Supplementary appendix to

Randomized trial of ciclosporin with two-hour monitoring versus tacrolimus with trough monitoring in liver transplantation; DELTA study

Dutch Trial Registry, number NTR489. Clinicaltrials.gov, number NCT00149994.

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List of investigators:

Leiden University Medical Centre, University of Leiden, Leiden, The Netherlands:
Dept. of Gastroenterology and Hepatology and Transplantation Center: Bastian Ruijter*, M.D., Akin Inderson*, M.D., Bart van Hoek, M.D. ,Ph.D.; Izak Biemond, M.S. *) joint first authorship
Department of Surgery and Transplantation Center: Jeroen Dubbeld, M.D., Jan Ringers, M.D., Andrzej Baranski, M.D., Ph.D. , Sandro Schaapherder, M.D., Ph.D.; Transplantation Center: Danny van der Helm.
Study coordinators: Lida Beneken-Kolmer, R.N., Babs de Klerk, R.N.;
Nurse specialists: Els M.T. Rijnbeek, M.S., Josine Spek- van den Ing, M.S.
Dept. of Medical Statistics: M. Rodriguez-Girondo, R. Wolterbeek.

Erasmus Medical Centre, Erasmus University, Rotterdam, The Netherlands:
Gastroenterology and Hepatology and Erasmus MC Transplantation Institute: Herold Metselaar, M.D., Ph.D. ;
Department of Surgery, Division of HPB and Transplant Surgery, Erasmus MC Transplantation Institute: Wojciech Polak, M.D., Ph.D., Geert Kazemier, M.D., Ph.D.; Nurse specialist: Lara Elshove, M.S.

University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands:
Department of Gastroenterology and Hepatogy: Aad van den Berg, M.D., Ph.D.;
Department of Surgery, Section HPB surgery and Liver Transplantation: Robert Porte, M.D., Ph.D.;
Data manager: Jan Bottema, M.S.

Supplementary Methods

Inclusion and exclusion criteria

Eligible patients were aged 18-75 years, scheduled to receive a primary orthotopic LT (including living donor, non-heart beating donor or split liver) and expected to be capable of study participation for at least 6 months post-OLT. Patients were excluded if requiring a multi-organ transplant, or if transplanted previously, if the patient was not eligible to receive at least 10mg/kg/day at the initial dosing of CsA, if recipient was a HIV carrier, if urine production was <200ml within the first 12 hours after reperfusion of the graft, if the immunosuppressive regimen prescribed post-transplantation was expected to include an mTOR-inhibitor like rapamycin, if severe coexisting or unstable disease was present expected to affect the study objectives, or if an unlicensed drug or therapy had been administered within one month prior to study entry. If needed use of mycophenolate mofetil (MMF) and/or azathioprine was allowed.

Immunosuppression

All patients received a 20mg dose of basiliximab (Simulect) intravenously and 500mgs of methylprednisolone in the anhepatic phase and a second intravenous dose of 20mg basiliximab at day 4. Oral prednisolone 20mg QD was given in the first week, 10 mg QD thereafter, and prednisolone was tapered and stopped if possible between 3 to 6 months post-transplant. Both CsA and Tac were initiated within 24-48 hours post-operatively. CsA (Neoral capsules, Novartis Pharma, Basel CH) was initiated at 10 mg/kg/day in two divided doses (BID) and adjusted to maintain the C2 level by monoclonal fluorescent polarization assay between800-1200 ug/l from month 0-3 and 700-900 ug/l from month 4-12. Tacrolimus (Prograft, Astellas Pharma B.V, Leiden, NL) was given at a starting

dose of 0,1-0,15mg/kg/day divided in two oral doses (BID), and adjusted to maintain the 12-hour trough level (T0) just above 10 ug/l with maximum 15 ug/l at month 0-3 and between 5-10 ug/l at month 4-12. All methods are specific for parent compound. The use of mycophenolate mofetil or azathioprine was allowed if deemed necessary due to renal dysfunction by the treating physician in order to lower levels of CsA or Tac as much as possible. In case of a suspected acute rejection, based on liver enzymes, an allograft biopsy had to be performed before the initiation of anti-rejection therapy. Methyl-prednisolone pulse therapy following the local standard dosage and schedule was then administered for anti-rejection therapy. For steroid-resistant rejection anti-thymocyte globulin was allowed as per local protocol. In case of rejection, the current study medication could be changed at the discretion of the prescribing physician and changes were recorded in the study database.

Concomitant medications

Concomitant medications that could interfere with CsA or Tac were avoided as much as possible. Other concomitant medications normally used in liver allograft recipients were allowed. Perioperative antibiotics and post-transplant antimicrobial prophylaxis were given as prescribed by the local protocols.

Visits and Evaluation

Baseline measurements consisted of complete physical examination, vital signs, HBV and HCV serology and viral load quantification and comprehensive metabolic panel. Patients received standard post-operative care with measurement of C2 or T0 thrice-weekly until discharge. Thereafter, weekly clinic visits until month one and at least at month 2, 3, 6 and 12 were scheduled. Additional visits could be made if necessary. Each visit vital signs,

laboratory determinations (including complete blood count, serum creatinine, electrolytes, liver enzymes and function, hemoglobin A1c, blood glucose and lipid panel), and C2/T0 whole blood levels were obtained. At 6 months post-LT a liver biopsy was performed as per protocol. Extra liver biopsies were obtained in case of suspected acute cellular rejection. ITT analysis was on all patents allocated to study treatment. According to protocol PP analysis was on all patients started and kept on the allocated study medication without more than 14 days interruption until 6 months after LT or until death or re-transplantation.

Data management supplement

After completion of the study and after the three centers participating uploaded all study data through the TRIALINK software to the server with the central database, the database was locked. and the data were converted to Microsoft Access tables. Retrieval of the full database form the server was delayed because TRIALINK -where the data were stored on a server- ceased to exist. We checked all tables for consistency. It appeared that in one table three patients had not been indicated as deceased, while they were in all other tables. We could confirm that these three patients indeed had deceased. In the presence of representatives of Novartis the database was unlocked, these three patients were indicated as deceased in the mentioned table, and the database was locked again before analysis. No interim analysis had been performed before. Data on medication for PTDM, new-onset hyperlipidemia and new-onset hypertension were checked with the original patient charts. Preliminary results were published on clinicaltrial.gov in 2011.

Supplementary Results

ITT analysis continued

Figure S1. Mean cyclosporine 2-hour levels during the first year after liver transplantation.

