Liver retransplantation in adult recipients: analysis of a 38-year experience in the Netherlands

Takagi, K.; Domagala, P.; Porte, R.J.; Alwayn, I.; Metselaar, H.J.; Berg, A.P. van den; ... ; Polak, W.G.

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PLENARY SESSION

Liver retransplantation in adult recipients: analysis of a 38-year experience in the Netherlands

Kosei Takagi · Piotr Domagala · Robert J. Porte · Ian Alwayn · Herold J. Metselaar · Aad P. van den Berg · Bart van Hoek · Jan N. M. Ijzermans · Wojciech G. Polak

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Abstract

Background Liver retransplantation (re-LT) accounts for up to 22% after primary liver transplantation (LT), and using donor livers for retransplantation can only be justified by successful outcomes.

Methods A total of 2,387 adult recipients with 2,778 LT, between 1979 and 2017, were analyzed to determine risk factors and outcome of re-LT in the Netherlands.

Results Of 2,778 LT, 336 (12.1%) were first, 43 (1.5%) were second, and 12 (0.5%) were third or fourth re-LT. The 5-year patient survival for primary LT, and first, second, and third or fourth re-LT were 74.0%, 70.8%, 63.3%, and 57.1%, respectively ($P = 0.10$). Recipient age (≤60 years) (OR 1.96, $P < 0.001$), era (1979–2006) (OR 1.56, $P = 0.003$), donor after circulatory death (DCD) (OR 1.96, $P < 0.001$), and cold ischemia time (CIT) (>9 h) (OR 1.42, $P = 0.007$) were significant risk factors for retransplantation after primary LT.

Conclusions Recipient age, era, DCD, and prolonged CIT were identified as parameters for retransplantation. The outcome after the first re-LT was good, and comparable to those of primary transplants. Survival after multiple re-LT was not significantly different from the first retransplant group, legitimizing third and fourth re-LT to well-selected patients.

Keywords Liver retransplantation · Outcome

K. Takagi · P. Domagala · J. N. M. Ijzermans · W. G. Polak (✉)
Division of HPB & Transplant Surgery, Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
e-mail: w.polak@erasmusmc.nl

R. J. Porte
Division of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, Department of Surgery, University Medical Center Groningen, Groningen, The Netherlands

I. Alwayn
Department of Surgery, Transplant Center, Leiden University Medical Center, Leiden, The Netherlands

H. J. Metselaar
Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands

A. P. van den Berg
Department of Gastroenterology and Hepatology, University Medical Center Groningen, Groningen, The Netherlands

B. van Hoek
Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

Introduction

Liver retransplantation (re-LT) is the only effective option to treat irreversible graft failure after primary liver transplantation (LT). Despite recent improvements in surgical technique, perioperative management and donor selection, LT leads to graft loss in approximately 5–22% of all LT recipients [1–3]. In many cases, patient survival may be preserved by offering a retransplantation to those who may again endure such a major surgical procedure. We should note, however, that retransplantation increases the need for donor organs and may only be allowed if the outcome legitimizes repetitive placement on the wait list of patients in need for a new liver graft. As the demand for re-LT may increase due to the utilization of extended criteria donors on one hand and the growing number of primary LT due to upcoming diseases like nonalcoholic steatohepatitis on the other, we may expect a further shortage of liver grafts [4]. Therefore, using donor livers for retransplantation can only be justified if the outcome is successful and may compete with primary transplants.

As previously reported inferior outcomes of retransplantations compared to primary LT were reported by some centers [3–7], we initiated the present study to evaluate the outcome of primary LT and retransplantation in the Netherlands.

The Dutch Transplant Registry (NOTR) has been established for the purpose of providing the transplant centers with transplant outcome in order to improve the quality and efficiency of the transplant programs in the Netherlands. The NOTR is a mandatory data registry; however, incidence, outcome, and risk factors of re-LT have not been investigated yet.

