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ORIGINAL ARTICLE

# Ischemic-type biliary lesions: A leading indication of liver retransplantation with excellent results

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**KEYWORDS**
Liver retransplantation;
Ischemic-type biliary lesion;
Performance status;
Organ shortage

**Summary**
*Background:* Liver retransplantation (RLT) is the only life-saving treatment option for patients with a failing graft, but it remains a major challenge because of inferior outcomes and technical difficulties.
*Methods:* This study aimed to evaluate the outcomes of and risk factors for adult RLT in a single center, focusing on the etiology of graft failure. Between 1987 and 2011, 1592 liver transplants (LTs) and 143 RLTs (9%) were performed at our institution.
*Results:* The 1-, 5- and 10-year patient survival rates after RLT were 60%, 52% and 39%, and the graft survival rates were 55%, 46% and 32%. The 90-day mortality rate was 32%, mainly

*Abbreviations:* LT, liver transplantation; RLT, liver retransplantation; ITBL, ischemic-type biliary lesion; PNF, primary non-function; HAT, hepatic artery thrombosis; CMV, cytomegalovirus; MRI, magnetic resonance imaging; ERCP, endoscopic retrograde cholangio-pancreatography; ICU, intensive care unit.

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due to septic complications (45% of deaths). Ischemic-type biliary lesions (ITBL) were the leading indication for RLT (23%), and patient survival was significantly better in patients retransplanted for ITBL than for any other indication ($P < 0.02$). Indications other than ITBL ($P = 0.015$), the transfusion of more than 7 units ($P = 0.006$) and preoperative dialysis ($P = 0.005$) were the three parameters associated with poor survival after RLT.
*Conclusion:* Patients with ITBL benefit the most from elective RLT.


## Introduction

Liver transplantation (LT) has become an established therapy for end-stage liver disease, enabling one-year survival rates higher than 80% in experienced centers [1—3]. In the event of graft failure, liver retransplantation (RLT) is the only life-saving option, corresponding to 5% to 22% of total LT activity in most countries, including in Europe and the USA [1—3].

The results of RLT are significantly worse than those of primary LT: patient survival is 20% lower at both 1 and 5 years [3,4]. Because of the increasing shortage of liver grafts (about one graft for two potential recipients in most western countries), in-depth discussions are necessary in order to determine whether certain RLT subgroups might have a better prognosis and stronger indication than others, which could unfortunately be considered as ''futile'' indications for LT.

Although several series have been reported [1,3,5,6], outcomes as a function of indication are still poorly defined because of the lack of reports focusing on the postoperative and long-term outcomes of RLT. The principal late indications for RLT are recurrent liver diseases, currently dominated by HCV recurrence and ischemic-type biliary lesions (ITBL), whereas early indications remain primary graft non-function (PNF) and hepatic artery thrombosis (HAT). However, over time, PNF and HAT have become marginal indications for RLT, and recurrent hepatitis C is now easily cured using direct antiviral agents. It is therefore likely that ITBL will become the leading indication for RLT in the near future, and it is wise to determine whether it is a useful indication for RLT. This retrospective study of the experience of a single large center in Europe thus compared the respective results of different indications for RLT over three different periods, in terms of long-term patient and graft survival.

## Patients and methods

Between 1984 and 2011, a total of 1592 LTs were performed at Cochin and Saint-Antoine Hospitals in Paris (by the same surgical and medical teams). In this population, 143 RLTs (9%) were performed in patients > 16 years as from 1987 and were included in this retrospective analysis. Fourteen patients had initially been transplanted in childhood (age < 16) and undergone a subsequent RLT in adulthood. All patients received a full-size organ, except for four patients who received full left liver grafts, with one from a living-related donor. There were no non-heart beating donors in this series. The three periods studied ran from 1987 to 1994 (P1), from 1995 to 2004 (P2) and from 2005 to 2011 (P3).

Pre-, intra- and postoperative data on the recipient were collected regarding age, gender, blood group (recipient and graft), cytomegalovirus (CMV) status, immunosuppression prior to RLT, graft type, transfusion requirements, veno-venous bypass, preoperative dialysis or mechanical ventilation, cold ischemia time, technical aspects (types of caval, portal, arterial and biliary anastomoses) and postoperative complications (arterial, portal, caval, biliary and digestive). The donor data analyzed included age, gender, blood group and CMV status. Surgical techniques in LT and RLT have undergone several changes over time. The piggyback technique for caval anastomosis has been used by our team since 1995. A temporary end-to-side portocaval shunt is widely performed during transplantation, except for recipients with significant spontaneous shunts. End-to-end portal, arterial and biliary anastomoses are subsequently performed. Veno-venous bypass is used in the event of difficult dissection, unstable patients in the case of cava replacement, and in the absence of spontaneous shunts and hemorrhage in the context of portal hypertension.

