ORIGINAL ARTICLE

Repeated kidney re-transplantation—the Eurotransplant experience: a retrospective multicenter outcome analysis

Volker Assfalg[1,2], Katharina Selig[3], Johanna Tolksdorf[3], Marieke van Meel[4], Erwin de Vries[4], Anne-Marie Ramsoebhag[4], Axel Rahmel[4†], Lutz Renders[1,5], Alexander Novotny[1,2], Edouard Matevossian[1,2], Stefan Schneeberger[6], Alexander R. Rosenkranz[7], Gabriela Berlakovich[8], Dirk Ysebaert[9], Noël Knops[10], Dirk Kuypers[11], Laurent Weekers[12], Anja Muehlfeld[13], Lars-Christian Rump[14], Ingeborg Hauser[15], Przemyslaw Pisarski[16], Rolf Weimer[17], Paolo Fornara[18], Lutz Fischer[19], Volker Kliem[20], Urban Sester[21], Dirk Stippel[22], Wolfgang Arns[23], Hans-Michael Hau[24], Martin Nitschke[25], Joachim Hoyer[26], Stefan Thorban[1,2], Julia Weinmann-Menke[27], Katharina Heller[28], Bernhard Banas[29], Vedat Schwenger[30], Silvio Nadalin[31], Kai Lopau[32], Norbert Hüser[1,2] & Uwe Heemann[1,5]

1 School of Medicine, TransplanTUM, Munich Transplant Center, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
2 Department of Surgery, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
3 Department of Mathematics, Technical University of Munich, Garching near Munich, Germany
4 Eurotransplant International Foundation, Leiden, The Netherlands
5 Department of Nephrology, School of Medicine, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany
6 Universitätsklinik für Visceral-, Transplantations- und Thoraxchirurgie Innsbruck, Medical University of Innsbruck, Innsbruck, Austria
7 Division of Nephrology, Medical University of Graz, Graz, Austria
8 Division of Transplantation, Department of Surgery, Medical University of Vienna, Wien, Austria
9 Department of Surgery, Antwerp University Hospital, Antwerp University, Edegem, Belgium
10 Department of Pediatric Nephrology, University Hospitals Leuven, Leuven, Belgium

SUMMARY

In Eurotransplant kidney allocation system (ETKAS), candidates can be considered unlimitedly for repeated re-transplantation. Data on outcome and benefit are indeterminate. We performed a retrospective 15-year patient and graft outcome data analysis from 1464 recipients of a third or fourth or higher sequential deceased donor renal transplantation (DDRT) from 42 transplant centers. Repeated re-DDRT recipients were younger (mean 43.0 vs. 50.2 years) compared to first DDRT recipients. They received grafts with more favorable HLA matches (89.0% vs. 84.5%) but thereby no statistically significant improvement of patient and graft outcome was found as comparatively demonstrated in 1st DDRT. In the multivariate modeling accounting for confounding factors, mortality and graft loss after 3rd and ≥4th DDRT ($P < 0.001$ each) and death with functioning graft (DwFG) after 3rd DDRT ($P = 0.001$) were higher as compared to 1st DDRT. The incidence of primary nonfunction (PNF) was also significantly higher in re-DDRT (12.7%) than in 1st DDRT (7.1%; $P < 0.001$). Facing organ shortage, increasing waiting time, and considerable mortality on dialysis, we question the current policy of repeated re-DDRT. The data from this survey propose better HLA matching in first DDRT and second DDRT and careful selection of candidates, especially for ≥4th DDRT.

Transplant International 2020; 33: 617–631

Key words

allocation, child, fourth, graft, kidney, loss, repeated, re-transplantation, survival, third

Received: 24 March 2019; Revision requested: 9 May 2019; Accepted: 27 December 2019; Published online: 30 January 2020

Correspondence

PD Dr. med. Volker Assfalg, Department of Surgery, School of Medicine, TransplanTUM, Munich Transplant Center, Klinikum rechts der Isar, Technical University of Munich, Ismaningerstr. 22, D-81675 Munich, Germany.
Tel.: +49-(0)89-4140-2121; fax: +49-(0)89-4140-4870;
e-mail: volker.assfalg@tum.de

doi:10.1111/tri.13569

11 Depertmant of Nephrology, University Hospitals Leuven, Leuven, Belgium
12 Departement de Nephrologie, Centre Hospitalier Universitaire de Liège, Domaine Universitaire du Sart Tilman, Liège, Belgium
13 Klinik für Nieren- und Hochdruckkrankheiten, Rheumatologische und Immunologische Erkrankungen, Uniklinik RWTH Aachen, Aachen, Germany
14 Department of Internal Medicine/Nephrology, Universitätsklinikum Düsseldorf, Düsseldorf, Germany
15 Department of Nephrology, Goethe University Frankfurt, University Clinic Frankfurt, Frankfurt/M, Germany
16 Department of Surgery, Universitätsklinikum Freiburg, Freiburg, Germany
17 Transplant Center, Universitätsklinikum Gießen und Marburg GmbH, Gießen, Germany
18 Department of Urology, Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg, Universitätsklinikum Halle, Halle, Germany
19 Department of Hepatobiliary and Transplant Surgery, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
20 Nephrologisches Zentrum Niedersachsen, Transplantationszentrum Hann. Münden, Hannoversch Münden, Germany
21 Transplantationszentrum des Saarlandes, Universitätsklinikum Homburg, Homburg, Germany
22 Department of Surgery, Universitätsklinikum Köln, Köln, Germany
23 Department of Nephrology, Krankenhaus Köln-Merheim – Klinikum der Universität Witten/Herdecke, Köln, Germany
24 Department of Surgery, Universitätsklinikum Leipzig, Leipzig, Germany
25 Department of Nephrology, Universitätsklinikum Schleswig-Holstein, Lübeck, Germany
26 Klinik für Innere Medizin, Nephrologie und Internistische Intensivmedizin, Universitätsklinikum Marburg, Marburg, Germany
27 Department of Nephrology, I. Medizinische Klinik und Poliklinik, Johannes Gutenberg-Universität, Mainz, Germany
28 Department of Nephrology, Universitätsklinikum Erlangen, Erlangen, Germany
29 Department of Nephrology, Universitätsklinikum Regensburg, Regensburg, Germany
30 Transplantationszentrum, Klinikum Stuttgart, Katharinenhospital, Stuttgart, Germany
31 Department of Surgery, Universitätsklinikum Tübingen, Tübingen, Germany
32 Nephrologie, Zentrum Innere Medizin, Universitätsklinikum Würzburg, Würzburg, Germany

[†]Present address: Deutsche Stiftung Organtransplantation, DSO, Deutschherrnufer 52, D-60594 Frankfurt, Germany
Volker Assfalg and Katharina Selig contributed equally to this work.
Norbert Hüser and Uwe Heemann contributed equally to this work.

Introduction

Kidney transplantation increases recipient survival and quality of life in patients suffering from end-stage renal disease (ESRD) [1]. Furthermore, graft and patient survival after deceased donor renal transplantation (DDRT) continuously improved over the last decades. Numerous investigations compared the outcome of re-transplantation with the continuation of dialysis after failure of the first graft and clearly demonstrated the benefit of re-DDRT for patients [2–4] and socio-economic considerations [5,6]. However, any advantages of repeated re-DDRT (third, fourth kidney transplant) remain unclear due to scarce data.

In the Eurotransplant (ET) area, the number of patients being re-waitlisted after returning to dialysis steadily ranges between 17.9% and 18.9% [7]. Mortality in these patients has been reported to be high, and re-transplantation is therefore recommended [2–4]. The outcome of re-DDRT has improved significantly because of better panel reactive antibody (PRA) screening, crossmatching, HLA matching, postoperative management, and immunosuppression protocols [8,9]. The outcome of a second graft has been reported to be similar to first DDRT [8,10]. The longest survival of a secondary graft was observed in recipients with a graft survival of the first kidney of more than three years [11]. Nephrologists are recommended to evaluate re-transplantation as soon as possible after return to dialysis, even in elderly candidates [12]. However, the number of immunized re-listed patients on the waiting list grows and aggravates organ shortage, which could be assumed to push transplant physicians to accept marginal and unsatisfyingly matched organs with scientifically proven minor outcome and early graft loss [13]. Furthermore, repeated re-DDRT inevitably leads to complex and high-level immunization of the patients [14,15]. Additionally, recipients with previously failed grafts frequently have a long history of comorbidities, side effects of long-term immunosuppression, and numerous surgical interventions with an increased risk of technical problems during re-transplantation, all associated with reduced outcome [8,16,17].

To alleviate this vicious cycle of repeated re-DDRT, it might be necessary to adjust allocation policy and possibly restrict repeated re-DDRT in order to allocate kidneys to more promising donor–recipient constellations.

