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Retransplantation of the liver in adults: outcome and predictive factors for survival

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Abstract Hepatic retransplantation is considered to carry a higher risk than primary transplantation. Survival might improve with more experience and better immunosuppression. We studied all 55 patients who were adults at the time of their first retransplantation and who underwent retransplantation between 1979 and May 2001. Patient survival at 1, 5 and 10 years was 73%, 63%, and 63%, respectively. Multivariate analysis of pre-transplant variables revealed prothrombin time, creatinine level, and indication for retransplantation, as independent predictive factors. Survival was highest in patients who had undergone retransplantation for hepatic artery thrombosis. Multivariate analysis, including pre-, per-, and post-operative variables, showed that era of transplantation, prothrombin time, blood loss, and intensive care unit (ICU) stay, were independent predictive factors. Survival at 1 and 5 years improved from 56% and 48%, respectively, before 1996 to 89% and 81%, respectively, after 1996. In conclusion, survival after hepatic retransplantation improved significantly through the years. Independent pre-transplant predictive factors were prothrombin time, creatinine level, and indication for retransplantation.

Keywords Survival · Liver transplantation · Retransplantation · Risk factors

Introduction

Retransplantation of the liver (reOLT) after failure of the first graft is considered to carry a higher risk, with higher morbidity and lower survival than for the first transplantation [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. In consideration of the often lower survival rate after reOLT, the increasing donor shortages, the pressure of increasing numbers of retransplant candidates on the waiting lists, and the higher costs of such procedures, it is important for one to evaluate the results of reOLT in order to compare the outcome. From the literature, different predictive factors for survival after reOLT are known [4, 5, 6, 7, 12, 13, 14, 15, 16, 17, 18], but they were not always acquired by multivariate analysis [4, 6, 7, 12, 13, 14]. The present study evaluates the results of reOLT in adult patients at our institution, with special emphasis on outcome and independent predictive factors for survival.

Patients and methods

The Groningen Liver Transplant Programme started in March 1979, and the first retransplantation was performed in March 1983. The present study consisted of the patients who were adult (> 17 years) at the time of retransplantation and who had undergone retransplantation before May 2001, which implies a minimum follow-up time of 1 year at the end of the study in May 2002. Data were collected from medical records and included patient characteristics, causes of graft failure, interval to reOLT, causes and time of death and several

Table 1 Pre-transplant characteristics of 55 patients who underwent a second transplantation

Variable	Median (range) or no. (%)
Age at retransplantation (years)	38 (18–61)
Gender	
Male	22 (40)
Female	33 (60)
Year of retransplantation	
≤ 27 January 1996	27 (49)
> 27 January 1996	28 (51)
Interval to retransplantation (days)	186 (4–4361)
Indication for retransplantation	see Table 2
Pre-transplantation status	
In-patient or out-patient status	
1 ICU	13 (23)
2 Hospitalized	24 (44)
3 Stable at home	18 (33)
Prothrombin time (s)	17.6 (4.6–57.0)
Creatinine (μmol/l)	85 (30–606)
Total bilirubin (μmol/l)	200 (9–991)
Leukocytes ($\times 10^9$/l)	6.7 (1.9–23.1)
Infected liver	
Yes	12 (22)
No	43 (78)

Table 2 Indications for retransplantation. Number of patients and interval to reOLT

Indication	No. of patients (%)	Interval in days	
		Median	(Range)
Chronic rejection	17 (31)	219	(23–1,512)
Hepatic artery thrombosis	15 (27)	43	(5–1,817)
Ischaemic type biliary lesions	13 (24)	845	(46–4,361)
Primary non-function	5 (9)	5	(4–7)
Hepatitis C	2 (4)	2,643	(1,533–3,752)
Hepatitis B	1 (2)	1,190	
Acute rejection	1 (2)	10	
Portal vein thrombosis	1 (2)	14	

peri-operative parameters, which were considered as possible predictive factors for survival (Tables 1, 2 and 3). Between March 1979 and May 2001, 410 adults received a primary transplantation at our centre.

Statistical analysis

The Kaplan–Meier method was used for survival analysis. Influence of possible risk factors on patient survival were first analysed by Cox univariate regression. Variables that achieved a significance level below 0.20 were subsequently analysed in forward and backward stepwise Cox multivariate regression. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS). A two-tailed P value of less than 0.05 was considered to be statistically significant.

