0041-1337/00/6909-1873/0
TRANSPLANTATION
Vol. 69, 1873–1881, No. 9, May 15, 2000
Printed in U.S.A.

PORTAL VEIN THROMBOSIS IN ADULTS UNDERGOING LIVER TRANSPLANTATION

RISK FACTORS, SCREENING, MANAGEMENT, AND OUTCOME[1]

MEHMET ALI YERDEL,[2] BRIDGET GUNSON,[3] DARIUS MIRZA,[3] KAAN KARAYALÇIN,[2] SIMON OLLIFF,[3] JOHN BUCKELS,[3] DAVID MAYER,[3] PAUL MCMASTER,[3] AND JACQUES PIRENNE[3,4]

Liver and Hepatobiliary Unit, Birmingham, United Kingdom

Background. **Portal vein thrombosis (PVT) has been seen as an obstacle to liver transplantation (LTx). Recent data suggest that favorable results may be achieved in this group of patients but only limited information from small size series is available. The present study was conducted in an effort to review the surgical options in patients with PVT and to assess the impact of PVT on LTx outcome. Risk factors for PVT and the value of screening tools are also analyzed.**

Methods. **Adult LTx performed from 1987 through 1996 were reviewed. PVT was retrospectively graded according to the operative findings: grade 1: <50% PVT +/− minimal obstruction of the superior mesenteric vein (SMV); grade 2: grade 1 but >50% PVT; grade 3: complete PV and proximal SMV thrombosis; grade 4: complete PV and entire SMV thrombosis.**

Results. **Of 779 LTx, 63 had operatively confirmed PVT (8.1%): 24 had grade 1, 23 grade 2, 6 grade 3, and 10 grade 4 PVT. Being male, treatment for portal hypertension, Child-Pugh class C, and alcoholic liver disease were associated with PVT. Sensitivity of ultrasound (US) in detecting PVT increased with PVT grade and was 100% in grades 3–4. In patients with US-diagnosed PVT, an angiogram was performed and ruled out a false positive US diagnosis in 13%. In contrast with US, angiograms differentiated grade 1 from grade 2, and grade 3 from grade 4 PVT. Grade 1 and 2 PVT were managed by low dissection and/or a thrombectomy; in grade 3 the distal SMV was directly used as an inflow vessel, usually through an interposition donor iliac vein; in grade 4 a splanchnic tributary was used or a thrombectomy was attempted. Transfusion requirements in PVT patients (10 U) were higher than in non-PVT patients (5 U) ($P<0.01$). In-hospital mortality for PVT patients was 30% versus 12.4% in controls ($P<0.01$). Patients with PVT had more postoperative complications, renal failure, primary nonfunction, and PV rethrombosis. The overall actuarial 5-year patient survival rate in PVT patients (65.6%) was lower than in controls (76.3%; $P=0.04$). Patients with grade 1 PVT, however, had a 5-year survival rate (86%) identical to that of controls, whereas patients with grades 2, 3, and 4 PVT had reduced survival rates. The 5-year patient survival rate improved from the 1st to the 2nd era in non-PVT patients (from 72% to 83%; $P<0.01$), in grade 1 PVT (from 53% to 100%; $P<0.01$), and in grades 2 to 4 PVT (from 38% to 62%; $P=0.11$).**

Conclusions. **The value of US diagnosis in patients with PVT depends on the PVT grade, and false negative diagnoses occur only in incomplete forms of PVT (grades 1–2). The degree of PVT dictates the surgical strategy to be used, thrombectomy/low dissection in grade 1–2, mesoportal jump graft in grade 3, and a splanchnic tributary in grade 4. Taken altogether, PVT patients undergo more difficult surgery, have more postoperative complications, have higher in-hospital mortality rates, and have reduced 5-year survival rates. Analysis by PVT grade, however, reveals that grade 1 PVT patients do as well as controls; only grades 2 to 4 PVT patients have poorer outcomes. With increased experience, results of LTx in PVT patients have improved and, even in severe forms of PVT, a 5-year survival rate >60% can now be achieved.**

Portal vein thrombosis (PVT) has, in the past, been considered an absolute contra-indication to liver transplantation (LTx) because of the technical difficulties it entails (*1*, *2*). In the recent years, innovative surgical techniques have been introduced (thrombectomy, use of venous jump graft, use of PV tributaries), and many technical obstacles have been overcome (*3*). As a result, PVT is no longer regarded as a contra-indication to LTx and several series have reported encouraging results of LTx in patients with this problem (*3–8*). However, no large series with extended follow-up has yet been reported, and the exact impact of PVT on the short and particularly long-term outcome of adult LTx remains unknown (Table 1). A source of difficulty in interpreting previous reports is that PVT is not an all or none phenomenon and there are various degrees of PVT, from incomplete and segmental thrombosis to total obstruction of the portal system. Various degrees of PVT may cause differences in the difficulty of the transplantation operation, thus there would be differences in graft and patient outcome. In addition, the value of pretransplant screening tools in detecting PVT has not been studied in detail. We reviewed results of LTx in patients with intraoperatively confirmed PVT at this center. We analyzed those results according to the extent of thrombosis. We also looked at the evolution of those results during two consecutive eras. In addition, we sought to delineate pretransplant risk factors for PVT and we looked at the value of pretransplant screening tools in detecting PVT. Finally, on

[1] This study, in part was sponsored by the NATO Science Fellowship Programme distributed by the Scientific and Technical Research Council of Turkey. A brief part of this study was presented at the 23rd Annual Scientific Meeting of the American Society of Transplant Surgeons, May 14–16, 1997, Chicago, Illinois.

[2] Department of General Surgery, Ankara University Medical School, Ankara, Turkey.

[3] Liver and Hepatobiliary Unit, Birmingham, UK.

[4] Address correspondence to: Jacques Pirenne, Abdominal Transplant Surgery Department, U.Z. Leuven, Herestraat 49, B-3000 Leuven, Belgium. E-mail: Jacques.Pirenne@uz.kuleuven.ac.be.

TABLE 1. Results of previously reported series on LTx patients having preoperative PVT

Author	Center	No. PVT/ No. patients (%)	% Rethrombosis	% PNF[a]	% Pancreatitis	Perioperative mortality (%)	1-year survival (%)
Stieber (1991)	Pittsburgh	34/1585 (2.1)	?	?	?	32.4	67.6
Langnas (1992)	Omaha	16/495 (3.2)	1 (6.25%)	0	2 (12.5%)	19	81
Cherqui (1993)	Cretéil	11/69 (15.9)	0	1 (9.1%)	0	11.1	73
Gonzales (1993)	Madrid	14/174 (8.0)	4 (28.5%)	1 (7.1%)	0	35.7	57.2
Davidson (1994)	London	14/132 (10.6)	3 (21.43%)	0	0	42	58
Gayowski (1996)	Pittsburgh	23/88 (26)	0	4 (17.3%)	0	19	88
Seu (1996)	Los Angeles	70/1423 (4.9)	2 (3%)	?	?	14	74
Lerut (1997)	Brussels	38/326 (11.7)	4 (10.5%)	3 (7.9%)	0	26.3	73.7
Yerdel (1999)	Birmingham	60/709 (8.4)	3 (5%)	4 (6.6%)	1 (1.6%)	30.5	65.6

[a] PNF, Primary nonfunction.

the basis of the presented series, which represents the largest series of adult LTx patients with PVT, we propose guidelines for the evaluation and management of PVT in LTx recipients.

