ORIGINAL ARTICLE

Portal Vein Thrombosis and Survival in Patients with Cirrhosis

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The effects of occlusive portal vein thrombosis (PVT) on the survival of patients with cirrhosis are unknown. This was a retrospective cohort study at a single center. The main exposure variable was the presence of occlusive PVT. The primary outcome measure was time-dependent mortality. A total of 3295 patients were analyzed, and 148 (4.5%) had PVT. Variables independently predictive of mortality from the time of liver transplant evaluation included age [hazard ratio (HR), 1.02; 95% confidence interval (CI), 1.01-1.03], Model for End-Stage Liver Disease (MELD) score (HR, 1.10; 95% CI, 1.08-1.11), hepatitis C (HR, 1.44; 95% CI, 1.24-1.68), and PVT (HR, 2.61; 95% CI, 1.97-3.51). Variables independently associated with the risk of mortality from the time of liver transplant listing included age (HR, 1.02; 95% CI, 1.01-1.03), transplantation (HR, 0.65; 95% CI, 0.50-0.81), MELD (HR, 1.08; 95% CI, 1.06-1.10), hepatitis C (HR, 1.50; 95% CI, 1.18-1.90), and PVT (1.99; 95% CI, 1.25-3.16). The presence of occlusive PVT at the time of liver transplantation was associated with an increased risk of death at 30 days (odds ratio, 7.39; 95% CI, 2.39-22.83). In conclusion, patients with cirrhosis complicated by PVT have an increased risk of death. ***Liver Transpl 16:83-90, 2010.*** © **2009 AASLD.**

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Occlusive portal vein thrombosis (PVT) is a common complication of chronic liver disease with a prevalence ranging from 1% to 16% of patients.[1-5] The occurrence of PVT is influenced by local factors (cirrhosis with associated liver architectural changes and increased resistance to flow), systemic factors (acquired or inherited abnormalities leading to hypercoagulability), and the development of hepatocellular carcinoma.[4,6] In the majority of patients with cirrhosis, PVT is diagnosed on radiographic studies as an incidental finding, although in some patients, PVT may present with decompensation of their chronic liver disease.[1,7]

Importantly, the natural history of PVT in patients with cirrhosis is largely unknown.[1,7,8] Certainly, many patients with well-compensated liver disease and PVT do well in the long term with medical management. Historically, patients with PVT were considered to be at increased risk of mortality related to bleeding complications, but improvements in the prophylactic management of esophageal varices have significantly reduced these risks.[9,10] Conversely, patients with occlusive PVT can be difficult to manage with respect to ascites and hepatohydrothorax. In general, patients who fail aggressive diuretic treatment for their ascites or hepatohydrothorax will be referred for a transjugular intrahepatic portosystemic shunt.[8,11,12] Unfortunately, transjugular intrahepatic portosystemic shunts are rarely an option for patients with PVT, and as a result, these patients may require frequent paracentesis or thoracentesis.

Within this context, our hypothesis is that occlusive PVT is associated with inferior survival in patients with chronic liver disease. This hypothesis is based on our anecdotal, clinical experience that patients with occlusive PVT and clinical decompensation have a higher risk of infectious complications and death. Unfortunately, there is little previous work focusing on the natural history of patients with cirrhosis and PVT. To

Abbreviations: CI, confidence interval; EtOH, ethanol; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PVT, portal vein thrombosis; Txp, transplantation.

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address this issue, we report on the survival of over 3000 adult patients with chronic liver disease who were evaluated for a liver transplant and stratified by the presence of occlusive PVT.

PATIENTS AND METHODS

This study was approved by the institutional review board at the University of Michigan. We used a 100% sample of all adult patients with cirrhosis evaluated in the multidisciplinary liver transplant clinic at our center between January 1, 1995 and March 30, 2007 who had not previously undergone transplantation. Data were obtained from a prospectively collected transplant database and from a review of the medical record. Patients with hepatocellular carcinoma were eliminated from all survival analyses. This was a clinical decision based on the observation that PVT in the setting of hepatocellular cancer is physiologically and clinically different from PVT in the setting of cirrhosis. Patients who received a liver transplant and were noted to have incidental hepatocellular carcinoma were not eliminated from the survival analysis. The Model for End-Stage Liver Disease (MELD) score at the time of evaluation, listing, and transplantation was calculated for each patient with primary laboratory data from our transplant database.