Table 3 Per-operative and post-operative characteristics of 55 retransplant patients, and the donor characteristics

Variable	No. of patients	Median (range) or no. (%)
Recipient operation		
Operation time (h:min)	35	9:00 (5:10–23:00)
Blood loss (l)	54	6.1 (0.2–40.0)
Arterial anastomosis	53	
Normal (without conduit)		41 (77)
Infra-renal conduit		9 (17)
Supracoeliac conduit		3 (6)
Bile-duct reconstruction	55	
Duct-to-duct anastomosis		43 (78)
Hepatico-jejunostomy		12 (22)
Cold ischaemia time (h:min)	51	8:46 (2:46–16:30)
Warm ischaemia time (h:min)	51	0:53 (0:33–1:49)
Donor variables		
Age (years)	54	36 (13–61)
Gender	53	
Male		31 (58)
Female		22 (42)
Steatosis donor liver	52	
None		34 (65)
Steatosis		18 (35)
Duration hospital stay (days)	52	1 (1–36)
ABO compatibility	54	
Identical blood group		37 (69)
Compatible blood group		17 (31)
Post-transplantation		
ICU stay (days)	55	7 (2–101)
Total hospital stay (days)	55	38 (3–114)

Results

Retransplantation rates

The cumulative incidence of a first retransplantation was 10%, 16%, 19%, and 22% at 1, 5, 10 and 15 years after primary transplantation, respectively. There was no significant difference in the retransplantation rates before and after January 1996 (Fig. 1).

Group description

Fifty-five adult patients underwent a second transplantation. Their median age was 38 years (range 18–61); a majority of 60% was female (Table 1). Half of the 55 patients received their retransplant after 27th January 1996. The interval between the first and second transplantation was wide, as illustrated in Fig. 1. The median interval was 186 days, with a wide range of 4 to 4,361 days. Seven patients (13%) received retransplants within 1 week, 15 patients (27%) within 1 month and 36 patients (65%) within 1 year.

The main aetiological process that led to ultimate graft failure for which retransplantation was performed, and the interval to retransplantation, are listed in

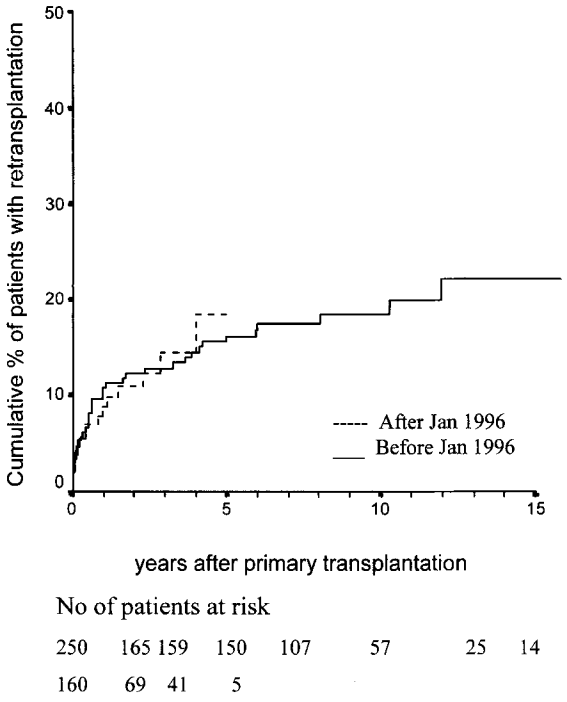

Fig. 1 Retransplantation rates before and after 27 January 1996 of patients who received transplants between March 1979 and May 2001