PATIENTS AND METHODS

Patient population. Information stored prospectively at the Unit Database was reviewed. Records of adult patients with chronic liver disease who underwent orthotopic LTx between October 1987 and August 1996 at the Liver Unit, Queen Elizabeth Hospital, Birmingham, UK, were retrieved. This study period was divided into 2 consecutive eras (1st era, October 1987–December 1991; 2nd era, January 1992–August 1996). Patients with intraoperatively-confirmed PVT formed the study group. PVT per se has not been a contraindication for LTx at our center except in patients with a liver tumor or in those with associated significant morbid factors. Pediatric transplantation and transplantation for fulminant hepatic failure were excluded from the analysis for standardization purposes. Donor management, harvesting, preservation, recipient operation techniques, and immunosuppression protocols have been previously published (*9–11*).

Grading of PVT. All patients with intraoperatively-confirmed PVT were identified. PVT was retrospectively classified into the following 4 grades, according to the extent of thrombosis assessed intraoperatively.

Grade 1—Minimally or partially thrombosed portal vein (PV), in which the thrombus is mild or, at the most, confined to <50% of the vessel lumen with or without minimal extension into the superior mesenteric vein (SMV).

Grade 2—>50% occlusion of the PV, including total occlusions, with or without minimal extension into the SMV.

Grade 3—Complete thrombosis of both PV and proximal SMV. Distal SMV is open.

Grade 4—Complete thrombosis of the PV and proximal as well as distal SMV.

Assessment of pretransplant risk factors for PVT. The following potential risk factors for PVT were studied: age, sex, primary disease, Child-Pugh Class (class A vs. B vs. C), previous treatment for portal hypertension (sclerotherapy, transjugular intrahepatic portosystemic shunt (TIPS), or shunt surgery), previous splenectomy, previous upper abdominal surgery, and presence of malignancy in the native cirrhotic liver. Statistical analysis was performed using the software program STATA. Chi-square test with Yates correction was used for the analysis of categorical variables, and the student's *t*-test was used for the analysis of quantitative variables.

Assessment of the efficiency of pretransplant imaging. All patients underwent a protocol ultrasound (US) investigation of their hepatic vasculature with special attention to PV morphologic features and flow. US records were reviewed. The majority of patients with US findings compatible with PVT underwent either conventional angiography or magnetic resonance angiography (MRA) and/or contrast-enhanced computed tomography. The results of US examination were compared with intraoperative findings, and a true or false positive/negative US result was recorded, accordingly. The sensitivity, specificity, positive, and negative predictive values of US imaging were then calculated using standard formulas. Finally, all angiograms and MRA were compared with both US and intraoperative findings, and all imaging results were further analyzed according to the grade of PVT.

Further progression of study. Surgical techniques used were analyzed according to the grade of PVT. Type of bypass used was also noted. Warm ischemia time, amount of operative blood transfusion, and duration of surgery were determined and analyzed according to the grade of PVT and the era. Early and late postoperative complications were studied according to the grade of PVT. In-hospital mortality was studied according to the grade of PVT and the era. Finally, graft and patient survival were analyzed according to the grade of PVT and the era. Lifetable analysis was performed by Kaplan-Meier method, and differences were compared by the log-rank test.

RESULTS

Incidence and grade of PVT. Between October 1987 and August 1996, 709 adult patients with chronic liver disease underwent 779 LTx (709 primary grafts, 70 regrafts). Of that entire population, 63 patients had operatively-confirmed PVT during their transplantation, giving a rate of 8.1% among 779 LTx. Sixty incidences of PVT were encountered during a primary, one during a secondary, and two during a tertiary LTx. The rate of PVT in primary grafts was 8.4% and in regrafts was 4.3% ($P=0.35$). Of the 63 patients with PVT, 24 had grade 1 PVT (38%), 23 had grade 2 PVT (37%), 6 had grade 3 PVT (9.5%), and 10 had grade 4 PVT (15.5%).

Pretransplant risk factors for PVT. Age, previous upper abdominal surgery, and cancer in the cirrhotic liver did not augment the risk of PVT. However, male sex, previous treatment for portal hypertension (sclerotherapy, TIPS, shunt surgery, previous splenectomy), Child-Pugh class C, and alcoholic liver disease were associated with PVT.

Of males and females undergoing LTx, 11% and 6% had PVT, respectively ($P=0.016$). The incidence of PVT differed in patients who had undergone previous sclerotherapy compared with those who had not, 12.4% versus 6.8%, respectively ($P=0.015$). When all treatment for portal hypertension-related bleeding (sclerotherapy, TIPS, shunt, surgery, splenectomy) were evaluated together, patients who underwent at least one of those interventions had a PVT rate of 12.5%, versus 6.6% in those who did not ($P=0.013$). The incidence of PVT was increased with worsening liver disease:

in Child-Pugh class A 2.5%, Child-Pugh class B 5.6% and Child-Pugh class C 10.4% ($P=0.04$, B vs. C). Finally, there was a higher incidence of PVT in patients undergoing LTx for alcoholic liver disease (17% vs. 10% for nonalcoholic liver disease; $P<0.01$). The incidence of PVT in patients undergoing LTx for other indications was not significantly different from that in the overall group: 16% in posthepatitis B, 13% in cryptogenic cirrhosis, 12% in autoimmune hepatitis, 10% in primary sclerozing cholangitis patients, 7% in liver tumor patients, 6% in posthepatitis C, 4.3% in retransplant, and 4% in primary biliary cirrhosis (P=NS).

Value of pretransplant imaging. US had technically failed in three patients (because of obesity n=1; intestinal air n=2). The sensitivity, specificity, and positive and negative predictive values of US in detecting presence or absence of PVT were 73%, 99%, 86%, and 98%, respectively. Sensitivity of US in detecting PVT increased with PVT grade: 48% in grade 1; 82% in grade 2; 100% in grades 3 and 4. There were no false negative results among patients with complete obstruction of the PV (grades 3 and 4). In fact, false negative US-diagnosis occurred exclusively in incomplete forms of PVT, that is, grades 1 and 2. The incidence of those false negative results was significantly higher in grade 1 than in grade 2 ($P=0.03$). In all grades 3 and 4 PVT, US performed had correctly diagnosed complete obstruction of the PV. US, however, could not differentiate grade 3 from grade 4 PVT.

