Occult Hepatocellular Carcinoma Associated With Transjugular Intrahepatic Portosystemic Shunts in Liver Transplant Recipients

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Transplant eligibility for hepatocellular carcinoma (HCC) is determined by the imaging identification of tumor burden within the Milan criteria. Transjugular intrahepatic portosystemic shunt(s) (TIPS) reduce portal hypertension but may impact HCC visualization. It was hypothesized that the presence of pretransplant TIPS would correlate with occult HCC and reduced survival. A single-center, retrospective, case control study was performed among liver transplant recipients with HCC (2000-2017). The primary endpoint was occult disease on explant pathology. Backward stepwise logistic regression was performed. The secondary endpoints disease-free survival (DFS) and overall survival (OS) were evaluated with Kaplan-Meier curves and Cox regression analysis. Of 640 patients, 40 had TIPS and more frequently exhibited occult disease (80.0% versus 43.1%; $P < 0.001$; odds ratio [OR], 4.16; $P < 0.001$). Portal vein thrombosis (PVT) similarly correlated with occult disease (OR, 1.97; $P = 0.02$). Explant tumor burden was equivalent between TIPS subgroups; accordingly, TIPS status was not independently associated with reduced DFS or OS. However, exceeding the Milan criteria was associated with reduced DFS (hazard ratio, 3.21; $P = 0.001$), and TIPS status in patients with a single suspected lesion (n = 316) independently correlated with explant tumor burdens beyond these criteria (OR, 13.47; $P = 0.001$). TIPS on pretransplant imaging are associated with occult HCC on explant pathology. Comparable occult disease findings in patients with PVT suggest that the mechanism may involve altered hepatic perfusion, obscuring imaging diagnosis. TIPS are not independently associated with reduced DFS or OS but are associated with exceeding the Milan criteria for patients with a single suspected lesion. The presence of TIPS may necessitate a higher index of suspicion for occult HCC.

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Hepatocellular carcinoma (HCC) is the most common primary malignant neoplasm in patients with cirrhosis and the second leading cause of cancer-related death worldwide. Only 28% of patients with unresectable HCC survive 3 years without intervention.[(1)] Transplantation provides the best outcome, but organ availability is insufficient.[(2)] Organs are therefore allocated to patients who fall within the Milan criteria, which consist of 1 lesion smaller than 5 cm in diameter or up to 3 lesions each smaller than 3 cm in diameter without macroscopic vascular invasion. Under these circumstances, overall and recurrence-free survival rates at 4 years reach 85% and 92%, respectively.[(3)]

Evaluation for HCC is unique among solid tumors in that the diagnosis is largely determined by

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; LI-RADS, Liver Imaging Reporting and Data System; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; N/A, not applicable; OR, odds ratio; OS, overall survival; PVT, portal vein thrombosis; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TIPS, transjugular intrahepatic portosystemic shunt(s).

pretransplant imaging.[4] However, despite evaluation at regular intervals, up to 42% of liver explants reveal unexpected (occult) intrahepatic HCC on explant pathology.[5] Patients with tumor burdens within the Milan criteria on explant pathology demonstrate longer recurrence-free survival compared with those who exceed the Milan criteria.[3]The clinical utility of these parameters is therefore rooted in how well the tumor burden can be determined by pretransplant imaging,[6] with strong reliance on characteristic perfusion patterns such as arterial hyperenhancement and venous washout that are dependent on the blood supply to the lesions.[7]

Transjugular intrahepatic portosystemic shunt(s) (TIPS) connect the portal and hepatic veins to reduce manifestations of portal hypertension. There are many conceivable mechanisms by which TIPS could impact the development of occult disease, but there exists little evidence that they cause tumor seeding or progression. Rather, data demonstrate that TIPS alter perfusion to hepatic parenchyma, which may have consequences on imaging characteristics. In an experimental noncirrhotic swine model, the presence of TIPS led to alterations in hepatic arterial blood flow on scintigraphy.[8] Increased arterial blood flow was subsequently demonstrated in patients with cirrhosis and TIPS, with 88% of the 25 patients demonstrating a rise in arterial peak velocity by intravascular Doppler sonography after TIPS placement.[9] Noninvasive volume perfusion computed tomography (CT) in 23 patients with portal hypertension similarly demonstrated that TIPS increased hepatic arterial perfusion and decreased total portal vein perfusion to the liver.[10] These alterations reflect the compensatory changes that take place through autonomic regulation of hepatic arterial tone to maintain constant hepatic perfusion, known as the arterial buffer response.[11]

Portal vein thrombus (PVT) similarly decreases portal venous blood flow and increases hepatic arterial blood flow.[12] PVT is associated with atypical characteristics of HCC on axial imaging such as decreased arterial phase hypervascularity[13] and venous washout,[13,14] leading to delays in diagnosis.[14] It was therefore hypothesized that the alterations in vascular flow induced by the presence of TIPS would negatively impact the ability to accurately detect the presence of HCC among patients undergoing surveillance and that these occult lesions could portend inferior survival among liver transplant recipients.

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Patients and Methods

STUDY POPULATION

A single-center, retrospective, case control study was performed among patients who underwent liver transplantation between November 2000 and July 2017 and were found to have HCC or hepatocholangiocarcinoma on explant pathology. No patients were excluded. The study was evaluated by our institutional review board and met eligibility criteria for review exemption (protocol no. 832467).

IMAGING

Magnetic resonance imaging (MRI) was performed at 1.5 T or 3.0 T with gadolinium. Our routine scanning includes T-1 weighted and opposed phase gradient echo, T-2 weighted, diffuse weighted, and fat suppressed T-1 weighted imaging obtained before and after gadolinium administration. All CT imaging was performed with intravenous contrast.