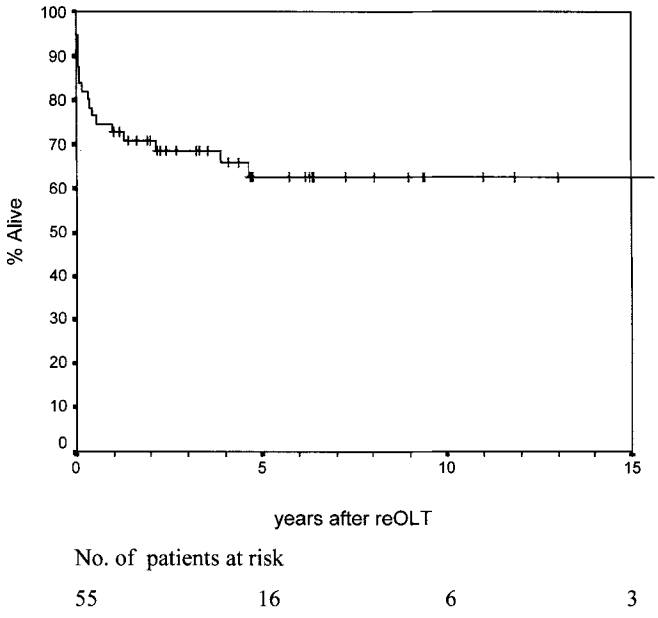

Fig. 2 Survival after retransplantation in 55 patients

Table 2. Chronic rejection (31%), hepatic artery thrombosis (HAT) (27%) and ischaemic-type biliary lesions (ITBLs) (24%) were the main indications. Primary non-function (9%) and viral disease (5%) were amongst the rarer indications. The interval to retransplantation for each indication showed a rather wide range (Table 2), but viral disease (median 1,533 days), ITBL (845 days) and chronic rejection (219 days) showed the longest intervals. Early HAT (within 15 days) was the indication for reOLT in four patients; late HAT in 11 patients (73%), with the latest after 5 years.

Two-thirds of the patients were hospitalized before their retransplantation; however, one-third could wait at home. Of the patients, 24% suffered from bacterial and/or candida infection in the liver, secondary to HAT or biliary problems. Most patients were jaundiced, but clotting and renal function were within normal limits in most patients, although a wide range was noticed (Table 1).

Operation and donor characteristics are listed in Table 3. Median operating time was 8.5 h and median blood loss 6 l, both with wide ranges. Of the patients, 23% needed an iliac conduit for arterial anastomosis. Of the 47 patients who had a duct-to-duct biliary anastomosis with their first graft, 43 received the same type of anastomosis with the second graft. Steatosis was judged by the pathologist from the donor liver biopsies taken before the actual transplantation. Eighteen (35%) of the donor livers showed some degree of steatosis, of which only five were severe. Median donor age was 36 years (13–61). After the operation, median hospital stay was 38 days (3–114), including a median of 7 days (2–101) on the intensive care unit that concluded with discharge or death.

Survival and causes of death

Patient survival at 3, 6, and 12 months was 82%, 76% and 73%, respectively; 1-year, 5-year, and 10-year survival rates were 73%, 63% and 63%, respectively (Fig. 2). Two patients developed graft failure after which they received a third graft; 1-year, 5-year and 10-year graft survival rates were 73%, 59%, and 59%, respectively.

Nineteen patients died; although causes of death were often multifactorial, the main reasons were as follows: ten patients died in relation to serious problems with the graft [primary non-function (PNF) 3×, HAT 2×, rejection 2×, ITBL 2×, venous outflow obstruction 1×]; six died primarily from infections (aspergillosis 2×, candida 2×, bacteria 2×); two died from post-transplantation lymphoproliferative disease and recurrent liver cancer, respectively, and one from bowel ischaemia. The reasons for graft failure in the two patients who received a third graft were venous outflow obstruction and HAT.

Predictive factors for survival

The variables listed in Tables 1, 2 and 3 were analysed by univariate analysis, the result of which is also shown

in those tables. Significant pre-transplant risk factors for an unfavourable outcome were found to be: transplantation before 1996, transplantation for indications other than HAT (especially chronic rejection), high creatinine level, and high bilirubin level. Of the per-transplant and post-transplant variables, high blood loss and long warm ischaemia time were related to decreased survival. In contrast to expectations, the presence of steatosis in the donor liver was favourable for outcome. A trend (*P* value between 0.05 and 0.10) was seen for duration of stay in the intensive care unit (ICU) and total hospital stay, in that a short ICU stay, but a long hospital stay, was favourable for outcome.

Subsequent multivariate analysis of the pre-transplant variables revealed prothrombin time, serum creatinine level and indication for retransplantation to be independent predictive factors (Table 4, Fig. 3). Multivariate analysis, including all pre-, per-, and post-operative variables, showed that year of transplantation (before or after 27th January 1996; Fig. 4), prothrombin time, blood loss, ICU stay, and total hospital stay were independent predictive factors for survival (Table 5).