Of 51 patients with a US diagnosis of PVT (44 true positive, 7 false positive), the PV was further examined by additional imaging in 40. No further imaging was done in 9 patients with minimally thrombosed PV at US examination (7 true positive; 2 false positive), and in another 2 patients with operatively-confirmed grade 4 PVT. Of the 40 patients further explored, a conventional angiogram alone was performed in 34; MRA and an angiogram were performed in one; MRA was associated with enhanced computerized tomography in one; and MRA alone was performed in another 4 patients.

An angiogram revealed patency of the PV and absence of thrombus in 5 patients with a false-positive US diagnosis of PVT. In contrast with US, angiograms differentiated grade 1 from grade 2 PVT, and grade 3 from grade 4. Grades of PVT defined by an angiogram corresponded to operative findings. All angiograms performed in grade 3 patients revealed a distally patent SMV, which was subsequently used as a portal inflow (see below). Angiograms, besides diagnosing totally occluded SMV in all grade 4 PVT, further revealed a patent collateral vessel which could subsequently be used as a portal inflow in 4 patients (see below). Morbidity (puncture site hemorrhage from the angiogram) was limited to one patient. MRA provided correct information regarding the grade of PVT all 6 times it was used.

Operative Management (Fig. 1, 2, 3)

Grade 1 PVT. In four patients, the minimal thrombotic segment was confined to the PV segment close to the liver hilum and no special technique had to be used for PV reconstruction. In 17 patients, low dissection of the recipient PV toward the SMV-splenic junction allowed a suitable PV segment proximal to the thrombus to be used for the anastomosis. In three patients, however, a thrombectomy had to be performed in addition to low dissection to provide a suitable recipient PV segment.

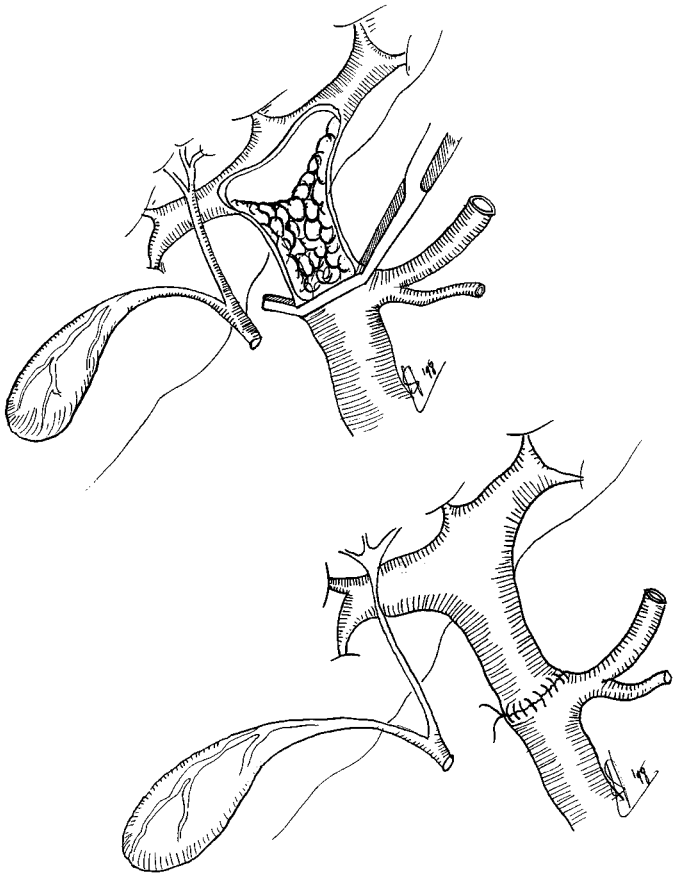

FIGURE 1. Thrombectomy and low dissection is the method of choice for revascularization in grades 1 and 2 PVT patients. It provides a suitable segment of donor portal vein distal to the thrombus.

Grade 2 PVT. Three patients underwent low dissection alone, but the majority (20) needed a thrombectomy (alone in 13 and combined with low dissection in 7).

Grade 3 PVT. At operative confirmation of extensively thrombosed PV and proximal SMV, but distally open SMV, the latter was directly prepared, as described elsewhere (*3*), to serve as a venous inflow. In all these patients but one, an interposition iliac vein graft from the donor was used between the distal SMV (end-to-side) and the donor PV (end-to-end). In one patient, however, the donor PV was long enough to be directly attached end-to-side to the distal SMV. All venous conduits were tunneled through the mesocolon behind the stomach and duodenum and anterior to the pancreas.

Grade 4 PVT. In six patients, there was a suitable PV tributary to which the donor PV was anastomosed end-to-side. A dilated coronary vein was used in four of them, with the technique described previously (*12*) (see Fig. 3). A branch of the SMV and a dilated choledochal vein were used in the other two patients. An interposition iliac vein graft was needed in only one of these six patients.

In four patients, however, no collateral vessel was available, and PV revascularization was attempted by repetitive, but only partially successful, thrombectomies. In one of these patients, in addition to the thrombectomy, a collateral SMV branch was anastomosed end-to-side to the donor PV to in-

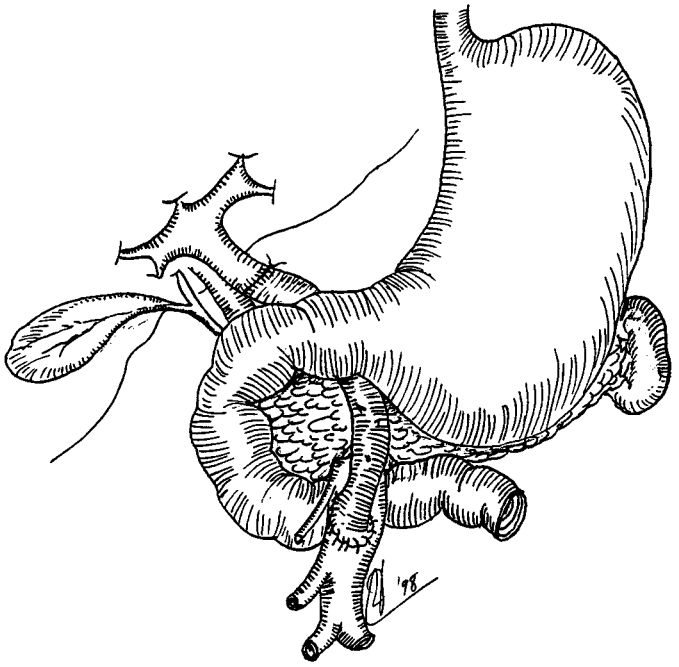

FIGURE 2. In grade 3 PVT, a donor iliac vein graft is interposed between the donor distal SMV and the graft portal vein. The conduit is placed anterior to the pancreas and posterior to the pylorus region.