DETERMINATION OF TIPS STATUS AND OCCULT DISEASE

TIPS status was determined at the time of the last pretransplant imaging. CT and MRI images at our institution are reviewed in a multidisciplinary tumor

conference by expert body radiologists. The identification of malignancy and indeterminate nodules on pretransplant imaging was based on report extraction. Occult malignancy was defined as the presence of any HCC lesions on explant pathology that were not identified on the last pretransplant imaging. A completely necrotic treated lesion on imaging or explant was considered an HCC lesion. Dysplastic nodules were excluded.

VARIABLES AND ENDPOINTS

The primary endpoint was occult disease on explant pathology. Secondary endpoints included disease-free survival (DFS) and overall survival (OS). Demographic and clinical variables were abstracted for inclusion in the multivariable model for occult disease, including the allocation and biochemical Model for End-Stage Liver Disease (MELD) scores, alpha-fetoprotein (AFP) level, etiology of liver disease, time between diagnosis of liver disease and transplantation, time between diagnosis of cancer and transplantation, type and number of pretransplant treatments (systemic or liver directed), time between last imaging and transplantation, type of last pretransplant imaging, presence and extent of PVT on imaging based on a classification system in the literature,[15] and presence of indeterminate lesions on imaging. To account for the fact that some patients received multiple imaging modalities, we reported the most sensitive and specific modality performed within 3 months of the final imaging, prioritizing MRI first, CT second, and ultrasound third.[16] Histopathological characteristics of the tumor, including differentiation and invasion, were determined by a liver pathologist. The most dedifferentiated grade identified in each specimen was coded. Warm and cold ischemia times were also abstracted to incorporate as potential confounders in the survival analysis.

STATISTICAL ANALYSIS

Descriptive statistics are reported as frequencies for binary or categorical variables, mean and standard deviation for normally distributed continuous variables, and median and interquartile range (IQR) for nonparametric continuous variables. Normality of continuous variables was evaluated by skewness and kurtosis testing. Univariate analysis between the 2 TIPS subgroups was performed with proportion tests for categorical values, *t* tests for normal continuous values, and Wilcoxon rank sum for nonparametric continuous values. To determine the relationship between clinical variables and occult disease, backward stepwise elimination of candidate variables was modeled with logistic regression for categorical dependent variables and linear regression for continuous dependent variables, combining forward selection using a *P* value for variable entry set to 0.10 and variable removal with a *P* value set to 0.20 for elimination.[17-19] Goodness of fit was determined by R^2 or pseudo R^2 values and is listed with the corresponding table for each model. Given that the patients with TIPS retained some differences from those without TIPS such as higher MELD score, we performed a secondary propensity score analysis that included independent variables hypothesized to be associated with occult disease including patient age, biochemical MELD score, preoperative AFP, pretransplant treatments, wait time, and most recent imaging before transplant. Propensity score was confirmed to be balanced graphically and objectively.[20] One match was used per observation. For all statistical analysis, α was set to 0.05.

For the evaluation of DFS and OS, Kaplan-Meier survival curve analysis was performed. Recurrence incorporated local or distant disease. Censorship occurred for death by another cause, lack of follow-up, or the end of this study. Univariable Cox regression analysis was used to identify relationships between clinical characteristics and survival. Covariates demonstrating modest significance ($P < 0.20$) on univariate analysis and clinically relevant variables were tested in the multivariable model and removed using manual backward elimination until only variables with $P < 0.10$ remained. The prediction models were evaluated with the Harrell C concordance statistic, and the number of covariates was limited to maintain model stability. Statistical analysis was performed using Stata version 15.1 (StataCorp LLC, College Station, TX).

Results

COHORT CHARACTERISTICS AND DEMOGRAPHICS

The database was composed of 640 patients who underwent transplantation and had HCC (n = 633, 98.9%) and/or hepatocholangiocarcinoma (n = 23, 3.6%). The median age at the time of transplant was 58.6 years (IQR, 53.9-64.0) in this largely male (82.5%) population. The leading etiology of liver disease was hepatitis

C virus (73.0%), and the majority (85.8%) had a diagnosis of HCC before transplant. The median time between transplant and last follow-up was 79 months (IQR, 34-125) in all patients and 103 months in patients who survived throughout the study period (IQR, 67-140). Of the 63 patients exhibiting PVT, 36 (57.1%) were present only in the trunk, and 18 (28.6%) were present only in 1 or more branches. A total of 23 (36.5%) were occlusive, and 15 (23.8%) extended into the mesenteric and/or splenic veins.

Forty patients in this study had TIPS. The indication for TIPS placement was exclusively variceal bleeding and/or ascites management. No patients rapidly decompensated after TIPS placement. Of the patients with known pre-TIPS imaging evaluations, 85.0% underwent CT or MRI a median of 54 days (IQR, 10-126) before shunt placement, and only 1 patient had malignancy at that time. Transplant was performed a median of 674 days (IQR, 309-1414) after TIPS placement. Interval ultrasounds were available in 32 patients (80.0%) with TIPS. Thirty-one of the evaluated shunts (96.9%) were patent by ultrasound.

The groups of patients with and without TIPS were not statistically different in terms of age, sex, etiology of liver disease, time on the waiting list, type of donation received (donation after brain death, donation after circulatory death, living donation, extended criteria donation), time between the most recent pretransplant imaging and transplant, the incidence of 1 or more indeterminate lesions on pretransplant imaging, and the presence of hepatocholangiocarcinoma. They also did not differ in terms of the incidence of PVT, extent of PVT into the splenic and/or mesenteric veins, presence of occlusive PVT, or thrombotic involvement of both the portal trunk and its branches (Table 1). A significant difference between subgroups included a higher biochemical MELD score in patients with TIPS (17 [IQR, 15-22] versus 12 [IQR, 9-18]; $P < 0.001$). Allocation MELD scores were not dissimilar between groups (24 [IQR, 21-28] versus 25 [IQR, 22-29]), as fewer exception points were granted to the TIPS group given their less frequent identification of pretransplant HCC. Patients were equally dispersed over time, such that the allocation systems used were consistent between groups. Patients with TIPS were also more likely to not have undergone pretransplant HCC therapy (70.0% versus 27.4%; $P < 0.001$), a difference that persisted when excluding patients with no known pretransplant malignancy (80.5% versus 57.1%; $P = 0.009$).

