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Pretransplant dialysis modality and long-term patient and kidney allograft outcome: a 15-year retrospective single-centre cohort study

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SUMMARY

Among factors determining long-term kidney allograft outcome, pretransplant renal replacement therapy (RRT) is the most easily modifiable. Previous studies analysing RRT modality impact on patient and graft survival are conflicting. Studies on allograft function are scarce, lack sufficient size and follow-up. We retrospectively studied patient and allograft survival together with allograft function and its decline in 2277 allograft recipients during 2000–2014. Pretransplant RRT modality ≥60 days as grouped into "no RRT" (n = 136), "haemodialysis (HD)" (n = 1847), "peritoneal dialysis (PD)" (n = 159), and "HD + PD" (n = 135) was evaluated. Kaplan–Meier analysis demonstrated superior 5-/10-/15-year patient (93.0/81.8/73.1% vs. 86.2/71.6/49.8%), death-censored graft (90.8/85.4/71.5% vs. 84.4/75.2/63.2%), and 1-year rejection-free graft survival (73.8% vs. 63.8%) in PD versus HD patients. Adjusted Cox regression revealed 34.5% [1.5–56.5%] lower hazards of death, whereas death-censored graft loss was similar [HR = 0.707 (0.469–1.064)], and rejection was less frequent [HR = 0.700 (0.508–0.965)]. Allografts showed higher 1-/3-/5-year estimated glomerular filtration rate (eGFR) in "PD" versus "HD" groups. Living donation benefit for allograft function was most pronounced in groups "no RRT" and "PD". Functional allograft decline (eGFR slope) was lowest for "PD". Allograft recipients on pretransplant PD versus HD demonstrated superior all-cause patient and rejection-free graft survival along with better allograft function (eGFR).

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Introduction

Chronic kidney disease (CKD) affects 1 in 10 people worldwide. In the United States, more than half a million patients have currently progressed to end-stage renal disease (ESRD). ESRD cases increase by 5–6% annually worldwide. Patients with CKD have up to fivefold increased mortality [1], and ESRD survival rate is often worse than for many solid tumours, highlighting the importance and urgency of the problem [2]. Compared with dialysis, kidney allograft transplantation offers substantial survival [3,4] and quality of life [5] benefits for ESRD patients, and it is cost-effective in the long run [6]. However, organ shortage warrants optimal

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use of organ donations in order to improve patient outcomes and to make use of available resources most effectively. While short-term outcomes after kidney transplantation have improved significantly, long-term graft survival remains a major challenge [7].

Long-term allograft outcome is determined by factors (both modifiable and nonmodifiable) relating to transplant procedure, recipient and donor, respectively. Among those factors, dialysis modality prior to allograft transplant seems the most readily modifiable. Previous studies demonstrated conflicting results with regard to pretransplant dialysis modality and patient and allograft outcomes [8–12]. A recent meta-analysis found that compared with HD, pretransplant PD was associated with better post-transplant patient survival, decreased risk for delayed graft function (DGF), and similar graft survival [13]. However, most studies lacked sufficient sample size. While studies with large sample size do exist, owing to the nature of large registry databases, analysis is focused on hard endpoints and functional allograft data are not available [8–12]. Published evidence suggests that a higher level of residual renal function (RRF) is independently associated with a better survival in dialysis patients [14–16].While pretransplant RRF does not impact on graft survival or function in pre-emptive renal transplants [17], it is unclear whether this holds true for patients on dialysis and whether the higher RRF in PD versus HD patients exerts benefit beyond kidney transplantation. To the best of our knowledge, there are only 2 studies looking at allograft function with respect to pretransplant dialysis modality [18,19], both demonstrating similar graft function in recipients with pretransplant HD versus PD regimens. However, sample size was small [18,19], functional graft data were available only up to 1 year [18], and generalizability might be impaired because only donors after cardiac death were studied [18]. We therefore analysed patient and allograft outcome with respect to pretransplant modality and included kidney allograft function and the trajectory of its decline in our analysis.

Patients and methods

Study design and patient population

In this study, we performed a retrospective cohort analysis of kidney transplant recipients at Hannover Medical School during a period from 1 January 2000 to 31 December 2014. It was approved as a retrospective cohort study of routinely collected data by the local medical ethics board and conformed to the Declaration of Helsinki of 1975, as revised in 2000. Specific informed consent was waived because of the retrospective and noninvasive nature of the study. Only transplants in adults (≥18 years) were studied. Our cohort did not include any graft donation after cardiac death. Both living and deceased donors were included in the analysis and were analysed separately. For recipients of multiple kidney transplants, the most recent one was considered the target transplantation. Recipients of multi-organ transplants other than kidney/pancreas were excluded as per Fig. 1.

Outcome variables

Primary study outcomes were all-cause patient death and graft survival. As allograft failure and death act as competing events after kidney transplantation, we calculated death-censored graft survival (survival with a functioning graft) as suggested by the European best practice guidelines for renal transplantation [20]. Both outcomes were modelled by using continuous survival time variables. As analyses for graft survival (noncensored for death) presented similar results, data are not shown in the manuscript.

Secondary outcomes included long-term graft function as measured by serum creatinine and estimated glomerular filtration rate (eGFR) at time points 1, 3 and 5 years post-transplantation, respectively. GFR was estimated using the Modification of Diet in Renal Disease formula. We also assessed long-term graft function decline measured by patient-individual eGFR slope derived from eGFR measurements. Patients with graft loss were omitted from graft function analyses. Finally, we analysed incidence rates of DGF, defined as need for dialysis within 7 days post-transplant, and episodes of acute rejection (AR, defined as biopsy-proven acute T cell- or antibody-mediated rejection requiring treatment as per Banff classification [21]) within 1 year post-transplant.

Independent variables

The primary variable of interest was RRT modality prior to transplantation. We applied the "60-day rule" as per USRDS convention stating that a dialysis modality that lasts ≥60 days can be considered stable. Hence, patients were grouped into one of the following categories as per dialysis status prior to kidney transplant: Patients who had been on HD or PD for at least 60 days without a switch were classified as "HD" and "PD", respectively. Patients who had been on both RRT

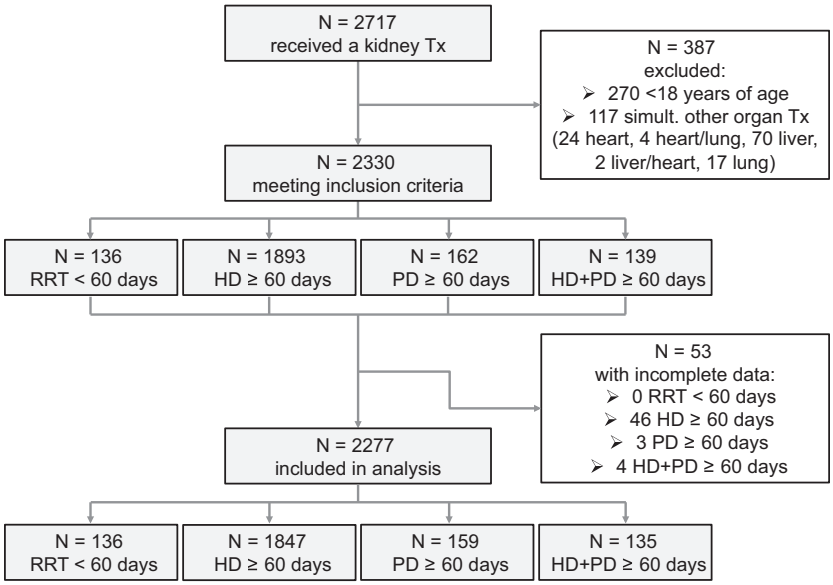

Figure 1 Flowchart of study population. HD, haemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; Tx, transplant.

modalities for at least 60 days and were switched at one or more time points were assigned to the group "HD + PD". Patients who had been on the same dialysis modality for less than 60 consecutive days or received pre-emptive transplants were classified as "no RRT ≥60 days".