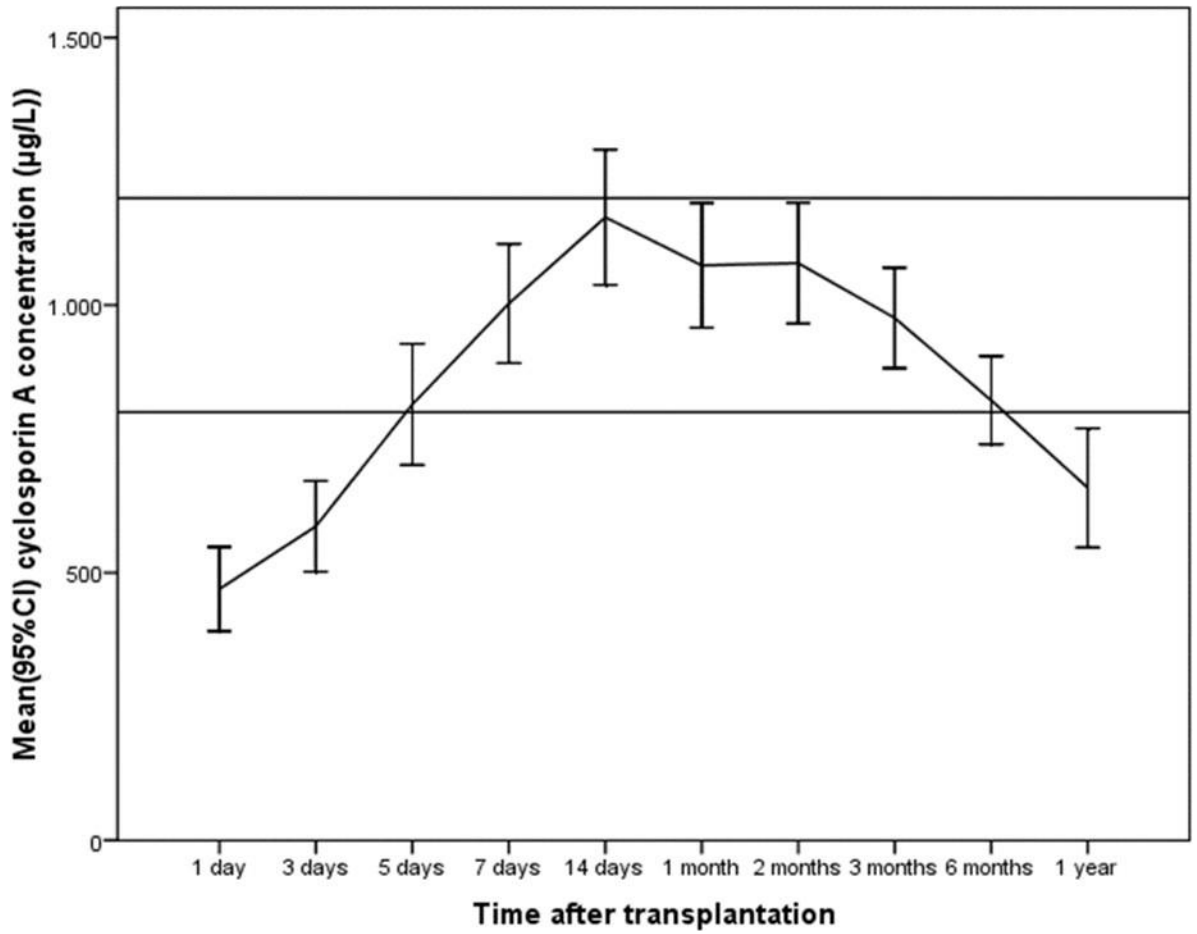

Figure S2. Mean tacrolimus trough levels during the first year after liver transplantation.

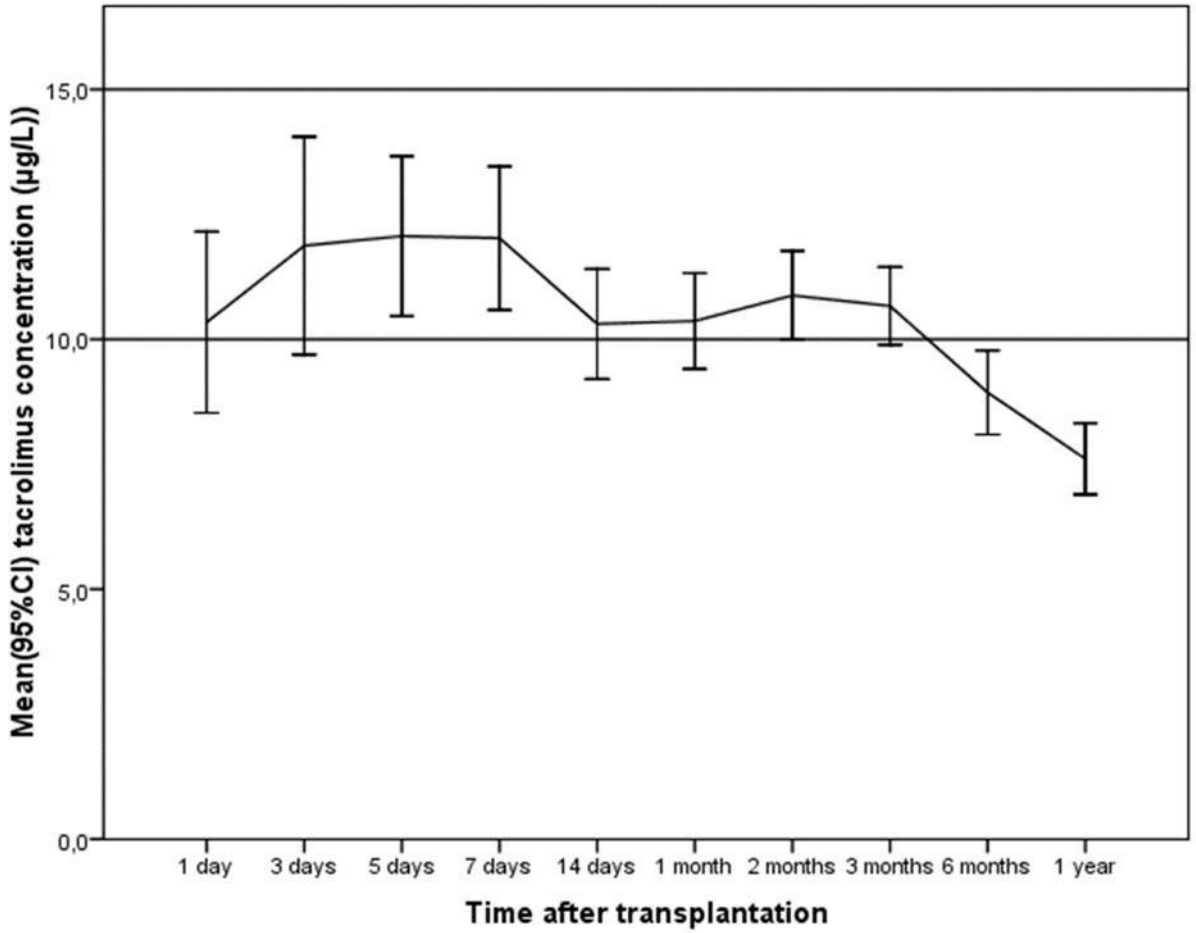

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Table S1. Number of patients in both T0 and C2 groups using other immunosuppression next to T0 or C2 and prednisolone -and induction with basiliximab and methyl-prednisolone- is indicated in this table.

			MMForAZA					
			no	AZA	MMF	sirolimus	everolimus	Total
Treatment allocation	Tacrolimus	Count	66	5	12	1	1	85
		% within Treatment allocation	77,6%	5,9%	14,1%	1,2%	1,2%	100,0%
	Cyclosporin A	Count	58	9	16	0	1	84
		% within Treatment allocation	69,0%	10,7%	19,0%	0,0%	1,2%	100,0%
Total		Count	124	14	28	1	2	169
		% within Treatment allocation	73,4%	8,3%	16,6%	0,6%	1,2%	100,0%

AZA=azathioprine, MMF= mycophenolate mofetil

Conversion of immunosuppression

At 12 months 72/85 patients allocated to tacrolimus were still on tacrolimus, while 51/84 patients allocated to ciclosporin were still on ciclosporin (Fisher exact Chi-square p=0.0005). Of patients allocated to tacrolimus 1/85 had been switched to ciclosporin, while 11/84 patients allocated to ciclosporin had been switched to tacrolimus in the first year (Fisher exact Chi-square p=0.0024). In both groups 4 patients had been converted to calcineurin-inhibitor free immunosuppression (IS) during the first year.

Causes of graft loss (ITT)

Table S2 summarizes the causes of graft loss (death or re-transplantation). Most occurrences of graft failure are related to biliary or acute hepatic artery complications and chronic rejection. Of the 30 patients with death-uncensored graft failure, 18 died and the other 12 underwent re-transplantation. One patient in the CsA group who suffered from chronic rejection could not be re-transplanted because of urosepsis, leading to death. Sepsis tended to be a more frequent cause of death in the C2 group, with 8 cases of sepsis vs. 2 in the T0 group ($p=0.057$). No other differences in causes of graft loss or death within the treatment groups could be identified, although death by malignancy occurred in four cases in the first year, all in the C2 group ($p=0.12$ versus T0 group): recurrence of epithelioid hemangioendothelioma, two recurrences of hepatocellular carcinoma, and one new epithelioid sarcoma.