The medical management of transplant recipients has also evolved over time. Before 1995, patients received cyclosporine, while after that time, their immunosuppressive therapy included tacrolimus and mycophenolate mofetil. Throughout the study period, the basic immunosuppressive regimen included low doses of prednisolone that were tapered and usually discontinued 6 months after RLT, except in patients with autoimmune liver disease (receiving prednisone 5 mg/d lifelong). Doses were adapted to maintain blood levels of cyclosporine between 100 and 300 ng/mL and of tacrolimus between 8 and 15 ng/mL. Patients who were CMV-positive prior to RLT, or CMV-negative patients receiving a CMV-positive graft, were administered CMV prophylaxis (aciclovir until 2000, ganciclovir until 2005 and then valganciclovir), which was maintained for 3 or 6 months in the absence of any contraindications or confirmed ongoing clinical CMV infection. Since 2008, all patients have routinely received acetylsalicylic acid (100 mg/d) to prevent arterial thrombosis as soon as their platelet count reaches $50 \times 10^9$/L, in the absence of any hemorrhagic manifestations.

The diagnosis of ITBL was based on non-anastomotic intrahepatic bile duct strictures, patency of the hepatic artery and repeated episodes of cholangitis without histological signs of recurrent PSC or rejection. New diagnostic

tools such as magnetic resonance imaging (MRI) and endoscopic retrograde cholangio-pancreatography (ERCP) have become available over time and enabled the more detailed diagnosis and management of vascular and biliary abnormalities during LT follow-up. The diagnosis of ITBL by means of recent non-invasive and endoscopic methods has certainly contributed to a more precise definition of this emerging indication.

The MELD score was introduced in France in 2007. Liver graft allocation was initially managed between 1994 and 2004 using a center-based national allocation system. As from 2004, liver graft allocation was based on a national nominal waiting list. Exceptional national priority is given to candidates presenting with primary non-function (PNF) or hepatic artery thrombosis (HAT) during the first seven days after their initial LT. After these seven days, the allocation of liver grafts to RLT candidates follows the same rules as those which apply to candidates for primary LT [7].

## Statistical analysis

For the present study, categorical variables were compared across samples using the chi-squared test, while quantitative variables were compared using the Wilcoxon test. Overall survival was defined using the time elapsing between the first RLT and death. Graft survival was defined as the time from the first RLT to death or the second RLT, whichever occurred first. Patients alive after RLT were censored for death at the time of the last news on their case. A Kaplan-Meier analysis was used to estimate survival. The Cox proportional hazard model was used to test for the influence of co-variables on survival. For comparisons of survival as a function of the indications for RLT or the severity of the recipients, we used the Bonferroni-Hochberg method to adjust for multiple comparisons (six comparisons). Multiple imputation was used for missing variables. All reported *P*-values are two-sided. We concluded a significant difference at *P*-values smaller than 0.05. All computations were performed using R software.

## Results

### Study population

Among the study population of 143 patients over 16 years that were retransplanted, representing 9% of our activity, there were 93 men and 50 women, with a median age of 45 years (IQR [32, 53]). Twelve patients underwent a second RLT, and two a third RLT. Eight retransplanted patients received combined liver-kidney transplants. The median required volume of intraoperative PRBCs was 7 units (range: 0 to 145 units). The mean cold ischemia time did not change significantly over time.

The indications for primary LT and RLT are detailed in Table 1. The characteristics of the principal indications are summarized in Table 2. We examined different periods (P1, P2, P3) and some significant changes occurred over time, as summarized in Table 3. The donors were significantly older in P3, with a median age of 37 years in P1 compared to 46 years in P3 ($P = 0.02$). The indications for RLT changed over time, with primary non-function (PNF) decreasing from 31% in P1 to 12% in P3, and ITBL increasing from 10% in P1 to 29% in P3 ($P = 0.016$). Consequently, in P1, the median time elapsing between LT and RLT was 14 days (range: 5 to 161 days), while in P2 it was 132 days (range: 12 to 852 days), and in P3 228 days (range: 21 to 3649 days) ($P < 0.001$).