Other covariates included transplant, recipient and donor variables. Transplant covariates included urgency status, number of mismatches for human leucocyte antigen (HLA)-A, HLA-B and HLA-DR, respectively, AB0 incompatibility, full house match and cold ischaemia time (CIT).

Recipient covariates included gender, blood group, height, weight, body mass index (BMI), body surface area (BSA), age at transplantation, primary kidney disease [categorized as glomerulonephritis, cystic kidney disease, diabetic nephropathy, interstitial nephritis/pyelonephritis/reflux nephropathy, vascular nephropathy, congenital and hereditary (excl. cystic), thrombotic microangiopathy (TMA), other and unknown], dialysis vintage prior to transplantation, current and highest panel reactive antibodies (PRA), previous kidney transplantation, simultaneous pancreas transplantation, comorbidities as per Charlson comorbidity index (myocardial infarction, heart failure, peripheral artery vascular disease, stroke, hemiplegia, diabetes mellitus, chronic lung disease, chronic liver disease, connective tissue disease, ulcus disease, malignancy, acquired immunodeficiency syndrome and dementia) plus additional information on coronary artery disease, status post percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass graft [CABG] and atrial fibrillation.

Donor covariates included donor type (deceased versus living), gender, blood group, height, weight, BMI, BSA and age.

Statistical analysis

Categorical variables in the subgroups were compared by using cross-tabulation, and continuous variables are summarized by means ± standard deviation unless stated otherwise. D'Agostino and Pearson omnibus test was used to test for normality. *t* tests, ordinary one-way ANOVA and nonparametric tests were used for comparison of means as applicable. Survival analyses comprised Kaplan–Meier graphs analysed by log rank test and multivariable Cox regression models. Observations were censored for all-cause death, graft failure (dialysis initiation) or loss to follow-up, whichever came first. To avoid collinearity between the primary variables of interest, separate Cox models were used. For covariates with nonproportional hazards, we added interaction of covariates with function of time to the model. Multivariable analysis was performed with a full model accounting for transplant, donor and recipient variables as well as with a reduced model that takes into account only pre-RRT variables, since the decision which RRT modality is used is far before the transplantation. In the reduced model, all transplant- or donor-related variables were therefore regarded as mediators rather than confounders of RRT modality and not included in that model to avoid overadjustment bias [22]. Since variable selection does not improve model stability [23], we conducted analyses without preselection (i.e. adjusting for all pre-RRT variables). For adjusted comparison of Cox regression

incidence plots, the confounders were set to zero or the most frequent value. Wald's backward and forward elimination models yielded the same results. We also performed separate analyses of all tests mentioned above after exclusion of patients with simultaneous kidney/pancreas transplant (n = 184). Results did not differ from the data presented here. Linear regression was used to estimate the per-patient slope of eGFR over time. Only those patients with three determinations of eGFR at time points 1, 3 and 5 years were used. Interaction was tested with general linear model analysis. All tests were two-tailed. $P < 0.05$ was considered to indicate statistically significant differences. IBM SPSS Statistics v22.0 and GRAPHPAD PRISM v6.0 were used for data analysis.

Results

Baseline characteristics

In total, 2277 kidney allograft patients with complete data were included in the analysis (Fig. 1). Demographics and baseline characteristics with respect to transplantation, recipient and donor are summarized in Table 1. Transplantations occurred at an equal rate across the study period (759, 757 and 761 in years 2000–2004, 2005–2009 and 2010–2014, respectively). Several baseline characteristics varied significantly between the four groups categorized according to pretransplant RRT modality and were therefore appropriately considered as confounders in multivariable analysis.

Primary outcome: all-cause death and death-censored graft survival

We recorded 553 events of death and 528 events of graft loss. Kaplan–Meier survival estimates of primary outcome parameters are shown in Fig. 2. Unadjusted 5-, 10- and 15-year survival rates were significantly better for allograft recipients on pretransplant PD compared with those on pretransplant HD for patient survival (93.0% vs. 86.2%, $P = 0.002$; 81.8% vs. 71.6%, $P = 0.002$; 73.1% vs. 49.8%, $P = 0.001$) as well as for death-censored graft survival (90.8% vs. 84.4%, $P = 0.024$; 85.4% vs. 75.2%, $P = 0.021$; 71.5% vs. 63.2%, $P = 0.017$). Patients with dialysis vintage ≥60 days for both HD and PD had similar 5-, 10- and 15-year overall survival rates compared with HD patients ($P = 0.319$, 0.385, and 0.340, respectively), whereas death-censored graft survival showed a tendency towards increased rates compared with HD patients ($P = 0.053$, 0.059, and 0.054, respectively). Compared with all other groups those patients with no RRT for ≥60 days prior to transplantation had the best overall survival after 5, 10 and 15 years (97.3, $P < 0.001$; 93.5, $P < 0.001$; 90.2%, $P < 0.001$) as well as the best death-censored graft survival (97.5, $P < 0.001$; 91.6, $P < 0.001$; 65.5%, $P = 0.001$).

Table S1 shows univariable survival data for all-cause patient death and death-censored graft survival. After multivariable adjustment for several baseline covariates, Cox regression analysis demonstrated superior overall survival (Fig. 3) in transplant recipients with pretransplant PD regimens compared with patients on pretransplant HD [34.5% lower hazards of death (95% confidence interval, CI 1.5–56.5%), $P = 0.042$], whereas hazards for death-censored graft loss (Fig. 4) were similar [HR = 0.71 (0.47–1.06), $P = 0.096$]. Compared with patients with pretransplant HD regimens, transplant recipients with no RRT for ≥60 days pretransplant had significantly lower HR for death [HR = 0.23 (0.10–0.51), $P < 0.001$] and for death-censored graft survival [HR = 0.36 (0.19–0.69), $P = 0.002$]. Regarding recipient variables, the reduced and the full Cox models demonstrated similar results. In addition to pretransplant dialysis modality, the full model showed that highly immunized (HI) and highly urgent (HU) urgency status, HLA-DR mismatches, higher cold ischaemia time, higher recipient age, primary kidney disease, hemiplegia, ulcus disease and Charlson comorbidity index showed effects on all-cause patient death (Fig. S1). Similarly, HLA-DR mismatches, pre-emptive transplant, recipient BMI, previous kidney transplant, living donor type and donor age showed effects on graft loss (Fig. S2). Cardiovascular diseases were predictive of patient death and graft loss in univariable (Table S1) but not in multivariable analyses. Simultaneous pancreas transplant was a predictor neither in univariable nor in multivariable Cox proportional hazard models and results did not differ when patients were analysed separately.