PVT is defined as occlusive thrombosis of the main portal vein. Most patients were initially diagnosed with PVT on liver ultrasound, but all cases were confirmed in 1 of 3 ways: a dedicated liver magnetic resonance imaging study, percutaneous mesenteric venography (an angiographic procedure), or identification in the operating room at the time of the liver transplant operation. Partially occluding thrombus in the portal vein was not considered PVT. In addition, an occlusive thrombus in the right portal vein, left portal vein, splenic vein, or superior mesenteric vein was not considered PVT unless there was an occlusive thrombus in the main portal vein.

Analysis

We first determined patient-specific risk factors for PVT. For this analysis, the primary outcome measure was time-dependent PVT. Patients were censored at the diagnosis of PVT, transplant, or death. Using a univariate Cox regression, we determined candidate covariates for a multivariate model. All candidate covariates reaching a statistical limit of significance of $P < 0.10$, in addition to other clinically important covariates, were entered into the multivariate model to determine variables independently associated with a diagnosis of PVT. For this analysis, patients with the diagnosis of cancer were included.

A patient level analysis was performed, with the main exposure variable being the presence of PVT, which was treated as a time-dependent variable. The primary outcome variable was mortality.

Among patients with and without PVT, we compared patient age, race, diagnosis, mean follow-up, listing rate, transplant rate, and unadjusted survival at the end of follow-up. These univariate analyses were completed with chi-square analysis for categorical variables and an unpaired *t* test for continuous variables.

Mortality rates were calculated for all patients by the Kaplan-Meier method, and statistical differences were determined by the log-rank test. Kaplan-Meier survival curves were created from the time of patient evaluation to death and from the time of transplantation to death. Patient survival was censored at death or loss to follow-up. Less than 1% of patients were lost to follow-up.

The independent effects of PVT on patient survival were assessed with multivariate Cox proportional hazards models. Three separate models were created to analyze time-to-event outcomes (mortality) from the time of liver transplant evaluation, time of listing for liver transplantation, and time of transplantation. Potential covariates for entry into the multivariate model were determined to be clinically relevant and/or to have a significant level in a univariate assessment of $P < 0.10$. Both PVT status and transplant status were treated as time-dependent covariates. All tests used were 2-sided, and a *P* value less than 0.05 was considered to be statistically significant.

The independent effects of PVT on perioperative survival (death within 30 days of liver transplantation) were assessed with a stepwise, multivariate logistic regression model.

SPSS version 15.0 (SPSS, Chicago, IL) was used for data analysis.

RESULTS

Patient Demographics and Clinical Management

Overall, 3897 patients were formally evaluated in liver transplant clinics at the University of Michigan between January 1, 1995 and March 30, 2007. Patients were excluded from further analysis (n = 602) if they did not have chronic liver disease, were younger than 18 years at the time of liver transplant evaluation, or had a previous liver transplant. Therefore, a total of 3295 patients met the study criteria for analysis. Of these, 148 patients (4.5%) were noted to have PVT at the time of evaluation or during the pretransplant period.

In general, patients with PVT and patients without PVT had similar demographics and etiologies of liver disease (Table 1). The mean follow-up period was longer in the PVT group (57.6 ± 50.4 versus 49.6 ± 42.6 months, $P = 0.058$). At the end of the follow-up period, 54.7% of the patients with PVT had died versus 37.2% of the patients without PVT ($P < 0.0001$, unadjusted analysis).

Overall, 2995 patients evaluated for liver transplantation had a screening ultrasound examination to evaluate hepatic flow. Three hundred thirty of these patients were noted to have had an ultrasound examination that documented either PVT (n = 123) or a suspicion thereof (n = 207). Three hundred of these patients went on to have additional imaging, and 148

TABLE 1. Descriptive Statistics of Patients Evaluated for a Liver Transplant With or Without Complete Occlusion of the Portal Vein (n = 3295)