Table S2. Causes of graft loss (death or re-transplantation) in the first year after OLT

	CsA (n=84)	Tac (n=85)
Death with a functioning graft	N = 13	N = 5
Infections (1 with chronic rejection)	8	2
Massive hemorrhagic necrosis	-	1
Intra-abdominal bleeding	-	1
Epileptic state with respiratory failure	-	1
malignancy	4	-
suicide	1	-
Graft loss with re-transplantation	N=8	N=4
Veno occlusive disease		1
Hepatic artery bleeding		1
Hepatic artery thrombosis	1	
Cholestatic recurrence hepatitis C		1
Non-anastomotic biliary strictures (NAS)	2	1
Chronic rejection	2	
Infected liver segment	1	
Primary non-function	1	
Bile duct necrosis	1	

More secondary endpoints (ITT)

Table S3. Cumulative raw incidences (n,%), and Kaplan-Meier estimates of the cumulative incidences with hazard ratio (HR) and 95% confidence interval of HR (CI) for patients reaching these secondary endpoints at 3, 6 and 12 months after LT in the C2 group (n=84) versus those in the T0 group (n=85) (ITT analysis).

		Cumulative raw incidence			Kaplan-Meier estimate of cumulative incidence and HR			
	Group	C 2 (n=84)	T0 (n=85)	Fisher p	C2 (CI)	T2 (CI)	HR (CI)	logrank p
Endpoint		N (%)	N (%)					
BPAR	3 mo	27 (32.1%)	20 (23.5%)	0.23	66.2% (55.6-76.8)	76.2% (67.0-85.4)	1.371 [0.772-2.46]	0.28
	6 mo	31 (36.9%)	21 (24.7%)	0.10	60.9% (49.9-71.9)	75.0% (65.6-84.4)	1.529 [0.882-2.633]	0.13
	12 mo	31 (36.9%)	21 (24.7%)	0.10	60.9% (49.9-71.9)	75.0% (65.6-84.4)	1.529 [0.882-2.633]	0.13
tACR	3 mo	28 (32.9%)	28 (33.3%)	0.99	34.8% (24.4-45.2)	33.4% (29.2-43.4)	0.954 [0.884-1.505]	0.87
	6 mo	29 (34.1%)	32 (38.1%)	0.63	40.0% (29.2-50.8)	34.6% (24.4-44.8)	1.067 [0.950-1.612]	0.79
	12 mo	29 (34.1%)	32 (38.1%)	0.63	40.0% (29.2-50.8)	34.6% (24.4-44.8)	1.067 [1.018-2.460]	0.79

Figure S1 shows mean cyclosporine 2-hour levels during the first year after liver transplantation.

Figure S2 shows mean tacrolimus trough levels during the first year after liver transplantation.

Figure S3 shows cumulative incidence of tACR (ITT) (KM and logrank analysis).

Figure S4 and Table 2 show the cumulative incidence of retransplantation or mortality (death-uncenrored graft failure). (ITT) (KM and logrank analysis).

Histological grading of acute cellular rejection (ITT)

Of the 21 BPARs in the T0 group, 11 were mild, 7 moderate and 3 severe on liver biopsy. In the C2 group of 31 BPARs, rejection was mild in 16, moderate in 11, and severe in 4 cases. No intergroup differences were observed between histological grades (p=0.96).

Long-term outcome

In ITT analysis after 2, 3, 5 and 10 years 76%, 75 %, 76% and 67% of CsA-treated patients survived, compared to 85%, 85%, 81% and 70% of Tac-treated patients (p=0.169, p= 0.12, p=0.14 and p=0.60) respectively.

Table S4 shows biometrics.

Table S5 shows adverse events according to the MeDRA classification.

Table S4. Biometrics

Biometric data per treatment group						
	Tacrolimus			Neoral		
	Baseline	3 months	6 months	baseline	3 months	6 months
Mean Blood pressure (mmHg)						
Systolic	130(±24,4)	132(±18,7)	128(±16,4)	131(±20,3)	139(±18,4)	137(±22,1)[a]
Diastolic[b]	74(±12,2)	82(±10,4)	79(±9,6)	73(±13,7)	85(±9,3)	83(±12,3)
Hypertension (RR >140/80) (N=)	9		7	9		14[c]
Weight (kg)[d]	77,5(±13,9)	75,3(±14,3)	78,6(±15,5)	75,6(±13,3)	76,0(±12,2)	76,2(±12,3)

(SD): standard deviations between brackets

a. Systolic blood pressure is significantly higher in Neoral group at 6 months, P=0,014

b. Diastolic blood pressure is higher compared to baseline after 6 months, P=0,002 and 0,001; no difference between tacrolimus and neoral

c. No significant differences in hypertension at baseline and 6 months

d. No significant differences in weight between and within treatment groups

Table S5. Adverse events according to MeDRA classification

			Treatment allocation		
			Tacrolimus	Cyclosporin A	Total
MedDRA SOC term		Count	2	2	4
		% of Total	,1%	,1%	,2%
	Blood and lymphatic system disorders	Count	51	35	86
		% of Total	2,0%	1,4%	3,4%
	Cardiac disorders	Count	23	28	51
		% of Total	,9%	1,1%	2,0%
	Congenital, familial and genetic disorders	Count	0	1	1
		% of Total	,0%	,0%	,0%
	Ear and labyrinth disorders	Count	4	1	5
		% of Total	,2%	,0%	,2%
	Endocrine disorders	Count	1	0	1
		% of Total	,0%	,0%	,0%
	Eye disorders	Count	11	5	16
		% of Total	,4%	,2%	,6%
	Gastrointestinal disorders	Count	368	261	629
		% of Total	14,6%	10,4%	25,0%

Table S5. Adverse events according to MeDRA classification (continued a)

		Treatment allocation		Total
		Tacrolimus	Cyclosporin A	
General disorders and administration site conditions	Count	150	144	294
	% of Total	6,0%	5,7%	11,7%
Hepatobiliary disorders	Count	30	40	70
	% of Total	1,2%	1,6%	2,8%
Immune system disorders	Count	3	1	4
	% of Total	,1%	,0%	,2%
Infections and infestations	Count	19	35	54
	% of Total	,8%	1,4%	2,1%
Injury, poisoning and procedural complications	Count	61	52	113
	% of Total	2,4%	2,1%	4,5%
Investigations	Count	10	13	23
	% of Total	,4%	,5%	,9%
Metabolism and nutrition disorders	Count	73	70	143
	% of Total	2,9%	2,8%	5,7%
Musculoskeletal and connective tissue disorders	Count	66	51	117
	% of Total	2,6%	2,0%	4,7%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Count	1	1	2
	% of Total	,0%	,0%	,1%
Nervous system disorders	Count	91	90	181
	% of Total	3,6%	3,6%	7,2%
Psychiatric disorders	Count	101	93	194
	% of Total	4,0%	3,7%	7,7%

Table S5. Adverse events according to MeDRA classification (continued b)

		Treatment allocation		Total
		Tacrolimus	Cyclosporin A	
Renal and urinary disorders	Count	80	84	164
	% of Total	3,2%	3,3%	6,5%
Reproductive system and breast disorders	Count	6	3	9
	% of Total	,2%	,1%	,4%
Respiratory, thoracic and mediastinal disorders	Count	65	88	153
	% of Total	2,6%	3,5%	6,1%
Skin and subcutaneous tissue disorders	Count	38	33	71
	% of Total	1,5%	1,3%	2,8%
Surgical and medical procedures	Count	9	5	14
	% of Total	,4%	,2%	,6%
Vascular disorders	Count	54	62	116
	% of Total	2,1%	2,5%	4,6%
Total	Count	1317	1198	2515
	% of Total	52,4%	47,6%	100,0%

Per Protocol Analysis

Per Protocol (PP) results are shown in Table S6 and supplementary figures. In the C2 group 69 patients and in the T0 group 82 patients were analysed per protocol. According to protocol PP analysis was on all patients started and kept on the allocated study medication without more than 14 days interruption until 6 months after LT or until death or re-transplantation.