Secondary outcome: 1-, 3-, 5-year graft function and eGFR slope

Allograft function after 1, 3 and 5 years post-transplant differed significantly between pretransplant RRT modality groups (Fig. 5). Lowest serum creatinine and highest eGFR were seen in recipients with no pretransplant RRT, followed by pretransplant PD, HD and HD + PD groups, respectively. Results were consistent across years 1, 3 and 5 post-transplant. Multiple comparisons demonstrated that serum creatinine was significantly lower in allograft recipients with pretransplant PD regimens than in those with HD regimens at 1 year [142.0

Table 1. Demographics and baseline transplantation, recipient and donor characteristics

Characteristic	Total (*N* = 2277)	No RRT (*N* = 136)	HD (*N* = 1847)	PD (*N* = 159)	HD + PD (*N* = 135)	*P*
Transplantation						
Urgency status, *n* (%)						
T	1959 (86.0)	116 (85.3)	1590 (86.1)	141 (88.7)	112 (83.0)	0.003
I	255 (11.2)	19 (14.0)	203 (11.0)	17 (10.7)	16 (11.9)	
HI	47 (2.1)	1 (0.7)	43 (2.3)	1 (0.6)	2 (1.5)	
HU	16 (0.7)	0 (0.0)	11 (0.6)	0 (0.0)	5 (3.7)	
No. of mismatches (mean ± SD)						
HLA-A	0.75 ± 0.70	0.96 ± 0.67	0.74 ± 0.70	0.70 ± 0.68	0.75 ± 0.63	0.003
HLA-B	0.99 ± 0.74	1.16 ± 0.66	1.00 ± 0.74	0.94 ± 0.75	0.86 ± 0.67	0.006
HLA-DR	0.77 ± 0.73	0.51 ± 0.71	0.81 ± 0.73	0.66 ± 0.75	0.71 ± 0.70	<0.001
Full house match, *n* (%)	372 (16.3)	8 (5.9)	301 (16.3)	41 (25.8)	22 (16.4)	<0.001
AB0 incompatibility, *n* (%)	69 (3.0)	19 (14.0)	36 (1.9)	7 (4.4)	7 (5.2)	<0.001
Cold ischaemia time, hours (mean ± SD)	12.6 ± 7.3	4.1 ± 4.1	13.3 ± 7.1	10.6 ± 7.2	12.8 ± 7.5	<0.001
Recipient						
Gender, *n* (%)						
f	896 (39.4)	54 (39.7)	692 (37.5)	79 (49.7)	71 (52.6)	<0.001
m	1381 (60.6)	82 (60.3)	1155 (62.5)	80 (50.3)	64 (47.4)	
Blood group, *n* (%)						
A	980 (43.0)	60 (44.1)	785 (42.5)	67 (42.1)	68 (50.4)	0.185
AB	118 (5.2)	6 (4.4)	96 (5.2)	12 (7.5)	4 (3.0)	
B	260 (11.4)	19 (14.0)	215 (11.6)	20 (12.6)	6 (4.4)	
0	919 (40.4)	51 (37.5)	751 (40.7)	60 (37.7)	57 (42.2)	
Height, cm (mean ± SD)	172 ± 10	173 ± 10	172 ± 10	172 ± 10	171 ± 12	0.739
Weight, kg (mean ± SD)	73.9 ± 14.6	72.8 ± 14.8	74.2 ± 14.7	73.3 ± 13.8	71.8 ± 15.2	0.484
BMI, kg/m^2 (mean ± SD)	24.9 ± 4.0	24.3 ± 3.7	25.0 ± 3.9	24.7 ± 3.8	24.3 ± 4.3	0.019
BSA, m^2 (mean ± SD)	1.87 ± 0.22	1.86 ± 0.23	1.88 ± 0.22	1.87 ± 0.21	1.84 ± 0.24	0.723
Age at Tx, years (mean ± SD)	50.4 ± 13.5	43.5 ± 16.0	51.6 ± 13.1	46.4 ± 12.7	45.2 ± 13.1	<0.001
Primary kidney disease, *n* (%)						
Glomerulonephritis	610 (26.8)	38 (27.9)	481 (26.0)	45 (28.3)	46 (34.1)	<0.001
Cystic kidney disease	329 (14.4)	36 (26.5)	270 (14.6)	14 (8.8)	9 (6.7)	
Diabetic nephropathy	300 (13.2)	20 (14.7)	243 (13.2)	29 (18.2)	8 (5.9)	
Interstitial nephritis/pyelonephritis/reflux nephropathy	223 (9.8)	17 (2.5)	174 (9.4)	16 (10.1)	16 (11.9)	
Vascular nephropathy	137 (6.0)	3 (2.2)	119 (6.4)	4 (2.5)	11 (8.1)	
Congenital and hereditary (excl. cystic)	65 (2.9)	6 (4.4)	48 (2.6)	8 (5.0)	3 (2.2)	
TMA	27 (1.2)	2 (1.5)	22 (1.2)	1 (0.6)	2 (1.5)	
Other	80 (3.5)	2 (1.5)	65 (3.5)	5 (3.1)	8 (5.9)	
Unknown	506 (22.2)	12 (8.8)	425 (23.0)	37 (23.3)	32 (23.7)	
Dialysis vintage prior to Tx, months (mean ± SD)	60.7 ± 37.9	3.7 ± 14.5	65.5 ± 36.1	44.0 ± 30.8	73.0 ± 32.6	<0.001
Current PRA, % (mean ± SD)	5.9 ± 18.8	3.4 ± 12.2	6.2 ± 19.4	3.4 ± 12.7	7.8 ± 21.2	0.502
Highest PRA, % (mean ± SD)	11.8 ± 26.0	4.7 ± 15.8	12.2 ± 26.5	7.2 ± 20.9	19.0 ± 30.7	<0.001

Table 1. Continued.

Characteristic	Total (*N* = 2277)	No RRT (*N* = 136)	HD (*N* = 1847)	PD (*N* = 159)	HD + PD (*N* = 135)	*P*
Previous kidney Tx, *n* (%)	321 (14.1)	13 (9.6)	266 (14.4)	13 (8.2)	29 (21.5)	0.004
Simultaneous pancreas Tx, *n* (%)	184 (8.1)	17 (12.5)	136 (7.4)	25 (15.7)	6 (4.4)	<0.001
Coronary artery disease, *n* (%)	516 (22.7)	21 (15.4)	443 (24.0)	25 (15.7)	27 (20.0)	0.013
PTCA, stent or CABG, *n* (%)	363 (15.9)	14 (10.3)	309 (16.7)	23 (14.5)	17 (12.6)	0.140
Atrial fibrillation, *n* (%)	265 (11.6)	9 (6.6)	233 (12.6)	14 (8.8)	9 (6.7)	0.023
Charlson comorbidity score	4.1 ± 1.9	3.6 ± 1.8	4.2 ± 1.9	3.7 ± 1.6	3.7 ± 2.0	<0.001
Donor						
Donor type, *n* (%)						
Cadaveric	1829 (80.3)	24 (17.6)	1580 (85.5)	113 (71.1)	112 (83.0)	<0.001
Living	448 (19.7)	112 (82.4)	267 (14.5)	46 (28.9)	23 (17.0)	
Gender, *n* (%)						
f	1167 (51.3)	83 (61.0)	924 (50.0)	87 (54.7)	73 (54.1)	0.057
m	1110 (48.7)	53 (39.0)	923 (50.0)	72 (45.3)	62 (45.9)	
Blood group, *n* (%)						
A	931 (40.9)	57 (41.9)	743 (40.2)	64 (40.3)	67 (49.6)	0.247
AB	96 (4.2)	4 (2.9)	80 (4.3)	10 (6.3)	2 (1.5)	
B	240 (10.5)	17 (2.5)	196 (10.6)	19 (11.9)	8 (5.9)	
0	1010 (44.4)	58 (42.6)	828 (44.8)	66 (41.5)	58 (43.0)	
Height, cm (mean ± SD)	172 ± 10	171 ± 9	173 ± 10	172 ± 11	172 ± 9	0.082
Weight, kg (mean ± SD)	77.0 ± 15.0	73.8 ± 12.4	77.5 ± 15.0	75.7 ± 16.7	74.8 ± 14.2	0.001
BMI, kg/m^2 (mean ± SD)	25.8 ± 4.1	25.1 ± 3.5	25.9 ± 4.1	25.5 ± 4.6	25.2 ± 3.8	0.016
BSA, m^2 (mean ± SD)	1.91 ± 0.22	1.87 ± 0.19	1.92 ± 0.22	1.89 ± 0.25	1.89 ± 0.21	0.001
Age, years (mean ± SD)	50.3 ± 15.9	50.0 ± 12.1	50.6 ± 16.2	47.7 ± 15.7	49.3 ± 14.9	0.062

BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CKD, chronic kidney disease; HD, haemodialysis; HI, highly immunized; HLA, human leucocyte antigen; HU, highly urgent; I, immunized; PD, peritoneal dialysis; PRA, panel reactive antibodies; PTCA, percutaneous transluminal coronary angioplasty; RRT, renal replacement therapy; SD, standard deviation; T, transplantable; TMA, thrombotic microangiopathy; Tx, transplantation.

P is given for statistical differences between pretransplant RRT modality groups.

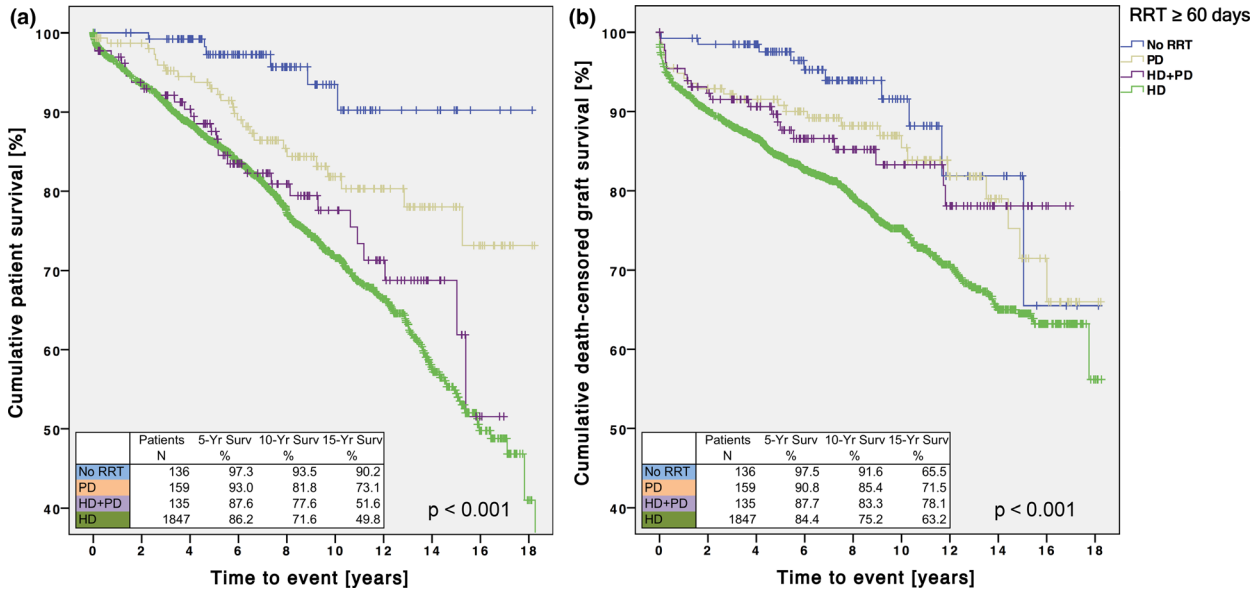

Figure 2 Unadjusted (Kaplan–Meier) primary outcomes comparing allograft recipients according to pretransplant RRT modality. Shown are patient survival (a) and death-censored graft failure (b). Maximum follow-up was 18.3 years, log rank (Mantel–Cox) $P < 0.001$ for (a) and (b). HD, haemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy.

(95% CI 130.8–153.3) vs. 152.5 (149.4–155.6) μmol/l, $P = 0.007$], 3 years [151.6 (134.3–168.9) vs. 158.8 (154.8–162.9) μmol/l, $P = 0.048$] and 5 years post-transplant [143.1 (130.0–156.2) vs. 159.4 (155.1–163.6) μmol/l, $P = 0.012$], respectively. Compared to recipients with no pretransplant RRT, who had the best allograft function, those with pretransplant HD demonstrated significantly lower eGFR at 1 year [47.7 (46.7–48.8) vs. 52.5 (49.7–55.3) ml/min/1.73 m^2, $P < 0.001$], 3 years [46.0 (45.0–47.0) vs. 52.5 (48.4–56.6) ml/min/1.73 m^2, $P < 0.001$] and 5 years post-transplant [45.4 (44.2–46.5) vs. 50.0 (46.4–53.5) ml/min/1.73 m^2, $P = 0.008$], respectively, whereas eGFR in patients on pretransplant PD was similarly good at 1 year [49.9 (46.9–52.9) ml/min/1.73 m^2, $P = 0.134$], 3 years [47.2 (43.9–50.5) ml/min/1.73 m^2, $P = 0.220$] and 5 years post-transplant [48.9 (45.2–52.7) ml/min/1.73 m^2, $P = 0.397$], respectively. We also analysed allograft function with respect to subgroups for possible influential covariates: As expected, living donation allografts demonstrated significantly better function as compared to deceased donation allografts [5-year serum creatinine 147.6 (140.8–154.2) vs. 160.3 (155.9–164.8) μmol/l, $P = 0.027$; 5-year eGFR 48.8 (46.7–50.9) vs. 44.9 (43.7–45.9) ml/min/1.73 m^2, $P < 0.001$]. Interestingly, as demonstrated by significant interaction between donor type and pretransplant RRT ($P = 0.001$), this benefit was particularly more pronounced in patients with either no RRT ($\Delta = 6.5$ ml/min/1.73 m^2) or on PD ($\Delta = 4.6$ ml/min/1.73 m^2) compared with a relatively small benefit for HD ($\Delta = 2.6$ ml/min/1.73 m^2) and HD + PD ($\Delta = 2.8$ ml/min/1.73 m^2) patients, respectively ($P < 0.001$; Fig. 6a). On the other hand, linear regression analyses demonstrated that there was a fairly robust inverse relationship between donor age and long-term eGFR, which was only present in patients who had received pretransplant dialysis, whereas 5-year eGFR was not related to donor age in patients with no RRT prior to allograft transplantation (Fig. 6b).

Allograft function decline measured by eGFR slope during post-transplant years 1–5 was slowest in recipients on pretransplant PD (−0.56 ml/min/1.73 m^2 per year), followed by HD (−0.86 ml/min/1.73 m^2 per year), HD + PD (−0.97 ml/min/1.73 m^2 per year) and patients with no pretransplant RRT (−1.47 ml/min/1.73 m^2 per year). However, differences between pretransplant RRT groups were not statistically significant ($P = 0.283$). Repeated measures linear mixed-effects modelling accounting for living versus deceased donation status yielded similar results (data not shown). In addition to that, secondary analysis of eGFR slopes comparing subgroups of living versus deceased donation allografts within the respective pretransplant RRT groups revealed significant benefits only for recipients on pretransplant PD, who profited the most from living donation and even demonstrated eGFR gain, as compared to all other subgroups that lost allograft function to varying degrees and did not differ significantly (Fig. 7).