	No PVT (n = 3147)	PVT (n = 148)	*P* Value
Gender	1905 males (60.5%)	91 males (61.5%)	0.817
Race			
Black	218 (6.9%)	7 (4.7%)	0.325
Nonblack	2545 (80.9%)	131 (88.5%)	
Unknown	385 (12.2%)	10 (6.8%)	
Cause of liver disease			
Autoimmune	95 (3.0%)	8 (5.4%)	0.138
Biliary cirrhosis	173 (5.4%)	7 (4.7%)	0.835
Cancer	62 (2.0%)	6 (4.1%)	0.125
Cryptogenic	369 (11.7%)	24 (16.2%)	0.118
EtOH	672 (21.4%)	31 (20.9%)	1.00
Hepatitis B	124 (3.9%)	8 (5.4%)	0.386
Hepatitis C	1129 (35.9%)	42 (28.7%)	0.065
NASH	72 (2.3%)	0	0.076
Other	449 (14.3%)	22 (14.9%)	0.810
Age at evaluation (years)	51.5 ± 11.2	50.9 ± 10.8	0.581
Age at transplant (years)	50.6 ± 11.8	49.7 ± 9.8	0.670
MELD at evaluation	12.1 ± 7.2	13.3 ± 8.3	0.245
MELD at transplant	16.5 ± 8.3	15.2 ± 9.0	0.985
Mean follow-up (months)	49.6 + 42.6	57.6 + 50.4	0.058
Dead at follow-up (%)	**37.2%**	**54.7%**	<**0.0001**

Abbreviations: EtOH, ethanol; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PVT, portal vein thrombosis.

were eventually diagnosed with PVT. All 123 patients in whom PVT was diagnosed on ultrasound were confirmed to have PVT on additional imaging, whereas only 20 (out of 207) with a suspicion of PVT on ultrasound were eventually diagnosed with PVT upon additional testing. With respect to confirmatory testing, we considered a diagnosis of PVT to be valid only when it was diagnosed via magnetic resonance imaging, mesenteric venography, or operative findings. Of the 148 patients diagnosed with PVT, magnetic resonance imaging was used to make the diagnosis in 142 cases, mesenteric venography was used in 5 cases, and intraoperative diagnosis was used in 1 case.

In univariate analysis, risk factors independently associated with a diagnosis of PVT included only the MELD score at the time of evaluation [hazard ratio (HR), 1.043; 95% confidence interval (CI), 1.010-1.077; $P = 0.010$]. In multivariate analysis, only the MELD score (HR, 1.060; 95% CI, 1.030-1.090; $P = 0.0001$) and cancer diagnosis (HR, 3.875; 95% CI, 1.069-14.020; $P = 0.039$) were included.

Of the 148 patients noted to have PVT, 70 (47.3%) were listed for transplantation (Fig. 1). In contrast, among the 3147 patients without PVT, 1124 (35.7%) were listed for transplantation ($P = 0.005$). Of the 70 patients listed for transplantation with PVT, 30 (42.9%) received a transplant versus 544 (48.4%) among the patients listed for transplantation who did not have PVT ($P = 0.390$).

Overall, 71 of the patients with PVT (60.2%) who did

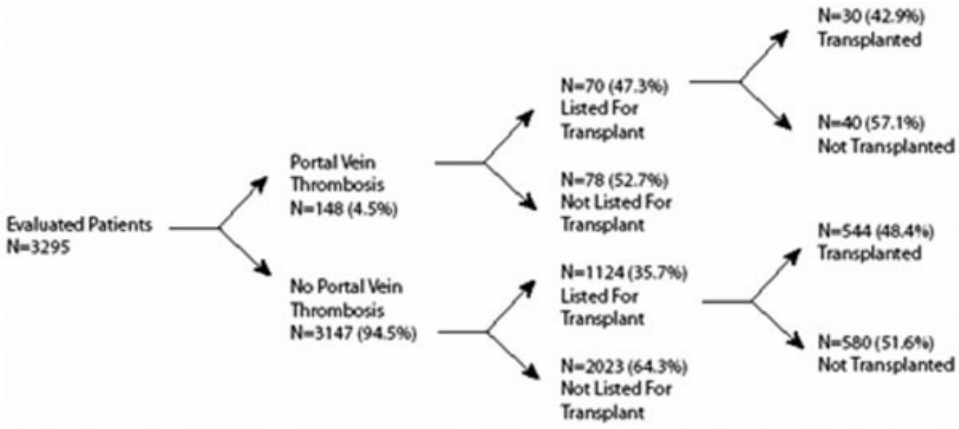

Figure 1. Evaluation, liver transplant listing, and transplant rates among patients at the University of Michigan with and without portal vein thrombosis.