Most patients underwent MRI (85.9%) or CT (10.7%) as the last imaging modality a median of 42 days (IQR, 21-74) before transplant. In all study patients and in the subgroup of patients with visualized pretransplant malignancy, the median number of lesions on pretransplant imaging was 1 (IQR, 1-2). Although patients with TIPS were more likely to have undergone imaging with ultrasound (15.0% versus 2.0%; $P = 0.003$), 14 of the 19 (73.7%) patients with TIPS and unidentified pretransplant HCC had undergone CT or MRI evaluation before transplant, similar to the 39 of 64 (60.9%; $P = 0.26$) patients without TIPS fitting the same criteria. Patients with TIPS were more likely to not have HCC identified on that imaging (47.5% versus 10.7%; $P < 0.001$), and their highest pretransplant AFP was notably lower (10 ng/mL [IQR, 5-34] versus 18 ng/mL [IQR, 7-83]; $P = 0.02$). For those with known pretransplant malignancy, the median diameter of the dominant lesion on imaging was not statistically significantly different for patients with or without TIPS. The level of missingness was 5% or less for all variables used in final multivariable regression models with the exception of the type of pretransplant imaging in the non-TIPS group (8.2%).

OCCULT HCC

Of all the patients, 45.6% exhibited occult disease on explant pathology, which was far more likely in patients with TIPS than without (80.0% versus 43.1%; $P < 0.001$; Table 1 and Fig. 1). By univariate analysis, TIPS was associated with occult disease with an odds ratio [OR] of 5.22 ($P < 0.001$; Table 2). The presence of PVT (OR, 2.02; $P = 0.007$) and the presence of at least 1 indeterminate lesion on pretransplant imaging (OR, 1.47; $P = 0.02$) also correlated with occult disease. When excluding patients with TIPS, occult disease was more common in patients with partial or occlusive PVT than in those without (54.5% versus 40.7%; $P = 0.02$), with an occult malignancy incidence of 57.9% in patients with complete PVT (n = 11). Among patients with an indeterminate lesion and TIPS or PVT, the incidences of occult disease increased to 92.9% and 60.0%, respectively.

The remaining factors associated with occult disease on univariate analysis included biochemical MELD score at the time of transplant (OR, 1.05; $P < 0.001$)

TABLE 1. Demographic, Clinical, Imaging, and Pathologic Characteristics of All Patients by TIPS Status

Patient Characteristics	No TIPS (n = 600)	TIPS (n = 40)	*P* Value
Age at transplant, years	58.4 (54.0-64.0)	57.3 (52.7-64.7)	0.57
Male sex	45 (82.5)	33 (82.5)	0.99
Etiology of liver disease			
Hepatitis C virus	438 (73.0)	29 (72.5)	0.95
Hepatitis B virus	42 (7.0)	0 (0.0)	0.08
Alcohol	42 (7.0)	4 (10.0)	0.48
Autoimmune	14 (2.3)	2 (5.0)	0.29
Nonalcoholic steatohepatitis	14 (2.3)	2 (5.0)	0.29
Cryptogenic/other	38 (6.3)	3 (7.5)	0.78
Unknown	12 (2.0)	0 (0.0)	0.37
MELD score			
Allocation	25 (22-29)	24 (21-28)	0.08
Biochemical	12 (9-18)	17 (15-22)	<0.001
Exception granted	479 (80.0)	24 (60.0)	0.003
AFP, ng/mL			
At time of listing for transplant	14 (6-41)	6 (3-15)	0.004
Highest before transplant	18 (7-83)	10 (5-34)	0.02
Most recent before transplant	10 (4-28)	5 (2-17)	0.02
Days on waiting list	195 (64-397)	267 (85-990)	0.09
Pretransplant treatment*			
None	163 (27.4)	28 (70.0)	<0.001
TACE	378 (63.1)	10 (25.0)	<0.001
RFA	76 (12.7)	3 (7.5)	0.33
Resection	14 (2.3)	0 (0.0)	0.33
Radioembolization	5 (0.8)	1 (2.5)	0.28
Percutaneous ethanol injection	3 (0.5)	0 (0.0)	0.65
Number of treatments	1 (0-2)	2 (1-3)	0.001
PVT			
Incidence	57 (9.5)	6 (15.0)	0.26
Site			
Only trunk	35 (61.4)	1 (16.7)	0.04
Only branch	14 (24.6)	4 (66.7)	0.03
Trunk and branches	6 (10.5)	0 (0.0)	0.40
Degree			
Occlusive	19 (33.3)	4 (66.7)	0.11
Nonocclusive	31 (54.4)	1 (16.7)	0.08
Extent of portal vein system occlusions			
None	38 (66.7)	4 (66.7)	1.00
Splenic and/or mesenteric vein	14 (24.6)	1 (16.7)	0.85
Most recent pretransplant imaging			
None	2 (0.3)	0 (0.0)	0.72
MRI	478 (79.7)	26 (65.0)	0.03
CT	55 (9.2)	8 (20.0)	0.08
Ultrasound	12 (2.0)	6 (15.0)	0.003
Unknown	53 (8.9)	0 (0.0)	0.05
Days from imaging to transplant	43 (21-74)	34 (15-79)	0.40
Indication for TIPS	N/A		N/A
Ascites		18 (45.0)	
Variceal bleeding		10 (25.0)	