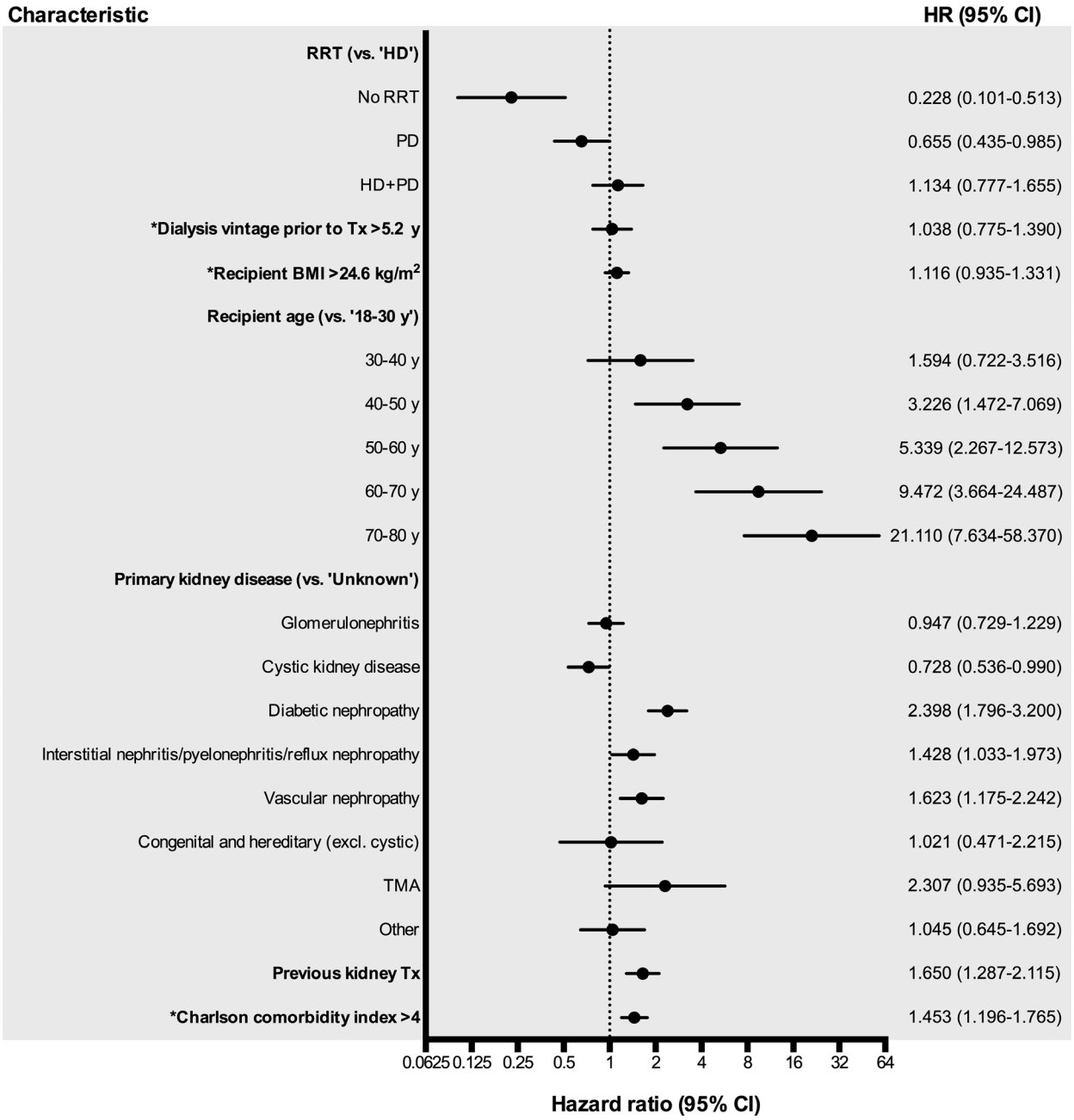

Figure 3 Multivariable Cox proportional hazard (reduced) model analysing all-cause patient death. The model accounts for recipient variables only. *Continuous variables dialysis vintage prior to Tx, recipient BMI and Charlson comorbidity index were dichotomized using the median. BMI, body mass index; CI, confidence interval; HD, haemodialysis; HR, hazard ratio; PD, peritoneal dialysis; RRT, renal replacement therapy; TMA, thrombotic microangiopathy; Tx, transplantation.

Secondary outcome: delayed graft function and early acute rejection episodes

Our data raise the question about a possible mechanism by which PD would improve outcomes. If one postulates such a mechanism to be procedure-related and not related to patient characteristics, its effect should be manifested mainly during the early post-transplant period. We therefore were interested to evaluate effects of pretransplant RRT on early post-transplant outcomes such as the incidence of DGF and AR episodes within 1 year of transplant.

We recorded 546 events of DGF. The rates were 2.9%, 14.5%, 26.6% and 21.5% for groups "no RRT",