Chronic rejection (PP)

Chronic rejection occurred in PP analysis in 2/69 (2.9 %) with C2 versus 0/82 with T0 (Fisher exact testp=0.21, logrank p=0.11).

Table S6. Cumulative raw incidences (n,%), and Kaplan-Meier estimates of the cumulative incidences with hazard ratio (HR) C2 versus T0 of patients reaching endpoints at 3, 6 and 12 months after LT in the C2 group (n=69) versus those in the T0 group (n=82) (**PP analysis**).

		Cumulative raw incidence			Kaplan-Meier estimate of cumulative incidence and HR			
	Group	C 2 (n=84)	T0 (n=85)	Fisher p	C2 (CI)	T2 (CI)	HR (CI)	logrank p
Endpoint \		N (%)	N (%)					
tBPAR *	3 mo	8 (11.6%%)	6 (7.3%)	0.41	7.6% (1.1-14.1)	7.4% (1.7-13.1)	1.624 [0.588-4.477]	0.24
	6 mo	10 (14.5%)	7 (8.5%)	0.31	10.9% (3.3-18.5)	7.4% (1.7-13.1)	1.778 [0.700-4.517]	0.24
	12 mo	10 (14.5%)	7 (8.5%)	0.31	15.9% (6.9-24.9)	8.8% (2.2-15.0)	1.778 [0.700-4.517]	0.24
Mortality	3 mo	5 (7.2%)	4 (4.9%)	0.75	7.2% (1.1-13.3)	4.9% (0.2-9.6)	1.507 [0.439-5.183]	0.54
	6 mo	6 (8.7%)	5 (6.1%)	0.55	8.7% (2.0-15.4)	6.1% (1.0-11.2)	1.451 [0.471-4.477]	0.74
	12 mo	8 (11.6%)	5 (6.1%)	0.26	8.7% (2.0-15.4)	6.1% (1.0-11.2)	1.941 [0.669-5.642]	0.24
re-LT * *	3 mo	5 (7.2%)	3 (3.7%)	0.47	7.2% (1.1-13.3)	3.7% (0.4-7.0)	2.016 [0.534-7.634]	0.33
	6 mo	5 (7.2%)	3 (3.7%)	0.47	7.2% (1.1-13.3)	3.7% (0.4-7.0)	2.016 [0.534-7.634]	0.33
	12 mo	8 (11.6%)	4 (4.9%)	0.11	11.6% (4.0-19.2)	4.9% (0.2-9.6)	2.444 [0.784-7.634]	0.13
re-LT or	3 mo	9 (13.0%)	6 (7.3%)	0.28	13.0% (5.0-21.0)	7.3% (1.6-13.0)	1.840 [0.682-4.959]	0.24
mortality	6 mo	10 (14.5%)	7 (8.5%)	0.31	14.5% (6.3-22.7)	8.2% (2.3-14.6)	1.760 [0.693-4.467]	0.25
	12 mo	**15 (21.7%)**	**8 (9.8%)**	0.07	**21.7% (11.9-31.5)**	**9.8% (3.3-16.73**	**2.344 [1.018-5.393]**	**0.045**
tBPAR or	3 mo	17 (24.6%)	12 (14.6%)	0.15	24.6% (14.4-34.8)	14.6 (7.0-22.2)	1.736 [0.843-3.576]	0.14
re-LT or	6 mo	20 (29.0%)	14 (17.1%)	0.12	29.0% (18.2-39.8)	17.1 (8.9-25.3)	1.780 [0.912-3.479]	0.10
mortality	**12 mo**	**23 (33.3%)**	**15 (18.3%)**	**0.04**	**33.3% (22.1-44.5)**	**18.8 (9.9-26.7)**	**1.935 [1.020-3.668]**	**0.04**
BPAR *	3 mo	20 (29.0%)	18 (22.0%)	0.35	30.6% (19.4-41.8)	22.2% (13.2-31.2)	1.339 [0.715-2.503]	0.37
	6 mo	23 (33.3%)	19 (23.7%)	0.20	35.6% (23.8-47.4)	23.5% (14.3-32.7)	0.815 [0.882-2.698]	0.20
	12 mo	23 (33.3%)	19 (23.7%)	0.20	35.6% (23.8-47.4)	23.5% (14.3-32.7)	0.815 [0.882-2.698]	0.20
tACR *	3 mo	21 (30.4%)	26 (31.7%)	1.00	31.9% (20.5-43.3)	32.1% (21.9-42.3)	0.917 [0.909-1.612]	0.94
	6 mo	24 (34.8%)	27 (32.9%)	0.86	36.8% (25.0-48.6)	33.4% (23.2-43.6)	1.021 [0.942-1.662]	0.94
	12 mo	24 (34.8%)	27 (32.9%)	0.86	36.8% (25.0-48.6)	33.4% (23.2-43.6)	1.021 [0.980-1.731]	0.94

For KM analysis *) censored for re-LT or mortality or **) for mortality.

Legend to Supplementary Figures:

Figure S1. Mean cyclosporine 2-hour levels during the first year after liver transplantation.
Figure S2. Mean tacrolimus trough levels during the first year after liver transplantation.
Figure S3. Cumulative incidence of tACR (ITT) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S4. Cumulative incidence of retransplantation or mortality (death-uncensored graft failure, which is the inverse of retransplantation-free survival). (ITT) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S5. Cumulative incidence of tBPAR, (PP) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S6. Cumulative incidence of tACR (PP) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S7. Cumulative incidence of BPAR (PP) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S8. Cumulative incidence of mortality (PP) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S9. Cumulative incidence of re-transplantation (PP) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S10 . Cumulative incidence of re-transplantation or death (PP) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.
Figure S11 . Cumulative incidence of combined endpoint of tBPAR, retransplantation or death (PP) with hazard ratio and 95% confidence interval (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.

Figure S3. Cumulative incidence of tACR (ITT)(KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.

