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Risk factors and impact of portal vein thrombosis in liver transplantation

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ABSTRACT

Introduction: portal vein thrombosis is a relatively common complication of advanced cirrhosis that increases perioperative risk in liver transplant recipients. This condition was characterized in a cohort of patients, including risk factors and their influence on survival.

Material and methods: a retrospective study of liver transplant recipients at the Clínica Universidad de Navarra was performed between 2000 and 2015. Differences in clinical and biological characteristics and survival were analyzed in subjects with and without portal vein thrombosis. A predictive index was also developed.

Results: a total of 288 patients were included in the study, portal vein thrombosis was recorded in 46 (16%) cases and seven (15.2%) had stage 3/4 disease according to Yerdel's classification. Factors associated with the presence of esophageal/gastric varices (OR = 3.7; p = 0.03) included variceal ligation or sclerotherapy (OR = 2.3; p =

0.01), being overweight/obesity (OR = 2.1; p = 0.04) and thrombocytopenia (OR = 3.6; p = 0.04). There were no significant differences between the groups with and without portal vein thrombosis in terms of survival according to Kaplan-Meier curve analysis (p = 0.7). However, the mortality rate was higher for Yerdel stages 3-4 (p < 0.01). A predictive index was developed that included varices, body mass index (BMI), thrombocytopenia and activated partial thromboplastin time (APTT). This index had a sensitivity of 76.1% and a specificity of 53.7% for the development of portal thrombosis.

Conclusions: the presence of esophageal/gastric varices, variceal ligation/sclerotherapy, thrombocytopenia and being overweight/obesity was associated with a higher rate of portal vein thrombosis. Advanced stages had an impact on survival.

Key words: Portal thrombosis. Liver transplantation. Liver cirrhosis. Gastric and esophageal varices. Obesity.

INTRODUCTION

Currently, liver transplantation represents the therapeutic strategy of choice for patients with advanced-stage liver disease. Until recently, portal vein thrombosis (PVT) was considered to be an absolute contraindication due to the sizable technical difficulties. The first successful liver transplant in a patient with these characteristics was performed in 1985 (1) and both medical and surgical approaches have changed considerably ever since. An estimated 9.7% ± 4.5% of patients undergoing liver transplantation have PVT (2), which had not been previously diagnosed in 50% of cases (3).

Not all the mechanisms involved in the pathophysiology of PVT in cirrhotic patients are well understood. However, selected predictive factors have been described, including reduced portal flow (2), the presence of collateral circulation (4), prior damage to the portal vein system (5) and focal inflammatory injuries (6). Cirrhosis-associated rebalanced hemostasis, where procoagulant factors may predominate, adds to this condition (7-9). Approximately 43% of patients with PVT remain asymptomatic (10) and Doppler ultrasonography is the modality of choice for diagnosis. Among

symptomatic patients, 39% present with gastrointestinal bleeding and 18% with abdominal pain (10). Laboratory test results are nonspecific. However, some studies report moderate reductions in prothrombin and other coagulation factor levels, as well as increased D-dimer levels (2,11-13).

PVT increases technical difficulties during transplantation and requires special techniques for thrombus removal or vascular reconstruction. Longer surgery duration, greater transfusion requirements and higher surgical re-intervention rates have been reported (3,14). The identification of patients with PVT may condition the course of liver transplantation in that appropriate perioperative management may anticipate relevant complications. Thus, the specific goals of this study included: a) establishing the impact of PVT on the clinical course of liver transplant patients; and b) assessment of the influence of patient and liver disease-related factors on a higher incidence of PVT.

PATIENTS AND METHODS

The study included a retrospective series of 288 patients who received a liver transplant between January 2000 and December 2015 at Clínica Universidad de Navarra (Pamplona, Spain). Inclusion criteria included the presence of liver cirrhosis, age over 18 years at the time of the procedure and no prior liver transplant procedure. Of the 288 patients included in the study, 46 (16%) had PVT. Patients with tumoral PVT were not included. The study was carried out in compliance with Good Clinical Practice standards and was approved by the Ethics Committee of Universidad de Navarra (25/10/2017).