The aim of this study was to examine the incidence, long-term outcomes, and risk factors for re-LT using a long-term follow-up cohort representing data from all three liver transplant centers in the Netherlands.

Methods

Study population

The NOTR prospectively collects LT data from three centers (Erasmus Medical Center, University Medical Center Groningen and Leiden University Medical Center) in the Netherlands all working with the same national program for indication and follow-up for LT and ensures data quality and validity by annual audit. We performed a retrospective analysis of all adult recipients (≥16 years) who underwent primary deceased donor LT between January 1979 and December 2017 using the NOTR database. This study was approved by the Dutch Liver Transplantation Advisory Committee (approval number: 40504). According to national legislation, this type of retrospective analysis using anonymous data is allowed in the Netherlands and does not require informed consent from the individual patients or approval by a local institutional review board.

Data collection

Using the NOTR database, the recipient and donor data of all LTs were collected. The recipient data included age, sex, date of transplantation, etiology of disease, outcome at last follow-up (survival or death), the date of graft loss, the cause of graft loss (acute cellular rejection [ACR], chronic cellular rejection, primary non function [PNF], primary graft dysfunction, hepatic artery thrombosis [HAT], hepatic vein thrombosis, biliary complications, liver complications, recurrence of primary diseases, and unknown), retransplantation (presence or absence), and time interval between primary transplantation and first re-LT. The following donor data were collected: age, sex, body mass index, the type of donor (donor after brain death [DBD] or donor after circulatory death [DCD]), the type of graft (whole or split liver), warm ischemia time (WIT), and cold ischemia time (CIT). The study period was divided into two eras: era (1979–2006) and era (2007–2017) based on the policy changes for allocation of donor livers [8]. Time interval between primary LT and first re-LT was divided into three groups: within the first month (0–30 days), within the first year (31–365 days), and after the first year (>365 days) after the primary LT. All recipients had been followed from the date of LT until either the date of death or the date of the last known follow-up.

Primary and secondary endpoints

Primary endpoint was the risk factors for retransplantation after primary LT. Secondary outcomes included patient survival after primary LT, first, second, and third or fourth re-LT as well as patient survival after the first re-LT according to the era, the time interval, and the cause of graft loss. The cause of graft loss was classified into five groups: rejection (ACR and chronic cellular rejection), graft dysfunction (PNF and primary graft dysfunction), vascular complications (HAT and hepatic vein thrombosis), liver complications (biliary complications and liver complications), and recurrence. In addition, the prognostic factors associated with graft survival after primary LT were examined.

Statistical analysis

Characteristics in recipients with or without re-LT following primary LT were compared. In addition, characteristics, including the causes of graft loss, in recipients with first re-LT according to the time interval were examined. Categorical variables were analyzed using the Pearson's χ^2 test or the Fisher's exact test. Comparison of medians between two groups was evaluated using the Mann–Whitney *U*-test and the independent samples *t*-test, respectively. Overall patient survival was calculated using the Kaplan–Meier's method, and the differences between the groups were investigated using the log-rank test. The risk factors associated with retransplantation following primary LT was analyzed using a logistic regression model for univariate and multivariable analyses; odds ratio (OR) and 95% confidence interval (CI) were calculated. The prognostic factors associated with graft survival after primary LT was investigated by using the Cox proportional hazards