Immunosuppressive regimens prior to RLT have changed over time. Cyclosporine A was given to 46% of LT recipients during P1, while standard triple immunosuppressive therapy based on prednisone, mycophenolate mofetil and tacrolimus was used in 72% of recipients during P3 (Table 3). Surgical techniques for LT and RLT have also evolved over

**Table 1** Indications for primary LT and RLT.

| Indications for primary LT | *n* | % |
|---|---|---|
| Hepatitis C cirrhosis | 28 | 20 |
| Hepatocellular carcinoma | 24 | 17 |
| On viral B disease | 6 | |
| On viral C disease | 6 | |
| On alcohol-related liver disease | 8 | |
| On cryptogenic liver disease | 4 | |
| Biliary disease | 22 | 16 |
| Primary sclerosing cholangitis | 7 | |
| Primary biliairy cirrhosis | 1 | |
| Biliary atresia | 7 | |
| Byler's disease | 5 | |
| Alagille disease | 1 | |
| Histiocytosis | 1 | |
| Alcohol-related cirrhosis | 22 | 15 |
| Hepatitis B cirrhosis | 12 | 8 |
| Fulminant hepatitis | 9 | 6 |
| Metabolic liver disease | 8 | 5 |
| Cystic fibrosis | 3 | |
| Wilson's disease | 2 | |
| Type IV glycogenosis | 1 | |
| $\alpha$1-antitrypsin deficiency | 1 | |
| Proprionic acidemia | 1 | |
| Other | 15 | 12 |
| Metastasis | 5 | |
| Hemangioendothelioma | 2 | |
| Amyloid neuropathy | 1 | |
| Toxic | 1 | |
| Cryptogenic | 6 | |
| Autoimmune cirrhosis | 3 | |
| Indications for RLT | | |
| Ischemic type biliary lesion (ITBL) | 33 | 23 |
| Hepatic artery thrombosis (HAT) | 25 | 17 |
| Primary non function (PNF) | 29 | 20 |
| Chronic rejection | 24 | 17 |
| Recurrent disease | 11 | 8 |
| Other | 21 | 15 |
| Hyperacute rejection | 1 | |
| Portal thrombosis | 2 | |
| Necrotic graft | 3 | |
| Acquired hepatitis B cirrhosis | 2 | |
| Undetermined cirrhosis | 4 | |
| Intrahepatic lymphoma | 2 | |
| Acute Budd-Chiari Syndrome | 2 | |
| Nodular regenerative hyperplasia | 1 | |
| Unknown | 4 | |

**Table 2** Characteristics of the patients according to the indication for RLT.

| *n* = 143 | ITBL (*n* = 33) | PNF (*n* = 29) | HAT (*n* = 25) | Rejection (*n* = 24) | Recurrence (*n* = 11) | Other (*n* = 21) |
|---|---|---|---|---|---|---|
| *Gender F/M* | 11/22 | 14/15 | 6/19 | 6/15 | 5/6 | 8/13 |
| *Mean age at LT [yrs]* | 37 ± 17 | 45 ± 12 | 40 ± 15 | 35 ± 18 | 48 ± 13 | 40 ± 19 |
| *Mean age at RLT [yrs]* | 41 ± 14 | 45 ± 12 | 40 ± 14 | 39 ± 14 | 50 ± 14 | 46 ± 12 |
| *Interval LT-RLT [yrs]* | 3,9 ± 5,9 | 0,03 ± 0,08 | 0,44 ± 1,4 | 3,4 ± 5,0 | 2,13 ± 2,2 | 6,4 ± 8,5 |
| *Follow-up after RLT [yrs]* | 5.4 ± 4.9 | 3.9 ± 5.4 | 5.2 ± 6.1 | 4.0 ± 5.6 | 1.9 ± 4.0 | 1.6 ± 2.7 |
| *Mortality at 90 days* | 9% (3) | 45% (13) | 32% (8) | 29% (7) | 55%(6) | 43% (9) |
| *Mean donor age* | 41 ± 14 | 39 ± 15 | 36 ± 16 | 43 ± 18 | 49 ± 17 | 46 ± 19 |
| *Donor CMV+* | 51% (17) | 48% (14) | 36% (9) | 37% (9) | 18% (2) | 47% (10) |
| *Initial disease* | | | | | | |
| Autoimmune cirrhosis | 3% (1) | 3% (1) | 4% (1) | 0% (0) | 0% (0) | 0% (0) |
| Hepatocellular carcinoma | 12% (4) | 14% (4) | 16% (4) | 12% (3) | 27% (3) | 29% (6) |
| Hepatitis B cirrhosis | 6% (2) | 10% (3) | 8% (2) | 12% (3) | 9% (1) | 5% (1) |
| Hepatitis C cirrhosis | 12% (4) | 17% (5) | 16% (4) | 29% (7) | 45% (5) | 14% (3) |
| Alcohol-related cirrhosis | 15% (5) | 21% (6) | 16% (4) | 12% (3) | 0% (0) | 19% (4) |
| Fulminant hepatitis | 3% (1) | 7% (2) | 4% (1) | 8% (2) | 9% (1) | 10% (2) |
| Metabolic liver disease | 12% (4) | 0% (0) | 4% (1) | 4% (1) | 0% (0) | 5% (1) |
| Biliary disease | 24% (8) | 7% (2) | 24% (6) | 17% (4) | 9% (1) | 10% (2) |
| Other | 12% (4) | 21% (6) | 8% (2) | 4% (1) | 0% (0) | 10% (2) |
| *Dialysis before RLT* | 6% (2) | 28% (8) | 12% (3) | 8% (2) | 18% (2) | 33% (7) |
| *Ventilation before RLT* | 9% (3) | 72% (21) | 28% (7) | 12% (3) | 18% (2) | 38% (8) |
| *Transfusion during RLT (packed red blood cells)* | 11.4 ± 13.7 | 7.3 ± 4.7 | 16.7 ± 33.4 | 10.5 ± 7.9 | 17.4 ± 10.6 | 13.9 ± 15.8 |