TABLE 1. *Continued*

Patient Characteristics	No TIPS (n = 600)	TIPS (n = 40)	*P* Value
Ascites and bleeding		3 (7.5)	
Unknown		9 (22.5)	
Pre-TIPS hepatic imaging	N/A		N/A
MRI		8 (20.0)	
CT		9 (22.5)	
Ultrasound		3 (7.5)	
Unknown		20 (50.0)	
Days between imaging and TIPS placement		54 (10-126)	
Malignancy identified on imaging		1 (2.5)	
Days between TIPS and transplant	N/A	674 (309-1414)	N/A
Pretransplant imaging			
Number of visualized lesions			
0	64 (10.7)	19 (47.5)	<0.001
1	303 (50.5)	13 (32.5)	0.03
2	152 (25.4)	4 (10.0)	0.03
3 or more	79 (13.2)	4 (10.0)	0.56
Unknown	2 (0.3)	0 (0.0)	0.72
Incidence of indeterminate lesions	190 (31.7)	14 (35.0)	0.66
Diameter of dominant lesion, mm†	22 (17-31)	25 (22-28)	0.24
Total diameter of all lesions, mm‡	28 (17-43)	20 (0-40)	0.009
Explant evaluation			
Number of lesions	2 (1-3)	2 (1-4)	0.67
Total diameter of all lesions, mm	35 (23-56)	30 (18-53)	0.18
Occult malignancy	257 (43.1)	32 (80.0)	<0.001
Single occult lesion	143 (23.9)	18 (45.0)	0.003
More than 1 occult lesion	115 (19.2)	14 (35.0)	0.02
Outside the Milan criteria	166 (28.3)	14 (35.0)	0.37
Differentiation			
Well differentiated	102 (17.1)	6 (15.0)	0.73
Moderately differentiated	301 (50.3)	26 (65.0)	0.07
Poorly differentiated	90 (15.0)	6 (15.0)	0.99
Invasion			
Micro lymphovascular invasion	305 (50.9)	22 (55.0)	0.62
Major vascular invasion	26 (4.4)	3 (7.5)	0.79
Hepatocholangiocarcinoma	20 (3.3)	3 (7.5)	0.67
Ischemic time			
Warm ischemia, minutes	54 (48-59)	55 (50-59)	0.29
Cold ischemia, hours	306 (249-368)	287 (238-349)	0.29

NOTE: Data are provided as n (%) or median (IQR).
*Patients who underwent multiple therapies are repeated in each applicable row.
†Diameter of dominant lesion on the last pretransplant image in patients with at least 1 suspected lesion.
‡Total diameter of all lesions includes patients with no reported malignancy on preoperative imaging.

and the use of CT (OR, 1.98; $P = 0.01$) or ultrasound (OR, 6.72; $P = 0.003$) for pretransplant imaging rather than MRI. As such, these factors were incorporated into the multivariable model along with other factors that were distinct between TIPS subgroups and potentially explanatory of the outcome such as pretransplant AFP and pretransplant HCC therapy. Logistic regression revealed that TIPS presence was independently associated with occult HCC (OR, 4.16; $P < 0.001$). Evaluation with CT (OR, 1.82; $P = 0.03$)

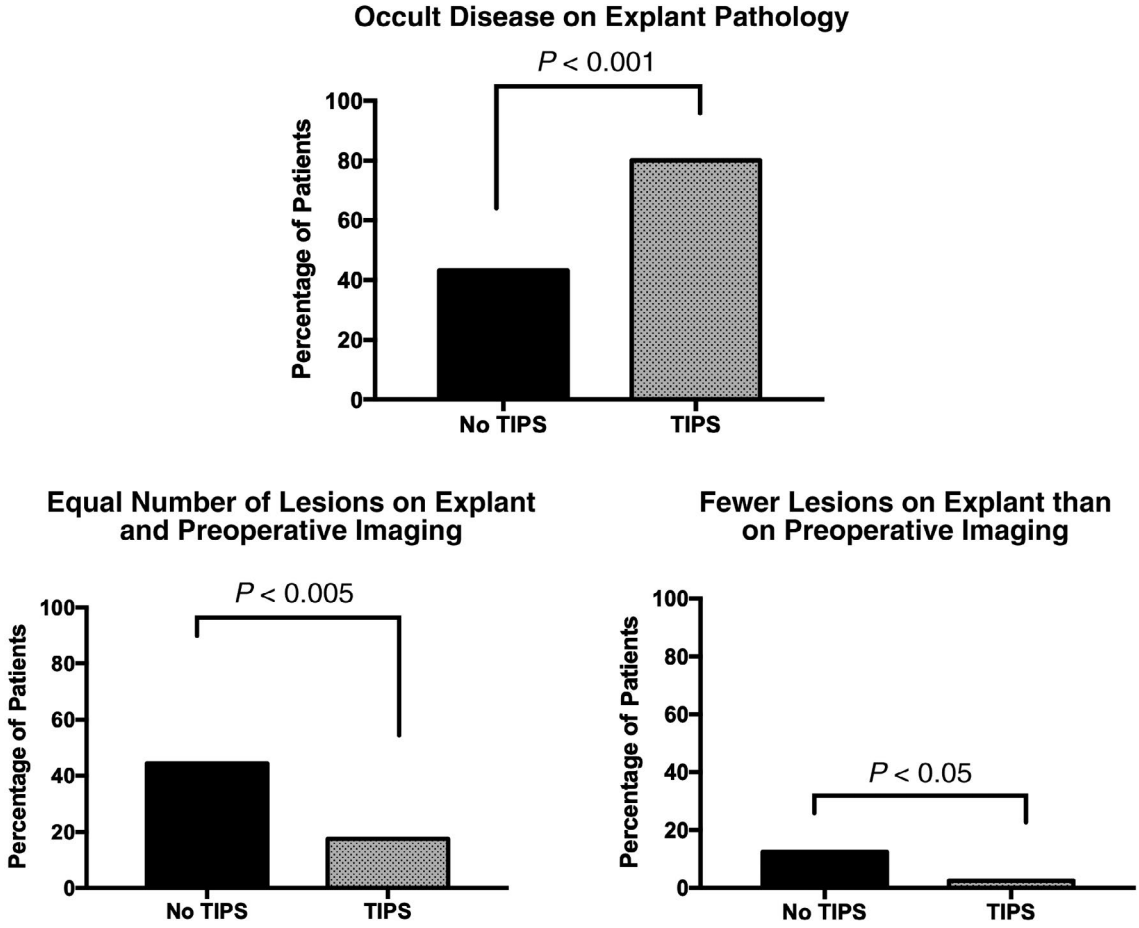

FIG. 1. Differences between expected and actual tumor burden on explant by TIPS status. Patients with TIPS were statistically significantly more likely to have occult disease on explant pathology and less likely to have equal or fewer lesions than expected based on pretransplant imaging.