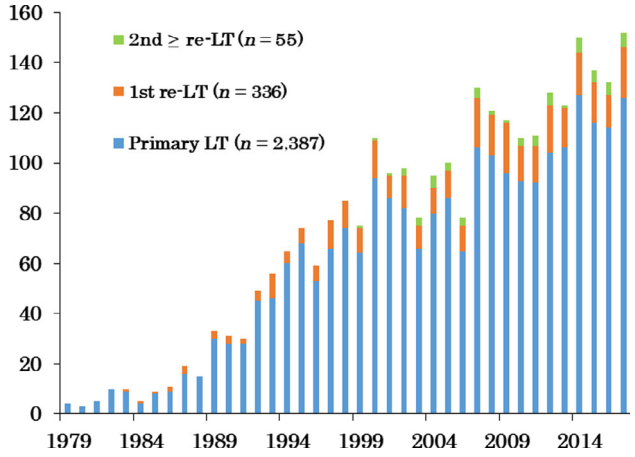


Fig. 1 Annual number of adult liver transplantations between 1979 and 2017 in the Netherlands

model with hazard ratio (HR) and 95% CI. All available and clinically relevant factors with a significance of $P < 0.20$ were included in the model. Two-sided $P < 0.05$ is considered significant. The statistical analyses were performed with JMP version 11 software (SAS Institute, Cary, NC, USA).

Results

Study population

The annual volume of LT between 1979 and 2017 in the Netherlands is shown in Figure 1. Over a 38-year period, a total of 2,778 LT was performed in the Netherlands (Table 1). Of 2,778 LT, 391 (14.1%) were re-LT, including 336 (12.1%) first, 43 (1.6%) second, and 12 (0.5%) third or fourth. In the era (1979–2006), 172 (12.5%) out of 1,376 LT were re-LT, whereas 219 (15.6%) among 1,402 LT were re-LT in the era (2007–2017). Furthermore, the incidence of multiple re-LT increased from 1.3% in the era (1979–2006) to 2.6% in the era (2007–2017). Regarding donor characteristics, the type of donor consisted of 2,309 DBD and 469 DCD, including 2,727 whole livers and 51 split livers. Most of DCD (444 out of 469, 94.7%) and split liver (49 out of 51, 96.0%) were used for primary LT.

Characteristics of 2,387 recipients (1,412 male and 975 female) with a median age of 51 years are shown in Table 2. The main indications for the first LT included primary sclerosing cholangitis (n = 364, 15.2%), malignant diseases (n = 321, 13.4%), alcoholic disease

Table 1 Recipient and donor characteristics of liver transplantation in the Netherlands between 1979 and 2017

Variable	Total	Primary LT	1st re-LT	2nd re-LT	3rd or 4th re-LT
No. of LT	2,778	2,387	336	43	12
Recipient					
Age (years)	50 (40–58)	51 (41–58)	48 (36–57)	45 (29–50)	47 (31–54)
Sex					
Male	1,639	1,412	191	26	10
Female	1,139	975	145	17	2
Era					
1979–2006	1,376	1,204	154	13	5
2007–2017	1,402	1,183	182	30	7
Donor					
Age (years)	47 (34–56)	47 (34–56)	46.5 (30.3–56)	48 (31–61)	49 (39–57)
Sex					
Male	1,435	1,250	163	18	4
Female	1,343	1,137	173	25	8
Donor type					
DBD	2,309	1,943	315	41	10
DCD	469	444	21	2	2
Graft type					
Whole	2,727	2,338	334	43	12
Split	51	49	2	0	0
WIT (min)	38.5 (30–52)	38 (30–53)	40 (31–50)	38 (29.3–43.3)	35 (34–37)
CIT (h)	7.9 (6.2–10.3)	8 (6.2–10.5)	7.6 (6–9.8)	7.5 (6–9.3)	6.7 (5.6–9.0)

CIT cold ischemia time, *DBD* donor after brain death, *DCD* donor after circulatory death, *LT* liver transplantation, *re-LT*, liver retransplantation, *WIT* warm ischemia time

Table 2 Characteristics in recipients with or without retransplantation following primary LT (n = 2,387)