time (Table 3). Classic end-to-end caval anastomosis was performed in all recipients during the early years of our experience, and the piggyback technique with side-to-side caval anastomosis was performed in almost one third of our patients in recent years (Table 3). Biliary anastomosis was performed with a Roux-en-Y loop in 48% of cases (*n* = 69), and duct-to-duct anastomosis in 30% (*n* = 44). An arterial conduit on the aorta for arterial reconstruction was performed in 39% of all cases (*n* = 47). A veno-venous bypass was required during RLT in 39% of recipients (*n* = 47).

## Morbidity and mortality

Recipient survival rates after RLT were 60%, 52%, and 39% at 1 year, 5 years and 10 years, respectively, while graft survival were 55%, 46% and 32% at 1 year, 5 years and 10 years, respectively (Fig. 1). Survival rates at 1, 5 and 10 years as a function of the different indications were 91%, 83% and 56%, respectively, for ITBL; 63%, 48% and 48% for chronic rejection; 56%, 56% and 41% for HAT; 44%, 37% and 32% for PNF; 36%, 24% and 24% for recurrent disease, and 56%, 43% and 34% for other indications (Fig. 2). Regarding the different indications for RLT, survival was significantly better in patients retransplanted for ITBL than in those who were retransplanted for any other indication ($P < 0.05$, adjusted for multiple testing). The mean time elapsing between LT and RLT was 2.7 ± 5.2 years, with intervals ranging from a minimum of 0.4 ± 1.4 years for HAT to a maximum of 3.9 ± 5.9 years for ITBL (Table 2). Follow-up for the different indications after RLT is given in Table 3.

