12)	*P* Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
2 or more criteria			<0.001	100% (73.5%−100%)	87.2% (74.3%−95.2%)	66.7% (41.0%−86.7%)	100% (91.4%−100%)
Yes	6 (12.8)	12 (100)					
No	41 (87.2)	0 (0)					
3 or more criteria			<0.001	100% (73.5%−100%)	93.6% (82.5%−98.7%)	80% (51.9%−95.7%)	100% (92.0%−100%)
Yes	3 (6.4)	12 (100)					
No	44 (93.6)	0 (0)					
4 or more criteria			<0.001	66.7% (34.9%−90.1%)	97.9% (88.7%−100%)	88.9% (51.8%−99.7%)	92% (80.8%−97.8%)
Yes	1 (2.1)	8 (66.7)					
No	46 (97.9)	4 (33.3)					
5 criteria			<0.001	41.7% (15.2%−72.3%)	100% (92.4%−100%)	100% (47.8%−100%)	87% (75.1%−94.6%)
Yes	0 (0)	5 (41.7)					
No	47 (100)	7 (58.3)					

NOTE: Data are given as n (%) and median (IQR).