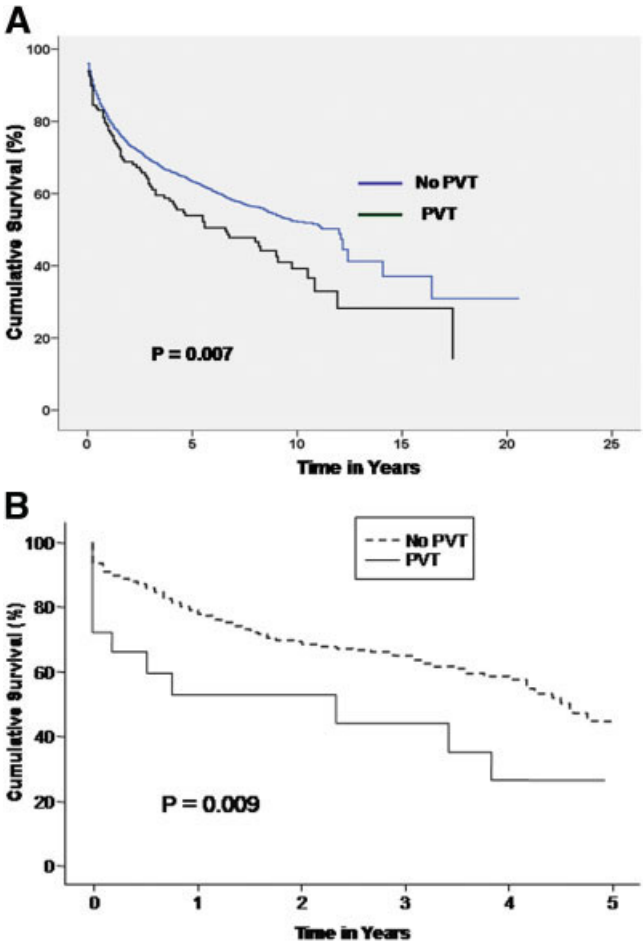

Figure 2. Kaplan-Meier survival curves from the time of (A) liver transplant evaluation and (B) transplantation for adult patients with chronic liver disease stratified by the presence of occlusive PVT.

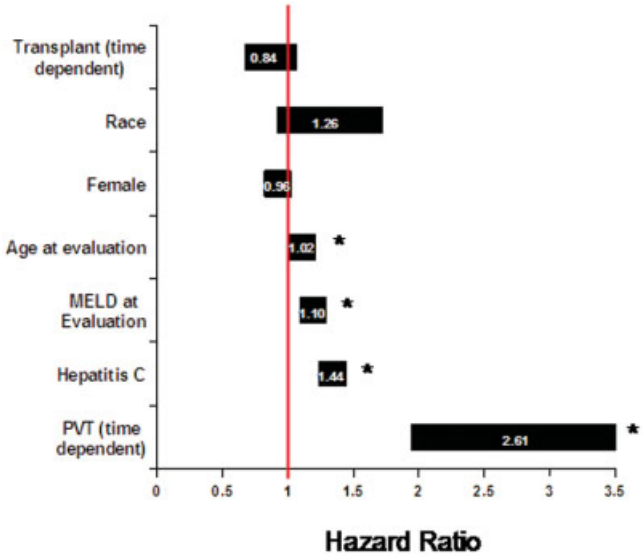

Figure 3. Time-dependent Cox regression model of the risk of mortality among patients who presented for evaluation for a liver transplant. Patients with PVT had a significantly higher risk of mortality versus patients without PVT (hazard ratio, 2.61; 95% confidence interval, 1.97-3.51). Both transplant status and PVT were managed as time-dependent covariates in this model. The *x* axis displays the hazard ratio and 95% confidence interval for mortality. *$P < 0.05$.

not receive a transplant were dead at the end of follow-up. Because of the clinical complexity of these patients, the determination of a specific cause of death was difficult. Among patients with PVT who died in our hospital prior to transplantation (n = 55), liver disease contributed to the deaths of all these patients. In addition, spontaneous bacterial peritonitis was the most common initial diagnosis (n = 35, 63.6%) for the admission during which these patients with cirrhosis and PVT died. No PVT patients died of refractory gastrointestinal bleeding in our institution.