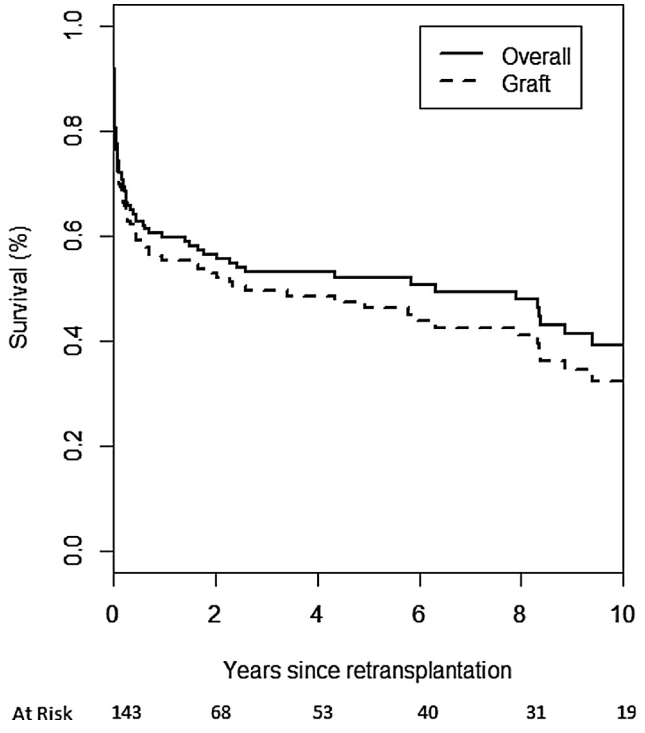


**Figure 1** Overall and graft survival (Kaplan-Meier analysis) after RLT.

**Table 3** Evolution over time of the characteristics of the patients at and after RLT.

| | *n* | P1 (1987—1994) *n* = 48 | P2 (1995—2004) *n* = 43 | P3 (2005—2011) *n* = 52 | *P* |
|---|---|---|---|---|---|
| Mortality at 90 days | 143 | 36% | 28% | 33% | NS |
| Mortality at 1 year | 143 | 46% | 33% | 42% | NS |
| Mortality at 5 years | 143 | 59% | 35% | 48% | NS |
| Donor age (median, years, interval) | 131 | 37 (23—51) | 40 (23—57) | 46 (30—62) | 0.02 |
| Donor CMV positive | 114 | 16 (55%) | 20 (54%) | 25 (52%) | NS |
| Recipient CMV positive | 119 | 30 (86%) | 25 (69%) | 34 (71%) | NS |
| Median cold ischemia time (min) | 139 | 551 (320—782) | 580 (430—730) | 501 (344—658) | 0.09 |
| Interval between LT and RLT (days) | 143 | 14 (5—161) | 132 (12—852) | 228 (21—3649) | < 0.001 |
| Indications for RLT | 143 | | | | 0.016 |
| ITBL | 33 | 5 (10%) | 13 (30%) | 15 (29%) | |
| PNF | 29 | 15 (31%) | 8 (19%) | 6 (12%) | |
| HAT | 25 | 9 (19%) | 10 (23%) | 6 (12%) | |
| Rejection | 24 | 11 (23%) | 6 (14%) | 7 (13%) | |
| Recurrence | 11 | 4 (8%) | 0 | 7 (13%) | |
| Other | 21 | 4 (8%) | 6 (14%) | 11 (21%) | |
| Biliary anastomosis | 123 | | | | 0.05 |
| Roux-in-Y | | 29 (78%) | 25 (64%) | 25 (53%) | |
| Duct-to-duct | | 8 (22%) | 14 (36%) | 22 (47%) | |
| Caval anastomosis | 126 | | | | 0.003 |
| End-to-end | | 37 (100%) | 32 (80%) | 35 (71%) | |
| Piggyback | | 0 | 8 (22%) | 14 (29%) | |
| Immunosuppressive regimen | 98 | | | | 0.001 |
| Ciclosporine | | 12 (46%) | 6 (18%) | 9 (23%) | |
| Tacrolimus | | 2 (8%) | 22 (67%) | 28 (72%) | |
| Other | | 12 (46%) | 5 (15%) | 2 (5%) | |

NS: not significant.

The overall 90-day mortality rate was 32% (*n* = 46). The lowest rate was 9% for patients retransplanted for ITBL and the highest rates were 55% and 45% for patients retransplanted for recurrent primary disease and PNF, respectively (Table 2). There was no significant difference in this mortality rate over the different time periods (Table 3). Nearly half of these deaths (48%) occurred within 7 days of RLT, 30% within 8 to 30 days and 22% within 30 to 90 days. The main causes of death were bacterial infections in 33% of cases (*n* = 15), fungal infections in 11% (*n* = 5) and hemorrhage in 13% (*n* = 6). Multi-organ failure occurred in 13% of the patients (*n* = 6), and heart failure or brain death in 11% (*n* = 5). Two hemodynamically unstable patients died intraoperatively (4%) from reperfusion syndrome. Seven patients (15%) died for miscellaneous other reasons. The mortality rates at 1 year and 5 years over the three study periods were 46% and 59% in P1, 33% and 35% in P2 and 42% and 48% in P3, without significant difference over time (Table 3).

## Prognostic factors

Multiple preoperative and intraoperative donor and recipient factors were tested under univariate and multivariate analyses to identify their influence on patient outcomes (Table 4). None of the following was found to exert any significant influence on survival: time interval to RLT, donor-recipient gender mismatch, donor age > 40 years, cold ischemia time > 12 h, mechanical ventilation prior to RLT, use of veno-venous bypass and duration of RLT. Under univariate analysis, we found that etiologies other than ITBL, such as positive CMV status in a donor or recipient, preoperative dialysis and the intraoperative transfusion of more than 7 units of PRBCs, were associated with impaired survival (Table 4). Under multivariate analysis, only preoperative dialysis and the intraoperative transfusion of more than 7 units of PRBCs were found to be independent factors for survival.