	Primary LT (n = 2,387)	1st re-LT (−) (n = 2,048)	1st re-LT (+) (n = 339)	P-value
Recipient				
Age (years)	51 (41–58)	52 (42–59)	45 (33–53)	<0.001
Sex (male/female)	1,412/975	1,218/830	194/145	0.44
Era (1979–2006/2007–2017)	1,204/1,183	997/1,051	207/132	<0.001
Etiology				
Acute liver failure	216	185	31	<0.001
Subacute liver failure	17	15	2	
Benign tumor	73	66	7	
Malignancy	321	290	31	
Cirrhosis				
HBV/HCV	278	239	39	
Alcoholic	281	256	25	
PSC	364	289	75	
PBC	160	140	20	
Other cholestatic disease	26	18	8	
AIH	101	79	22	
Biliary disease	27	22	5	
Cryptogenic	250	223	27	
Metabolic disease	145	129	16	
Budd Chiari syndrome	25	20	5	
Others	103	77	26	
Donor				
Age	47 (34–56)	47 (34–57)	48 (35–56)	0.89
Sex (male/female)	1,250/1,137	1,067/981	183/156	0.52
BMI	24.2 (22.2–26.1)	24.2 (22.2–26.1)	24.2 (22.2–26.1)	0.43
DBD/DCD	1,943/444	1,677/371	266/73	0.14
Whole/split	2,338/49	2,008/40	330/9	0.42
WIT (min)	38 (30–53)	38 (30–52)	42 (31–57)	0.002
CIT (h)	8 (6.2–10.5)	7.8 (6.2–10.4)	8.4 (6.8–10.8)	<0.001

AIH autoimmune hepatitis, *BMI* body mass index, *CIT* cold ischemia time, *DBD* donor after brain death, *DCD* donor after circulatory death, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *LT* liver transplantation, *PBC* primary biliary cholangitis, *PSC* primary sclerosing cholangitis, *re-LT* liver retransplantation, *WIT* warm ischemia time

(n = 281, 11.8%), and hepatitis B virus and/or hepatitis C virus (n = 278, 11.6%).

Characteristics of retransplantation

Out of 2,387 LT recipients, 339 (14.2%) required re-LT following primary LT. The results in recipients with or without re-LT are represented in Table 2. Recipients with re-LT were significantly younger than those without re-LT (45 vs. 52 years, $P < 0.001$). Out of 1,204 recipients in the era (1979–2006), 207 (17.2%) received re-LT, as compared to 132 (11.2%) of 1,183 recipients in the era (2007–2017) ($P < 0.001$). The retransplant rate based on the etiology of diseases was as follows: autoimmune hepatitis, 22.8% (22 of 101); primary sclerosing cholangitis, 20.6% (75 of 364); Budd–Chiari syndrome, 20.0% (5 of 25); acute liver failure, 14.4% (31 of 216); hepatitis B virus and/or hepatitis C virus related cirrhosis, 14.0% (39 of 278); and primary biliary cholangitis, 12.5% (20 of 160). Regarding donor data, there was no significant difference in terms of donor type (P = 0.14) and graft type (P = 0.42); however, the retransplant group had significantly longer WIT (42 vs. 38 min, P = 0.002) and CIT (8.4 vs. 7.8 h, $P < 0.001$).

The causes of graft loss in patients with re-LT are shown in Table 3. The main causes of graft loss were biliary complications (n = 101, 29.8%), HAT (n = 71, 20.9%), PNF (n = 37, 10.9%), and recurrence of primary diseases (n = 31, 9.1%).

The demographic characteristics in 339 recipients with first re-LT according to the time interval were also summarized in Table 3. The median time interval between primary LT and first re-LT was 6.2 months (range 0.3–44.3 months).