Whereas outcome of repeated re-transplantation has been analyzed in the UNOS/OPTN area and some single-transplant centers [16,18–25], there exists no comprehensive analysis on the respective collective of repeated re-DDRT recipients in the Eurotransplant Kidney Allocation System (ETKAS) and Eurotransplant Senior Program (ESP).

Eurotransplant kidney allocation system was first introduced in 1996 [26] and thereafter continuously refined to improve patient and graft outcome based on medical and immunological criteria and to streamline use of available donor organs. DDRT allocation is based on histocompatibility, waiting time, sensitization, logistic aspects with the objective of minimizing ischemia time, a child bonus, and medical urgency [27,28]. The ESP started in 1999 to meet the problem of increasing numbers of both older donors and recipients. ESP allocation directs kidneys from postmortem donors of ≥65 years to recipients of ≥65 years without HLA matching and aims at short cold ischemia times by regional allocation [29]. Both ETKAS and ESP admit immunologically sensitized candidates [29]. Hitherto, neither the number of transplants received nor expected graft or patient survival is part of the allocation algorithms.

This study analyses the outcome of repeated re-DDRT (3rd and ≥4th transplants) from 42 kidney transplant centers in comparison with the results from 1st DDRT within the ET area.

Patients and methods

The long-term outcome of repeated kidney only re-transplantation from brain death deceased donors within ETKAS and ESP in the ET area between 1996 and 2010 was investigated. In this time period, all transplant centers within the ET area performed in total 45 435 DDRTs.

Data completeness at the ET registry turned out to be unsatisfactory due to inconsistent obligation for the transplant centers to input data. Therefore, a digitalized questionnaire like previously performed by the ET community for another issue [30] was sent to all 65 ET transplant centers. Outcome of 1st DDRT has previously been demonstrated to be comparable to results after 2nd DDRT [2,4,5,8,15,31]. Therefore, and because of the high number of cases (n = 5950) and the impossibility to encourage transplant centers to complete this huge amount of datasets, the latter patients were excluded from our survey and the questionnaire focused on 3rd and ≥4th DDRT only.

The request was issued between July 2013 and April 2015 and asked for sequence of organ transplantation, date of last follow-up, graft loss and date of loss, patient's death and date of death, and death with functioning graft (DwFG), respectively. DwFG is an appropriate measure to analyze the number of deaths not associated with graft failure and therefore gives insights into the concomitant health status of the affected recipients. Information on gender, age at transplant, HLA match, waiting time, transplant period, and general information on the overall ET waiting list and transplantations was obtained from the ET database. Forty-two centers (42/65; 64.6%) returned the questionnaires, and data completeness increased markedly. For statistical analyses, all records without follow-up were removed and noninformative censoring was assumed for all data analyzed to cope with different follow-up times and the problem of patients lost to follow-up [32]. Figure 1 displays the patient selection process. In 88 cases, recipients appeared repeatedly within the investigated period and 280 donors donated both kidneys for repeated re-DDRT patients. Last follow-up data were accomplished in October 2017, and final mean and median follow-up times for both 1st DDRTs and repeated re-DDRTs were 3040 and 2922 days vs. 2752 and 2496 days. Follow-up was capped at 15 years after DDRT for the analysis.

According to ET data protection policy, all data were anonymized for patient's and center's identity and nationality at the ET registry department and then analyzed by the authors.

Comparisons of patient characteristics among groups were performed using generalized estimating equations (GEE) to account for dependent observations of patients with multiple transplants or sharing the same donor. Cumulative incidence curves were calculated for patients' death, DwFG, and graft loss, thereby accounting for the problem of competing risks between DwFG and graft loss and dependent observations using robust standard error estimates based on an infinitesimal jackknife estimate [33]. Censored patient survival and cumulative incidence of DwFG and graft loss were compared to all investigated subgroups and to all standard ETKAS and ESP first transplantations between 1996 and 2010 (n = 38 173) whereof data were available in the ET database (survival: n = 33 637 and DwFG/graft loss: n = 31 263, respectively). For factors with more than two groups, Bonferroni correction was applied to account for multiple pairwise comparisons. For patient survival, Cox proportional hazards models were used with a robust covariance matrix for the confidence intervals accounting for dependent observations, and for DwFG and graft loss, the Fine Gray proportional regression models were used with semiparametric random effects for multivariate competing risk data [34,35] for the analysis.

Multivariable models for patient survival, DwFG, and graft loss included covariates previously identified to affect graft failure and mortality after DDRT, such as age and gender of recipient, waiting time, and HLA mismatches for comparison between 1st, 3rd, and ≥4th DDRT [36]. Additional models for analysis within repeated re-DDRT recipients included age and gender of the donor, cold ischemia time, PRA% at transplant, and presence of HLA antibodies as additional confounding variables to the ones mentioned above. Hazard ratios and subdistribution hazard ratios are reported with 95% confidence intervals.

Primary nonfunction (PNF) was assumed when graft failure was recorded within 90 days after transplantation and before recipient's death. These patients were then excluded from all investigations on graft loss.

The numbers of HLA mismatches including HLA-A, HLA-B, and HLA-DR loci were analyzed with regards to transplant outcome. In view of pleasing results for 1st DDRTs with numerous matches, we additionally divided all 1st DDRT and repeated re-DDRT recipients in two groups according to the configuration of HLA matches: all matches with at least one HLA-DR and at least one HLA-A or one HLA-B match were assigned for the group of "favorable matches", and all other matches were defined "unfavorable matches."

Facing relevant numbers of recipients with missing follow-up, we performed an analysis to identify subgroups with statistically higher rates of missing data. Whereas no differences in patients with and without follow-up could be revealed with regards to age, gender, waiting time, transplant sequence, PNF, and HLA match, more patients transplanted between 2006 and 2010 had no follow-up within the repeated re-DDRT collective, respectively (Table 1a). For comparison, among 1st DDRT recipients no follow-up was more frequently observed in patients of younger age, female gender, a good HLA match, without PNF, and transplantation between 2001 and 2010 (Table 1b).

A two-sided level of significance of 0.05 was used for all analyses. Statistical analysis was performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) with the packages survival and timereg [37,38]. All data ascertainments and analyses were performed in accordance with ethical standards as laid down in the Declaration of Helsinki.

Results

1st DDRT recipients were significantly older than recipients of a 3rd or ≥4th DDRT (mean age 50.2 years, SE 0.1 vs. 43.0 years, SE 0.4; $P < 0.001$; Fig. 2). Comparison of average waiting time for repeated re-DDRTs versus 1st DDRT revealed no significant difference (1323.2 days, SE 30.9 vs. 1339.2 days, SE 5.1; $P = 0.792$). For this subanalysis only, patients with a waiting time less than or equal to 180 days were excluded, assuming these short times were due to a preceding PNF, conserving waiting time for the subsequent allocation. Mean waiting time was shorter in children because of the pediatric bonus in ETKAS, and recipients of ≥65 years participating in the ESP in all subgroups investigated within this study.

Relevant basic patient demographics, transplant-specific information, and subgroup-related transplant outcome are outlined in Tables 2, and 3 summarizes results for the multivariable models for patient survival as well as the competing risks DwFG and graft loss.

After accounting for confounding variables, the multivariable models for all recipients showed significantly worse patient and graft survival for 3rd and ≥4th DDRT compared to 1st DDRT. Further, 3rd DDRT recipients had a significantly higher risk of DwFG compared to 1st DDRT, whereas comparison to ≥4th DDRT was not significant (Table 3a). The cumulative incidence curves regarding transplant sequence for patient death, DwFG, and graft loss are depicted in Fig. 3.

For the comparison between 3rd DDRT recipients and ≥4th DDRT recipients the multivariate models revealed no significant difference in DwFG and graft loss, but patient survival was significantly worse for ≥4th DDRT compared to 3rd DDRT ($P = 0.039$; Table 3b). It should be noted, that patient survival, graft loss, and DwFG did not differ significantly in repeated re-DDRT recipients between the three investigated time periods after accounting for the different length of follow-up by truncating at 8 years after DDRT (Table 2).

Older age was significantly associated with an increased risk of patients' death and DwFG, and with a decreased risk of graft loss in both the models for all recipients and repeated re-DDRT (Table 3), supporting the results of the univariate analysis (Table 2; Fig. 4).

Table 1. Overview on data completeness for follow-up of (a) repeated re-DDRT and (b) 1st DDRT with regard to patient- and transplant-specific factors.