The presence or absence of PVT was recorded preoperatively (based on imaging tests) and at the time of transplantation (intratransplant). Patients were followed up in an evolutionary manner, considering the end of the study observational period (September 2017) or patient demise as the completion date. The following variables were collected: a) clinical parameters: age, gender, BMI, diabetes mellitus (DM), comorbidities, etiology, hepatocellular carcinoma, Child-Pugh stage, RBC concentrates and surgery duration; b) laboratory parameters: hemoglobin, platelets, albumin, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), creatinine, sodium, international normalized ratio (INR), APTT,

antithrombin, fibrinogen and D-dimer; and c) follow-up: re-intervention, hemodialysis and mortality.

Patients with PVT identified before transplantation were managed with TIPS or low-molecular weight heparin, at the discretion of the treating physician (15). Intraoperative PVT management included thrombectomy and portoportal anastomosis whenever possible. Low-molecular weight heparin was then initiated early during the postoperative period.

Statistical analysis

Categorical variables were expressed as proportions and continuous variables as the mean and standard deviation for parameters with a normal distribution, or otherwise, the median and interquartile range were used. A descriptive analysis of the data was performed that compared clinical and demographic factors between patients with and without PVT. First, a Shapiro-Wilk test was performed to assess variable normality. The following methods were used for the descriptive analysis: Student's t-test or Mann-Whitney U-test for quantitative variables and the Pearson's χ^2 or Fisher's exact test for qualitative variables. The probability of PVT development based on patient characteristics was determined by multivariate analysis using logistic regression and was expressed as the odds ratio (OR) with the corresponding 95% confidence interval (CI). Survival analysis was performed using the Kaplan-Meier method and the log-rank test. The Chi-squared test was used to assess mid-term (one year) mortality.

With regard to the analysis of laboratory data, some parameters were categorized according to normal reference values. Anemia and thrombocytopenia categories that were based on reference values were included for hemoglobin. Albumin was categorized into three groups depending on whether the values were above, within or below the reference interval. AST, ALT and PA were included when above the normal levels. Similarly, ORs for values above the normal range were included with regard to INR.

The statistical analysis was performed using the Stata 15 (StataCorp. 2017) software and statistical significance was set at $p < 0.05$. Values of $p < 0.1$ were deemed to represent a trend, although not statistically significant. All p values were reported as two-tailed.

RESULTS

Descriptive analysis

PVT was identified in 46 (16%) of 288 liver transplant recipients, six were females (13.8%) and 40 were males (86.2%). The PVT diagnosis was incidental in 13 cases (28.2%). The between-group comparisons of demographic, clinical and laboratory characteristics for both patients and transplants are shown in table 1. This also includes thrombosis grade and extension, according to Yerdel's classification (16). Half of patients had grade-1 PVT and seven had stage 3 or 4 PVT. Of these, the PVT was detected preoperatively and imaging tests identified a thin portal vein without thrombosis in the remaining subjects. Thrombectomy and porto-portal anastomosis were performed in 43 patients. Three cases underwent anastomosis of the donor portal vein to the recipient left renal vein, with significant splenorenal shunt in one case. Two patients underwent an anastomoses to large-caliber collaterals.

A history of esophageal/gastric varices (p = 0.02) and variceal ligation or sclerotherapy (p = 0.01) was more frequent in patients with PVT compared to subjects without PVT. Similarly, a trend to an increased frequency of variceal bleeding was identified (30.4% *vs* 19%; p = 0.08). With regard to other laboratory parameters, patients with PVT had lower fibrinogen levels (193 mg/dl) compared to those without PVT (211.5 mg/dl), with a tendency to statistical significance (p = 0.07). Table 2 shows the follow-up variables, including overall mortality, re-intervention rates and hemodialysis requirements.

Univariate and multivariate analysis

According to univariate analysis (Table 3), overweight subjects or those with any degree obesity had an OR 2.1 times higher for PVT compared to subjects that were not overweight. This association was statistically significant. A significant correlation was found between the presence of varices and PVT, with a 3.7 times higher OR for PVT in comparison to cases without varices. Other factors were identified that were associated with portal thrombosis, including variceal ligation or sclerotherapy (OR = 2.3) and presence of thrombocytopenia (OR = 3.6). According to the multivariate

analysis (Table 3) using model variables, the presence of esophageal/gastric varices (p = 0.01) and being overweight/obesity (p = 0.03) were statistically significant.