or ultrasound (OR, 4.15; $P = 0.03$), higher biochemical MELD score (OR, 1.02; $P = 0.048$), the presence of PVT (OR, 1.97; $P = 0.02$) on imaging or explant, and the presence of at least 1 indeterminate lesion on imaging (OR, 1.50; $P = 0.04$) were significant in the final regression (Table 2). The regression was also performed with the number of indeterminate lesions as a continuous variable, which remained statistically significantly associated with the outcome of occult disease (OR, 1.40; $P = 0.04$).

Although occult disease was more common in patients with TIPS, the total tumor burden on explant pathology was not different between groups, as measured by the number of lesions, total summed diameter of all lesions, percentage of explants exceeding the Milan criteria, degree of differentiation, and presence of micro lymphovascular or major vascular invasion (Table 1). By linear regression, TIPS status was also not associated with greater total summed diameter of lesions on explant minus summed diameter of lesions on imaging when considering patients with the same number of lesions identified on explant pathology.

Propensity score matching included variables such as time between imaging and transplantation, time on the waiting list, biochemical MELD score, pretransplant therapy, the presence of PVT, pretransplant AFP, and the last imaging obtained before transplant. No variables were statistically significantly different between groups after matching. The presence of TIPS remained independently associated with occult disease between matched cohorts (coefficient, 0.26; $P = 0.004$).

TABLE 2. Univariate and Multivariable Logistic Regressions to Evaluate Factors Associated With Occult Disease in All Patients

	Univariate			Multivariable		
Independent Variables	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age at transplant	1.00	0.98-1.02	0.99	–	–	–
Female sex	0.77	0.52-1.12	0.18	–	–	–
Etiology of liver disease						
Hepatitis C virus	0.76	0.54-1.06	0.11	–	–	–
Hepatitis B virus	0.86	0.48-1.53	0.60	–	–	–
Alcohol	1.45	0.80-2.64	0.22	–	–	–
Biochemical MELD score at time of transplant	1.05	1.03-1.07	<0.001	1.02	1.00-1.05	0.048
Most recent AFP before transplant	1.00	1.00-1.00	0.40	–	–	–
Days on waiting list	1.00	1.00-1.00	0.93	–	–	–
Received pretransplant treatment						
TACE	0.57	0.42-0.78	<0.001	–	–	–
RFA	0.78	0.50-1.21	0.27	–	–	–
Resection	1.26	0.46-3.46	0.65	–	–	–
Radioembolization	0.39	0.10-1.47	0.16	–	–	–
Percutaneous ethanol injection	2.57	0.24-27.12	0.43	–	–	–
Number of treatments	0.79	0.67-0.92	0.003	–	–	–
Most recent pretransplant imaging						
MRI	Reference	–	–	Reference	–	–
CT	1.98	1.18-3.31	0.01	1.82	1.07-3.11	0.03
Ultrasound	6.72	1.93-23.31	0.003	4.15	1.11-15.48	0.03
Findings on preoperative imaging						
PVT	2.02	1.22-3.39	0.007	1.97	1.14-3.40	0.02
TIPS	5.22	2.37-11.49	<0.001	4.16	1.84-9.40	<0.001
Indeterminate lesion(s)	1.47	0.87-1.48	0.02	1.50	1.02-2.18	0.04
Days from imaging to transplant	1.00	1.00-1.00	0.16	–	–	–

NOTE: Pseudo $R^2 = 0.05$ for multivariable regression.

SENSITIVITY ANALYSIS

Given that ultrasound imaging is inferior to axial imaging in identifying lesions and that patients with TIPS were more likely to have received this modality, occult disease was evaluated excluding those patients whose last pretransplant imaging was ultrasound or an unknown modality. Occult disease remained more common in patients with TIPS (79.4% versus 40.9%; $P < 0.001$). In the multivariable regression, TIPS remained statistically significantly associated with occult disease (OR, 3.68; $P = 0.02$). In addition, given the implications of alternate pathology and the nearly statistically significant increase in occult disease for patients with hepatocholangiocarcinoma (69.6% versus 45.0%; $P = 0.056$), the regression was performed excluding this pathology. TIPS remained associated with occult disease (OR, 4.01; $P = 0.001$).

OCCULT HCC IN PATIENTS WITH A SINGLE SUSPECTED LESION

A total of 316 patients underwent transplant for a single lesion identified on pretransplant imaging (Table 3). Patients with TIPS within this subgroup continued to exhibit a higher biochemical MELD score than their counterparts without TIPS (14 [IQR, 13-17] versus 12 [IQR, 9-16]; $P = 0.04$). However, the other baseline differences that existed in the entire cohort between TIPS groups, such as pretransplant tumor interventions and imaging modalities, were negated. The diameter of the lesion by imaging and pretransplant AFP values were not statistically significantly different between groups.