Table 3 Characteristics in recipients with first retransplantation according to the time interval between primary LT and first re-LT

	Total (n = 339)	≤30 days (n = 118)	31–365 days (n = 86)	>365 days (n = 135)	P-value
Recipient					
Age (years)	45 (33–53)	47 (33.8–57)	46 (29.5–56)	40 (32–50)	0.009
Sex (male/female)	194/145	56/62	56/30	82/53	0.02
Era (1979–2006/2007–2017)	207/132	67/51	45/41	95/40	0.013
Cause of graft loss					
ACR	3	3	0	0	<0.001
CCR	31	0	16	15	
PNF	37	37	0	0	
Primary graft dysfunction	11	7	3	1	
HAT	71	46	13	12	
HVT	7	5	1	1	
Biliary complications	101	8	39	54	
Liver complications	12	3	3	6	
Recurrence	31	0	2	29	
Unknown	35	9	9	17	

ACR acute cellular rejection, *CCR* chronic cellular rejection, *HAT* hepatic artery thrombosis, *HVT* hepatic vein thrombosis; *PNF* primary non function

Out of 339 re-LT, 118 (34.8%) recipients had re-LT within the first month, 86 (25.4%) had within the first year (31–365 days), and 135 (39.8%) had after the first year. The main causes of graft loss within the first month were HAT (39.0%) and PNF (31.4%), within the first year biliary complications (45.3%) and chronic cellular rejection (11.6%), and after the first year biliary complications (40.0%) and recurrence of the primary diseases (21.5%).

Patient survival

Patient survival after primary LT, first, second and third or fourth re-LT are shown in Figure 2a. After a median follow-up time of 5.1 years (range 0–36 years), the 1-, 3-, 5-, and 10-year patient survival rates were 84.5%, 78.0%, 74.0%, and 64.4% for primary LT, 79.3%, 74.3%, 70.8%, and 60.7% for first re-LT, and 79.9%, 73.5%, 63.3%, and 57.5% for second re-LT, respectively. The 1-, 5-, and 10-year survival rates for third or fourth re-LT were 57.1% at all time points. No significant differences between the groups were found (P = 0.10).