Predictive index

A predictive index was constructed to identify patients with a higher risk for PVT, where prophylactic measures may be considered. To this end, data provided by the logistic regression were used and the following formula for PVT prediction was obtained: 2 + 3 * varices + 2 * BMI + 3 * thrombocytopenia + 2 * APTT.

Where, for varices: 0 = absence of varices and 1 = presence of varices. For BMI: 0 = underweight and normal weight and 1 = overweight or obesity. For thrombocytopenia: 0 = platelets within or above the normal range and 1 = thrombocytopenia. For APTT: 0 = within the normal range and 1 = prolonged (ratio > 1.3).

Scores equal or above 7 were established as the cut-off for high PVT risk. The sensitivity was 76.1%, specificity was 53.7%, PPV was 23.8% and NPV was 92.2%. Data are shown in a ROC curve (Fig. 1).

Survival analysis

Survival analysis was performed using the Kaplan-Meier method. The first follow-up date was defined as the date on which the liver transplantation was performed and the last follow-up date was defined as the date of the event (death), loss to follow-up or the end of the study follow-up. The two latter conditions were considered as censored data. The results provided by this analysis are shown in figure 2.

A log-rank test was used to compare survival rates between the groups with and without portal vein thrombosis. The results indicated that pre-transplant PVT was not associated with a greater mortality (p = 0.07). The mean survival was 12.0 years (95% CI: 11.14-12.87) for patients without PVT and 12.5 years (95% CI: 10.7-14.4) for patients with PVT. Mortality at one year was 7.1% (20/281) for cases without PVT or Yerdel's stages 1-2, *versus* 42.8% (3/7) for subjects with Yerdel's stage 3-4, which was statistically significant (p < 0.01). The causes of death of the three deceased patients with stage 3/4 PVT were variceal GI bleeding, infection and anoxic encephalopathy following an intraoperative arrest.

DISCUSSION

This study assessed the role of PVT in an ample patient cohort that underwent a liver transplantation in order to establish its predictive value, either as a standalone factor or in combination with other clinical and laboratory parameters. A significant relationship was found between BMI, the presence of pharyngeal/gastric varices, variceal ligation/sclerotherapy, thrombocytopenia and presence of PVT. However, the limitations posed in the assessment of BMI in patients with ascites must be highlighted, as this involved 2/3 of subjects in our study.

The prevalence of PVT in patients with cirrhosis varies from 4.6% to 17.9% (17). The prevalence in our cohort was 16%, which is similar to that in the study by Koh et al. (18). Among the cardiovascular risk factors assessed, obesity acts as a prothrombotic factor that favors chronic inflammation and impairs coagulation and fibrinolysis (19-21). In our series, patients that were overweight or obese had twice the risk of PVT compared to those with a normal weight or underweight. There was no statistically significant association between BMI and thrombotic complications in the study by Molina et al. (22). The authors concluded that obesity does not seem to be a risk factor that reduces graft or patient survival. However, Ayala et al. demonstrated that obesity may indeed represent an independent risk factor for PVT in cirrhotic patients that are eligible for liver transplantation (23). However, it is also associated with PVT in cases without cirrhosis (20). The higher incidence of PVT among patients with an increased BMI may be related to ascites, which also points to advanced liver disease. Furthermore, the higher incidence of PVT seen in overweight/obese individuals may also be related to the prothrombotic tendency that is characteristic of this metabolic syndrome (24).