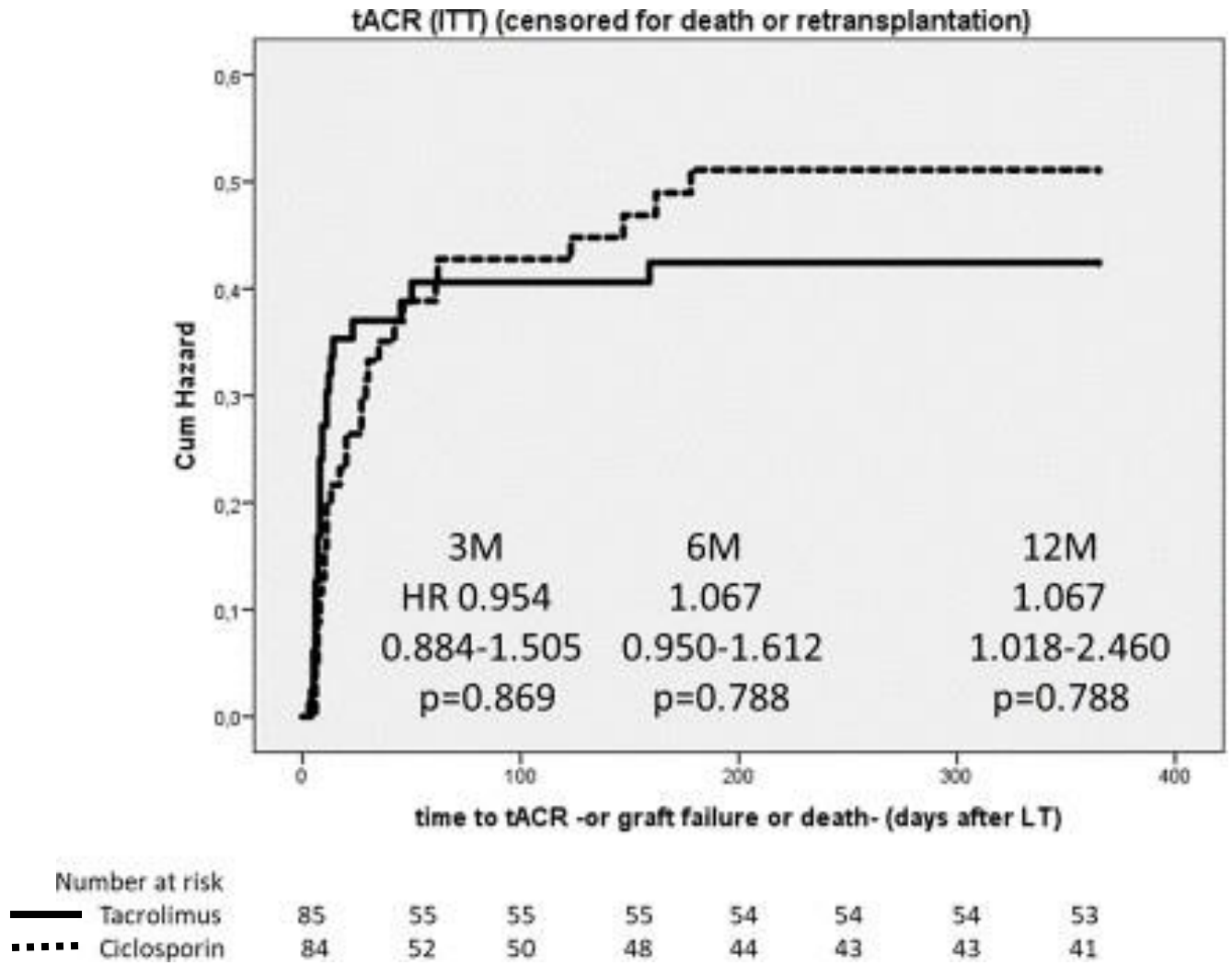


Figure S4. Cumulative incidence of retransplantation or mortality (death-uncensored graft failure). (ITT)(KM and logrank analysis).

Solid line: Tacrolimus. Interrupted line: Cyclosporin.

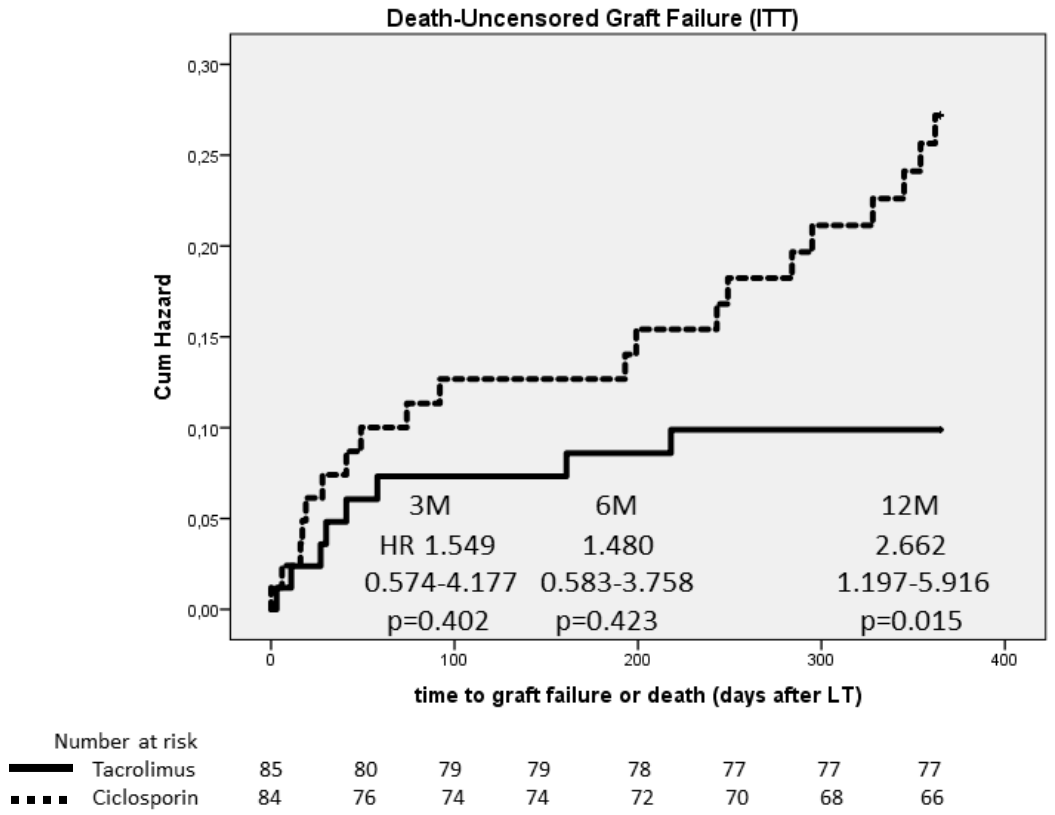
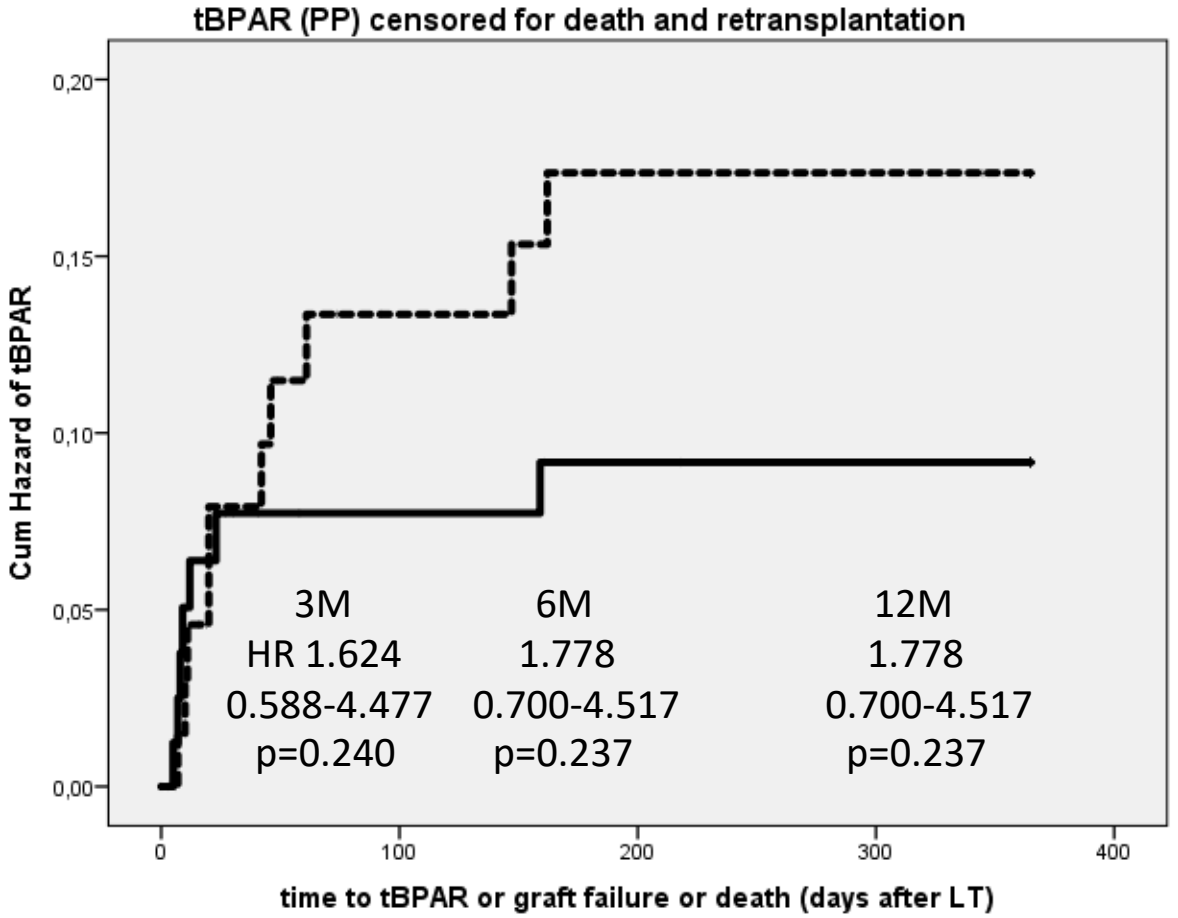


Figure S5. Cumulative incidence of tBPAR, (PP)(KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.