Survival comparison after primary transplantation and retransplantation before and after January 1996

Before January 1996, 1-year and 5-year survival rates were, respectively, 76% and 68% after primary transplantation (including retransplant patients), and 56% and 48%, respectively, after first retransplantation. After January 1996, 1-year and 5-year survival rates were 83% and 74% after primary transplantation, and 89% and 81% after retransplantation. The differences before and after January 1996 were not statistically significant for primary transplantation, in contrast to first retransplantation, as noted above (Figs. 4 and 5).

Table 4 Pre-transplant predictive factors for survival. List of pre-transplant variables that achieved a significance level < 0.20 by univariate analysis, and result of subsequent multivariate analysis (*NS* not significant)

Variable	Univariate analysis*	Multivariate analysis**
Age	< 0.20	NS
Gender	< 0.20	NS
Year of retransplantation ≤ 27 January 1996 > 27 January 1996	0.016	NS
Interval to retransplantation	< 0.20	NS
Indication for retransplantation Chronic rejection HAT ITBLs Miscellaneous	0.003	0.035
Prothrombin time	< 0.20	0.027
Creatinine level	< 0.0001	0.035
Total bilirubin	0.002	NS

* < 0.20 = *P* value between 0.05 and 0.20, **NS

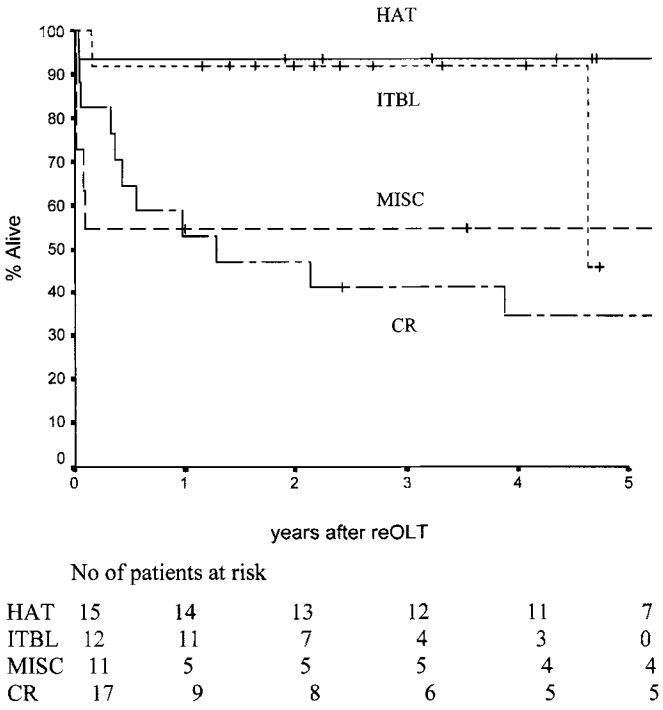

Fig. 3 Survival after retransplantation according to indication, respectively, 15, 12, 11, and 17 patients. *MISC* miscellaneous, *CR* chronic rejection

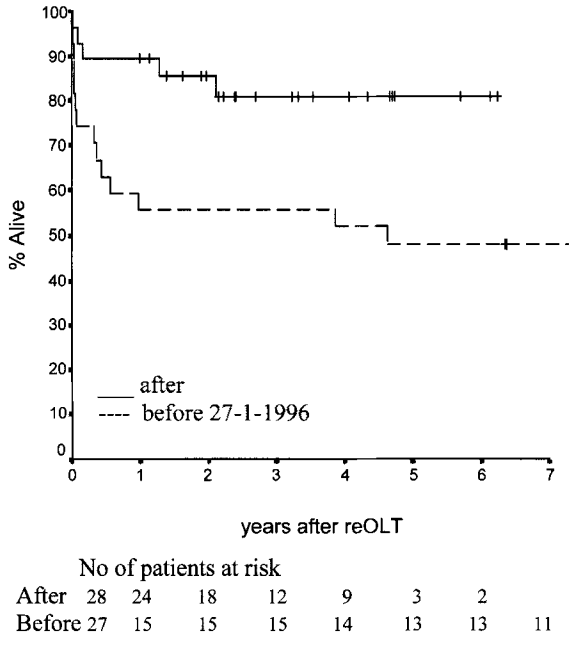

Fig. 4 Survival after retransplantation before and after 27 January 1996, respectively, 27 and 28 patients. $P = 0.016$