	(a) Repeated re-DDRT					(b) 1st DDRT				
	Patients with follow-up		Lost to follow-up			Patients with follow-up		Lost to follow-up		
	n	%	*n*	%	*P*-value	*n*	%	*n*	%	*P*-value
Transplant sequence repeated re-DDRT										
3rd transplant	956	82.3	50	79.4						
≥4th transplant	206	17.7	13	20.6						
Gender										
Female	511	44.0	21	33.3		12 885	38.3	1210	40.4	0.025
Male	651	56.0	42	66.7		20 752	61.7	1786	59.6	
Age*										
0–15 years	20	1.7	1	1.6		1245	3.7	86	2.9	0.003
16–55 years	964	83.0	48	76.2		17 955	53.4	1781	59.4	
56–64 years	139	12.0	11	17.5		7756	23.1	676	22.6	
≥65 years	38	3.3	3	4.8		6681	19.9	453	15.1	
Missing	1	0.1	0	0.0		0	0.0	0	0.0	
Transplant period										
1996–2000	406	34.9	13	20.6	0.022	10 596	31.5	425	14.2	<0.001
2001–2005	353	30.4	18	28.6		10 512	31.3	1303	43.5	
2006–2010	403	34.7	32	50.8		12 529	37.2	1268	42.3	
Waiting time										
0–11 months	257	22.1	16	25.4		7789	23.2	836	27.9	
12–23 months	230	19.8	11	17.5		5601	16.7	497	16.6	
24–59 months	406	34.9	20	31.7		11 649	34.6	845	28.2	
≥60 months	269	23.1	16	25.4		8598	25.6	818	27.3	
PNF										
No PNF	1015	87.3	56	88.9		31 263	92.9	2986	99.7	<0.001
PNF	147	12.7	7	11.1		2374	7.1	10	0.3	
Immunulogical HLA mismatches (grouping)										
Favorable match†	1033	88.9	55	87.3		28 353	84.3	2605	86.9	<0.001
Unfavorable match‡	128	11.0	8	12.7		5197	15.5	374	12.5	
Missing	1	0.1	0	0.0		87	0.3	17	0.6	
Number of immunulogical HLA mismatches										
0	240	20.7	13	20.6		5716	17.0	563	18.8	<0.001
1	120	10.3	8	12.7		2241	6.7	205	6.8	
2	293	25.2	10	15.9		8006	23.8	745	24.9	
3	311	26.8	21	33.3		10 052	29.9	918	30.6	
4	137	11.8	7	11.1		4679	13.9	356	11.9	
5	50	4.3	4	6.3		2140	6.4	144	4.8	
6	10	0.9	0	0.0		716	2.1	47	1.6	
Missing	1	0.1	0	0.0		87	0.3	18	0.6	

*Age classes were chosen according to ET categorization.

†At least one HLA-DR plus at least one HLA-A or one HLA-B match.

‡No HLA-DR or neither HLA-A nor HLA-B match.

Finally, a significant relationship was detected between longer cold ischemia time and increased risk of patients' death and DwFG as well as between higher donor age and worse patient and graft survival in the multivariable models for repeated re-DDRT (Table 3b).

The incidence of PNF was significantly higher in re-DDRT (12.7%) than in 1st DDRT (7.1%; $P < 0.001$). For the latter group, younger age was positively associated with a lower rate of PNF ($P < 0.001$, Table 4a).

Despite lower number of HLA mismatches (Table S1) and younger recipient age, the outcome was inferior in

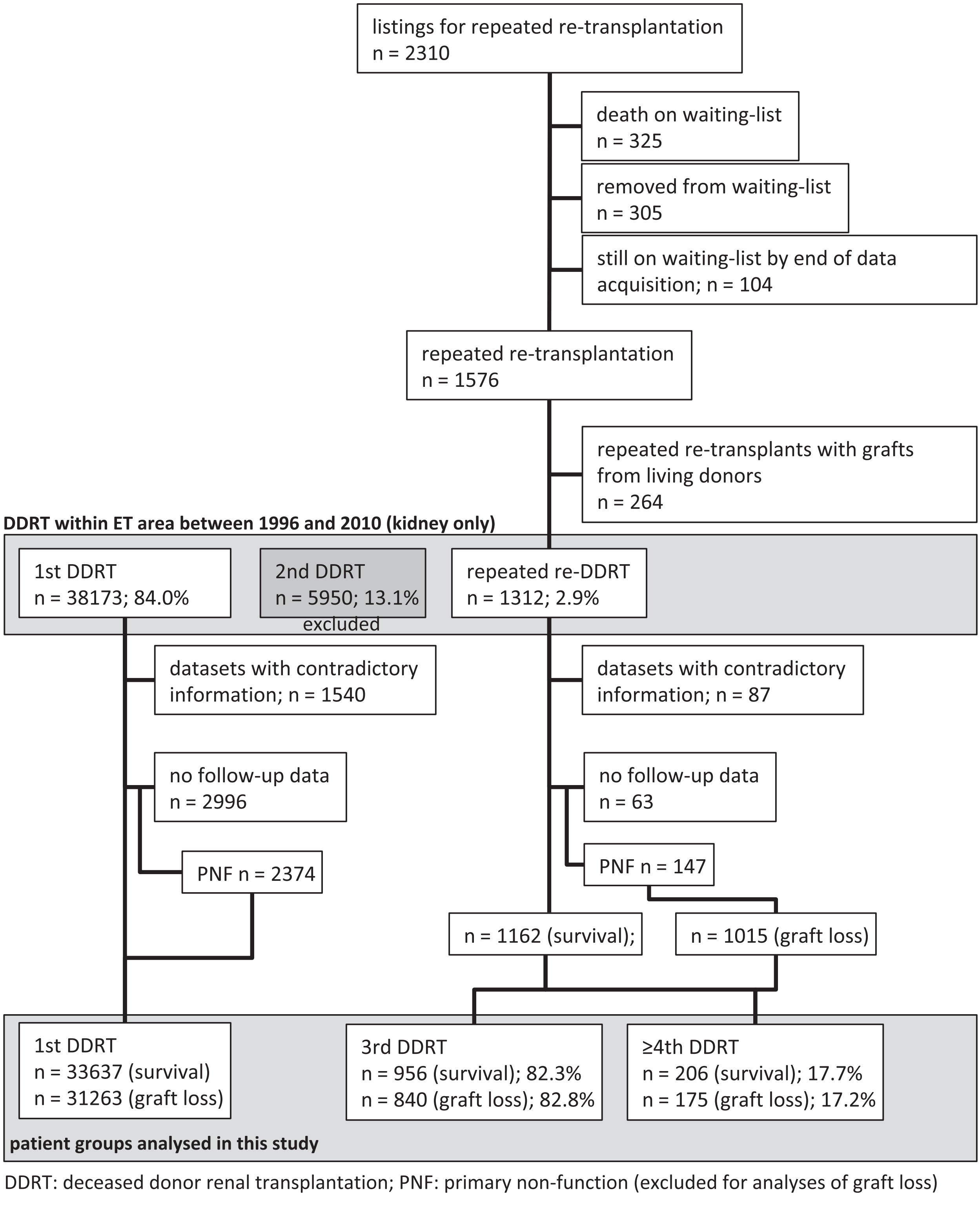

Figure 1 Flowchart: Selection process of patients analysed in this study. DDRT: deceased donor renal transplantation; PNF: primary non-function (excluded for analyses of graft loss)

3rd and ≥4th DDRT than in 1st DDRT recipients (Table 3a).

The rate of "favorable matches" was significantly higher in repeated re-DDRT compared to 1st DDRT recipients (Table 4b; 89.0% vs. 84.5%; $P < 0.001$), and "favorable matches" correlated positively with lower recipient's age in both 1st DDRTs ($P < 0.001$) and repeated re-DDRTs ($P = 0.011$; Table 4b). A

Table 2. Patient survival and cumulative incidence rates for DwFG and graft loss for 1st DDRT and repeated re-DDRT regarding sequence of transplantation and patient- and transplant-specific factors for repeated re-DDRTs.