Number at risk

Tacrolimus	82	71	70	70	68	67	67	67
Ciclosporin	69	54	51	50	48	48	48	46

Figure S6. Cumulative incidence of tACR (PP)(KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.

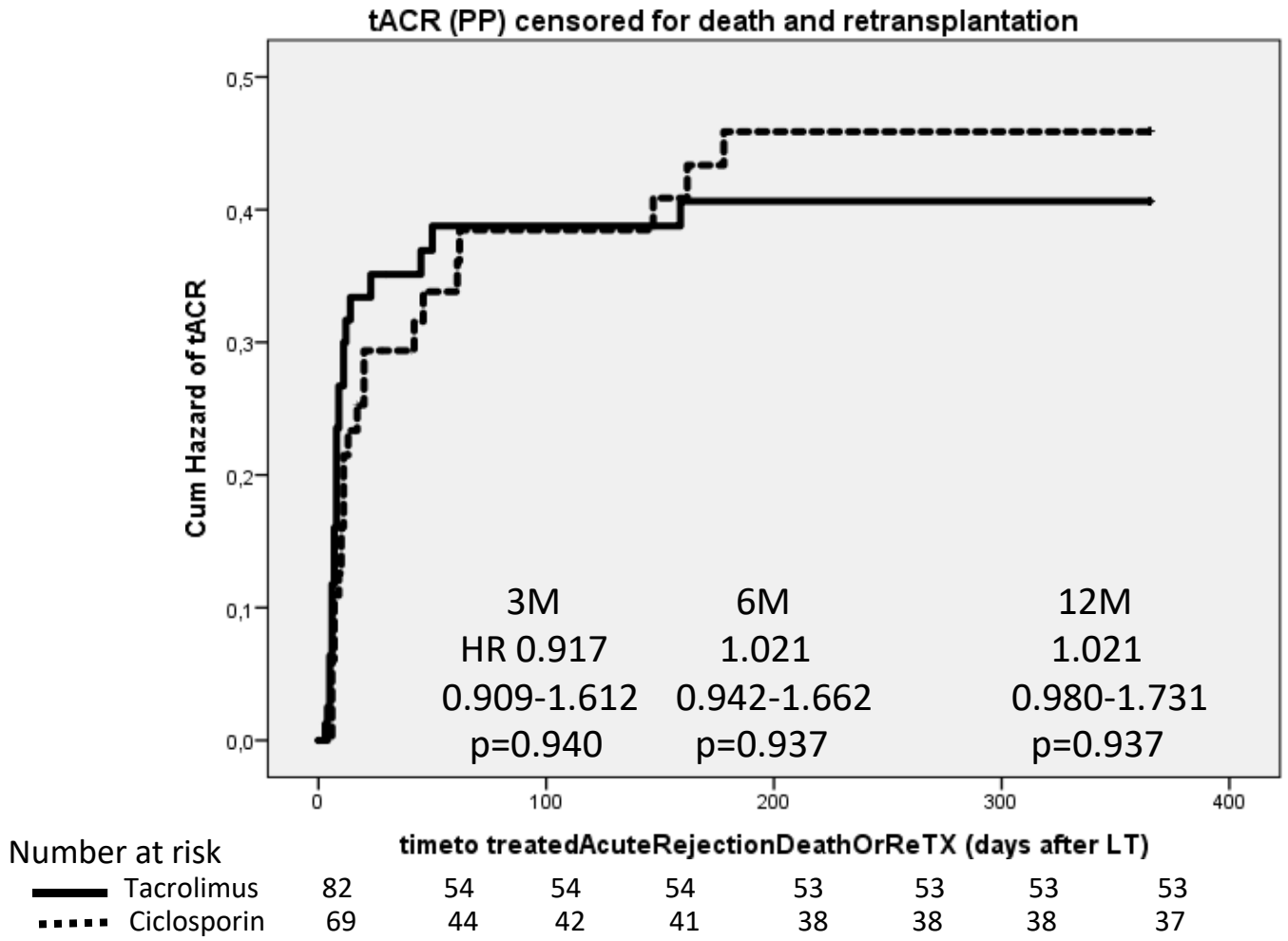
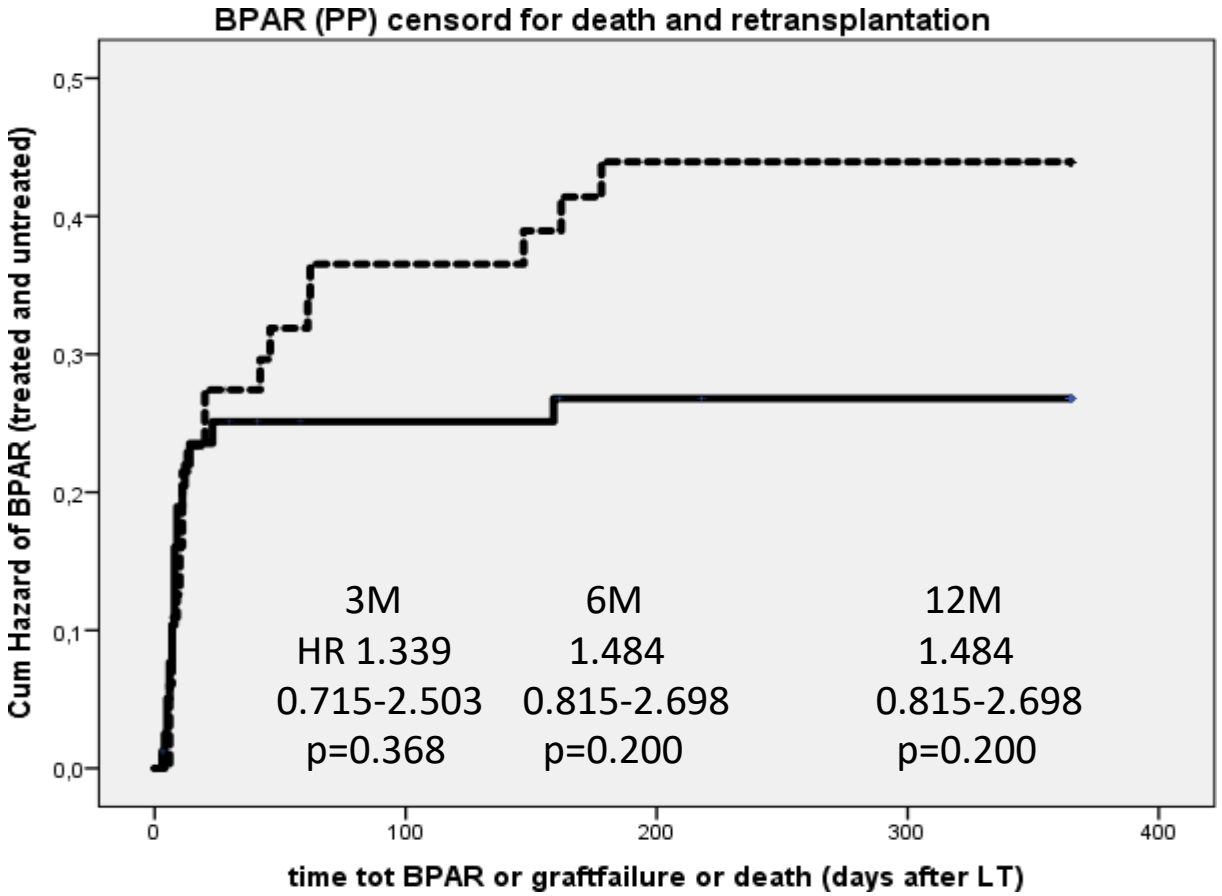


Figure S7. Cumulative incidence of BPAR (PP)(KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.