Survival from the Initial Evaluation

The Kaplan-Meier analysis of patient survival from the time of transplant evaluation, stratified by the presence or absence of PVT, is demonstrated in Fig. 2A. Unadjusted patient survival among those with pretransplant PVT was significantly lower than survival among those without PVT ($P = 0.007$).

An additional survival analysis was completed to assess the independent effects of PVT on patient survival from the time of evaluation for liver transplantation. Candidate variables for a multivariate model of mortality from the time of transplant evaluation were determined by univariate Cox analysis. Candidate variables included transplantation (time-dependent; HR, 1.21; 95% CI, 1.04-1.49), race (nonwhite; HR, 1.11; 95% CI, 0.89-1.38), gender (female; HR, 1.20; 95% CI, 1.10-1.31), age at evaluation (HR, 1.02; 95% CI, 1.01-1.03), MELD at evaluation (HR, 1.10; 95% CI, 1.08-1.12), hepatitis C (HR, 1.14; 95% CI, 1.04-1.24), and PVT (HR, 2.59; 95% CI, 2.08-3.29).

The candidate variables from the univariate analysis were used to create a multivariable Cox regression model (Fig. 3). Variables noted to be independently associated with mortality from the time of initial liver transplant evaluation included age at evaluation (HR, 1.02; 95% CI, 1.01-1.03), MELD at evaluation (HR, 1.10; 95% CI, 1.08-1.11), hepatitis C (HR, 1.44; 95% CI, 1.24-1.68), and PVT (HR, 2.61; 95% CI, 1.97-3.51).

In order to further describe the risk of mortality from the time of evaluation among patients with PVT, we compared their unadjusted mortality rate to that of patients without PVT with stratification by the MELD score at the time of liver transplant evaluation. Patients with PVT had a risk of mortality similar to that of patients who presented for evaluation with a MELD score of 26. The mean MELD score of patients with PVT at the time of liver transplant evaluation was 12. It is important to note that the follow-up period for the patients with PVT was longer (57.6 ± 50.4 versus 49.6 ± 42.6 months, $P = 0.058$), so their exposure to the risk of mortality was higher.

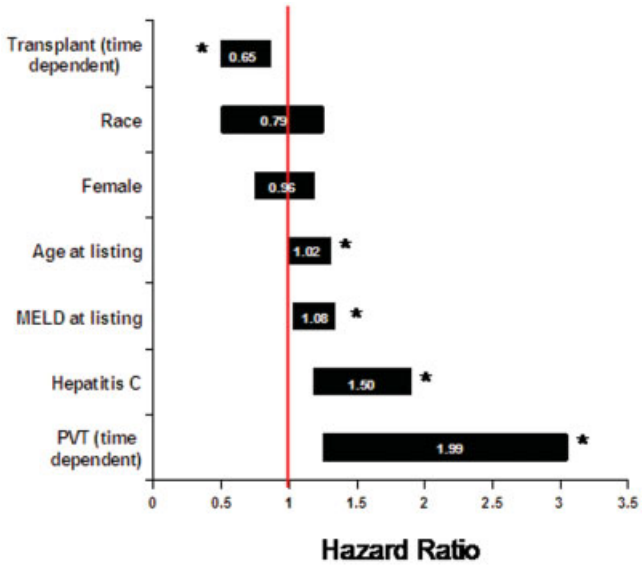

Figure 4. Time-dependent Cox regression model of the risk of mortality among patients who were listed for liver transplantation. Liver transplant candidates with PVT had a significantly higher risk of mortality versus candidates without PVT (hazard ratio, 1.99; 95% confidence interval, 1.25-3.16). Both transplant status and PVT were managed as time-dependent covariates in this model. The *x* axis displays the hazard ratio and 95% confidence interval for mortality. *P < 0.05.

Survival from the Time of Listing for a Liver Transplant

Survival analysis was completed in order to assess the independent effects of PVT on survival from the time of listing for a liver transplant. Candidate variables for a multivariate model (mortality from the time of transplant listing) were first determined by univariate analysis. Candidate variables included transplantation (time-dependent; HR, 0.83; 95% CI, 0.60-1.07), race (nonwhite; HR, 0.88; 95% CI, 0.59-1.20), sex (female; HR, 1.15; 95% CI, 0.96-1.34), age at listing (HR, 1.01; 95% CI, 1.01-1.02), MELD at listing (HR, 1.08; 95% CI, 1.06-1.11), hepatitis C (HR, 1.22; 95% CI, 1.03-1.40), and PVT (HR, 1.89; 95% CI, 1.28-2.49).