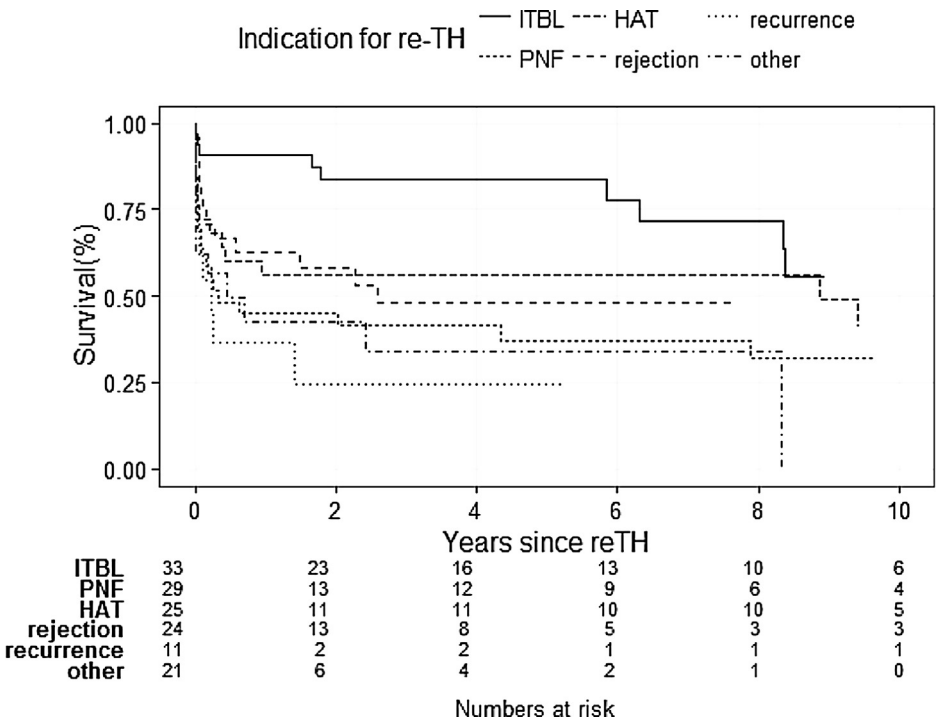


**Figure 2** Kaplan-Meier survival analysis according to the etiology of RLT.

**Table 4** Univariate and multivariate analyses of factors influencing survival after RLT.

| Patient characteristics | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *P* | Hazard ratio | | *P* |
| Time to first RLT | | | 0.26 | – | | |
| > 90 days | 1 | | | | | |
| 8 to 90 days | 1.3 | | | | | |
| < 7 days | 1.6 | | | | | |
| Donor-recipient Sex mismatch | 1.5 | [0.95, 2.3] | 0.08 | – | | |
| Donor age > 40 y | 1.0 | [0.6,1.7] | 0.88 | – | | |
| CMV + (R or D) | 3.5 | [1.1, 11.3] | 0.04 | – | | |
| Ventilation | 1.6 | [0.96, 2.7] | 0.07 | – | | |
| Red blood cell transfusion (> 7 units) | 2.0 | [1.2, 3.4] | 0.006 | 1.7 | 1.1, 2.7 | 0.02 |
| Cold ischemia (> 12 h) | 1.2 | [0.7, 2.1] | 0.56 | – | | |
| Veno-venous bypass | 1.5 | [0.9, 2.4] | 0.09 | – | | |
| Dialysis | 2.4 | [1.3, 4.2] | 0.005 | 1.9 | 1.1, 3.1 | 0.02 |
| Time period | | | 0.22 | – | | |
| 1987 to 1994 (P1) | 1 | | | | | |
| 1995 to 2004 (P2) | 0.6 | | | | | |
| 2005 to 2011 (P3) | 0.7 | | | | | |
| Indication for RLT | | | 0.015 | – | | |
| ITBL | 1 | | | | | |
| HAT + PNF | 2.0 | | | | | |
| Others | 2.5 | | | | | |

The MELD score was only introduced in France in 2007 and was therefore not available for the majority of the patients covered by this study. To investigate the performance status of the RLT candidates in different indications, we used the percentage of patients who were intensive care unit (ICU)-bound and required mechanical ventilation or dialysis prior to RLT (Tables 2 and 3). The survival was significantly reduced in those patients, when compared to those not ICU-

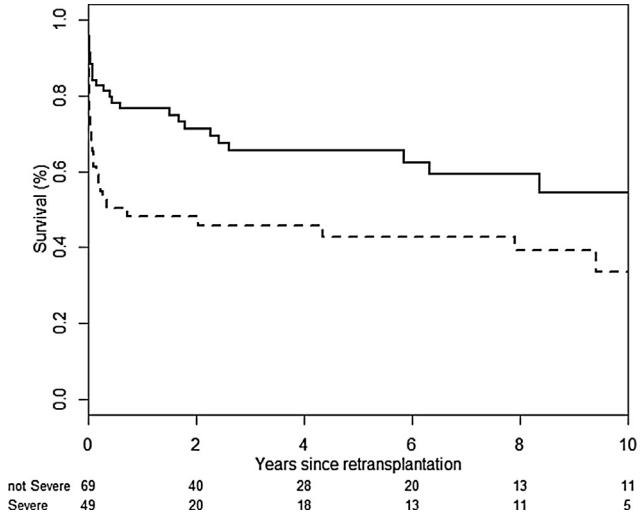


**Figure 3** Kaplan-Meier survival analysis according to initial severity (severe: dialysis and/or ventilation, dashed vs. non severe, plain).

bound (Fig. 3), with survival at 90 days, 1 year and 5 years of 55%, 48% and 43% in ICU-bound patients vs. 83%, 77% and 66%, respectively, in the other patients ($P = 0.008$).