Number at risk

Tacrolimus	82	61	60	60	58	57	57	57
Ciclosporin	69	44	42	41	38	38	38	36

Figure S8. Cumulative incidence of mortality (PP) (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.

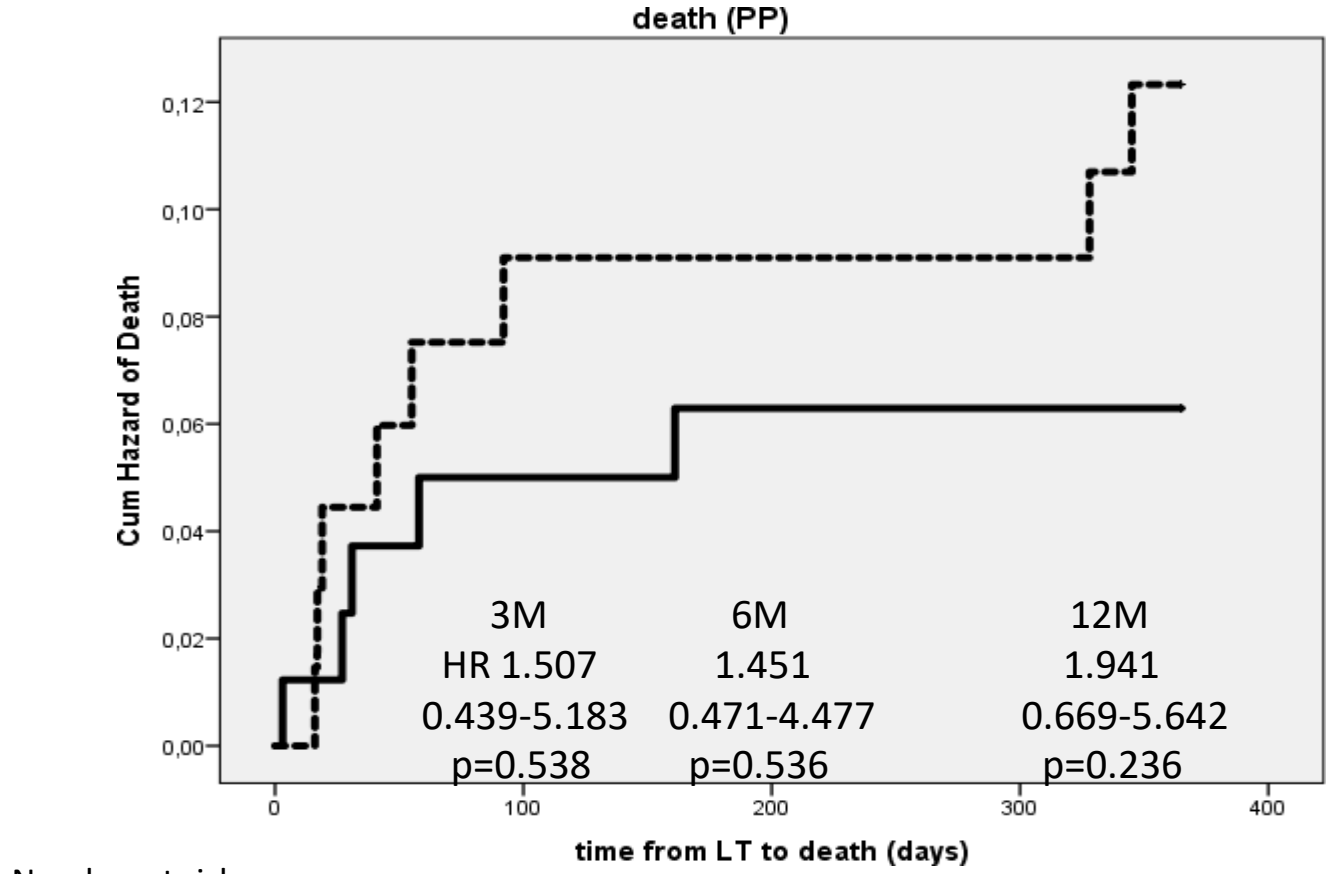


Figure S9. Cumulative incidence of retransplantation (PP)(KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.

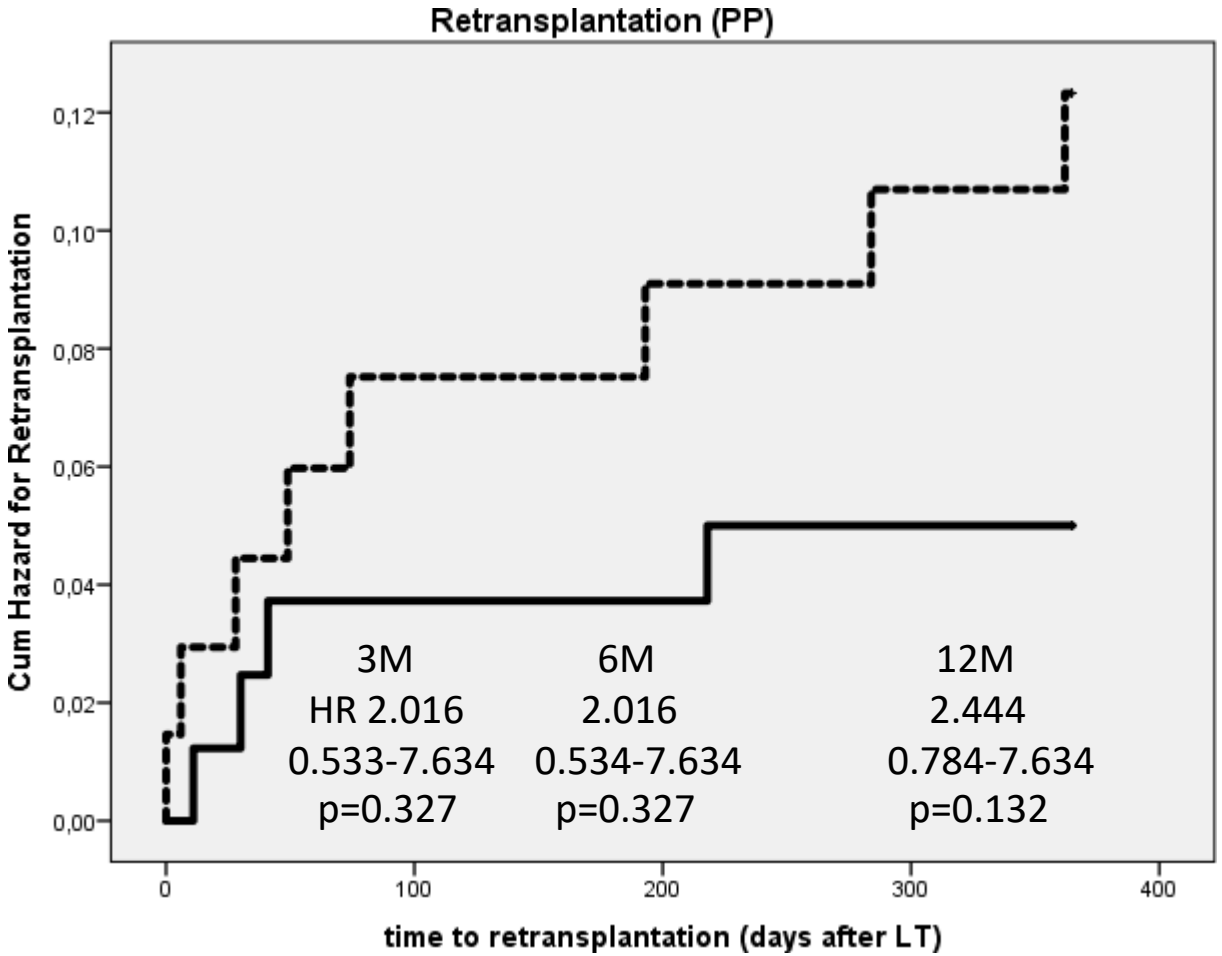


Figure S10 . Cumulative incidence of re-transplantation or death (PP) (KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.