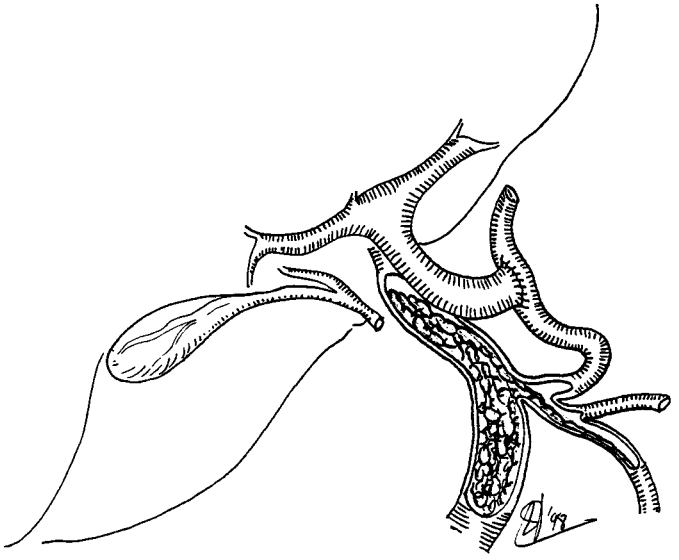

FIGURE 3. In grade 4 PVT, a collateral of the portal system is used as an inflow vessel (in this case, a dilated coronary vein).

crease flow. In another patient, the blood flow after the thrombectomy remained unsatisfactory, and an end-to-side anastomosis between the donor PV and a retroperitoneal varix was performed.

Veno-venous bypass was used selectively. There were 22 patients who received full caval and portal bypasses using the PV in 16, and the inferior mesenteric vein in 6; 11 patients received a portal bypass only, using the PV in 4, the inferior mesenteric vein in 6, or a collateral of the PV in 1; 17 patients received a caval bypass only; and no bypass was used in another 13.

Effect of PVT on intraoperative parameters by PVT grade and by era. The overall median duration of surgery was 6 hr in both PVT and non-PVT patients. It dropped significantly from the 1st to the 2nd era in the non-PVT patients (from 6 to 5 hr, $P=0.0001$). It also dropped from the 1st to the 2nd era in the non-PVT patients (from 7 to 6 hr), but this did not reach significance ($P=0.19$). Median duration of surgery in PVT patients was significantly longer than in non-PVT patients during the 2nd era (6 vs. 5 hr, $P<0.0001$).

The overall median transfusion requirement in PVT patients (10 U) was significantly higher than that in non-PVT patients (5 U) ($P<0.0001$). Transfusion requirements dropped significantly in both PVT and non-PVT patients from the 1st to the 2nd era: from 14 to 8 U ($P<0.015$) in PVT patients, and from 7 to 4 U in non-PVT patients ($P<0.0001$), respectively. Finally, warm ischemia time was not influenced by presence or absence of PVT, PVT grade, or era.

Postoperative complications by PVT grade (Table 2). The rate of post-LTx hepatic artery thrombosis, relaparatomy, and postoperative pancreatitis were similar in both PVT and non-PVT patients. There was a trend for more infectious complications in PVT patients and particularly in advanced grades of PVT, although the difference did not reach significance. Renal failure requiring dialysis, the rate of primary nonfunction, and the incidence of thrombosis of the PV was significantly higher in PVT patients.

Postoperative in-hospital mortality by PVT grade and by era (Table 3). The in-hospital mortality for patients with PVT was 30%. In comparison, the in-hospital mortality for transplantations without PVT was 12.4% ($P<0.001$).

In patients with grade 1 PVT (n=23), there were 3 deaths in total and all occurred within 30 days after LTx, giving an in-hospital mortality rate of 13%. Reasons for deaths were septic complications in two and acute hemolysis resulting from an uncontrollable humoral graft-versus-host disease in one patient.

In patients with grade 2 PVT (n=21), there were 10 deaths in total during the post-LTx period. Two were late deaths

TABLE 2. Distribution of postoperative complications according to presence or absence of PVT and PVT grade

	Non-PVT (%) N=716	Grade 1 PVT (%) N=24	Grade 2 PVT (%) N=23	Grade 3 PVT (%) N=6	Grade 4 PVT (%) N=10	Grade 1–4 (%) N=63	PVT vs. non-PVT
Hepatic arterial thrombosis	2.6 n=17	0	4.7 n=1	0	0	1.7 n=1	P=NS
Relaparotomy for any reason	13.7 n=89	8.7 n=2	14.2 n=3	0	20 n=2	11.6 n=7	P=NS
Pancreatitis	0.6 n=4	0	0	0	10 n=1	1.7 n=1	P=NS
Infectious complications of any kind	18 n=118	26 n=6	28.5 n=6	33.3 n=2	40 n=4	30 n=18	P=NS
Renal failure requiring dialysis	9.4 n=61	21.8 n=5	19.4 n=4	16.6 n=1	20 n=2	20 n=12	P=0.01
Primary nonfunction	1.4 n=9	0	14.2 n=3	16.6 n=1	0	6.6 n=4	P=0.02
Rethrombosis	1.1 n=7	0	9.5 n=2	0	10 n=1	5 n=3	P=0.04

TABLE 3. In-hospital mortality rates according to PVT grade and era[a]

Grade of PVT	Overall in Hospital Mortality (%)	First Era in Hospital Mortality (%)	Second Era in Hospital Mortality (%)	First Era vs. Second Era
Non-PVT	12.4	17.8	9	$P<0.01$
PVT 1–4	30	53	22	$P=0.03$
1	13	50	0	$P=0.01$
2	38.1	50	30.8	NS
3	33.3	100	20	NS
4	50	50	50	NS
	$P<0.001$	$P<0.001$	$P<0.01$	

[a] Non-PVT vs. Grades 1–4 PVT.

occurring 8 and 4 months after discharge and caused by metastatic disease and late acute rejection, respectively. The other 8 deaths occurred during the in-patient stay, giving an in-hospital mortality of 38.1%. The reasons for these 8 fatalities were the following: primary nonfunction of the graft (n=3), rethrombosis of the PV (n=2), hepatic arterial thrombosis (n=1), uncontrollable sepsis (n=1), and reperfusion coagulopathy leading to severe bleeding (n=1).

In patients with grade 3 PVT (n=6), there were two deaths in total, one caused by primary nonfunction on day 0 and another caused by sepsis at 34 days, giving an in-hospital mortality of 33.3%. In survivors, iliac vein grafts functioned well and remained patent.

In patients with grade 4 PVT (n=10), there were 5 deaths in total, all occurring within the first 30 days after LTx, giving an in-hospital mortality of 50%. All four patients having thrombectomies were among those who died: one died of acute left ventricular failure after declamping; a second died of retropancreatic bleeding and pancreatitis at 21 days; a third developed PV rethrombosis at 9 days and this caused fatal variceal bleeding; a fourth patient died at 8 days, of sepsis. In addition, one patient, in whom PV revascularization had been performed through an interposed vein between the donor PV and a recipient SMV branch, died of acute cardiac failure 1 day after LTx. In-hospital mortality decreased from the 1st to the 2nd era in control non-PVT patients (from 17.8% to 9%; $P<0.01$) and also in PVT patients (from 53% to 22%; $P=0.03$).