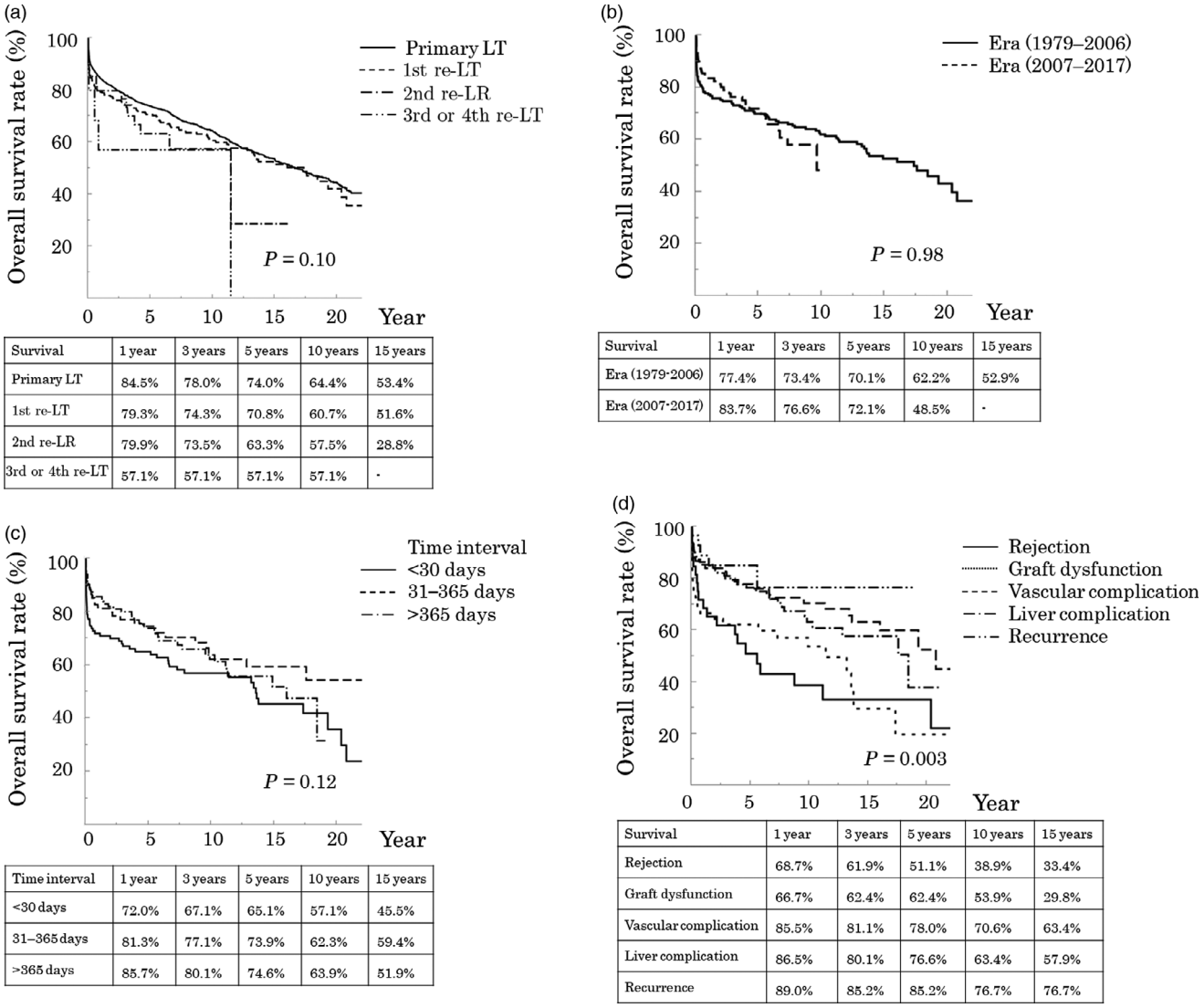
Patient survival after first re-LT according to the era, the time interval, and the cause of graft loss are demonstrated in Figure 2b–d. The 1-, 3-, and 5-year patient survival rates were 77.4%, 73.4%, and 70.1% in the era (1979–2006), and 83.7%, 76.6%, and 72.1% in the era (2007–2017) (Fig. 2b, P = 0.98). Regarding patient survival rates after first re-LT based on the time interval, the 1-, 3-, and 5-year survival rates were as follows: within the first month, 72.0%, 67.1%, and 65.1%; within the first year, 81.3%, 77.1%, and 73.9%; and after the first year, 85.7%, 80.1%, and 74.6%, as shown in Figure 2c. No significant differences between the groups were found (P = 0.12). Patient survival rates after first re-LT based on the cause of graft loss were significantly different (Fig. 2d, P = 0.003). Patients with rejection or graft dysfunction had poorer prognosis compared to those with vascular complications, liver complications, or recurrence.

Risk factors for retransplantation

Table 4 shows the results of univariate and multivariable analyses to investigate the risk factors associated with re-LT after primary LT. The multivariable logistic regression model revealed recipient age (≤60 years) (OR 1.96, 95% CI 1.34–2.94, P < 0.001), era (1979–2006) (OR 1.56, 95% CI 1.17–2.10, P = 0.003), DCD (OR 1.96, 95% CI 1.40–2.72, P < 0.001), and CIT (>9 h) (OR 1.42, 95% CI 1.10–1.83, P = 0.007) to be significant risk factors for re-LT after primary LT.

Prognostic factors associated with graft survival after primary LT

In a multivariable Cox proportional hazards model, recipient age (>60 years) (HR 1.29, 95% CI 1.08–1.52, P = 0.005), DCD (HR 1.28, 95% CI 1.06–1.55, P = 0.012), and CIT (>9 h) (HR 1.20, 95% CI 1.06–1.36, P = 0.005) were found to be significantly associated with decreased graft survival after primary LT (Table S1).