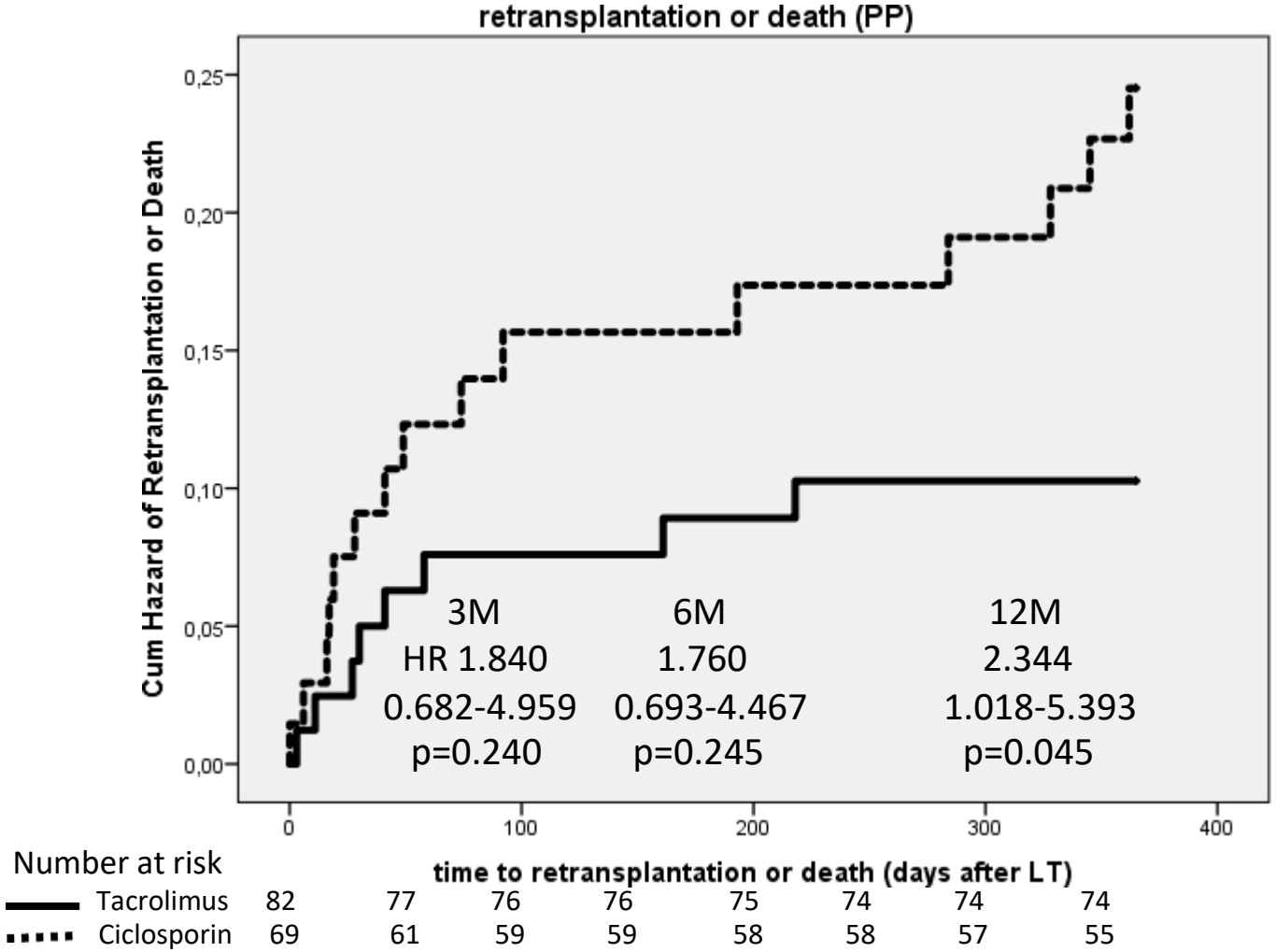
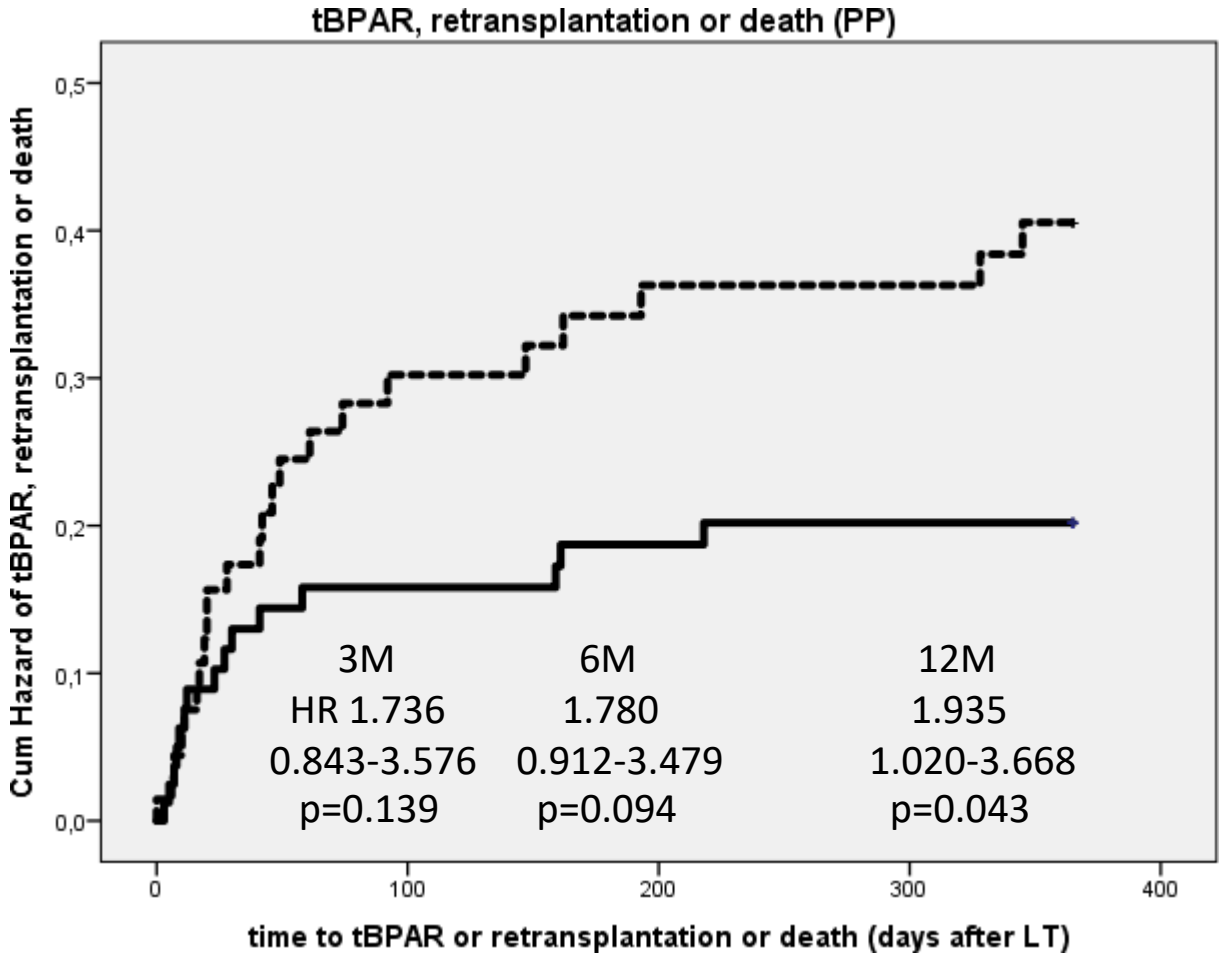


Figure S11 . Cumulative incidence of combined endpoint of tBPAR, retransplantation or death (PP)(KM and logrank analysis). Solid line: Tacrolimus. Interrupted line: Cyclosporin.



Number at risk

Tacrolimus	82	71	70	70	68	67	67	67
Ciclosporin	69	54	51	50	48	48	48	46