	Patients		Patient survival				Patients competing risk†		Cumulative incidence of DwFG				Cumulative incidence of graft loss			
	n	%	1 year % ±SE	5 years % ±SE	10 years % ±SE	*P*-value	*n*	%	1 year % ±SE	5 years % ±SE	10 years % ±SE	*P*-value	1 year % ±SE	5 years % ±SE	10 years % ±SE	*P*-value
1st DDRT	33 637	100.0	94.7 ± 0.1	84.9 ± 0.2	70.1 ± 0.3		31 263	100.0	4.1 ± 0.1	11.2 ± 0.2	21.5 ± 0.3	6; 3	2.5 ± 0.1	11.1 ± 0.2	22.1 ± 0.3	1; 1; 1
re-DDRT	1162	100.0	95.2 ± 0.6	85.0 ± 1.1	71.2 ± 1.7		1015	100.0	3.6 ± 0.6	10.3 ± 1.0	18.6 ± 1.4		6.4 ± 0.8	23.2 ± 1.4	38.3 ± 1.8	
3rd DDRT	956	82.6	95.9 ± 0.7	86.5 ± 1.1	72.8 ± 1.8		840	82.8	3.2 ± 0.6	9.8 ± 1.0	18.7 ± 1.5		6.2 ± 0.8	21.4 ± 1.5	37.4 ± 1.9	
≥4th DDRT	206	17.8	92.1 ± 1.9	78.4 ± 3.2	63.8 ± 4.2		175	17.2	5.2 ± 1.7	12.7 ± 2.6	18.6 ± 3.4		7.5 ± 2.0	31.9 ± 3.6	42.4 ± 4.3	
Gender																
Female	511	44.1	96.1 ± 0.9	87.8 ± 1.5	74.4 ± 2.4	4	452	44.5	3.1 ± 0.8	8.2 ± 1.3	16.2 ± 2.0	9	6.9 ± 1.2	24.1 ± 2.1	41.3 ± 2.8	
Male	651	56.2	94.6 ± 0.9	82.9 ± 1.6	68.7 ± 2.3		563	55.5	3.9 ± 0.8	11.9 ± 1.4	20.5 ± 1.9		6.0 ± 1.0	22.6 ± 1.8	36.0 ± 2.3	
Age*																
0–15 years	20	1.7	100.0 ± 0.0	100.0 ± 0.0	79.7 ± 9.9	5; 2	18	1.8	0.0 ± 0.0	0.0 ± 0.0	6.7 ± 6.5		11.1 ± 7.4	33.3 ± 11.1	74.4 ± 12.4	7
16–55 years	964	83.2	96.2 ± 0.6	88.1 ± 1.1	76.3 ± 1.7	1; 1	845	83.3	2.7 ± 0.6	7.4 ± 0.9	14.2 ± 1.4	1; 1	6.8 ± 0.9	23.8 ± 1.5	39.4 ± 1.9	
56–64 years	139	12.0	91.9 ± 2.3	70.3 ± 4.1	39.6 ± 6.0		116	11.4	6.9 ± 2.4	24.1 ± 4.1	44.6 ± 5.6		4.3 ± 1.9	20.6 ± 3.8	28.3 ± 4.8	
≥65 years	38	3.3	78.9 ± 6.6	50.9 ± 9.4	40.7 ± 11.8		35	3.4	14.3 ± 5.9	41.4 ± 9.1	54.0 ± 12.7		2.9 ± 2.8	14.4 ± 6.0	20.7 ± 8.1	
Missing	1	0.1	100.0 ± 0.0	100.0 ± 0.0	—		1	0.1	0.0 ± 0.0	0.0 ± 0.0	—		0.0 ± 0.0	0.0 ± 0.0	—	
Transplant period																
1996–2000	406	35.1	96.1 ± 1.0	86.7 ± 1.7	76.1 ± 2.2		353	34.8	2.3 ± 0.8	9.1 ± 1.5	16.5 ± 2.0		7.9 ± 1.4	25.4 ± 2.3	39.5 ± 2.6	
2001–2005	353	30.5	95.7 ± 1.1	85.7 ± 1.9	66.5 ± 3.0		310	30.5	4.2 ± 1.1	9.1 ± 1.6	19.8 ± 2.4		4.9 ± 1.2	22.2 ± 2.4	38.0 ± 3.0	
2006–2010	403	34.8	93.9 ± 1.2	82.7 ± 2.1	—		352	34.7	4.3 ± 1.1	12.3 ± 1.9	—		6.3 ± 1.3	21.6 ± 2.4	—	
Waiting time																
0–11 months	257	22.2	94.9 ± 1.4	83.8 ± 2.4	70.5 ± 3.5		222	21.9	3.6 ± 1.3	9.4 ± 2.0	19.8 ± 3.0		7.2 ± 1.7	25.6 ± 3.0	40.2 ± 3.8	
12–23 months	230	19.9	95.2 ± 1.4	85.4 ± 2.6	68.3 ± 3.8		198	19.5	3.6 ± 1.3	11.1 ± 2.3	20.1 ± 3.2		5.1 ± 1.6	23.4 ± 3.1	37.6 ± 3.9	
24–59 months	406	35.1	95.8 ± 1.1	85.2 ± 1.8	73.8 ± 2.8		355	35.0	3.4 ± 1.0	9.9 ± 1.6	15.6 ± 2.2		6.5 ± 1.3	22.5 ± 2.3	37.8 ± 3.0	
≥60 months	269	23.2	94.7 ± 1.4	85.6 ± 2.2	70.4 ± 3.6		240	23.6	3.8 ± 1.2	10.9 ± 2.1	21.3 ± 3.2		6.7 ± 1.6	21.9 ± 2.8	37.9 ± 3.8	
Gender (donor)																
Female	521	45.0	95.1 ± 1.0	85.1 ± 1.7	71.3 ± 2.5		450	44.3	3.3 ± 0.8	10.3 ± 1.5	17.6 ± 2.0		6.5 ± 1.2	25.0 ± 2.1	38.4 ± 2.6	
Male	641	55.4	95.3 ± 0.8	85.0 ± 1.5	71.1 ± 2.2		565	55.7	3.7 ± 0.8	10.3 ± 1.3	19.4 ± 1.9		6.4 ± 1.0	21.9 ± 1.8	38.2 ± 2.4	
Age* (donor)																
0–15 years	39	3.4	94.8 ± 3.6	83.6 ± 6.1	73.2 ± 7.8		38	3.7	5.3 ± 3.6	13.3 ± 5.6	23.3 ± 7.3		2.6 ± 2.6	24.0 ± 7.0	30.7 ± 7.8	
16–55 years	846	73.1	96.2 ± 0.7	86.7 ± 1.2	72.8 ± 1.9		753	74.2	3.1 ± 0.6	9.1 ± 1.1	18.8 ± 1.6		5.7 ± 0.8	21.2 ± 1.5	36.5 ± 2.0	11
56–64 years	228	19.7	93.8 ± 1.6	82.3 ± 2.8	67.3 ± 3.9		184	18.1	4.4 ± 1.5	12.4 ± 2.5	16.1 ± 3.0		9.3 ± 2.1	29.9 ± 3.5	45.5 ± 4.2	
≥65 years	49	4.2	85.4 ± 5.0	70.4 ± 6.9	61.0 ± 9.2		40	3.9	7.5 ± 4.2	18.6 ± 6.4	18.6 ± 6.4		10.0 ± 4.7	30.8 ± 7.9	50.4 ± 10.0	
Cold ischemia time																
<10 h	80	6.9	96.2 ± 2.2	87.8 ± 4.8	76.3 ± 6.9		69	6.8	2.9 ± 2.0	7.3 ± 3.1	9.6 ± 3.8		4.3 ± 2.5	25.5 ± 5.4	33.1 ± 6.4	
10–18 h	422	36.4	95.7 ± 1.0	86.4 ± 1.8	71.4 ± 2.8		370	36.5	3.5 ± 1.0	8.4 ± 1.5	17.7 ± 2.5	8	5.7 ± 1.2	26.4 ± 2.4	38.4 ± 3.0	
≥18 h	550	47.5	95.1 ± 0.9	83.6 ± 1.6	70.4 ± 2.2		480	47.3	3.8 ± 0.9	12.4 ± 1.5	20.6 ± 2.0		7.9 ± 1.2	22.2 ± 1.9	38.6 ± 2.4	
Missing	110	9.5	93.5 ± 2.4	85.8 ± 3.6	67.2 ± 8.4		96	9.5	3.1 ± 1.8	7.7 ± 2.8	21.6 ± 7.2		3.1 ± 1.8	14.8 ± 3.8	37.5 ± 8.5	
PRA% at transplant																
0–5	503	43.4	95.2 ± 1.0	85.0 ± 1.7	71.4 ± 2.5		454	44.7	4.0 ± 0.9	11.4 ± 1.5	20.3 ± 2.1		3.8 ± 0.9	18.3 ± 1.9	35.2 ± 2.6	
6–84	540	46.6	95.7 ± 0.9	85.3 ± 1.6	72.1 ± 2.4		464	45.7	2.8 ± 0.8	8.9 ± 1.3	17.2 ± 2.0		9.1 ± 1.3	26.1 ± 2.1	39.8 ± 2.6	
≥85	116	10.0	93.1 ± 2.3	83.9 ± 3.6	64.5 ± 5.9		94	9.3	5.3 ± 2.3	11.4 ± 3.4	18.0 ± 4.8		6.4 ± 2.5	33.6 ± 5.4	47.2 ± 6.6	
Missing	3	0.3	100.0 ± 0.0	100.0 ± 0.0	100.0 ± 0.0		3	0.3	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0		0.0 ± 0.0	33.3 ± 27.2	33.3 ± 27.2	
HLA antibodies																
No	338	29.2	96.7 ± 1.0	86.9 ± 1.9	74.2 ± 2.8	10	304	26.3	2.6 ± 0.9	9.4 ± 1.7	17.9 ± 2.6		3.9 ± 1.1	21.4 ± 2.4	35.5 ± 3.2	
Yes	823	71.1	94.6 ± 0.8	84.2 ± 1.4	69.9 ± 2.0		711	61.4	3.9 ± 0.7	10.6 ± 1.2	18.9 ± 1.7		7.5 ± 1.0	24.0 ± 1.6	39.4 ± 2.1	

SE, standard error.