Survival	1 year	3 years	5 years	10 years	15 years
Primary LT	84.5%	78.0%	74.0%	64.4%	53.4%
1st re-LT	79.3%	74.3%	70.8%	60.7%	51.6%
2nd re-LR	79.9%	73.5%	63.3%	57.5%	28.8%
3rd or 4th re-LT	57.1%	57.1%	57.1%	57.1%	-

Survival	1 year	3 years	5 years	10 years	15 years
Era (1979-2006)	77.4%	73.4%	70.1%	62.2%	52.9%
Era (2007-2017)	83.7%	76.6%	72.1%	48.5%	-

Time interval	1 year	3 years	5 years	10 years	15 years
<30 days	72.0%	67.1%	65.1%	57.1%	45.5%
31–365 days	81.3%	77.1%	73.9%	62.3%	59.4%
>365 days	85.7%	80.1%	74.6%	63.9%	51.9%

Survival	1 year	3 years	5 years	10 years	15 years
Rejection	68.7%	61.9%	51.1%	38.9%	33.4%
Graft dysfunction	66.7%	62.4%	62.4%	53.9%	29.8%
Vascular complication	85.5%	81.1%	78.0%	70.6%	63.4%
Liver complication	86.5%	80.1%	76.6%	63.4%	57.9%
Recurrence	89.0%	85.2%	85.2%	76.7%	76.7%

Fig. 2 Patient survival after primary LT, 1st, 2nd, and 3rd or 4th re-LT (a). Patient survival after first re-LT according to the era (b), the time interval between primary LT and first re-LT (c), and the cause of graft loss (d)

Discussion

The present study is the largest series of 2,387 adult recipients with 2,778 LT from three liver transplant centers in the Netherlands, investigating the incidence, long-term outcomes, and risk factors of re-LT using database of the NOTR. This study finds that re-LT is an effective modality for patients with irreversible graft failure after primary LT, and offers good long-term outcome even after multiple re-LT. Furthermore, we identified risk factors for retransplantation and prognostic factors for graft survival such as recipient age, DCD and prolonged CIT.

In the present study, the overall patient survival rate after first re-LT with 5-year of 70.8% and 10-year of 60.7% was relatively better compared to previous literature [7, 9, 10]. Previous studies reported poor outcome following multiple re-LT [10, 11]; however, our results showed superior outcomes with 5-year survival of more than 50% in terms of patient survival after second, and third or fourth re-LT. Although these survival rates were lower than that after primary LT, our findings suggested that multiple re-LT could be feasible because re-LT is the only treatment option for patients with irreversible graft failure. This has also been shown in a recent study from France [12].

The timing of re-LT is an important issue because the indication for re-LT, surgical difficulty, and outcome are different according to the time interval between primary LT and re-LT [3, 6, 10, 11]. Early re-LT could be technically easier than primary LT, however the status of recipients would be worse because of advanced liver failure, and severe hemodynamic impairment. In contrast, late

Table 4 Risk factors for retransplantation in patients following primary LT (n = 2,387)

Variable	Univariate			Multivariable		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Recipient age						
≤60 (vs. >60)	2.19	1.53–3.25	<0.001	1.96	1.34–2.94	<0.001
Recipient sex						
Male (vs. female)	0.91	0.72–1.15	0.44			
Era						
1979–2006 (vs. 2007–2017)	1.65	1.31–2.09	<0.001	1.56	1.17–2.10	0.003
Donor age						
>50 (vs. ≤50)	1.07	0.84–1.35	0.59			
Donor sex						
Male (vs. female)	1.08	0.86–1.36	0.52			
Donor BMI						
>25 (vs. ≤25)	0.93	0.72–1.18	0.54			
Donor type						
DCD (vs. DBD)	1.24	0.93–1.64	0.14	1.96	1.40–2.72	<0.001
Graft type						
Split (vs. whole)	1.37	0.62–2.72	0.42			
WIT (min)						
>45 (vs. ≤45)	1.23	0.97–1.56	0.09	1.02	0.78–1.33	0.87
CIT (h)						
>9 (vs. ≤9)	1.52	1.21–1.92	0.001	1.42	1.10–1.83	0.007