Occult disease in this subgroup remained more frequent in patients with TIPS (61.5% versus 34.3%; $P = 0.049$). Moreover, the presence of extensive occult

TABLE 3. Demographic, Clinical, Imaging and Pathologic Characteristics for Patients Who Exhibited a Single Identifiable Lesion on Pretransplant Imaging (n = 316)

Patient Characteristics	No TIPS (n = 303)	TIPS (n = 13)	*P* Value
Age at transplant	58.6 (53.7-64.3)	59.5 (53.0-65.0)	0.90
Male sex	240 (79.2)	12 (92.3)	0.25
Etiology			
Hepatitis C virus	220 (72.6)	10 (76.9)	0.73
Hepatitis B virus	25 (8.3)	0 (0.0)	0.28
Alcohol	19 (6.3)	1 (7.7)	0.85
Autoimmune	7 (2.3)	0 (0.0)	0.58
Nonalcoholic steatohepatitis	7 (2.3)	0 (0.0)	0.58
Cryptogenic/other	18 (5.9)	1 (7.7)	0.80
MELD			
Allocation	28 (24-29)	27 (22-29)	0.63
Biochemical	12 (9-16)	14 (13-17)	0.04
Exception granted	273 (90.4)	10 (76.9)	0.12
AFP, ng/mL			
At time of listing	12 (5-43)	6.0 (3-35)	0.36
Highest before transplant	16 (6-71)	34 (10-84)	0.38
Most recent before transplant	9.0 (4-27)	17 (6-41)	0.24
Days on waiting list	215 (82-404)	349 (147-724)	0.08
Pretransplant treatment			
None	61 (20.3)	5 (38.5)	0.12
TACE	209 (69.0)	6 (46.2)	0.08
RFA	48 (15.8)	3 (23.1)	0.49
Resection	5 (1.7)	0 (0.0)	0.64
Radioembolization	0 (0.0)	0 (0.0)	0.99
Percutaneous ethanol injection	0 (0.0)	0 (0.0)	0.99
Number of treatments	1 (1-1)	1 (0-1)	0.06
Most recent pretransplant imaging			
MRI	252 (83.4)	11 (84.6)	0.92
CT	27 (8.9)	1 (7.7)	0.88
Ultrasound	4 (1.3)	1 (7.7)	0.34
Days from imaging to transplant	46 (26-74)	54 (34-90)	0.66
Pretransplant imaging			
Diameter of lesion, mm	22 (16-33)	24 (20-38)	0.29
Explant evaluation			
Number of lesions	1 (1-2)	2 (1-3)	0.02
Diameter of dominant lesion, mm	25 (18-35)	29 (25-35)	0.36
Occult disease	104 (34.3)	8 (61.5)	0.049
Outside the Milan criteria	51 (16.8)	7 (53.9)	<0.001
4 or more lesions	18 (5.9)	3 (23.1)	0.02

NOTE: Data are provided as n (%) or median (IQR).

disease (4 or more lesions) was more likely in patients with TIPS (23.1% versus 5.9%; $P = 0.02$), who accordingly exceeded the Milan criteria on explant pathology with greater frequency (53.9% versus 16.8%; $P < 0.001$). In multivariable regression models, TIPS status was independently associated with a greater number of occult lesions (coefficient, 1.14; $P = 0.003$; Supporting Table 1) and extension beyond the Milan criteria on explant pathology (OR, 13.47; $P = 0.001$; Supporting Table 2).

SURVIVAL ANALYSIS

HCC recurrence was identified in 92 patients (14.4%). DFS was 94.9% at 1 year and 84.9% at 5 years in all

study patients. Patients outside of the Milan criteria on explant pathology experienced a shorter DFS of 87.6% at 1 year and 68.5% at 5 years. Factors independently associated with shorter DFS on multivariable analysis included poor histologic differentiation (hazard ratio [HR], 2.02; $P = 0.01$), major vascular invasion on explant pathology (HR, 2.43; $P = 0.01$), positive surgical margin (HR, 2.71; $P = 0.046$), and exceeding the Milan criteria on explant pathology (HR, 2.97; $P < 0.001$; Supporting Table 3). Among patients with a single identified lesion on pretransplant imaging, DFS was 94.9% at 1 year and 86.5% at 5 years (Fig. 2). Findings on explant pathology that were associated with shorter DFS in this subgroup included micro lymphovascular invasion (HR, 4.10; $P < 0.001$) and exceeding the Milan criteria (HR, 3.21; $P = 0.001$; Supporting Table 3). TIPS status was not independently associated with DFS, and patients with TIPS were not more likely to have local or distant recurrent disease.

A total of 240 patients (37.5%) died. Median OS was 15.6 years (1 year, 90.1%; 5 years, 72.5%) in all patients. Patients outside the Milan criteria on explant pathology had a shorter OS of 86.1% at 1 year and 62.4% at 5 years compared with 91.7% and 76.6%, respectively, for those within the Milan criteria. Factors associated with reduced OS included patient age (HR, 1.02; $P = 0.02$), poor histologic differentiation (HR, 1.51; $P = 0.01$), and recurrence (OR, 4.42; $P < 0.001$; Supporting Table 4). Increased OS was associated with more recent year of transplant (HR, 0.96; $P = 0.02$). For patients with a single lesion identified on pretransplant imaging, OS was 90.1% at 1 year and 74.4% at 5 years (Fig. 2). Factors associated with reduced OS in this subgroup included recurrence (HR, 4.65; $P < 0.001$) and poor histologic differentiation (HR, 1.76; $P = 0.02$; Supporting Table 4). When recurrence was removed from the multivariable models, explant Milan status became statistically significantly associated with OS (HR, 2.72; $P < 0.001$); the other factors remained consistent. TIPS status was not independently associated with OS.

Discussion

The Milan criteria incorporate the size and number of HCC lesions detected on pretransplant imaging and are used to identify liver transplant candidates who are best suited to have a successful outcome. Clinicians therefore rely on accurate imaging to determine appropriate candidacy for transplant. This study demonstrates that the presence of TIPS at the time of pretransplant imaging is independently associated with a greater incidence of occult malignancy on explant pathology.