Multiple clinical factors were previously associated with PVT development, including prior procedures for portal hypertension, endoscopic management of varices and thrombectomy (3). In our study, there was a statistically significant association between the presence of PVT and prior variceal ligation, with a frequency of 43.8% in this group. This association may result from an increase in thrombotic complications after surgery for portal hypertension, which most likely results from an increased inflammatory response and hampered blood flow. In fact, some studies described this as an independent risk factor (25). With regard to liver disease complications in our

cohort, patients with PVT had a higher prevalence of esophageal varices (93.5%) compared to subjects without PVT (79.3%). The presence of varices was associated with a 3-fold increase in PVT risk. A history of prior variceal bleeding increased the PVT risk by a factor of 1.9, which approached statistical significance. This association has previously been reported by Montenovo et al. (17) and may due to the presence of higher portal hypertension levels in these individuals (26). Several studies describe a higher rate of PVT among patients with advanced liver disease, with a prevalence that ranges from < 1% for compensated cirrhosis to > 25% for decompensated disease (14,16). There was no differences in PVT rate among subjects with advanced liver disease in our study, although the incidence (17.8%) was consistent with the above values. In this study, the presence of PVT was not correlated with other etiologies of liver disease such as hepatitis C virus-related cirrhosis, alcoholic cirrhosis, or hepatocellular carcinoma. Even though this has been reported in previous studies (27-29).

An increase in transfusion requirements has been previously described for patients with PVT (27,30) due to thrombocytopenia and advanced liver disease. Our data did not substantiate this finding as there was no such increased requirement compared to patients without PVT, although this may be due to the fact that only RBC concentrates and no other blood products were factored in. With regard to laboratory parameters, there was an inverse correlation (2,31) between platelet levels and PVT. This may be due to a reduced portal flow from portal hypertension overcoming the potential "protective" effect of thrombocytopenia in the thrombosis setting. Other factors that may lead to thrombocytopenia include splenic platelet sequestration, bone marrow suppression by hepatitis C virus (HCV) and antiviral therapy with interferon (32).

A novel, interesting finding in our study was the predictive index development that included the presence of esophageal/gastric varices, BMI, the presence of thrombocytopenia and APTT. This index had an acceptable sensitivity and specificity, with a high negative predictive value. Further studies will be needed to establish its prognostic significance for PVT.

PVT had been previously described as a factor that increases mortality within 30 days post-transplant (2,30). The study by Ghabril et al. (14) that used the OPTN database found that PVT represents an independent mortality risk factor in the first 90 days

post-transplant and in graft failure. Furthermore, Koh et al. (18) showed that overall survival and graft survival are similar in patients with and without PVT, which is consistent with the results obtained in the present study. Thus, survival does not seem to vary between both groups. In our series, one-year mortality was 7.1% among patients without PVT or Yerdel stage 1/2 and 42.8% in advanced stages. Of the three deceased patients, one died from persistent PVT (variceal bleeding) and one due to an increased intraoperative complexity. These results are similar to those reported by Zanetto et al. (33) in a recent meta-analysis. In this study, patients with stage 1/2 had a mortality rate of 18% within the first year, which increased to 50% for subjects with stage 3/4.

With regard to the diagnostic approach to pre-transplant PVT, we consider that all candidates for the procedure should be assessed by Doppler ultrasound. This should also be completed with angio-CT or angio-MRI scans in cases of a slow portal flow or suspected PVT, according to the recommendations issued by the Spanish Society of Liver Transplantation (SETH) (34). We recommend anticoagulation with low molecular weight heparin for patients with partial PVT, except when contraindicated or the waiting time is short. Cases where anticoagulation is contraindicated may be considered for TIPS (15). When thrombosis is complete or nearly complete, angio-CT should be used to assess the potential for an adequate intraoperative portal flow via large collaterals. If unfeasible, recanalization using interventional radiology may be considered (35). The fact that advanced-stage PVT is associated with increased postoperative mortality should be borne in mind, even though it is not considered as an absolute contraindication for liver transplantation (34).

Our research has the limitations that are typically associated with the assessment of observational data from a retrospective study. Furthermore, patient follow-up duration differs according to year of transplantation. A significant study limitation was the inability to correctly categorize PVT stage as per the classification by Yerdel et al. (16). Furthermore, the sample size was relatively small and may interfere with the conclusions drawn from a clinical or practical perspective.

To conclude, our study identified the presence of esophageal/gastric varices and their ligation or sclerotherapy as predictive variables for PVT. Among the laboratory parameters, thrombocytopenia represents an independent risk factor for the

development of PVT. Furthermore, the PVT risk doubles in overweight or obese individuals and PVT does not significantly impact on survival after liver transplantation. The results of this study provide data with prognostic significance, although further studies are needed to establish whether a perioperative preventive/therapeutic strategy to PVT may have a significant impact on the postoperative course of liver transplantation patients.