Patient and graft survival by PVT grade and by era. The overall actuarial 5-year patient survival rate in PVT patients (65.6%) was lower than in non-PVT patients (76.3%; $P=0.04$; Fig. 4). Survival rates in non-PVT patients were then compared with those of each grade of PVT patient (Table 4). Only in grade 1 PVT were the 5-year patient and graft survival

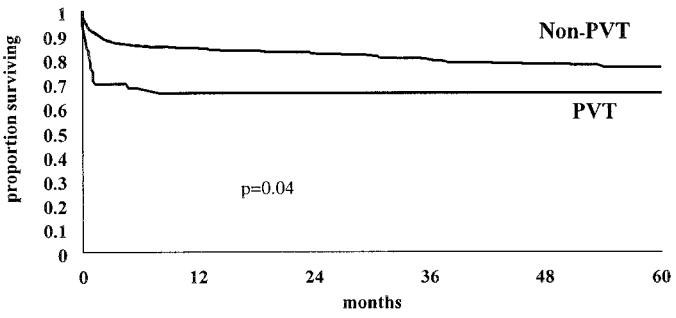

FIGURE 4. Overall patient survival rates in patients with and without PVT (1987–1996).

TABLE 4. Overall 1-year and 5-year patient and graft survival according to PVT grade[a]

	Patient survival		Graft survival	
	1 year (%)	5 years (%)	1 year (%)	5 years (%)
Non PVT	84.2	76.3	76.7	67.9
PVT	65.6	65.6	63.9	63.9
Grade 1	86	86	86	86
Grade 2	52	52	52	47
Grade 3	67	67	67	67
Grade 4	50	50	50	50

[a] See *P* values in the text.

rates (both 86%) identical to those of control patients without PVT ($P=0.5$ and 0.2 for patient and graft survival, respectively) (Table 4; Fig. 5). Corresponding survival rates in grades 2, 3, and 4 PVT were not different among each other (P=NS) and were inferior to those of controls ($P<0.01$). When grouping grades 2–4 PVT cases together, overall 5-year patient and graft survival rates were 55% and 52%, respectively; this was lower than corresponding survival figures in control, non-PVT patients (84.2% and 76.3%), and this difference was highly significant ($P<0.0001$ and $P<0.0004$, for patient and graft survival, respectively) (Fig. 5).

Analysis by era (2nd era vs. 1st era) showed significant improvement in 5-year patient survival rate in non-PVT patients (from 72% to 83%; $P=0.001$), in grade 1 PVT (from 53% to 100%; $P=0.006$), and an improvement, albeit not to a statistically significant extent in the combination of patients with grades 2 to 4 PVT (from 38% to 62%; $P=0.11$) (Fig. 6). As shown in Figure 6, patients with grade 1 PVT in the 2nd era continued to do as well as non-PVT patients ($P=0.12$); although results in patients with grades 2 to 4 PVT improved from the first to the 2nd era, these patients continued to be at higher risk for reduced 5-year survival rates, in comparison with controls ($P=0.0002$).

DISCUSSION

Fifteen years ago, LTx was considered technically not feasible in patients with PVT; in fact, Van Thiel et al. reported two operative deaths directly related to PVT (*1*). Shortly after that, however, Shaw reported successful LTx in the presence of PVT by using venous conduits to bypass the thrombotic segment (*13*). Since then, experience has been gained in various centers and a number of reports have emerged, indicating the feasibility of LTx even in the presence of PVT, by using various techniques, mainly low dissection of the recip-

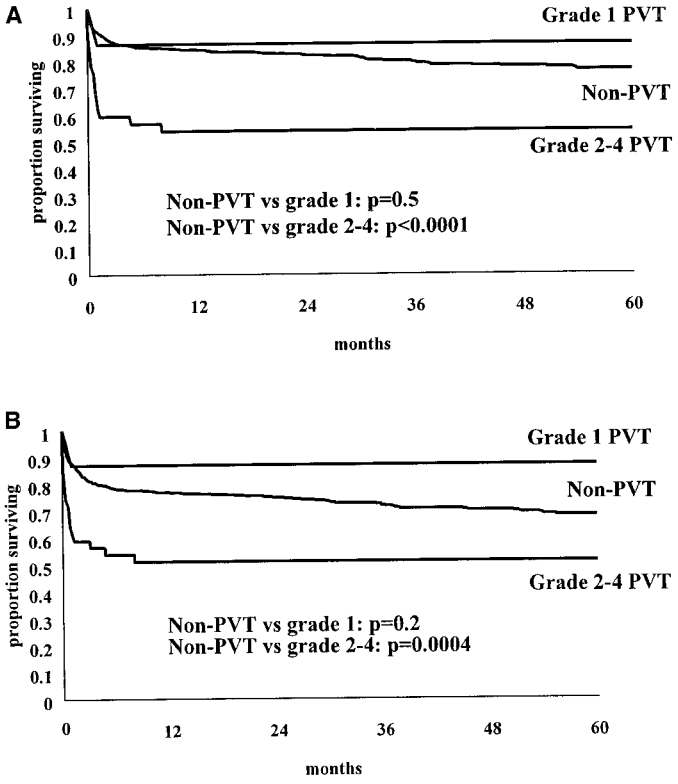

FIGURE 5. Overall (A) patient and (B) graft survival rates in non-PVT, grade 1 PVT, and combined grades 2–4 PVT patients (1987–1996).

ient PV, thrombectomy of the recipient PV, and interposition of venous graft between donor PV and recipient SMV (*3–8*). However, only few studies have looked in detail at the impact of PVT on LTx outcome, the risk factors for PVT, and the value of screening tools. Furthermore, those factors are likely to be influenced by the degree of PVT, a factor that has not been taken into account in previous studies.

The incidence of PVT in cirrhotic patients varies between 0.6% and 64.1%, depending on the diagnostic methods used and patient selection (*14–17*). The incidence of PVT in LTx series is usually lower, from 2.1% to 26%, partly because PVT has been seen as a relative contraindication to LTx (Table 1) (*3–8*, *18*, *19*). The incidence of PVT was 8.4% in our adult LTx series.