P-values: 1: <0.001; 2: 0.001; 3: 0.002; 4: 0.008; 5: 0.010; 6: 0.016; 7: 0.017; 8: 0.020; 9: 0.022; 10: 0.038; 11: 0.043.

*Age classes were chosen according to ET categorization.

†Patients without missing data for competing risks.

Table 3. Multivariable Cox regression models for patient survival and Fine Gray model with random effects for DwFG and graft loss of (a) 1st DDRT and repeated re-DDRT and (b) repeated re-DDRT including available confounding factors with units given in squared brackets.

	Patient survival			Competing risks			
				DwFG		Graft loss	
	Hazard ratio (95%-CI)	*P*-value		Subdistribution hazard ratio (95%-CI)	*P*-value	Subdistribution hazard ratio (95%-CI)	*P*-value
(a) 1st DDRT and repeated re-DDRT							
Transplant sequence group			Transplant sequence group				
1st DDRT	Reference		1st DDRT	Reference		Reference	
3rd DDRT	1.62 (1.43–1.83)	<0.001	3rd DDRT	1.35 (1.13–1.61)	0.001	1.73 (1.52–1.96)	<0.001
≥4th DDRT	2.40 (1.84–3.13)	<0.001	≥4th DDRT	1.34 (0.94–1.92)	0.110	2.13 (1.68–2.71)	<0.001
Age of recipient [10 years]	1.84 (1.80–1.88)	<0.001	Age of recipient [10 years]	1.89 (1.83–1.95)	<0.001	0.88 (0.87–0.89)	<0.001
Gender (recipient)			Gender (recipient)				
Female	Reference		Female	Reference		Reference	
Male	1.18 (1.13–1.23)	<0.001	Male	1.15 (1.09–1.21)	<0.001	1.02 (0.97–1.07)	0.472
Waiting time [years]	1.00 (0.99–1.01)	0.976	Waiting time [years]	1.00 (0.99–1.01)	0.866	0.99 (0.98–1.00)	0.006
Mismatch group			Mismatch group				
Favorable	Reference		Favorable	Reference		Reference	
Unfavorable	1.09 (1.04–1.15)	<0.001	Unfavorable	0.90 (0.84–0.97)	0.004	1.47 (1.38–1.57)	<0.001
(b) repeated re-DDRT							
Transplant sequence group			Transplant sequence group				
3rd DDRT	Reference		3rd DDRT	Reference		Reference	
≥4th DDRT	1.37 (1.02–1.85)	0.039	≥4th DDRT	1.11 (0.70–1.75)	0.670	1.23 (0.93–1.63)	0.150
Age of recipient [10 years]	1.66 (1.46–1.90)	<0.001	Age of recipient [10 years]	2.01 (1.69–2.39)	<0.001	0.81 (0.73–0.89)	<0.001
Age of donor [10 years]	1.14 (1.05–1.23)	<0.001	Age of donor [10 years]	0.99 (0.87–1.11)	0.805	1.17 (1.08–1.27)	<0.001
Gender (recipient)			Gender (recipient)				
Female	Reference		Female	Reference		Reference	
Male	1.25 (0.97–1.61)	0.085	Male	1.30 (0.91–1.86)	0.151	0.93 (0.74–1.17)	0.549
Gender (donor)			Gender (donor)				
Female	Reference		Female	Reference		Reference	
Male	1.12 (0.88–1.42)	0.352	Male	1.10 (0.77–1.57)	0.604	1.10 (0.87–1.38)	0.434
Waiting time [years]	1.00 (0.96–1.04)	0.966	Waiting time [years]	1.02 (0.96–1.08)	0.512	0.98 (0.94–1.02)	0.297
Mismatch group			Mismatch group				
Favorable	Reference		Favorable	Reference		Reference	
Unfavorable	1.28 (0.88–1.87)	0.192	Unfavorable	0.95 (0.52–1.75)	0.874	1.09 (0.75–1.57)	0.651
Cold ischemia time [h]	1.02 (1.00–1.04)	0.024	Cold ischemia time [h]	1.05 (1.03–1.08)	<0.001	1.01 (0.99–1.03)	0.197
PRA% at transplantation	1.00 (1.00–1.01)	0.132	PRA% at transplantation	1.00 (0.99–1.00)	0.522	1.00 (1.00–1.01)	0.052
HLA antibodies			HLA antibodies				
No	Reference		No	Reference		Reference	
Yes	1.27 (0.95–1.68)	0.097	Yes	1.06 (0.71–1.58)	0.775	1.03 (0.79–1.35)	0.819

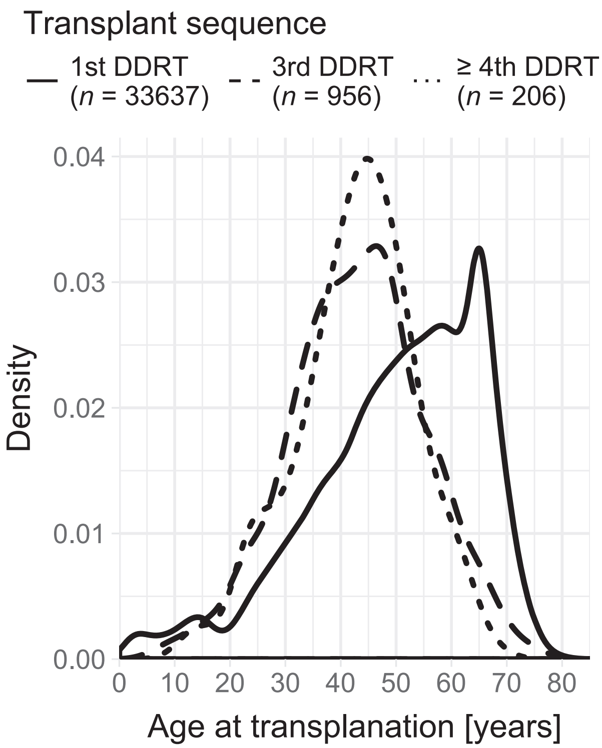

Figure 2 Age in years at deceased donor renal transplantation regarding transplant sequence.

conspicuously high number of unfavorable matches were found for the elderly of both 1st DDRTs (43.7%) and re-DDRTs (21.1%) which must be assumed to be a result of the waiver of HLA matching within the ESP. When recipients older than 64 years were excluded from the analysis, the difference in “favorable” matches across age was no longer significant for 1st DDRT recipients ($P = 0.090$) and repeated re-DDRTs ($P = 0.051$). Finally, the impact of “favorable” versus “nonfavorable” HLA matches on outcome was compared for both 1st DDRT and repeated re-DDRT recipients. Figure 5 displays the positive effects on patient death, DwFG, and graft loss in the 1st DDRT controls whereas no benefit of “favorable” HLA matches could be detected for the repeated re-recipients in the univariate and multivariable analysis after accounting for confounding variables, just as revealed in the HLA mismatch analysis (Tables 2 and 3; Fig. S1).

Discussion

With the booming success of transplantation, the rate of sequential DDRTs increased over time and will do so in the future due to better survival of recipients. However, reduced graft survival potentially results from the demographic change toward older donors and a consecutively increasing number of expanded criteria donors.

As 65 ET transplant centers performed re-DDRTs, both surgical difficulties due to precedent procedures [16] and immunological challenges because of immunization [39] do not act as a deterrent to refrain from sequential transplantations. However, as the number of organ donations declines and, consequentially, waiting time increases, this policy has to be challenged. We asked the question, whether there are data prompting an upper limit to sequential transplantations as there should be a balance between rate of success [8,40] and need [7].

Demographic data of repeated re-recipients

The rate of 2.9% repeated re-DDRTs among all DDRTs is comparable to previously published reports from other programs [6,16,20]. Although statistically increasing overall graft survival times might suggest repeated re-DDRT to be a problem of the elderly transplant patients, mean age in repeated re-DDRT recipients turned out to be significantly lower compared to 1st DDRT (Fig. 2). However, a younger mean age of re-DDRT recipients was previously reported for the UNOS/OPTN database as well [25,41].