## Surgical complications

Half of the recipients (55%) presented at least one surgical complication after RLT (Table 5). The most frequent complications were biliary in 25% ($n = 36$) and arterial complications in 12.5% ($n = 18$). Twenty-one of the biliary complications (58%) occurred on a Roux-in-Y anastomosis. Eleven of the arterial complications (61%) occurred within 90 days of RLT. Four patients (22%) died within three months of onset of the complication, two from hemorrhage after arterial rupture and two others from a liver abscess. The proportion of arterial complications remained stable over the three time periods ($P = 0.71$). None of the following factors showed significant influence on the development of biliary or arterial complications: duration of cold ischemia time (> 12 h), donor age (> 40 years), positive donor CMV serology, presence or absence of transfusion, need or not for veno-venous bypass and type of biliary (duct-to-duct or Roux-in-Y) or arterial (hepatic artery or conduit on the aorta) anastomosis. No cases of arterial thrombosis have occurred after RLT since 2005. There were seven (5%) portal vein complications, five of which (71%) occurred more than three months after RLT (Table 5). Seven complications (5%) were seen to affect the vena cava. Three stenoses occurred more than 90 days after RLT and three thromboses occurred within 7 days of RLT. Postoperative bleeding occurred in 20 patients (14%), six of whom died. Thirteen patients (9%) presented with digestive complications, all requiring surgical management (Table 5).

## Discussion

Because the long-term results of RLT show inferior survival rates when compared with primary LT, organ allocation in the context of a growing graft shortage is a broad ethical issue. In this context, it has become crucial to select the best candidates for RLT. This retrospective but large study may help to define the best indications for RLT.

The patient and graft survival rates seen in this series were in line with recent findings in the literature [1—6]. In our series, the vulnerable condition of recipients before RLT was defined by the patients being hospital or ICU-bound because of dialysis or mechanical ventilation. Dialysis support prior to RLT was found to be a significant independent factor predictive of poor survival, as has previously been reported [3,4,8—11]. There remains an unanswered question as to whether kidneys should be allocated simultaneously to candidates for RLT with renal failure [12,13]. A risk score index has recently identified predictive factors associated with graft failure after RLT [3]. This index includes recipient factors such as age > 55 years, MELD score > 27, mechanical ventilation and serum albumin < 2.5 g/dL at the time of RLT. In addition, we found that a need for intraoperative transfusion was a strong independent predictive factor for impaired survival, most likely reflecting the technical complexity of RLT. The cut-off (> 7 units of PRBCs) was lower than those previously reported, indicating an improvement in the perioperative and surgical management of these patients [3]. In particular, the technical complexity of RLT was also highlighted by the frequent use of a veno-venous bypass. A temporary portocaval shunt was considered and performed whenever possible in order to maintain hemodynamic stability and avoid splanchnic congestion during graft implantation, as reported by other investigators [8,14].

We observed significant overall mortality (32%) during the early postoperative course after RLT with great differences among indications, ranging from 9% for ITBL candidates to 55% for recurrent disease. Bacterial and fungal sepsis was the main cause of death (45%) with incidences comparable to those in the literature, ranging from 46.3% to 62.2% [2,3,8,15]. We also saw important postoperative morbidity, with significant rates of biliary and arterial complications, as known from the literature [4,16]. However, it should be noted that after the introduction of acetylsalicylic acid as routine prophylaxis for all our recipients in 2005, we did not observe any arterial thrombosis following RLT. In contrast to the literature, we found that the type of biliary anastomosis (duct-to-duct versus Y-in-Roux) did not influence the rate of biliary complications after RLT [17]. A significant number of digestive complications were observed, affecting 9% of our patients. This high incidence therefore calls for special attention being paid to this type of complication among recipients in the context of RLT.

However, and in contrast with the literature, no influence on survival was found for variables such as donor age and donor-recipient gender mismatch [3,8,18], cold ischemia time [8] and the time to RLT [1]. Nor did we find any significant influence on post-RLT outcomes of the time elapsing between primary LT and RLT, which ranged from early (< 7 days), to intermediate (8—90 days) to late (> 90 days). Results in the recent literature are contradictory on this point [3—5]. The definitions of ''early'', ''late'', ''urgent'' or ''elective'' RLT vary considerably between authors, so that the results may not be entirely comparable.