We sought to explore potential mechanisms behind the increased occult disease in patients with TIPS. We considered that pathologic evaluation may have been altered based on the presence of TIPS; however, all explants were sectioned and evaluated using an established internal protocol that involved removal of each TIPS and consistent, thin sectioning of all explants, minimizing bias in the pathologic assessment. Another consideration is that patients with TIPS exhibited higher biochemical MELD scores, which could represent more progressive or long-standing cirrhosis and therefore a higher propensity to develop malignancy. However, patients with TIPS had no greater burden of malignancy on explant pathology than patients without TIPS in terms of the size and number of lesions, the presence of tumor burden exceeding the Milan criteria, and tumor differentiation and vascular invasion. This similarity supports the theory that the entire degree of occult disease cannot be attributed to increased severity of liver disease predisposing to malignancy. The equivalence of tumor burden between the TIPS groups is consistent with prior histologic evaluations of liver explants, including a retrospective analysis of histopathologic data from 214 patients (68 patients with TIPS).[21] Furthermore, the biochemical MELD score was included in our multivariable models and propensity score matching, and TIPS status remained independently associated with occult disease, suggesting an alternative underlying mechanism.

Another difference between the TIPS subgroups worth considering is the lower rate of pretransplant transarterial chemoembolization (TACE) in patients with TIPS, which persisted even when excluding patients with no known pretransplant malignancy. Reduced pretransplant treatment may have contributed to some of the occult disease burden, although this factor was incorporated into the multivariable model and propensity score matching, and TIPS status remained independently associated with occult disease. In addition, among patients with a single lesion identified before transplant, TIPS subgroups were similar in terms of pretransplant interventions (Table 3), but TIPS remained independently associated with occult disease, the presence of 4 or more lesions, and extension beyond the Milan criteria on explant pathology.

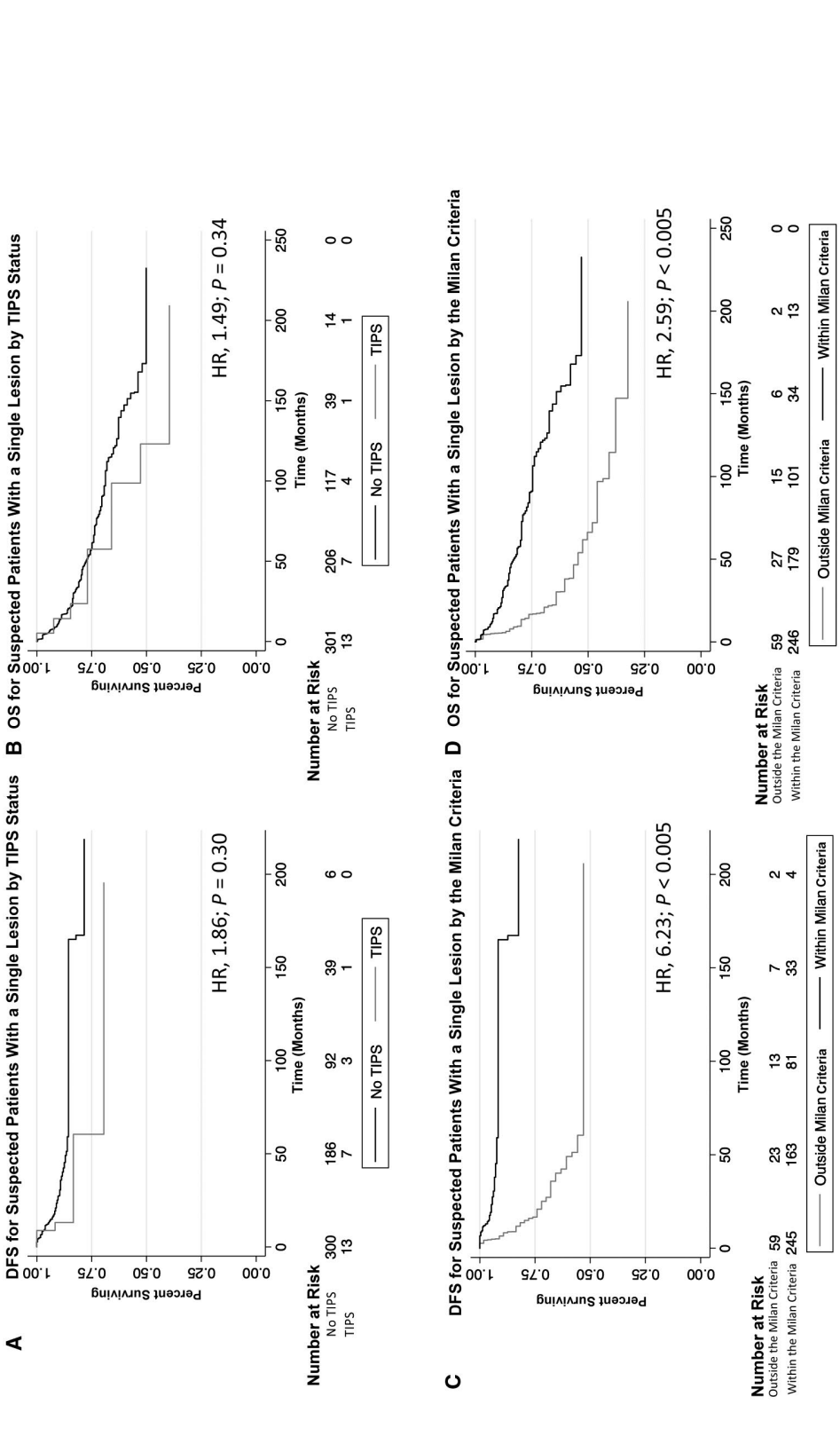

FIG. 2. Kaplan–Meier survival curve analysis of DFS and OS for patients with a single lesion identified on pretransplant imaging. (A) DFS and (B) OS demonstrated by TIPS status. (C) DFS and (D) OS demonstrated by the Milan criteria on explant pathology.