Table 5 Pre-, per-, and post-operative predictive factors for survival. List of pre-, per-, post-operative, and donor variables that achieved a significance level < 0.20 by univariate analysis, and result of subsequent multivariate analysis (*NS* not significant)

Variable	Univariate analysis*	Multivariate analysis**
Age	< 0.20	NS
Gender	< 0.20	NS
Year of retransplantation	0.016	0.002
≤ 27 January 1996		
> 27 January 1996		
Interval to retransplantation	< 0.20	NS
Indication for retransplantation	0.003	NS
Chronic rejection		
HAT		
ITBLs		
Miscellaneous		
Prothrombin time	< 0.20	0.03
Creatinine level	< 0.0001	NS
Total bilirubin	0.005	NS
Blood loss	< 0.0001	0.03
Arterial anastomosis	< 0.20	NS
No conduit		
Conduit		
Warm ischaemia time	0.005	NS
Steatosis donor liver	−0.042	NS
ABO compatibility	< 0.20	NS
Duration of ICU stay	< 0.20	< 0.0001
Total hospital stay	< 0.20	< 0.0001 (−)

* < 0.20 = *P* value between 0.05 and 0.20, **NS

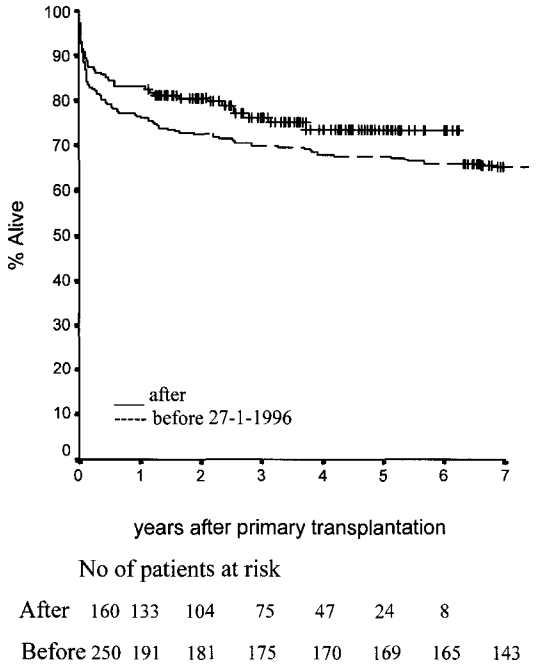

Fig. 5 Survival after primary transplantation before and after 27 January 1996, respectively, 250 and 160 patients. *P* = 0.15

Discussion

The present study was focused on patient survival after hepatic retransplantation in adult patients and the search for possible risk factors that affect survival. We included all patients who had undergone retransplantation since the start of our programme in 1979. An overall 1-year and 5-year survival rate of 73% and 63%, respectively, was found. A significant improvement was seen through the years: 1-year and 5-year survival rates were significantly better after January 1996 (89% and 81%) than before January 1996 (56% and 48%) (Fig. 4). These survival rates seem to compare favourably with those from the literature, although comparison is hampered by differences in, for example, study episodes and age groups (children and/or adults) [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11].

The first retransplantation at our centre was done in 1983. Although most retransplantations are performed within the first year of OLT (in our series 65%), the number of patients who are eligible for retransplantation later, and who have had stable and acceptable graft functions for many years, seems to increase. In our cohort these were patients with secondary biliary problems, mostly related to ITBLs, patients with sudden HAT, and patients with recurrent viral disease.

It is interesting to note that the cumulative incidence of retransplantation was 10% at 1 year, but this figure had doubled 10 years later (Fig. 1). In the future the cumulative incidence after retransplantation might increase further, as more patients with hepatitis C receive a first transplant nowadays. This is worrisome, as retransplant candidates are in competition with primary transplant candidates. In contrast, new drug regimens for prevention or treatment of recurrent viral disease might decrease the need for retransplantation in the future [19, 20].

Prothrombin time, serum creatinine level, and the indication for reOLT, were found to be pre-transplant predictive factors for survival. In Table 6 the results from other studies are summarized. Only studies that used multivariate analysis were included in this table [5, 15, 16, 17, 18]. In contrast to others, we did not find recipient age to be an independent predictive factor; however, in several studies children were included and they have, in general, better survival outcomes than adults.