In our study, we found the following factors to be associated with PVT: male sex, previous treatment for portal hypertension (sclerotherapy, TIPS, shunt surgery, previous splenectomy), Child-Pugh class C, and alcoholic liver disease. Male sex correlated with PVT, but it is likely that alcoholic cirrhosis and not male sex accounts for that finding. The association between PVT and treatment for bleeding probably reflects the fact that patients with the most pronounced portal hypertension are more susceptible to developing PVT, probably because of the hemodynamic changes in the PV (low flow or reverse flow eventually predisposing to thrombosis). In support of that hypothesis is the observation that not only patients with variceal bleeds but also those with repeated episodes of encephalopathy and severe ascites are at risk for developing PVT (*3–8*). Budd-Chiari syndrome and hypercoagulable status have been associated with PVT; indeed, a preserved coagulation could trigger the development of PVT, particularly in the setting of a reduced or reverse flow. Prothrombotic states, such as the Leiden mutation of factor V, could promote development of PVT, but this was not studied in our series. Unlike others, we did not observe a correlation between cancer and PVT, probably because patients with PVT and liver tumors are excluded from LTx in our program, given their poor prognosis (*3–8*).

Imaging of the hepatic vasculature and, in particular, of the PV is a routine part of the pre-LTx evaluation. US usually is the initial diagnostic tool used because it is noninvasive, is rapidly available, is inexpensive, and provides reasonable accuracy in experienced hands. The reported efficiency of US in detecting PVT varies between 26% and 87%, indicating extreme variability owing to the high incidence of false negative results in different series (*3–8*, *18*). Efficiency of US depends not only on the expertise of the individual radiologist but also on the extent of PVT. For example, Chergui mentioned that all their patients with total PVT were correctly diagnosed before transplantation, as opposed to patients with partial PVT in whom US had generated many false negative results (*5*). However, Davidson reported failure of US in identifying PVT even in patients with intraoperatively confirmed totally occluded PV (*7*). It was then hypothesized that PVT may have developed in the pre-LTx period after the last US had been performed. It is, thus, essential to regularly repeat US studies in patients on the waiting list to keep from missing intercurrent development of PVT. Most of these aforementioned series are small and, therefore, not adequate to study the diagnostic efficiency of US in detecting various degrees of PVT. In our larger patient population, US was revealed to be an efficient pre-LTx screening tool. Overall sensitivity and specificity of 73% and 99% were superior to previously published results. It is important that US never failed to detect PVT in patients with no PV flow, that is, complete, grade 3 and 4 PVT. In those patients, sensitivity and specificity was 100%. Our data confirm the relatively higher incidence of false negative US results in patients with preserved PV flow, that is, incomplete grade 2 and particularly grade 1 PVT. In contrast, to previous hypotheses, we failed to document a relationship between the time from the last US to the LTx, and the rate of false-negative US results (data not shown). We must emphasize, however, that our policy is to repeat US frequently while patients are on the waiting list, in particular in those whose clinical condition suddenly deteriorates (an event that can be precipitated by PVT). In all the "missed" PVT, the thrombus was in fact incomplete with partially preserved PV flow. Surgically, this underdetection of PVT had only little impact, because those mild forms of PVT could always be dealt with by using simple surgical techniques.

An angiogram is an essential element in the detailed investigation of patients with a US diagnosis of PVT for the following reasons. First, as demonstrated in this series, an angiogram rules out a false-positive US result. This is crucial because an erroneous pre-LTx diagnosis of PVT may falsely overestimate the particular risk of individual patients. Fortunately, the incidence of false positive US results is low (13%). There is a possibility that those false-positive US results correspond to the recanalization of a previously thrombosed PV, but we did not find any stigmata of that at surgery. The availability of i.v. US contrast agents can allow

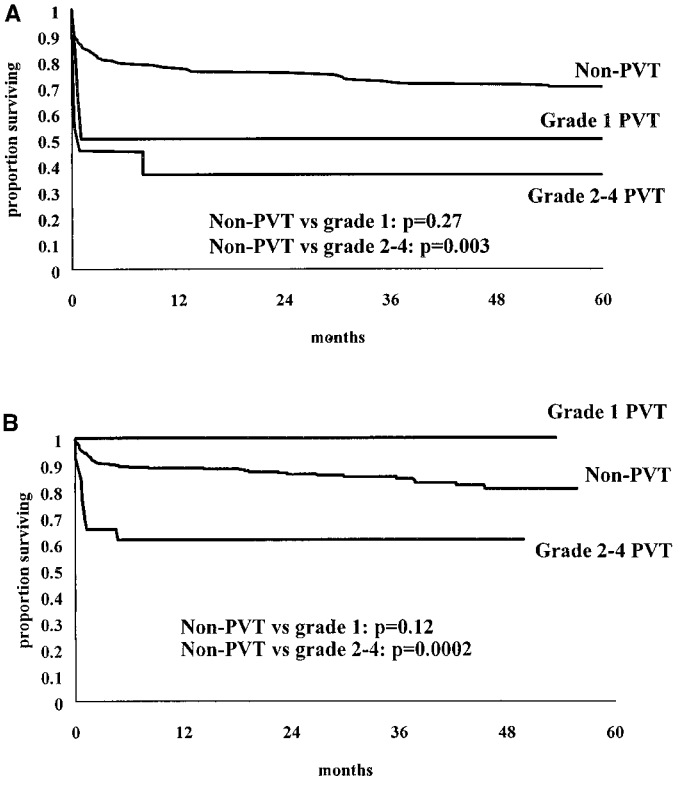

FIGURE 6. Survival of non-PVT patients, grade 1 PVT patients, and combined grades 2–4 PVT patients according to the era. (A) 1st era, 1987–1991. (B) 2nd era, 1992–1996.

the demonstration of portal vein flow when the conventional and color Doppler examination shows no flow. Such a use of US contrast agent could avoid the need for an angiogram or MRI angiogram when there is a false positive US diagnosis of portal vein thrombosis. Second, in contrast to US, an angiogram better delineates the severity, the extent, and the precise location of the intraportal thrombus and it can provide invaluable information regarding the patency of the splenic-SMV junction, the distal SMV, and possible venous collaterals that could be used as inflow vessels. An angiogram, therefore, is required to distinguish grade 1 from grade 2, and grade 3 from grade 4 PVT. This distinction is not just academic but also clinically relevant because various forms of PVT require different surgical strategies (see below). It is for that reason that for patients with an in-surgery "unexpected" diagnosis of PVT, intraoperative angiograms have been recommended by some (*3*).

The indication for an angiogram in LTx candidates varies between centers. Several units like ours reserve the angiogram only for those patients with a US diagnosis of PVT (*4*), whereas, others use it more liberally, even in patients with no US evidence of PVT but just reduced PV flow (*5*, *7*, *18*). Some centers even perform routine angiograms in all prospective LTx candidates. We believe that the most rational and cost effective approach is to perform an angiogram only in patients with a US diagnosis of PVT, providing that screening US is performed by experienced radiologists and that the incidence of false negative results is low and limited to mild forms of PVT. With multidimensional scanning ability, MRA can accurately detect portal-splenic-SMV abnormalities (*20–22*). In our experience, MRA was as accurate as an angiogram in grading PVT. In contrast to the conventional angiogram, MRA is noninvasive and can be safely performed in patients with renal impairment. Subject to availability, it is now our current practice to perform MRI rather than the conventional angiogram to evaluate the PV and PVT in LTx candidates when US is not sufficient.