Rather than the timing of RLT alone, the clinical condition of the RLT candidate and the actual indication for RLT

**Table 5** Surgical complications and treatments after RLT ($n = 143$).

| Type of complications | *n* | % | Treatment (*n*) |
|---|---|---|---|
| Biliary complications | 36 | 25 | |
| Type of anastomosis | | | |
| Roux-in-Y | 21 | 58 | |
| Stenosis | 25 | | Percutaneous dilatation (13), endoscopic stenting (7) Hepatico-jejunostomy (5) |
| Leakage | 7 | | Surgery (5), endoscopic stenting (2) |
| Other | 4 | | Surgery (4) |
| Arterial complications | 18 | 12.5 | |
| Type of anastomosis | | | |
| Arterial conduit on aorta | 8 | 44 | |
| Thrombosis | 11 | | Thrombectomy (4), local lysis and repeat anastomosis (4) Conservative (3) |
| Anastomotic stenosis | 5 | | Percutaneous angioplasty (3), repeat anastomosis (2) |
| Arterial rupture | 2 | | Embolization (1), surgery (1) |
| Venous complications | 14 | 10 | |
| Portal vein stenosis | 2 | | Percutaneous angioplasty (1), conservative (1) |
| Portal vein thrombosis | 5 | | Repeat anastomosis (1), conservative (4) |
| Vena cava stenosis | 3 | | Percutaneous angioplasty (3) |
| Vena cava thrombosis | 4 | | Conservative (4) |
| Intra-abdominal hemorrhage | 20 | 14 | All surgery (20) |
| Abdominal wall complications | 12 | 8 | All surgery (12) |
| Digestive complications | 13 | 9 | All surgery (13) |
| Colon perforation | 7 | | |
| Gastric perforation | 2 | | |
| Roux-in-Y loop perforation | 2 | | |
| Duodenal perforation | 1 | | |
| Small bowel volvulus | 1 | | |

may represent the most important clues to survival. This was suggested as early as in 1999 by a registry analysis [19], but the etiologies of RLT have dramatically changed since that time. The principal late indications for RLT were recently dominated by HCV recurrence and ischemic-type biliary lesions (ITBL), whereas early indications remain primary graft non function (PNF) and hepatic artery thrombosis (HAT). Over time, PNF and HAT have become marginal indications for LT, and recurrent hepatitis C is now easily cured direct-acting antiviral agents. This new therapy may indeed open the way towards a change in the management of future RLT candidates, and significantly affect indications and outcomes.

In our study, we showed that survival was significantly better in late elective cases of ITBL than in early urgent cases such as HAT and PNF. In the recent literature, ITBL has become a more frequent indication for RLT. This evolution may reflect the fact that better diagnostic tools are now available to enable accurate diagnosis and early management [20—23]. Patients with ITBL develop progressive graft failure despite aggressive treatment with endoscopic and interventional radiology, and mortality without RLT can be as high as 50—100% [20,24]. The multifactorial origin of ITBL is suggested to be ischemic, genetic and immunological, and bile salt-induced injury is a known risk factor [21,25,26]. The role of CMV infection in ITBL remains controversial [21,22,25]. In our series, a positive CMV status was a predictive factor for poor survival.

In the current context of a scarcity of liver grafts, the issue of the futility of RLT needs to be addressed. By considering predictive models of outcomes in RLT, as well as individual patient factors, local and national allocation policies, the final decision to list a patient and allocate a graft may be strongly influenced. These models do not take into account waiting list mortality which can equally affect primary LT recipients and RLT candidates, as can random operative and perioperative events [26,27]. The known inferior long-term survival of RLT recipients may cause an ethical conflict between an individual patient's benefit in receiving a graft for RLT and the scarcity of liver grafts available for primary LT recipients [27]. Patients with ITBL usually have had good and stable graft function for many years, and the findings from our series suggest that this subgroup of patients might greatly benefit from elective RLT and achieve an excellent long-term outcome, but present a high incidence of early mortality from sepsis. These patients are less frequently ICU-bound and therefore require less dialysis and ventilation prior to RLT when compared to other indications. This non-urgent elective status certainly plays a key role in the outcomes of these patients and should be taken into consideration before listing such a patient for RLT. [1,2]. Management should therefore be focused on improving clinical condition in RLT candidates by reducing the level of immunosuppressive therapy in order to preserve renal function and reduce the incidence of postoperative sepsis and opportunistic infections.

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The authors declare that they have no competing interest.

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