Most studies, but not all, found bilirubin level to be of predictive value; in our study bilirubin was only of significance in univariate analysis. An explanation might be that many of our patients had cholestatic disease with high bilirubin levels. Chronic rejection and biliary complications accounted for 55% of the causes of graft failure, and cause of graft failure was found to be an independent predictive factor by us.

Serum creatinine level seems to be a predictive factor in almost all studies, including ours. UNOS score, or

Table 6 Review of studies which by multivariate regression analysis identified pre-transplant variables as predictive factors for survival after retransplantation (*NT* not tested)

References	No. of patients	Recipient	Bilirubin	Creatinine	Miscellaneous
[15, 5, 16, 17, 18], respectively	Adults (a) and/or children (c)	Age			
Doyle et al., 1996 (Pittsburgh) [15]	418[a]a	+	+	+	Donor age, female donor gender, mechanical ventilation, immune suppression
Markmann et al., 1997 (UCLA) [5]	299 a, c	+	NT	NT	Interval to reOLT, no. of OLTs, UNOS status
Markmann, 1999 (UCLA) [16]	150 a, c	+	+	+	Mechanical ventilation cold ischaemia time (<, > 12 h) [b]
Rosen et al., 1999 (UNOS database) [17]	900 a	+	+	+	UNOS status, presence of PNF
Facciuto et al., 2000 [c] (Mount Sinai) [18]	48 a	+	–	+	Per-operative use of blood products[b]
Present study, 2004	55 a	–	–	+	Prothrombin time, indication for reOLT

[a]Studied graft survival in 314 patients receiving 418 reOLTs
[b]These studies included one or two variables which cannot be known pre-transplant
[c]Included only late reOLTS (> 6 months after primary OLT)

some other variant concerning in-patient or out-patient status, is another frequently found predictive factor, although that was not observed in our study. Interval to reOLT does not seem of much importance either, as only one of the studies that used multivariate analysis found a relationship with survival [5].

Rosen et al. [17] report on a more favourable outcome of PNF versus non-PNF in a study group, from the UNOS database, with 37% PNF as aetiology for graft failure. We also found indication for reOLT to be of significance; however, our study included only a small number of patients with PNF (9%). In contrast, HAT and biliary complications carried the most favourable prognosis. In our study four of the five PNF patients died. Thus, it is also possible that if the non-PNF group from Rosen et al. were subdivided into other diagnosis groups the outcome would be different.

A worrisome finding is the relatively low survival rate of our patients with chronic rejection. Factors that might play a role and which might be avoidable are: late re-listing, long waiting times once re-listed, high cumulative amounts of immunosuppression, with consequent side effect, for peri-operative renal function, infections, diabetes, etc. In this respect it should be mentioned that the incidence of retransplantation for chronic rejection is decreasing: 13 of our patients with chronic rejection were given retransplants before 1996, and only four thereafter. Better immunosuppression probably plays an important role.

Analysis of additional per-operative and post-operative variables showed that transplantation since 1996, low blood loss and short duration of stay in the ICU related independently to a good outcome. The last two are well-known risk factors, and the first shows that we have done better, overall, since 1996, as already stated above. Difference in indications to reOLT before and after January 1996 seems to be one of the reasons for better outcomes in recent years. The main differences in indications were present for chronic rejection (13 patients before January 1996, four thereafter) and ITBLs (two patients before, 11 after). As shown in Fig. 3 survival after reOLT was worst in patients with chronic rejection and good in patients with ITBLs.

Several other characteristics of retransplantation candidates might be of importance in relation to outcome, for example, the degree of immunosuppression, the presence of biliary tract complications and type and number of re-interventions. In part, these parameters are reflected in some of the parameters that were studied, such as the indication for retransplantation, operating time, and per-operative blood loss. In general, some caution as to the reliability of the predictive factors derived from our study is necessary. The number of reOLT patients (55) is not very large for subsequent univariate and multivariate analysis.

In conclusion, it can be stated that survival rate after reOLT is improving through the years, and is, presently, quite high in our institution. Consequently, reOLT can be considered to be very efficient as a way of saving lives. Further improvement might be achieved by improvement of renal function before the actual retransplantation.

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