Management options to revascularize the liver graft in patients with PVT range from low dissection of the PV or even the splenic-SMV bifurcation, to thrombectomy, venous grafting procedures, or use of PV collaterals (*3–8*, *18*, *19*). Most patients with incomplete PVT can successfully undergo LTx if simple operative maneuvers are used. PVT frequently starts intrahepatically and extends downward to the proximal PV. A well-preserved segment of PV without thrombosis can often be reached near the pancreas in most patients with mild PVT, and this segment can safely be used for PV anastomosis. In the large majority of our patients with grade 1 PVT (87.5%) and in 13% of patients with grade 2 PVT, this technique alone was sufficient to provide adequate portal revascularization. If the thrombus extends lower behind the pancreas into the splenic-SMV bifurcation and SMV, then the surgical technique depends on the severity/extent of the thrombus. In grades 1 and 2 patients with totally patent SMV, the thrombectomy is the procedure of choice, provided that sufficient blood flow can be reestablished. Often a combination of low dissection and thrombectomy is needed.

In patients with proximally occluded, but distally open, SMV (grade 3), we did not attempt low dissection and thrombectomy of the retropancreatic PV for fear of causing bleeding and pancreatitis (*4*). In those cases, we concur with Stieber, Langnas, and Gayowski on having a low threshold to use donor iliac vein grafts, and we directly proceeded with dissection of the distally patent SMV segment (*3*, *4*, *18*). In one patient, the donor PV was sufficiently long to reach the SMV. There has been concern that local left-sided portal hypertension may persist after construction of mesoportal conduits (*23*). However, this has not been observed in patients in this and other centers who received a bridge graft to the distal SMV (*3–8*, *18*).

Management options in patients with extremely extensive grade 4 PVT depends on the presence of a splanchnic collateral that can provide an adequate outflow for the portal system and which is not too distant from the liver hilum (*3*, *12*). In 6 of 10 of our grade 4 patients, we found such a collateral and all pre-LTx angiograms performed had successfully documented these collateral vessels. This re-emphasizes the importance of pre-LTx mapping of the PV system in planning the surgical procedure. Five of these six patients are still alive and well with normal graft function. However, all of the four other patients in whom no suitable collateral vessel was identified at the time of LTx and in whom only thrombectomies were attempted, died within 30 days after LTx. It is for this subgroup of patients identified by a pre-LTx angiogram that the technical feasibility and outcome of LTx remain questionable. However, Stieber reported successful outcomes in 5 similar patients after extensive thrombectomies (*3*). In similar cases of complete thrombosis of the PV system, arterialization of PV flow using donor splenic artery and cavoportal hemitransposition have been performed with success in a few patients (*3*, *24*, *25*). Combined liver-intestine transplantation is another possible alternative.

The use and type of veno-venous bypass in patients with PVT is dependent on the extent of PVT. In mild forms of PVT, full bypass using the thrombectomized PV is possible, provided that the PV is suitable and that special care is taken during the introduction of cannulae. In patients with a fragile PV, the inferior mesenteric vein can be used if bypass is to be used. It should be noted that in patients having totally occluded PVs, a portal bypass is not necessary and only a caval bypass can be safely used as an adaptation for the lack of portal vein flow that has already occurred.

In this series, and consistent with others, blood transfusion requirements were higher in patients with PVT, reflecting the more complex surgery in those patients having severe portal hypertension (*3*, *4*, *8*, *26*). Blood transfusion in both PVT and non-PVT patients decreased significantly from the first to the second era, a finding in accordance with Seu and reflects experience and refinement in surgical technique and hemostasis (*8*). In contrast to the literature, overall duration of surgery (6 hr) was not higher in PVT patients in our series. With more experience, duration of surgery was further reduced, from 6 hr during the 1st era to 5 hr during the 2nd era, only in control patients without PVT. It is interesting that the warm ischemia time of the graft was not influenced by PVT. This reflects the fact that vessels used to re-establish flow (e.g., native PV, iliac vein conduit) were prepared before graft implantation so that it did not prolong the anhepatic period.

The rate of post-LTx hepatic artery thrombosis, relaparatomy, and postoperative pancreatitis was similar in PVT and controls. Pancreatitis caused by extended retropancreatic dissection has been reported but occurred in only one of our 63 patients, probably because retropancreatic dissection was systematically avoided (*3*, *4*). There was a trend for more infectious complications and a significant increase in renal failure and dialysis requirement in PVT patients, particularly in advanced grades of PVT; this probably reflects the fact that these are more fragile patients who undergo more complex surgery with higher blood transfusion requirements. Similar to Shaked, we found a higher incidence of primary nonfunction and dysfunction in PVT patients, again particularly in higher grades of PVT (Table 1). This does not result from a prolonged warm ischemia time, because the warm ischemia time was identical in PVT and controls. Because we did not routinely measure PV blood flow, we cannot rule out that some degree of portal hypoperfusion may have contributed to liver graft dysfunction in some cases. However, we believe that the increased rate of liver dysfunction is multifactorial in origin and mostly reflects the fact that LTx in PVT patients is a complex surgical procedure associated with difficult dissections, and higher blood loss in fragile patients with severe portal hypertension (*8*, *18*, *26*).

Rethrombosis of the PV has occurred in only 5% of our PVT patients, which compares favorably with the literature where rethrombosis rates of up to 28% have been reported (Table 1). No anticoagulation was used. Aspirin, low molecular weight heparin, dextran, and coumadin derivatives have been used by others, but the role of these prophylactic measures remains unclear (*6*, *8*). We believe that, with the exception of those patients with hypercoagulable states, systemic anticoagulation is not mandatory. Indeed, the primary etiologic factor of PVT (elevated intrahepatic resistance and portal hypertension) is cured once the cirrhotic liver is replaced. Rethrombosis of the PV after LTx carries a bad prognosis, and mortality of rethrombosis in our series was 100%. However, a few case reports of successful outcome have been published, using thrombectomy, splenorenal shunt, reLTx or even conservative management (*7*).

It is thus apparent from our experience and that of others that LTx candidates with PVT are more prone to develop severe perioperative complications (*8*, *18*, *26*) (Table 1). First, PVT patients undergo more complex surgery (longer surgery, higher transfusion requirements) and these factors are known to negatively influence outcome (*4–8*). Second, most of these patients are more fragile than the average LTx candidate. In particular, most of our patients with PVT were Child-Pugh class C (data not shown). It is thus important to stress that the increased perioperative morbidity-mortality in these patients reflects not only the technical difficulty, but also the more critical status of those patients.