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Table 1. Anthropometric and clinical parameters for patients with/without portal vein thrombosis

	PVT (n = 46)	*NO PVT (n = 242)*	*p*
Age	59 (52-63.8)	58 (51-64)	0.73
Gender (M:F)	40 (13.9%): 6 (2.1%)	200 (69.4%): 42 (14.6%)	0.47
BMI	27.5 (± 3.1)	27 (± 4.7)	0.4
DM			
No	25 (54.3%)	102 (42.1%)	0.13
Pre-transplant	13 (28.3%)	78 (32.2%)	0.6
Comorbidities			
Ascites	30 (65.2%)	158 (65.3%)	0.99
Encephalopathy	24 (52.2%)	119 (49.2%)	0.71
Bleeding from varices	14 (30.4%)	46 (19%)	0.08
Spontaneous bacterial peritonitis	6 (13%)	34 (14%)	0.86
Esophageal/Gastric varices	43 (93.5%)	192 (79.3%)	*0.02*
Variceal ligation/sclerotherapy	18 (39.1%)	53 (21.9%)	*0.01*
Etiology			
HCV	16 (34.8%)	90 (37.2%)	0.76
Alcohol	24 (52.2%)	122 (50.4%)	0.83
Other	10 (21.7%)	54 (22.3%)	0.93
Hepatocellular carcinoma	24 (52.2%)	104 (43%)	0.25
Child-Pugh			
A	10 (21.7%)	64 (26.4%)	0.5
B	23 (50%)	116 (47.9%)	0.8
C	13 (28.3%)	60 (24.8%)	0.65
RBC concentrates			
1-5	20 (43.5%)	106 (43.8%)	0.97
5-10	14 (30.4%)	61 (25.2%)	0.46
10-15	1 (2.2%)	10 (4.1%)	0.5
> 15	2 (4.3%)	12(5%)	0.9
Surgery duration	360 (300-400)	360 (300-400)	0.55
Laboratory parameters			
Hemoglobin (g/dl)	11.8 (10.1-13.1)	11.8 (9.6-13.3)	0.83
Platelets (x 10^9/l)	75 (53-104.5)	79.5 (55-109.3)	0.38
Albumin (mg/dl)	3,090 (2,785-3,585)	3,180 (2,870-3,690)	0.41
Bilirubin (mg/dl)	2.78 (1.5-3.9)	2.57 (1.4-4.3)	0.75
AST (IU/l)	43 (29.3-51.5)	39.50 (28-61.5)	0.83
ALT (IU/l)	27.50 (21.3-43.8)	30 (20-49.3)	0.45
AP (IU/l)	152 (101.5-233.5)	160 (108.3-216.8)	0.77
Creatinine (mg/dl)	0.9 (0.7-1.1)	0.9 (0.8-1.1)	0.41
Sodium (mEq/l)	137 (135-140)	137 (134-139)	0.22
INR	1.4 (1.2-1.5)	1.3 (1.2-1.5)	0.19
APTT (sec)	39.8 (34.7-45.4)	39.75 (35.1-45.6)	0.74
Anti-thrombin (%)	41 (32-59)	49 (35-64)	0.15
Fibrinogen (mg/dl)	193 (141.8-258)	211.5 (157-290.3)	0.07
D-dimer (ng/ml)	625 (324.3-1,424.9)	641.5 (294.3-1,470)	0.81
Portal vein thrombosis grade (Yerdel) (16)	1 = 23 2 = 16 3 = 5 4 = 2		

OR: odds ratio; 95% CI: 95% confidence interval; PVT: portal vein thrombosis; BMI: body mass index; DM: diabetes mellitus; HCV: hepatitis C virus; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AP: alkaline phosphatase; INR: international normalized ratio; APTT: activated partial thromboplastin time.

Table 2. Follow-up with regard to the presence or absence of portal vein thrombosis

	PVT (n = 46)	*NO PVT (n = 242)*	*p*
Re-intervention (n = 6)	2 (4.3%)	4 (1.7%)	0.24
Hemodialysis (n = 3)	0	3 (1.2%)	0.45
Mortality (n = 93)	14 (30.4%)	79 (32.6%)	0.77

PVT: portal vein thrombosis. n (%).