The candidate variables were used to create a multivariable Cox regression model (Fig. 4). Variables noted to be independently associated with the hazard of mortality from the time of liver transplant listing included age at listing (HR, 1.02; 95% CI, 1.01-1.03), transplantation (HR, 0.65; 95% CI, 0.50-0.81), MELD at listing (HR, 1.08; 95% CI, 1.06-1.10), hepatitis C (HR, 1.50; 95% CI, 1.18-1.90), and PVT (HR, 1.99; 95% CI, 1.25-3.16).

In order to further describe the risk of mortality from the time of listing among patients with PVT, we compared their unadjusted mortality rate to that of patients without PVT with stratification by the MELD score at the time of liver transplant listing. Patients with PVT had a risk of mortality similar to that of patients who presented for listing with a MELD score of 31. The mean MELD score of patients with PVT at the time of liver transplant listing was 14. It is important to note that the follow-up period for the patients with PVT was longer, so their exposure to the risk of mortality was higher.

Survival Following a Liver Transplant

The clinical characteristics of patients with and without PVT who received a liver transplant were similar with respect to gender, race, cause of liver disease, and age. The patients with PVT that received a transplant had a significantly longer posttransplant follow-up period (79 versus 105 months, $P = 0.003$; Table 2). MELD scores at the time of transplant were similar between both groups (15.1 versus 16.3, $P = 0.55$). Survival was inferior among patients with PVT after transplantation at 30 days (17.7% versus 4.4%, $P = 0.07$), at 1 year (33.0% versus 25.0%, $P = 0.354$), and at follow-up (36.7% versus 28.4%, $P = 0.371$), but these differences were not statistically significant (unadjusted analysis). The causes of death among the 5 patients with PVT who died within 30 days included primary nonfunction related to a prolonged warm ischemia time, ruptured splenic vein varix on postoperative day 10, acute right heart failure, intraoperative pulmonary hemorrhage, and respiratory failure (severe pulmonary edema following liver transplantation after a massive transfusion). Clearly, a significant portion of these early deaths were directly attributable to PVT and the resultant difficult liver transplant operation. Among the patients without PVT who died within 30 days (n = 25), the primary causes of death included primary nonfunction (n = 10) and right heart failure (n = 8). There seems to be a trend toward less mortality within 30 days at our center. In the last 4 years, the 30-day survival for transplants has been 98.7%, with no deaths among patients with PVT within 30 days of transplantation. This is likely related to technical improvements and improvements in recipient and donor selection.

A multivariate logistic regression model was used to assess independent risk factors for perioperative death (30-day survival). The presence of occlusive PVT at the time of liver transplantation was associated with a significantly increased hazard of death at 30 days (odds ratio, 7.39; 95% CI, 2.39-22.83; Table 3). Other clinically relevant covariates, including age, race, sex, MELD, and hepatitis C, were not associated with a statistically significant increased risk of perioperative death.

As before, a univariate Cox regression analysis was used to generate candidate variables for a multivariate model for survival following transplantation. In multivariate analysis, only the MELD score at the time of transplantation was significantly associated with inferior survival following transplantation (HR, 1.024; 95% CI, 1.003-1.046; Fig. 5). There was a trend toward inferior survival among patients with hepatitis C (HR, 1.337; 95% CI, 0.906-1.971) and PVT (HR, 1.973; 95% CI, 0.992-3.921), but these trends were not statistically significant. In contrast, patients with PVT were noted to have inferior survival on Kaplan-Meier analysis ($P = 0.009$; Fig. 2B).

TABLE 2. Liver Transplant Recipients With or Without Complete Occlusion of the Main Portal Vein (n = 574)

	No PVT (544)	PVT (n = 30)	*P* Value
Race			
Black	36 (6.5%)	1 (3.3%)	0.389
Nonblack	491 (89.3%)	29 (96.7%)	
Unknown	23 (4.2%)	0 (0.0%)	
Age at evaluation (years)	49.3	47.5	0.358
Age at transplant (years)	50.6	49.7	0.618
Mean follow-up (months)	**79.0**	**105**	**0.003**
MELD at transplant	16.3	15.1	0.552
Dead at 30 days (%)	4.4	17.7	0.071
Dead at 1 year (%)	25.0	33.0	0.354
Dead at follow-up (%)	28.4	36.7	0.371

Abbreviations: MELD, Model for End-Stage Liver Disease; PVT, portal vein thrombosis.