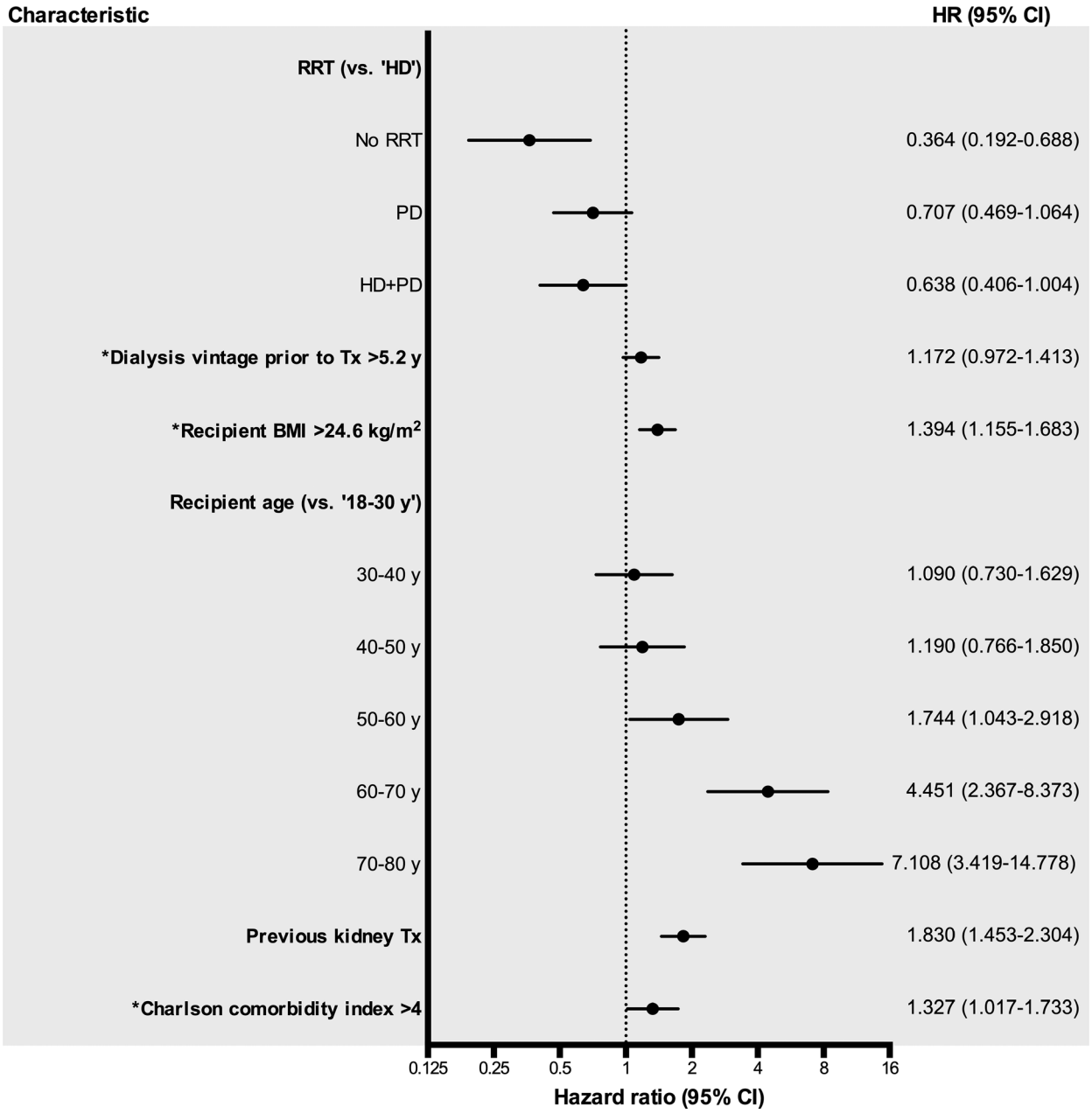

Figure 4 Multivariable Cox proportional hazard (reduced) model analysing death-censored graft loss. The model accounts for recipient variables only. *Continuous variables dialysis vintage prior to Tx, recipient BMI and Charlson comorbidity index were dichotomized using the median. BMI, body mass index; CI, confidence interval; HD, haemodialysis; HR, hazard ratio; PD, peritoneal dialysis; RRT, renal replacement therapy; Tx, transplantation.

"PD", "HD" and "HD + PD", respectively ($P < 0.001$), demonstrating reduced DGF prevalence in "PD" versus "HD" patients.

We recorded 771 patients who experienced ≥1 episode of AR requiring treatment within 1 year of transplantation. The rates were 25.7%, 25.8%, 35.1% and 34.8% for groups "no RRT", "PD", "HD" and "HD + PD", respectively ($P = 0.019$). Kaplan–Meier survival estimates of cumulative AR-free graft survival are shown in Fig. 8a and demonstrate similar survival for "no RRT" and "PD" patients. Unadjusted 3-month, 6-month and 1-year AR-free graft survival rates were significantly better for "PD" versus "HD" groups (82.8% vs. 72.8%, $P = 0.011$; 75.7% vs. 66.6%, $P = 0.012$; 73.8% vs. 63.8%, $P = 0.012$). Finally, multivariable Cox regression analysis demonstrated superior overall AR-free graft survival (Fig. 8b) in "PD" compared with "HD" patients [HR = 0.700 (95% CI 0.508–0.965), $P = 0.029$].

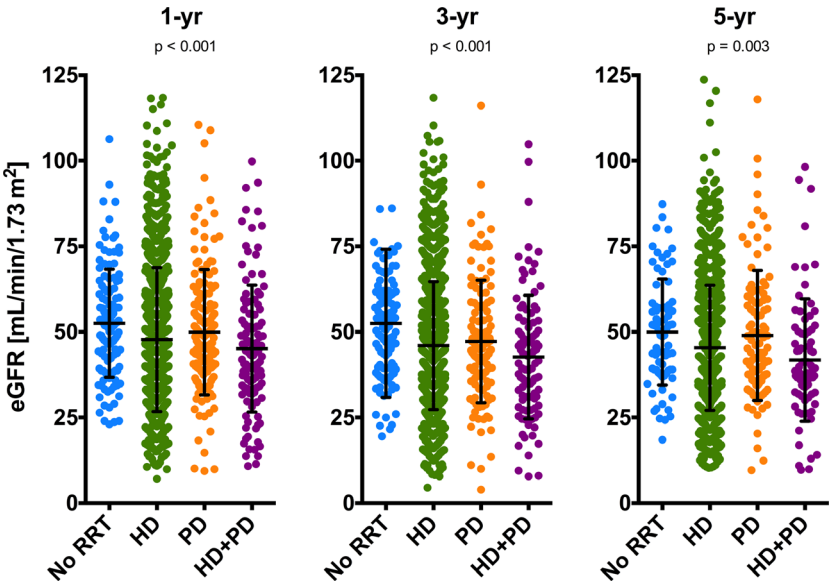

Figure 5 1, 3 and 5 years post-transplant allograft function. Mean eGFR ± SD is shown for pretransplant RRT groups. ANOVA *P* for log-transformed variables; eGFR, estimated glomerular filtration rate; HD, haemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SD, standard deviation.

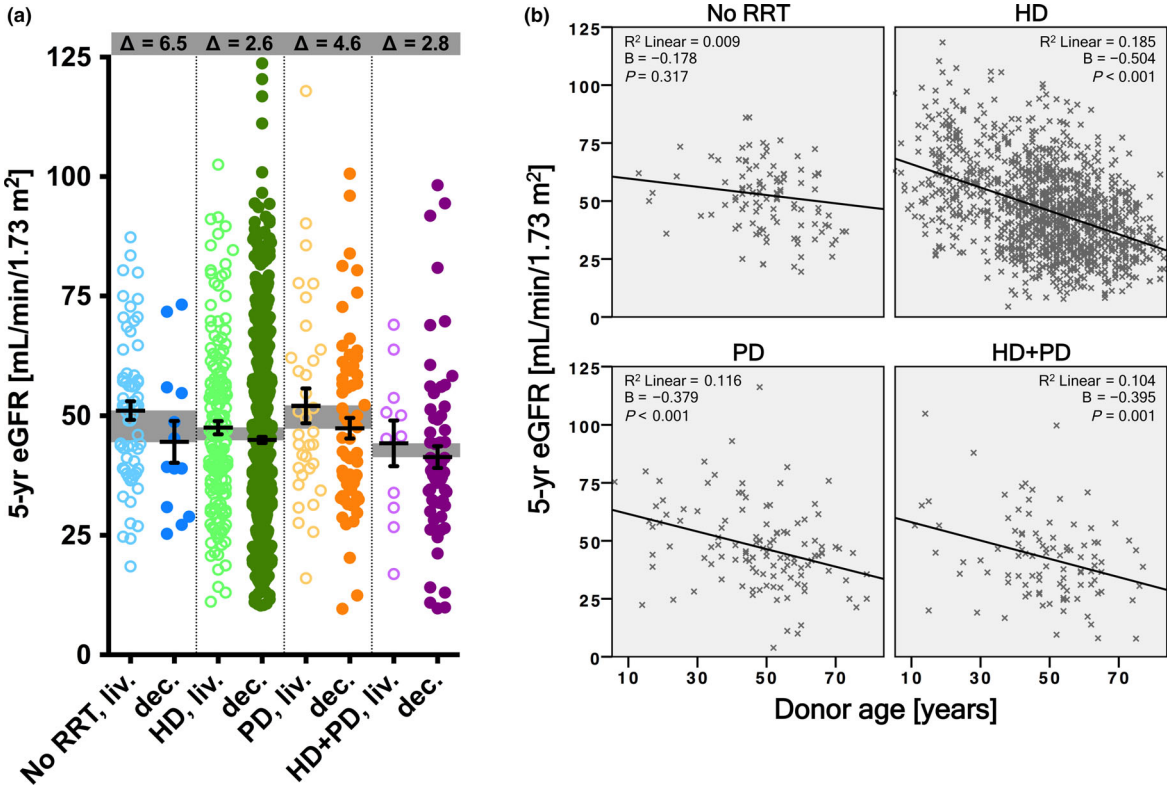

Figure 6 Influence of donor factors on allograft outcomes. (a) Benefit of living versus deceased donation type for 5-year allograft function given as ΔeGFR (shadowed area); 5 years post-transplant eGFR is given as means ± SEM, open symbols ○ denote living donation (liv.), closed symbols ● denote deceased (dec.) donation. $P < 0.001$ for living versus deceased donation comparison. (b) Relationship of donor age and 5-year eGFR. R^2, regression coefficient *B*, and *P* values are given for linear regression across individual pretransplant RRT groups. eGFR, estimated glomerular filtration rate; HD, haemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SEM, standard error of the mean.