Table 3. Univariate and multivariate logistic regression analysis of risk factors for the development of portal vein thrombosis

	Univariate analysis	*Multivariate analysis*

	OR	95% CI	p	OR	95% CI	p
Age	1	0.97-1	0.67			
Gender (M:F)	1.4	0.6-3.5	0.47			
BMI	2.1	1.1-4.5	*0.04*	2.4	1.1-5.4	*0.03*
DM						
No			ref	0.5	0.3-1	0.06
Pre-transplant	0.7	0.3-1.4	0.3			
Comorbidities						
Ascites	1	0.5-1.9	0.99			
Encephalopathy	1.1	0.6-2.1	0.71			
Bleeding from varices	1.9	0.92-3.8	0.08			
SBP	0.9	0.4-2.3	0.86			
Esophageal/gastric varices	3.7	1.1-12.5	*0.03*	6.4	1.5-28.2	*0.01*
Variceal ligation/sclerotherapy	2.3	1.2-4.5	*0.01*			
Etiology						
HCV	0.9	0.5-1.7	0.76			
Alcohol	1.1	0.6-2.0	0.83			
Other	0.9	0.5-2.1	0.93			
Hepatocellular carcinoma	1.5	0.8-2.7	0.25			
Child-Pugh						
A			ref			
B	1.3	0.6-2.8	0.6			
C	1.4	0.6-3.4	0.5			
Hemoglobin (g/dl)	1.4	0.7-2.4	0.35			
Platelets (x 10^9/l)	3.6	1.1-11.9	*0.04*			
Albumin (mg/dl)						
< 3,100	1.3	0.7-2.4	0.5			
> 4,300	0.7	0.2-3.4	0.7			
Bilirubin (mg/dl)	1.7	0.7-4.2	0.26			
AST (IU/l)	1	0.9-1	0.26			
ALT(IU/l)	1	0.98-1	0.15			
FA (IU/l)	0.8	0.6-1.2	0.3			
Creatinine (mg/dl)	1	0.4-2.4	0.99			
Sodium (mEq/l)	1.1	0.98-1.2	0.13			
INR	1.2	0.6-2.6	0.57			
PTT (sec)	0.7	0.5-1.1	0.14	0.4	0.2-1.1	0.08
Anti-thrombin (%)	1	0.97-1	0.12			
Fibrinogen (mg/dl)	1	0.97-1	0.05			
D-dimer (ng/dl)	1.2	0.6-2.6	0.57			