As patients with TIPS exhibited fewer lesions on pretransplant imaging but an equal burden of malignancy on explant pathology compared to patients without TIPS, we hypothesize that the increased burden of occult disease is attributed to an inability to visualize tumors on imaging among those with TIPS. Although patients with TIPS were more likely to have undergone ultrasound imaging and less likely to have received an MRI as the last pretransplant imaging, most patients with TIPS (73.7%) who did not have any lesions identified on pretransplant imaging had undergone CT or MRI evaluation, which was not dissimilar to the rate in patients without TIPS. As such, when patients who underwent ultrasound evaluation were excluded from the regression, TIPS status remained independently associated with occult disease. This association suggests that even axial imaging is insufficient to adequately diagnose pretransplant HCC in patients with TIPS. TIPS were not associated with an increase in the summed diameter of lesions on explant minus the summed diameter of lesions on imaging when comparing patients with the same number of explant lesions, suggesting that TIPS impact the identification of lesions more than they underestimate the size of identified lesions. Prior studies have not demonstrated a higher incidence of occult malignancy in patients with TIPS, but diagnoses have been made based on imaging modalities,[22-24] which we now suggest may be of decreased utility in these patients.

One theory behind this mechanism is that the nodularity in patients with TIPS and cirrhosis impacts the capacity to identify lesions by imaging. The degree of cirrhosis between TIPS groups can be evaluated in future studies. Another theory is that alterations in the contribution of portal venous and hepatic arterial flow[10,14] change the characteristics that typically inform the diagnosis of HCC. To further explore this idea, we investigated the role of PVT, as occlusion of the portal vein should cause a similar reduction in portal venous contribution to the hepatic parenchyma. Indeed, occult disease was statistically significantly more common in patients with any degree of PVT in our study. Individual factors of PVTs such as their occlusive nature and location within the portal vein were not associated with occult disease in our study, which may be a factor of small sample size or may imply that any degree of flow alteration can impact diagnostic accuracy. Further studies in this area may be warranted.

We also noted that a prior study identified more Liver Imaging Reporting and Data System (LI-RADS) 3 lesions in some patients with TIPS,[23] and we considered that these atypical lesions could corroborate our findings if ultimately found to be malignant on explant pathology. Although LI-RADS categorization was not available during the majority of our study time frame, we did confirm that the presence and number of indeterminate lesions on imaging were independently associated with occult disease. Strikingly, 92.9% of patients with TIPS and 60.0% of patients with PVT who had at least one indeterminate lesion on pretransplant imaging exhibited occult disease on explant pathology, suggesting that the presence of altered perfusion may have reduced the ability to definitively characterize these lesions as HCC. Another factor that may have contributed to poor visualization is a susceptibility artifact from TIPS, limiting the evaluation of the liver parenchyma immediately adjacent to the stent. Finally, shunting away from the liver parenchyma (because of TIPS or PVT) could predispose the liver to develop confluent fibrosis, producing a signal intensity that obscures malignancy.

The relevance of occult disease is its impact on recurrence and survival. Overall, TIPS status was not independently associated with shorter DFS or OS, which is consistent with the fact that patients with and without TIPS had similar extents of malignancy on explant pathology. However, in the low-risk group of patients with single suspected lesions based on pretransplant imaging, patients with TIPS were statistically significantly more likely to exceed the Milan criteria. Being outside the Milan criteria on explant pathology was independently associated with reduced DFS in the multivariable model. The Milan criteria was also independently associated with reduced OS when recurrence was removed from the model, suggesting an effect of Milan status on mortality through recurrence.

A unique concern in this study is that of sample bias, as patients are often identified as TIPS candidates because of a lack of suspected malignancy. Given that this series was composed of patients who ultimately exhibited HCC on explant pathology, patients with TIPS may have been more likely to be labeled as having occult malignancy. However, the relationship between TIPS and occult disease remained even when excluding patients with no known malignancy before transplant. We also did not capture the timing of pretransplant therapies to assess patients who underwent interventions between the last pretransplant imaging and transplant, which may have been higher in patients without TIPS given the more frequent use of pretransplant therapy in this group. We do not suspect that this would

significantly impact the findings, as patients with TIPS had relatively lower pretransplant AFP despite differences in intervention rates, and treated lesions were still captured as malignancies in this study. We also do not suspect this would be a large portion of the population given that 85.8% of the population underwent only 2 or fewer pretransplant interventions, and the median time between diagnosis and transplant (240 days) was more than 5 times longer than the median time between last imaging and transplant (42 days). Other limitations of this study include its retrospective nature and the use of single institution data, which may reduce the generalizability of the findings. The results will need to be further evaluated in large multicenter studies; however, the data support a hypothesis that has mechanistic plausibility. The contemporary relevance of these findings may also be reduced by the fact that imaging standards and assessment have evolved over time; however, the same criteria were applied to patients with and without TIPS, and the year of transplant was included in all regression models, reducing the probability that methodology impacted the association between TIPS and occult disease. We opted not to perform a retrospective review of the imaging to apply contemporary standards given that this would introduce bias in this study of patients with known HCC.

In an era with limited organ supply to meet the demand for liver transplantation, organs are directed toward patients with the highest likelihood of survival based on eligibility criteria. This study suggests that patients with TIPS are more likely to have a greater burden of occult malignancy on explant pathology than expected based on pretransplant imaging, especially when an indeterminate lesion is present. When those patients are outside the Milan criteria on explant pathology, the recurrence rates are higher. These findings suggest that there is a need to aggressively surveil patients with TIPS, which may include using adjusted diagnostic imaging criteria to incorporate altered flow characteristics associated with TIPS and a higher index of suspicion involving more liberal use of tissue biopsy to appropriately identify and manage malignancy.

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