Discussion

In 2277 kidney allograft recipients who were followed for up to 18 years post-transplantation, pretransplant treatment with PD was associated with superior patient survival (36% lower all-cause mortality risk) compared with pretransplant HD, which is consistent with results from large registry studies [8–12]. Despite efforts to

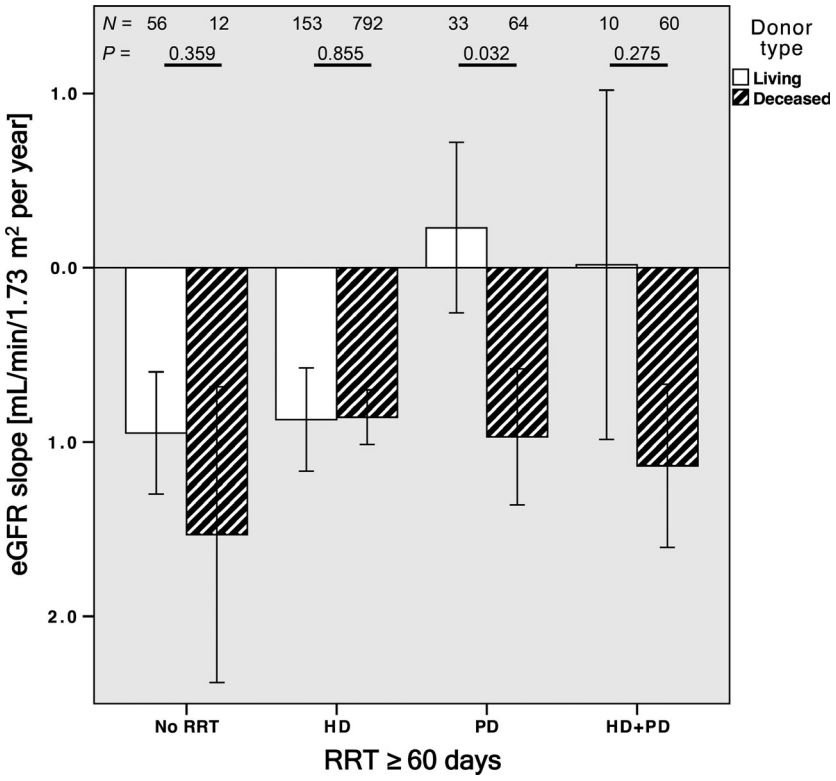

Figure 7 Allograft function decline during post-transplant years 1–5. Mean eGFR slope ± SEM is shown and statistically compared between living versus cadaveric donation within pretransplant RRT groups. eGFR, estimated glomerular filtration rate; HD, haemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SEM, standard error of the mean.

adjust for many covariates, even registry analyses have yielded conflicting results for post-transplant allograft outcome, highlighting the challenges in comparing inherent differences in HD versus PD patient populations: patients on PD are generally younger, healthier, have been on dialysis for a shorter time and additionally receive transplants at a higher rate than those on HD [12,13].

Along those lines, we found an AR-free allograft survival benefit associated with pretransplant PD versus HD treatment, hinting at a RRT modality-related rather than patient characteristics-related effect. We confirm recent results from others [9–11] but contradicting older findings of still others who reported pretransplant PD to be associated with either favourable [8] or deleterious [12] effects on allograft survival. However, the authors analysing USRDS registry data only evaluated all-cause, not death-censored graft survival and superior all-cause graft survival in PD patients was thus a consequence of a higher death rate in HD patients [8]. Moreover, some studies categorized pretransplant RRT according to the modality used either for the longest period [8], at the time of transplantation [12] or at study entry [10] and therefore did not further subgroup patients who had received both HD and PD in a sequential manner. When looking at pretransplant RRT modality as the primary variable of interest, one needs to consider the importance of stable long-term treatment with a single RRT modality versus bias owing to changes from one dialysis modality to another. In order to minimize adverse effects on internal validity, we therefore applied the "60-day rule" as per USRDS convention stating that a dialysis modality that lasts ≥60 days can be considered stable. We grouped patients accordingly and adverse outcomes for patients with HD + PD regimens demonstrate the necessity of doing so. Differences in results might also be explained by the fact that previous studies pertained to premillennial cohorts of 20–29 years ago [8,12] before significant changes in immunosuppressive regimens. While our sample size is noticeably smaller than those of large registry studies, their follow-up times of maximum 5 [8,9,11,12] and 6 years [10], respectively, are considerably shorter than our 18 years.

To the best of our knowledge, no single study so far reported on the trajectory of functional graft decline, as measured by eGFR slope. Herein, we report for the first time on a significant allograft function benefit of pretransplant PD over HD recipients as indicated by lower serum creatinine and higher eGFR at 1, 3 and 5 years post-transplant. This may in part be owing to between-group differences regarding predictors of allograft

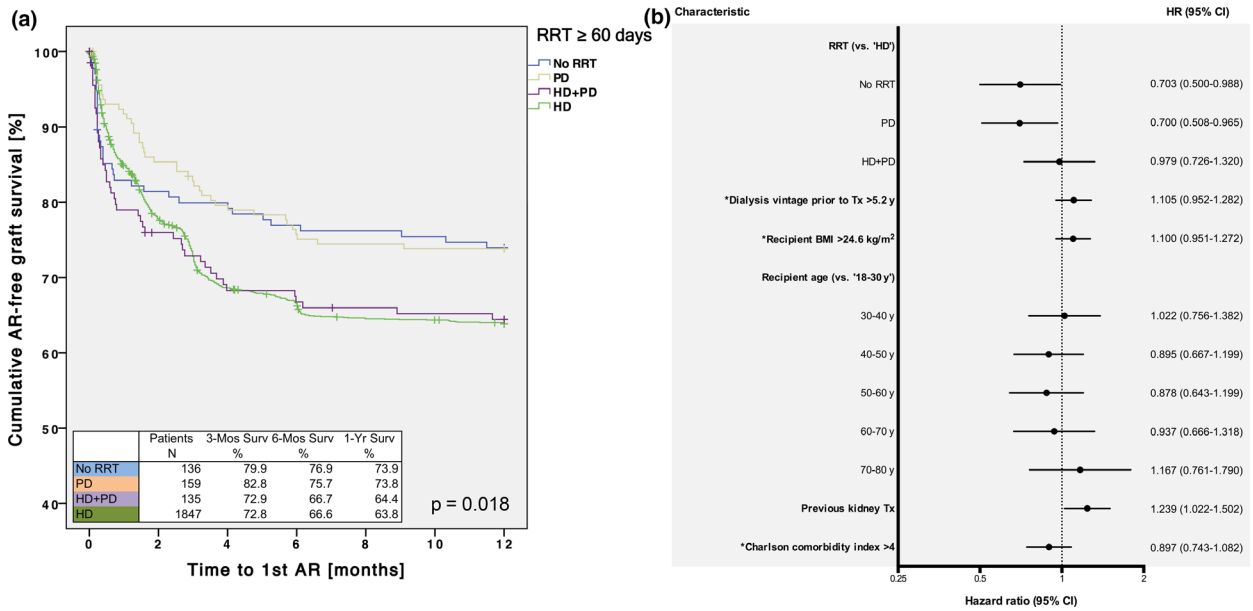

Figure 8 Acute rejection episodes within 1 year post-transplant according to pretransplant RRT modality. (a) Unadjusted (Kaplan–Meier) cumulative AR-free graft survival according to pretransplant RRT modality. Maximum follow-up was 12 months, log rank (Mantel–Cox) $P = 0.018$. (b) Multivariable Cox proportional hazard (reduced) model analysing AR. The model accounts for recipient variables only. *Continuous variables dialysis vintage prior to Tx, recipient BMI and Charlson comorbidity index were dichotomized using the median. AR, acute rejection; BMI, body mass index; CI, confidence interval; HD, haemodialysis; HR, hazard ratio; PD, peritoneal dialysis; RRT, renal replacement therapy; Tx, transplantation.