The overall 5-year patient survival in PVT patients (65.6%) was lower than in non-PVT patients (76.3%). It is interesting that 1-year and 5-year survival in PVT patients was identical, reflecting that those patients, once they have survived the perioperative period, enjoy long term survival that is identical to that of non-PVT patients, and irrespective of the PVT grade. We further analyzed survival rates according to the severity of PVT, and we found that patients with minimally thrombosed PV (grade 1) can undergo transplantation successfully, with results identical to those achieved in patients without PVT. Only more severe forms of PVT (grades 2–4) negatively influence outcome. Finally, experience in the management of these challenging patients is crucial. As described above, patients operated on during the second era had less bleeding, shorter operative times, and reduced in-hospital mortality, and this resulted in improved short-term and long-term survival.

In conclusion, the incidence of PVT in LTx candidates at our center is 8.4%. Risk factors for PVT include: male sex, previous treatment for portal hypertension, previous splenectomy, Child-Pugh class C, and alcoholic liver disease. In experienced hands, US is an efficient screening tool to detect PVT, particularly advanced forms with complete obstruction and interrupted venous flow. Positive US should be completed by further imaging. An angiogram, albeit invasive, rules out the rare false positive US diagnosis, and defines the grade of PVT, thereby allowing better surgical strategy in advance. The degree of PVT influences outcome and dictates the surgical strategy to be used, lower dissection and thrombectomy in grades 1 and 2, an iliac vein graft in grade 3, and a PV tributary in grade 4; absence of such a tributary is associated with very poor outcome. The degree of PVT influences the results, not only because of the technical difficulties, but also because of the severity of liver disease for which PVT is a surrogate. Grade 1 PVT patients do as well as non-PVT patients, irrespective of the era, whereas grades 2–4 patients have higher perioperative complications and reduced long-term survival. With increased experience results, of LTx in PVT patients have improved and, even in severe forms of PVT, a 5-year survival rate superior to 60% can now be achieved.

Acknowledgments. The authors are grateful to Mrs. Lydia Coolen for preparation of the manuscript, and to Mr. Frank Van Gelder for the illustrations.

REFERENCES

1. VanThiel DH, Schade RR, Starzl TE, et al. Liver transplantation in adults. Hepatology 1982; 2: 637.
2. VanThiel DH, Schade RR, Gavaler JS, Shaw BW, Iwatsuki S, Starzl TE. Medical aspects of liver transplantation. Hepatology 1984; 4: 795.
3. Stieber AC, Zetti G, Todo S, et al. The spectrum of portal vein thrombosis in liver transplantation. Ann Surg 1990; 213: 199.
4. Langnas AN, Marujo WC, Stratta RJ, et al. A selective approach to preexisting portal vein thrombosis in patients undergoing liver transplantation. Am J Surg 1992; 163: 132.
5. Cherqui D, Duvoux C, Rahmouni A, et al. Orthotopic liver transplantation in the presence of partial or total portal vein thrombosis: problems in diagnosis and management. World J Surg 1993; 17: 669.
6. Gonzalez EM, Garcia IG, Sanz RG, Pinto IG, Segurola CG, Romero CJ. Liver transplantation in patients with thrombosis of the portal, splenic or superior mesenteric vein. Br J Surg 1993; 80: 81.
7. Davidson BR, Gibson M, Dick R, Burroughs A, Rolles K. Incidence, risk factors, management, and outcome of portal vein abnormalities at orthotopic liver transplantation. Transplantation 1994; 57: 1174.
8. Seu P, Shackleton CR, Shaked A, et al. Improved results of liver transplantation in patients with portal vein thrombosis. Arch Surg 1996; 131: 840.
9. Mirza DF, Gunson BK, Da Silva RF, Mayer AD, Buckels JA, McMaster P. Policies in Europe on "marginal quality" donor livers. Lancet 1994; 344: 1480.
10. McMaster P, Mirza D. Optimal use of cyclosporin A in liver transplantation. Transplant Proc 1994; 26: 2662.
11. Mirza DF, Gunson BK, McMaster P. Liver transplantation in Birmingham: indications, results, and changes. Clin Transpl 1996; 217.
12. Czerniak A, Badger I, Sherlock D, Buckels J. Orthotopic liver transplantation in a patient with thrombosis of the hepatic, portal and superior mesenteric veins. Transplantation 1990; 50: 334.
13. Shaw BW Jr, Iwatsuki S, Bron K, Starzl TE. Portal vein grafts in hepatic transplantation. Surg Gynecol Obstet 1985; 161: 66.
14. Belli L, Sansalone C, Aseni P, Romani F, Rondinara G. Partial thrombosis in cirrhotics: a retrospective analysis. Ann Surg 1986; 203: 286.
15. Okuda K, Ohnishi K, Kimura K, et al. Incidence of portal vein thrombosis in liver cirrhosis: an angiographic study of 708 patients. Gastroenterology 1985; 89: 279.
16. Chang HP, McFadzean AJS. Thrombosis and intimal thickening in the portal system in cirrhosis of the liver. J Pathol Bacteriol 1965; 89: 473.
17. Sarfeh IJ. Portal vein thrombosis associated with cirrhosis. Arch Surg 1979; 114: 902.
18. Gayowski TJ, Marino IR, Doyle HR, et al. A high incidence of native portal vein thrombosis in veterans undergoing liver transplantation. J Surg Res 1996; 60: 333.
19. Lerut JP, Mazza D, Leeuw VV, et al. Adult liver transplantation and abnormalities of splanchnic veins: experience in 53 patients. Transpl Int 1997; 10: 125.
20. Lewis WD, Finn JP, Jenkins RL, Carretta M, Longmaid HE, Edelman RR. Use of magnetic resonance angiography in the pretransplant evaluation of portal vein pathology. Transplantation 1993; 56: 64.
21. Nghiem HV, Freeny PC, Winter III TC, Mack LA, Yuan C. Phase-contrast MR angiography of the portal venous system: preoperative findings in liver transplant recipients. AJR 1994; 163: 445.
22. Nghiem HV, Winter TC, Mountford MC, et al. Evaluation of the portal venous system before liver transplantation. Value of phase contrast MR-angiography. AJR 1995; 164: 871.
23. Sheil AGR, Thompson JF, Stephen MS, Eyers AA, Graham JC, Bookallil MJ. Mesoportal graft for thrombosed portal vein in liver transplantation. Clin Transplant 1987; 1: 18.
24. Sheil AGR, Thompson JF, Stephen MS, et al. Donor portal vein arterialization during liver transplantation. Transplant Proc 1989; 21: 2343.
25. Tzakis AG, Kirkegaard P, Pinna AD, et al. Liver transplantation with cavoportal hemitransposition in the presence of diffuse portal vein thrombosis. Transplantation 1998; 65: 619.
26. Shaked A, Busuttil RW. Liver transplantation in patients with portal vein thrombosis and central portacaval shunts. Ann Surg 1991; 214: 696.

Received 3 June 1999.
Accepted 18 October 1999.