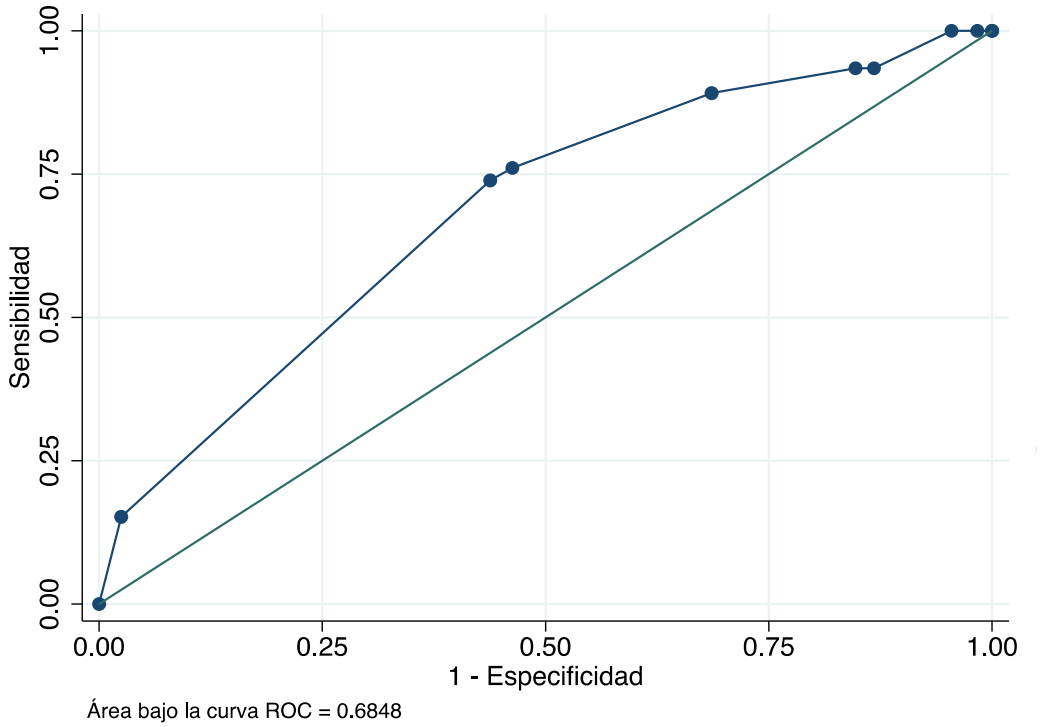

Fig. 1. ROC curve analysis of the accuracy of the predictive index with regard to portal vein thrombosis. A ROC curve was plotted, which incorporated the predictive index as a determinant factor of PVT. An AUC = 0.6848 was obtained.

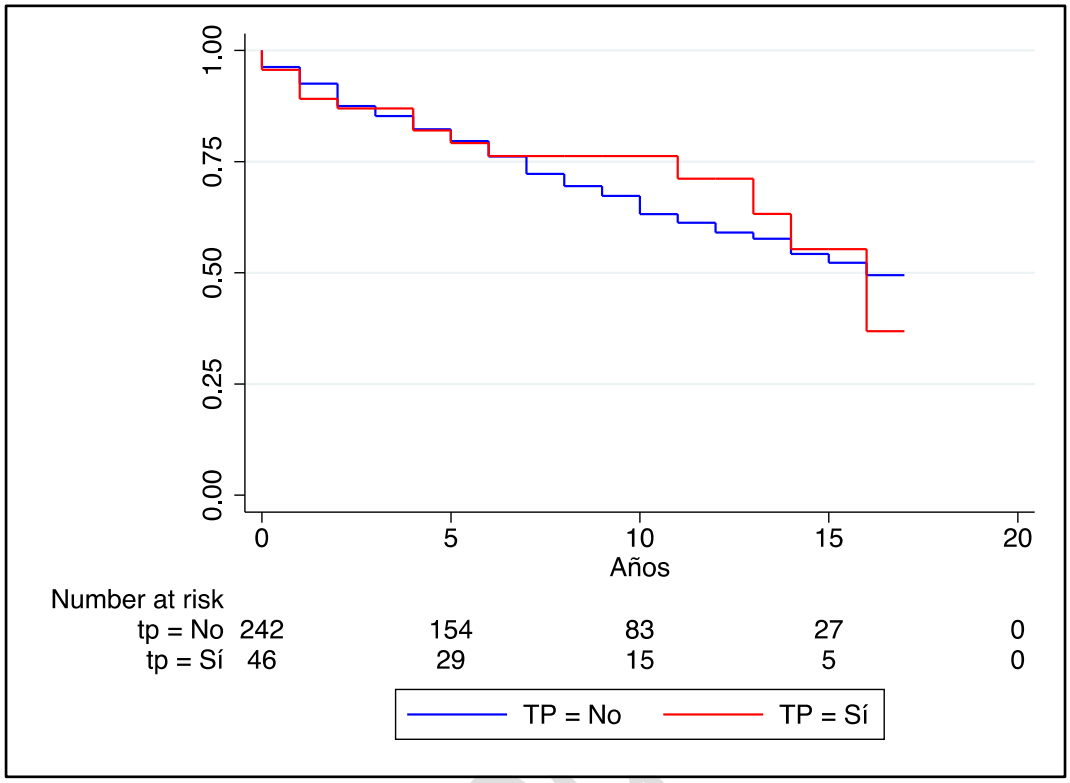

Fig. 2. Survival analysis in patients with and without portal vein thrombosis. Kaplan-Meier patient survival curve after liver transplantation in patients with (red) and without (blue) portal vein thrombosis. The number of patients at risk in each analyzed time period is shown.