survival as per multivariable Cox regress models. Although it is known that measurements of serum creatinine and eGFR may fail to detect a fair percentage of biopsy-proven episodes of acute rejection episodes [24] and development of interstitial fibrosis and atrophy may not be accurately represented in changes in serum creatinine [25], compared with invasive GFR measurement and protocol biopsies, serum creatinine and eGFR still represent by far the most feasible and cost-effective method of assessing graft function. Furthermore, changes in graft function over time as estimated by eGFR slope have been shown to be highly correlated with measured iothalamate GFR slopes in allograft recipients, thus providing valuable information for the trajectory of functional decline [26]. In addition, it has been shown that eGFR slope is a strong predictor of long-term kidney allograft outcome and may facilitate its prediction [27,28]. While the overwhelming number of studies analysing pretransplant RRT modality did not incorporate data on actual allograft function, there are only two reports taking into account creatinine or eGFR, both failing to demonstrate graft function differences in recipients with pretransplant HD versus PD regimens. However, sample size was small in both studies [18,19]. Moreover, functional graft data were available only up to 1 year [18] and solely donors after cardiac death were studied, impairing generalizability to a large extent [18].

Finally, we analysed long-term allograft function with respect to donor age as well as living versus deceased donation status within pretransplant RRT modality groups. Higher donor age was associated with decreased 5-year eGFR only in patients on dialysis prior to transplantation but not in patients who had been transplanted pre-emptively or received <60 days of dialysis ("no RRT"). This might be partly owing to a donor selection effect as the proportion of living donation was higher among this group. Moreover, we found the living donation benefit for 5-year eGFR to be most pronounced in groups "no RRT" and "PD". Again, this underpins the importance of residual renal function (RRF) at the time of transplant for allograft outcome, as compared to HD patients, and both recipients of pre-emptive allografts and PD patients are known to have better preserved RRF [14,29]. Higher RRF in PD patients may be associated with various effects influencing cardiovascular morbidity, thereby in part explaining the survival benefit of PD over HD patients [11]. We could not test this formally, though, as RRF at the time of transplant was not available and thus was not incorporated as a variable in our study. Finally, eGFR slopes did not differ significantly between pretransplant RRT modality groups. Interestingly,

however, functional allograft decline was lowest in PD patients. Those PD patients receiving living donation grafts even demonstrated eGFR gain during post-transplant years 1-5. However, owing to the small sample size significant interaction between donor type and pretransplant RRT could not be demonstrated for eGFR slope. Therefore, these results should be interpreted with caution. While it has been reported that more than half of patients can have stable or even positive GFR slopes, our results warrant careful interpretation, as there is considerable debate on the applicability of different eGFR formulas and their validity in transplant recipient cohorts [26]. The same authors have also reported that eGFR slope, particularly when calculated by MDRD-estimated GFR within the first post-transplant year, significantly underestimated the number of patients with declining graft function, which is why we used time points from 1 to 5 years post-transplant.

There are several limitations to our study. Owing to the retrospective nature of this study, we could not compare outcomes of ESRD patients with equal eligibility for HD versus PD. As patients eligible for PD are usually healthier, more autonomous, frequently professionally active and often have higher educational and socio-economic status, despite any effort in multivariable adjustment, PD status at the time of transplantation should therefore be interpreted as a marker of an unknown cluster of positive characteristics, rather than reflecting a causal relation. Estimates comparing HD versus PD are therefore likely to be biased by the pretransplant selection process responsible for baseline differences at the time of transplantation. Prospectively designed studies are needed in order to exclude this issue. Also, waiting times for a deceased donor kidney in Germany are comparatively long. PD technical failure occurs in up to 50% of patients during the 3 first years after dialysis initiation. The PD cohort might therefore be composed of patients who either received a living donation graft early on, had preferential early allocation by chance because of a deceased donor with superior matching or had technique survival until standard allocation. As median waiting times in Germany are >4 years, there might have been a selection of a population receiving either good quality kidneys early or having long-term PD technique survival. The last category of patients probably has characteristics that are difficult to adjust for in a classical multivariate model. Owing to the single-centre nature, our results may not extrapolate to other centres, especially as donation after cardiac death is not performed in Germany. Also, most studies analysing pretransplant dialysis modality excluded recipients of simultaneous organ transplants. While we excluded all simultaneous organ transplantations other than pancreas/kidney, we took special care in performing separate analyses for cohorts with and without simultaneous kidney/pancreas transplants. Simultaneous pancreas transplant was neither a predictor in Cox models nor did the results any of the other tests differ from the data presented herein. However, residual confounding cannot be definitely excluded. Also, the analysis of allograft function decline is conditional on a functioning graft and interpretation of results should take this fact into account. Compared with registry databases, our sample size might be relatively small. Still, we present long-term data of up to 18 years of follow-up with consistent properties of allograft transplant procedure. Moreover, outcome data of incident allograft recipients were prospectively collected. Data completeness and regularity are thus easier to control in a single-centre study than with registry data.

The strengths of our study include its long follow-up of up to 18 years, the homogeneity of clinical practice with regard to both RRT and transplant procedures, as well as the competing risk methodology for graft survival precluding interferences of competing events. Additionally, to our knowledge, this is the first analysis of long-term kidney allograft function >1 year post-transplant and of DGF and AR episodes in a comparatively large-size sample analysing pretransplant RRT as primary variable of interest.

In conclusion, our data are in line with recent registry studies confirming superior patient and AR-free graft survival for recipients on pretransplant PD versus HD. Moreover, this is the first study to demonstrate in a considerable sample size population a significant allograft function benefit of pretransplant PD over HD recipients at 1, 3 and 5 years post-transplant. Our findings demonstrate that additional investigations with respect to residual renal function (RRF) at the time of transplantation and its effect on long-term kidney allograft function are warranted, as preservation of RRF might prove a worthwhile goal not only pertaining to outcome on dialysis but also extending beyond transplantation to kidney allograft outcome.

Authorship

MSB and GE: conceived the research design and had full access to the data. MSB, SP, RC, ED, SR and GE: were involved in data acquisition; MSB, SP and GE: analysed the data; MSB: drafted the original version of the manuscript; all authors participated in the review and editing of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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SUPPORTING INFORMATION

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

Figure S1. Multivariable Cox proportional hazard (full) model analyzing all-cause patient death.

Figure S2. Multivariable Cox proportional hazard (full) model analyzing death-censored graft loss.

Table S1. Predictors of all-cause death and death-censored graft survival in univariable Cox regression analysis.

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