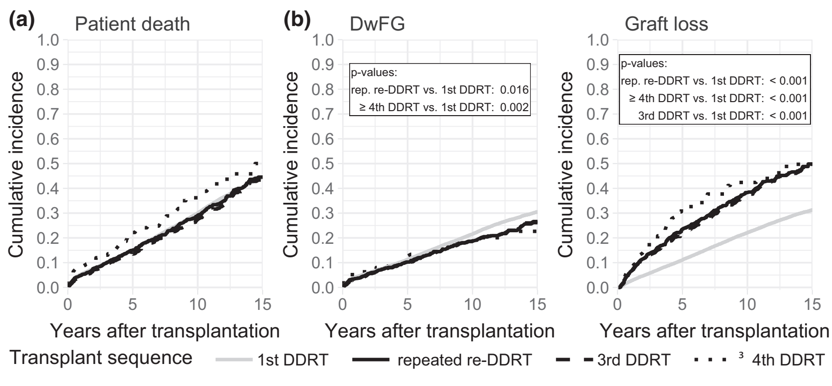

Figure 3 Cumulative incidence curves by transplant sequence for (a) patient death and (b) death with functioning graft and graft loss for 1st deceased donor renal transplantation (DDRT) and repeated re-DDRT.

Table 4. (a) Primary nonfunction and (b) HLA matches regarding sequence of transplantation and age at transplantation for 1st deceased donor renal transplantation (DDRT) and repeated re-DDRT.

	(a) PNF					(b) Immunological HLA matches				
	No PNF		PNF			Favorable match*		Unfavorable match†		
	n	%	*n*	%	*P*-value	*n*	%	*n*	%	*P*-value
1st DDRT	31 263	92.9	2374	7.1	1 1 2	28 353	84.5	5197	15.5	1 1 3
Age (1st DDRT)‡					4					4
0–15 years	1169	93.9	76	6.1		1158	93.1	86	6.9	
16–55 years	16 776	93.4	1179	6.6		16 448	91.6	1502	8.4	
56–64 years	7264	93.7	492	6.3		7028	90.6	726	9.4	
≥65 years	6054	90.6	627	9.4		3719	56.3	2883	43.7	
re-DDRT	1015	87.3	147	12.7		1033	89.0	128	11.0	
3rd DDRT	840	87.9	116	12.1		847	88.7	108	11.3	
≥4th DDRT	175	85.0	31	15.0		186	90.3	20	9.7	
Age (repeated re-DDRT)‡										5
0–15 years	18	90.0	2	10.0		20	100.0	—	—	
16–55 years	845	87.7	119	12.3		858	89.1	105	10.9	
56–64 years	116	83.5	23	16.5		124	89.2	15	11.0	
≥65 years	35	92.1	3	7.9		30	78.9	8	21.1	
Missing	1	100.0	—	—		1	100.0	—	—	

P-values: 1: < 0.001; 2: 0.020; 3: 0.022; 4: <0.001 (for continous age); 5: 0.011 (for continous age).

*At least one HLA-DR plus at least one HLA-A or one HLA-B match.

†No HLA-DR or neither HLA-A nor HLA-B match.

‡Age classes were chosen according to ET categorization.

These findings suggest the presence of a so far unspecified group of recipients who need a first transplant early in their life, then rapidly loose grafts and end up with repeated re-DDRTs at a median age of 43.0 years. Hypothetically, these patients can be characterized in future analyses by either an altered immunological pattern or distinct underlying and concomitant diseases or even nonadherence, all leading to early and repeated graft loss. Unfortunately, these data are currently not reported to the ET database. Facing the conspicuously younger mean age of repeated re-DDRT recipients, further analyses should be performed within this subgroup to identify and ideally eliminate factors that lead to repeated early graft losses. In 1st DDRT recipients, the peak at 65 years represents the increased allocation probability for candidates with longer waiting times who change to the ESP and then rapidly receive a transplant as reported before.

The observed higher rate of PNF in repeated re-DDRT patients (Table 4a) fits into the expected pattern of highly immunized patients who additionally suffer from serious comorbidities. Unfortunately, the ET database hitherto does not register any data on comorbidities.

Survival of repeated re-recipients

Multivariable modeling accounting for confounding factors revealed significantly worse survival for 3rd and ≥4th DDRTs as compared to recipients of a 1st DDRT contradictory to previous reports [6,16,22,25] (Table 3a; Fig. 3a).

The outcome of ≥4th DDRTs was worse compared to 3rd DDRT (Table 3b). This observation may be due to a higher prevalence of serious concomitant diseases, accumulated side effects of medications and long-term dialysis, and complications due to highly dosed immunosuppressants.

Currently, apart from our study, there are no data on patient survival or improvement of recipient's quality of life after ≥4th DDRT as compared to patients' outcome of continued renal replacement therapy. Moreover, a careful selection of potentially suited candidates registered for ≥4th DDRT can be

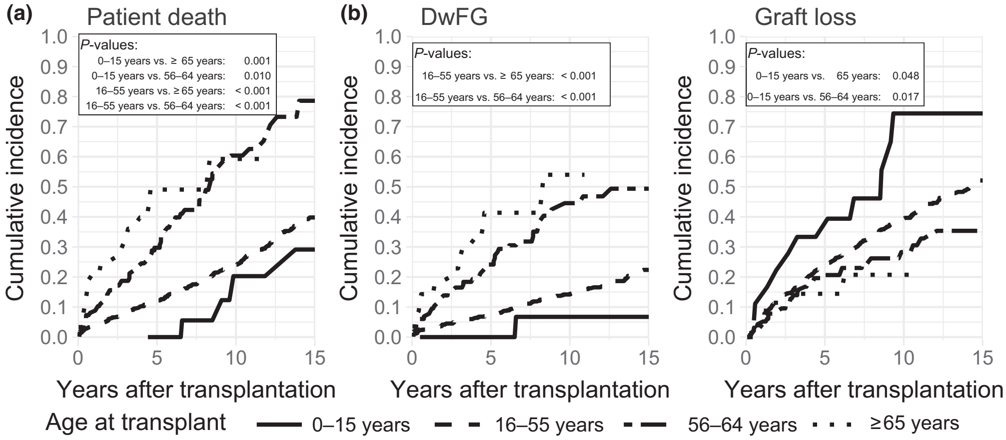

Figure 4 Cumulative incidence curves by age group at transplantation for (a) patient death and (b) death with functioning graft and graft loss for repeated re-DDRT.

assumed. Therefore, these findings are alarming. Death on waiting list while waiting for a third or fourth graft at ET is reported for 325 candidates during the investigated period. However, the estimated number of unreported deaths after delisting remains indeterminate because these data are neither systematically reported to ET nor to the transplant centers or another registry.

Graft loss in repeated re-recipients

In previous studies, graft survival in 3rd compared to 1st DDRT recipients was similar [20,23] or decreased [6,16,22,25]. In our study, a significantly increased cumulative incidence of graft loss for 3rd and ≥4th DDRTs as compared to 1st DDRTs was identified (Tables 2 and 3a; Fig. 3). These results can mainly be ascribed to accelerated rejection due to immunization and probably to an increased prevalence of comorbidities in the repeated re-DDRT group as stated above.

Especially immunization could be expected to be higher in 3rd and ≥4th DDRT recipients. Previously, the impact of HLA-DR mismatch and acute rejections could be identified as relevant factors influencing graft loss negatively even in first re-DDRT recipients [8]. During the 1990s, several developments such as the introduction of new calcineurin inhibitors, improvements in antibody screening, crossmatching and HLA matching, advanced prophylaxis and control for infections, and more effective anti-rejection therapy influenced graft survival rates positively [8]. However, all re-recipients from this survey had similar patient survival and cumulative incidences of DwFG and graft loss in the three time periods investigated (Table 2).

This survey at hand first revealed the encouragingly positive impact of "favorable" HLA matching on patient survival, DwFG, and graft loss in 1st DDRT and next reported on its statistical irrelevance in the repeated re-DDRT group for the very first time in literature (Table 3; Figs 5 and S1). Therefore, recipient-associated factors like comorbidities and short cold ischemia times (Table 3b) must be assumed to have much more impact on outcome than "favorable" matching in these recipients.

Together with these findings, the significant differences in patient survival between 3rd and ≥4th DDRT recipients on the one hand and in patient survival and DwFG between younger and elderly repeated re-recipients on the other hand (Tables 2 and 3; Figs 3 and 4) further strengthen the hypothesis that not only increased immunization but also side effects of therapy, health implications due to long-term renal replacement therapy, accumulating comorbidities, and complications due to poor organ function in the course of time lead to repeated organ losses and death and therefore display a severe problem especially in the ≥4th DDRT recipients.

Age-related outcome of repeated re-recipients

The analyses clearly demonstrate the significantly better patient survival of children compared to older recipients, lower DwFG and a disastrous ten-year graft loss (74.4%; Tables 2 and 3; Fig. 4). Previously published studies on graft outcome in pediatric recipients demonstrated comparably poor graft survival rates after first kidney transplantation [31] and both first and repeated re-DDRT [42], respectively.