TABLE 3. Thirty-Day Survival After Liver Transplantation

Variable	*P* Value	HR	Lower CI	Upper CI
Age at transplant	0.511	0.987	0.950	1.026
Hepatitis C	0.918	1.050	0.417	2.647
MELD at transplant	0.478	1.018	0.969	1.068
PVT	**0.001**	**7.389**	**2.392**	**22.827**
Male	0.891	1.068	0.413	2.761
Nonblack	0.404	0.511	0.106	2.468

Abbreviations: CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; PVT, portal vein thrombosis.

With respect to surgical methods, an endovenotomy was attempted in each case of PVT. In 90% of the cases (n = 27), this was successful in securing adequate portal venous inflow. In 10% of the cases, it was not. Alternative attempts included a superior mesenteric vein jump graft with a vein conduit (n = 1) and portocaval transposition (n = 2). Of the 3 patients in which endovenotomy was not successful, all died within 1 year.

DISCUSSION

In this study, the effects of occlusive PVT on the survival of patients with chronic liver disease were examined. This study is the largest and most comprehensive assessment of PVT in patients with cirrhosis. PVT was found to be independently associated with inferior survival among patients with cirrhosis who are being evaluated for a liver transplant and associated with inferior short-term survival following liver transplantation. These findings may inform decisions regarding the suitability and timing of transplantation for patients with cirrhosis and PVT.

The etiology and clinical management of patients with cirrhosis and PVT are poorly described. The expected pathophysiological consequences of PVT include a further increase in portal hypertension and a worsening of liver function due to the decreased portal flow.[1] Patients with cirrhosis and PVT have been shown to have inferior survival in comparison with patients without

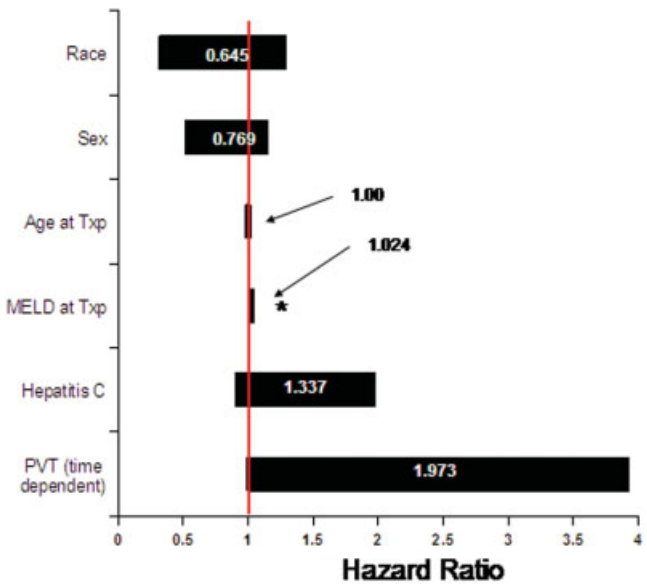

Figure 5. Time-dependent Cox regression model of the risk of mortality among patients who received a liver transplant. Only the MELD score at the time of Txp was significantly associated with inferior survival following Txp (hazard ratio, 1.024; 95% confidence interval, 1.003-1.046). The *x* axis displays the hazard ratio and 95% confidence interval for mortality. *P < 0.05.

PVT, but previous work has been unable to control for the degree of synthetic liver dysfunction.[1,6,7] In addition, previous work has primarily focused on the risk of mortality related to gastrointestinal bleeding. With advances in the management of esophageal varices, gastrointestinal bleeds are now a less common cause of death among patients with cirrhosis, and in our series, no patients with PVT who died had refractory gastrointestinal bleeding as the cause of death.[2,4,13,14]

Because access to liver transplantation in the United States is determined by the risk of mortality on the waitlist, a clear understanding of the independent contributions of PVT to mortality among patients with cirrhosis is needed. This analysis has observed a significantly increased risk of mortality among patients with PVT, even when controlling for the MELD score. For patients with PVT and decompensated liver disease (eg, ascites and encephalopathy), transplantation might be appropriate, even if the MELD score is low. The United Network for Organ Sharing regional review boards should carefully consider awarding MELD exception points to clinically unstable patients with PVT.