BMI body mass index, *CI* confidence interval, *CIT* cold ischemia time, *DBD* donor after brain death, *DCD* donor after circulatory death, *OR* odds ratio, *WIT* warm ischemia time

re-LT would be more complicated high-risk surgery due to severe adhesion and several posttransplant complications [6]. Outcomes based on the time interval have been reported differently. The European Liver Transplant Registry (ELTR) has demonstrated that early re-LT within the first month after primary LT had a significantly worse 5-year graft survival than late re-LT (45% vs. 50%, $P < 0.0001$) [11]. The United Network for Organ Sharing (UNOS) data has shown that re-LT within the first year after primary LT had below standard outcomes [5]. In the present study, the time interval was not associated with prognosis after re-LT.

Among recipient and donor risk factors for re-LT, younger recipient age, era, DCD, and prolonged CIT were significant risk factors associated with re-LT. CIT is considered the benchmark associated with organ function after allograft implantation [13]. In the comparison between younger recipients (≤60 years) and older recipients (>60 years), the time interval between primary LT and first re-LT and causes of graft loss were significantly different between the groups (Table S2). Among the retransplant recipients, 42.8% of younger recipients received re-LT after the first year (>365 days) after the primary LT due to mainly biliary complications and recurrence of primary disease. In contrast, 54.5% of older recipients underwent re-LT within the first month (0–30 days). Accordingly, younger recipients had higher chances of late re-LT following primary LT due to chronic complications in the present study.

The era was stratified by the policy changes for allocation of donor livers in the present study. In the Netherlands, a new allocation system based on the model for end-stage liver disease (MELD) score has been introduced since December 2006 [8]. The era was identified as a one of the risk factors for re-LT after primary LT. Although many differences between the eras were found in terms of recipients' and donors' factors (Table S3), longer follow-up period in the era (1979–2006) would have an effect on higher incidences of re-LT after the first year after the primary LT. In contrast, the era was not a predictor for graft survival after primary LT. Moreover, no significant differences were found in patient survival after first re-LT stratified by era.

The use of extended criteria donors, such as older grafts, higher body mass index, but mostly DCD, has been instrumental in expanding the available donor pool in LT [14, 15]. In the European countries, DCD is developed to overcome the organ shortage, and the number of DCD donations has been increasing even though they are still limited in several countries including the Netherlands,

Belgium, the United Kingdom, Spain and France [16, 17]. From 2001, there has been an increasing use of DCD livers in the Netherlands, which recently accounted for approximately 40% of all liver donors [18]. However, DCD grafts are reported to have higher incidences of biliary complications, especially like ischemic-type biliary lesions, with subsequent impaired graft survival requiring re-LT [19, 20]. Actually, DCD was an independent risk factor of re-LT as well as a significant predictor of graft survival following primary LT.

The present study has several limitations. Our findings were based on information registered in the NOTR database, therefore the results would be affected by the accuracy and consistency of the data entry. Furthermore, the indication and selection criteria for re-LT might be different between the centers. As a general rule, DCD livers are not accepted to patients with re-LT.

In conclusion, the incidence of re-LT has increased in recent years in the Netherlands mostly due to use of extended criteria donors, especially DCD. The present study showed good clinical outcomes after first re-LT and acceptable results after multiple re-LT. The time interval between primary LT and first re-LT was not associated with prognosis after re-LT. Recipient age, era of transplantation, DCD, and increased CIT were identified as risk factors for retransplantation.

Conflict of interest None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Prognostic factors for graft survival in patients following primary LT (n = 2,387).
Table S2. Characteristics in younger or older recipients who received primary LT (n = 2,387).
Table S3. Characteristics in younger or older recipients who received primary LT (n = 2,387).