Our findings strongly support the assertion that comorbidities and accumulation of therapeutic side

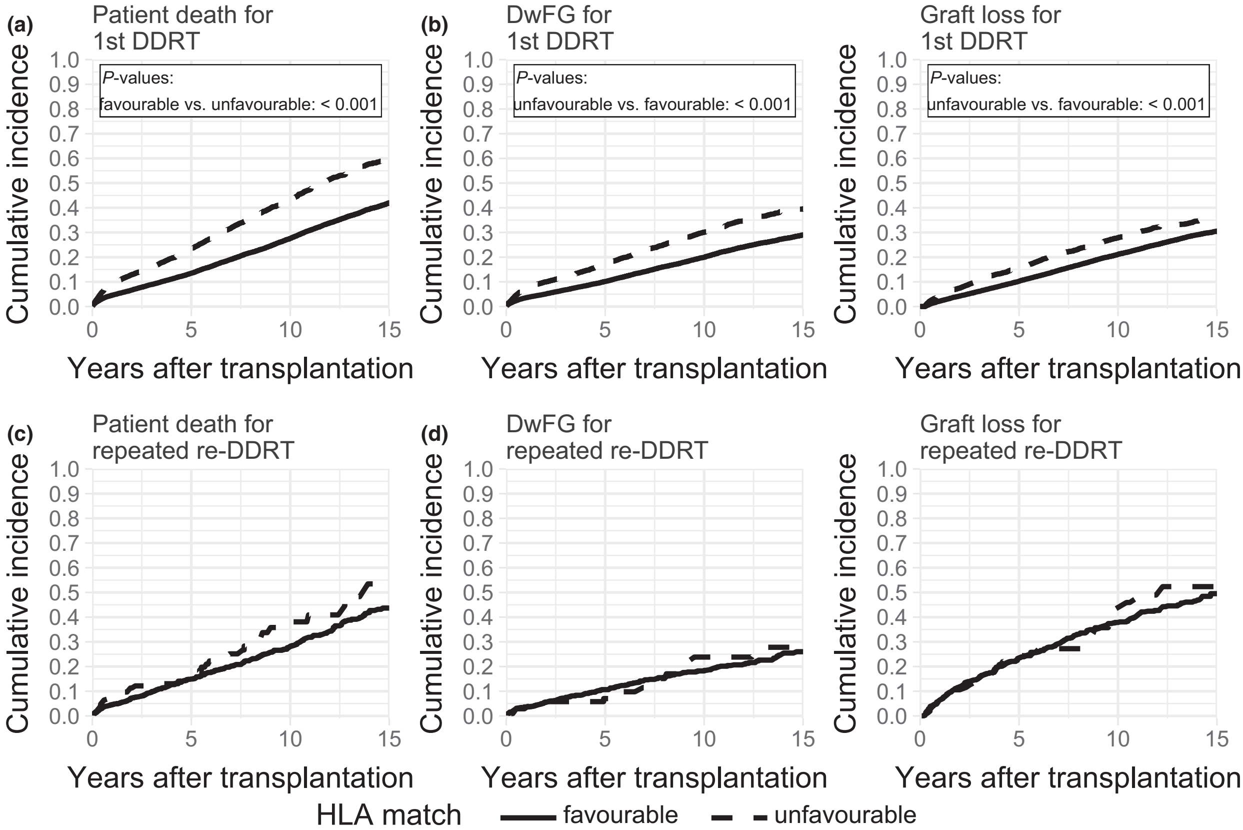

Figure 5 Cumulative incidence curves by HLA matches at transplantation for (a) patient death and (b) death with functioning graft (DwFG) and graft loss for 1st deceased donor renal transplantation (DDRT) and (c) patient death and (d) DwFG and graft loss for repeated re-DDRT.

effects are less prevalent in children and "mid agers" but cause death and DwFG in elderly repeated re-recipients (Fig. 4; Table 3b).

Children had significantly more favorable matches (Table 4b), which are most likely due to restrictive in-house regulations regarding HLA mismatches and organ quality in most centers. Furthermore, the significantly increased rate of unfavorable matches in seniors can most likely be ascribed to the reduced importance of HLA matching in the opinion of treating physicians for this group and the waiver of HLA matching in the ESP. The high cumulative ten-year incidence of graft loss in pediatric recipients (74.4%; Tables 2 and 3b) despite favorable HLA matching and graft selection is most likely related to nonadherence as highlighted before [43,44].

Data completeness in the Eurotransplant database

Data completeness differs between the ET member countries. While in some countries like the Netherlands and Belgium, data delivery to ET is compulsory; in others like Germany, it is up to the centers. This explains the in part suboptimal data completeness. However, by use of statistical censoring missing follow-up was correctly compensated for analyses of 1st DDRT and repeated re-DDRT.

Limitations

The main limitation of this study is the retrospective data assessment from a noncompulsory database and the consecutively limited information. Due to the participation of 64.6% of the ET transplant centers, data completeness was considerable after return of the questionnaires. Nevertheless, several interesting parameters like delayed graft function, rejection, one-year serum creatinine level, primary renal disease, concomitant diseases, and detailed features from deceased donor organs were not available.

Another bias of this study might derive from the fraction of patients without follow-up data as discussed above. However, the data suggest that especially observations with favorable outcome are missing in the control group, which may result in comparatively even worse outcomes after repeated re-DDRT.

Next, the comprehensive cohort might be inhomogeneous due to different therapeutic regimens in the centers. However, earliest data come from transplantations of the year 1996 when triple therapy with calcineurin inhibitors, mycophenolic acids, and steroids was well established and generally accepted. Analyzing the outcome regarding the three consecutive time periods revealed comparable results.

Finally, to reveal the true benefit of repeated re-transplantation, the outcome of repeated re-DDRT also ought to be compared to the course of those candidates qualifying for repeated re-DDRT after failure of their second or third transplant but continuing dialysis. In this ideal setting, the impact of long-term renal replacement therapy and lead time on dialysis could be identified and the actual benefit of repeated re-DDRT versus continued dialysis would be examined from the point of view of those candidates confronted to the decision whether to apply for another graft or not. However, data on patients eligible for repeated re-DDRT but abstaining from the procedure are not available at the present time too.

Conclusions

In our study, recipients of more than two sequential grafts had a shorter graft and patient survival than any other group. The results emphasize the benefit of HLA matching in first and second DDRT [15,20,22,31,45]. Further studies should be initiated to evaluate the expected positive impact of well-matched first and second kidney transplantations on a reduction of repeated re-transplantations on the one hand and a better graft survival of these 3rd and ≥4th grafts due to lower immunization levels on the other hand in future.

The study clearly indicates that a mandatory joined register to collect all data on donors and recipients, including concomitant diseases, is urgently needed to identify those candidates who do and who do not profit from repeated re-transplantation. Furthermore, long-term survival of repeated re-transplantation should be compared prospectively to continuation of dialysis.

The current and future aggravated organ shortage and the need to balance demand with success, forces us to look deeper into the matter and find out as soon as possible whether a fourth graft should be allowed in allocation. Allocation schemes should include factors such as immunization, concomitant diseases and underlying disease, a required minimum of HLA matches, duration of organ function and sequence of previously transplanted graft(s), nonadherence, and special regulations for distinct age groups. The long-term objective of kidney allocation could be an algorithm including both need and promising outcome just as the Lung Allocation Score (LAS) in lung transplantation. However, according to distinct differences in organ donation rates, waiting times, and death on waiting list between ET countries, the scope for generous repeated organ allocation is rated differently. As this future kind of allocation is far more complicated than anything around so far, its development will take a lot of time and needs reliable data (which are not available today). In the meantime, we should carefully consider whether a fourth transplantation is really a useful measure.

Funding

The authors have declared no funding.

Conflict of interest

The authors declare no conflict of interests.

Declaration

All results presented in this paper have not been published previously in whole or part.

Authorship

VA, MM, NH, AR, AN, UH: conception and design of study. VA, NH, MM, KS, JT, EV, AMR, LR, EM, SS, ARR, GB, DY, NK, DK, LW, AM, LCR, IH, PP, RW, PF, LF, VK, US, DS, WA, HMH, MN, JH, ST, JW, KH, BB, VS, SN, KL: acquisition of data. VA, KS, JT, NH, AN, UH: analysis and/or interpretation of data. VA, KS, JT, NH, AN, UH: drafting the manuscript. MM, AR, EV, AMR, LR, EM, SS, ARR, GB, DY, NK, DK, LW, AM, LCR, IH, PP, RW, PF, LF, VK, US, DS, WA, HMH, MN, JH, ST, JW, KH, BB, VS, SN, KL: revising the manuscript critically for important intellectual content.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Cumulative incidence curves by number of HLA-mismatches at transplantation for (a) patient death and (b) DwFG and graft loss for 1st DDRT and (c) patient death and (d) DwFG and graft loss for repeated re-DDRT.