That having been said, it is important to consider MELD exception points for PVT within the context of the observation that patients with PVT have inferior posttransplant survival. Both our analysis and work completed by the Scientific Registry of Transplant Recipients have noted inferior posttransplant survival among patients with PVT.[5,15] A poor posttransplant outcome is not a good argument for advocating for preferential access to transplantation for patients with PVT. Accordingly, patients with PVT, particularly those thought to be at increased risk of a difficult perioperative course, must be carefully selected for transplantation. This includes patients with significant debilitation, malnutrition, advanced age, or a nonliver end-organ disease. Overall, focusing on the benefit of liver transplantation might address the balance between wait-list and posttransplant survival. In all, a larger analysis using Scientific Registry of Transplant Recipients data and focusing on the relative benefit of transplantation among PVT patients compared to other patients on the wait-list is in progress by our group and is needed to more fully inform policy decisions regarding patients with PVT.

Although our study provides several novel insights, it has several limitations. First, all data for this study were obtained from a single center with a relatively small sample (n = 148) of patients with PVT. For this analysis, it was important that PVT be managed as a time-dependent covariate in survival models, and as a result, a very detailed retrospective assessment of the medical record is required. Such detailed data are not available in any clinical registry or database, and thus a more extensive assessment of PVT using larger data sets is not currently possible. Second, as mentioned earlier, PVT is poorly understood. As a result, unknown confounding factors may exist. Similarly, the MELD score was used to control for the degree of synthetic liver dysfunction, but certainly a true assessment of the severity of end-stage liver disease is more complex than simply the MELD score. More specifically, the MELD score was designed as a measure of liver transplant wait-list mortality and not as a measure of synthetic liver dysfunction. To address this with a sensitivity analysis, we used MELD components (international normalized ratio, creatinine, and bilirubin) in our multivariable models instead of the MELD score, and no significant differences were noted in the model results. Third, although we attempted to control for illness severity, our methods do not fully account for the dynamic nature of illness severity. Ideally, the MELD score or its components would have been treated as a time-dependent covariate, but we were not able to do this because of limitations of the data set. Similarly, a small proportion of patients who were transplanted were managed with warfarin (8% of PVT patients and 6% of non-PVT patients), and this would have elevated these patients' MELD scores at transplant. The PVT patients were largely treated with warfarin for their PVT, whereas the non-PVT patients were treated for either venous thromboembolism or atrial arrhythmia. Either the inclusion or exclusion of these patients from the analysis would introduce a confounding factor, and we have elected to include these patients in the analysis. The inclusion of warfarin therapy in the posttransplant models had no effect on model outputs. Another limitation of this study is that the observation period was from 1995 to 2007, and the study was limited to patients who were evaluated for liver transplantation. Certainly, the clinical management of end-stage liver disease and liver transplantation allocation changed significantly over this time period. For example, our group is currently more aggressive about transplanting patients with PVT than we were in the past. As a result, these era effects could have implications for the conclusions made on the basis of these data.

Consideration should be given to the potential implications of selection bias in this retrospective cohort. Only patients who were referred for liver transplant evaluation were studied. As a result, this study is an assessment not of all patients with cirrhosis and PVT but only of the subset of patients referred for liver transplant evaluation. In addition, patients with PVT may be more likely to be "passed over" for available organs because of the complexity of their operation, and this could lead to lower transplant rates and higher death rates. Similarly, with respect to the diagnosis of PVT, patients who were listed for a liver transplant may have been followed more closely and, as a result, were potentially more likely to receive a diagnosis of PVT. Presumably, these issues with selection not only affected this analysis but also will limit any future analysis of clinical registry data.

In summary, patients with cirrhosis complicated by PVT have a significantly increased risk of death. Policymakers and members of United Network for Organ Sharing regional review boards must consider not only the increased risk of pretransplant death among these patients but also the inferior posttransplant outcomes. Additional study is needed to clarify the management of patients with chronic liver disease complicated by occlusive PVT.

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