Table S1. Number of HLA-mismatches of 1st DDRT and repeated re-DDRT regarding transplant sequence and recipients' age at transplant.

REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, *et al*. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999; **341**: 1725.
2. Ojo A, Wolfe RA, Agodoa LY, *et al*. Prognosis after primary renal transplant failure and the beneficial effects of repeat transplantation: multivariate analyses from the United States Renal Data System. *Transplantation* 1998; **66**: 1651.
3. McCaughan JA, Patterson CC, Maxwell AP, Courtney AE. Factors influencing survival after kidney transplant failure. *Transplant Res* 2014; **3**: 18.
4. Rao PS, Schaubel DE, Wei G, Fenton SS. Evaluating the survival benefit of kidney retransplantation. *Transplantation* 2006; **82**: 669.
5. Hornberger JC, Best JH, Garrison LP Jr. Cost-effectiveness of repeat medical procedures: kidney transplantation as an example. *Med Decis Making* 1997; **17**: 363.
6. Matas AJ, Gillingham KJ, Payne WD, *et al*. A third kidney transplant: cost-effective treatment for end-stage renal disease? *Clin Transplant* 1996; **10**(6 Pt 1): 516.
7. Mehrabi S, Sohn S, Li DC, *et al*.Temporal Pattern and Association Discovery of Diagnosis Codes using Deep Learning. 2015 Ieee International Conference on Healthcare Informatics (Ichi 2015). 2015: 408–416.
8. Coupel S, Giral-Classe M, Karam G, *et al*. Ten-year survival of second kidney transplants: impact of immunologic factors and renal function at 12 months. *Kidney Int* 2003; **64**: 674.
9. Cho YW, Terasaki PI. Influence of rejection of the first transplant on the outcome of subsequent transplants. In: Touraine JL, ed. *Retransplantation*, Vol. **29**. Dordrecht: Kluwer Academic Publishers, 1997: 65–78.
10. Giessing M, Fuller TF, Friedersdorff F, *et al*. Comparison of first and second kidney transplants from the same deceased donor. *Nephrol Dial Transplant* 2010; **25**: 4055.
11. Arndorfer JA, Meier-Kriesche HU, Ojo AO, *et al*. Time to first graft loss as a risk factor for second renal allograft loss. *Transpl Proc* 2001; **33**: 1188.
12. Heldal K, Hartmann A, Lonning K, *et al*. Should patients older than 65 years be offered a second kidney transplant? *BMC Nephrol* 2017; **18**: 13.
13. Ojo AO, Hanson JA, Meier-Kriesche H, *et al*. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 2001; **12**: 589.
14. Redfield RR, Scalea JR, Zens TJ, *et al*. The mode of sensitization and its influence on allograft outcomes in highly sensitized kidney transplant recipients. *Nephrol Dial Transplant* 2016; **31**: 1746.
15. Gupta M, Wood A, Mitra N, Furth SL, Abt PL, Levine MH. Repeat kidney transplantation after failed first transplant in childhood: past performance informs future performance. *Transplantation* 2015; **99**: 1700.
16. Hagan C, Hickey DP, Little DM. A single-center study of the technical aspects and outcome of third and subsequent renal transplants. *Transplantation* 2003; **75**: 1687.
17. Kousoulas L, Vondran FW, Syryca P, Klempnauer J, Schrem H, Lehner F. Risk-adjusted analysis of relevant outcome drivers for patients after more than two kidney transplants. *J Transplant* 2015; **2015**: 712049.
18. Blanco M, Medina J, Gonzalez E, *et al*. Third kidney transplantation: a permanent medical-surgical challenge. *Transplant Proc* 2009; **41**: 2366.
19. Izquierdo L, Peri L, Piqueras M, *et al*. Third and fourth kidney transplant: still a reasonable option. *Transplant Proc* 2010; **42**: 2498.
20. Loupy A, Anglicheau D, Suberbielle C, *et al*. Long-term outcome of third kidney transplants. *Nephrol Dial Transplant* 2007; **22**: 2693.
21. Park SC, Moon IS, Koh YB. Second and third kidney transplantations. *Transplant Proc* 2006; **38**: 1995.
22. Dabare D, Kassimatis T, Hodson J, *et al*. Outcomes in third and fourth kidney transplants based on the type of donor. *Transplantation* 2019; **103**: 1494.
23. Horovitz D, Caumartin Y, Warren J, *et al*. Outcome of third renal allograft retransplants versus primary transplants from paired donors. *Transplantation* 2009; **87**: 1214.
24. Kienzl-Wagner K, Mark W, Maglione M, *et al*. Single-center experience with third and fourth kidney transplants. *Transpl Int* 2011; **24**: 780.
25. Redfield RR, Gupta M, Rodriguez E, Wood A, Abt PL, Levine MH. Graft and patient survival outcomes of a third kidney transplant. *Transplantation* 2015; **99**: 416.
26. Vanrenterghem Y, Persijn GG. The implementation of the new Eurotransplant kidney allocation system. *Eurotransplant Newslett* 1996; **131**: 4.
27. Mayer G, Persijn GG. Eurotransplant kidney allocation system (ETKAS): rationale and implementation. *Nephrol Dial Transplant* 2006; **21**: 2.
28. Persijn GG. Allocation of organs, particularly kidneys, within Eurotransplant. *Hum Immunol* 2006; **67**: 419.
29. Eurotransplant Manual, Version 3.1. Chapter 4 Kidney (ETKAS and ESP). https://www.eurotransplant.org/cms/mediaobject.php?file=H4+Kidney+November+17%2C+20171.pdf
30. Assfalg V, Huser N, van Meel M, *et al*. High-urgency kidney transplantation in the Eurotransplant Kidney Allocation System: success or waste of organs? The Eurotransplant 15-year all-centre survey. *Nephrol Dial Transplant* 2016; **31**: 1515.
31. Trnka P, McTaggart SJ, Francis A. The impact of donor/recipient age difference and HLA mismatch on graft outcome in pediatric kidney transplantation. *Pediatr Transplant* 2018; **22**: e13265.
32. Ranganathan P, Pramesh CS. Censoring in survival analysis: potential for bias. *Perspect Clin Res* 2012; **3**: 40.
33. Dignam JJ, Kocherginsky MN. Choice and interpretation of statistical tests used when competing risks are present. *J Clin Oncol* 2008; **26**: 4027.
34. Scheike TH, Sun Y, Zhang MJ, Jensen TK. A semiparametric random effects model for multivariate competing risks data. *Biometrika* 2010; **97**: 133.
35. Terry M, Therneau PMG. *Modeling Survival Data: Extending the Cox Model*. New York: Springer, 2000.

36. Heinze G, Dunkler D. Five myths about variable selection. *Transpl Int* 2017; **30**: 6.
37. Therneau TM, Lumley T. A Package for Survival Analysis in S. version 2.382015, 2015. Available from https://CRAN.R-project.org/package=survival.
38. Scheike TH, Zhang MJ. Analyzing competing risk data using the R timereg package. *J Stat Softw* 2011; **38**: i02.
39. Susal C, Opelz G. Current role of human leukocyte antigen matching in kidney transplantation. *Curr Opin Organ Transplant* 2013; **18**: 438.
40. Yeo SM, Kim Y, Kang SS, *et al*. Long-term clinical outcomes of kidney re-transplantation. *Transplant Proc* 2017; **49**: 997.
41. Khalil AK, Slaven JE, Mujtaba MA, *et al*. Re-transplants compared to primary kidney transplants recipients: a mate kidney paired analysis of the OPTN/UNOS database. *Clin Transplant* 2016; **30**: 566.
42. Lledo-Garcia E, Hernandez-Fernandez C, Subira-Rios D, *et al*. Cadaver donor kidney retransplantation in the pediatric patient: complications and long-term outcome. *J Urol* 2011; **185**(6 Suppl): 2582.
43. Dunn TB, Browne BJ, Gillingham KJ, *et al*. Selective retransplant after graft loss to nonadherence: success with a second chance. *Am J Transplant* 2009; **9**: 1337.
44. Van Arendonk KJ, James NT, Boyarsky BJ, *et al*. Age at graft loss after pediatric kidney transplantation: exploring the high-risk age window. *Clin J Am Soc Nephrol* 2013; **8**: 1019.
45. Broeders N, Racape J, Hamade A, *et al*. A new HLA allocation procedure of kidneys from deceased donors in the current era of immunosuppression. *Transplant Proc* 2015; **47**: 267.