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## **Pre-transplant dialysis modality and long-term patient and kidney allograft outcome: A 15-year retrospective single center cohort study**

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## **AUTHORSHIP STATEMENT**

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 analyzed the data; MSB drafted the original version of the manuscript, all authors participated in the review and editing of the manuscript.

## **DISCLOSURE**

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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## **KEYWORDS**

Kidney transplantation; outcome; graft failure; graft function; hemodialysis (HD); peritoneal dialysis (PD).

## ABBREVIATIONS

AR	acute rejection
BMI	body mass index
BSA	body surface area
CABG	coronary artery bypass graft
CKD	chronic kidney disease
DGF	delayed graft function
eGFR	estimated glomerular filtration rate
HD	hemodialysis
HI	highly immunized
HLA	human leukocyte antigen
HU	highly urgent
I	immunized
MDRD	modification of diet in renal disease
PD	peritoneal dialysis
PRA	panel reactive antibodies
PTCA	percutaneous transluminal coronary angioplasty
RRF	residual renal function
RRT	renal replacement therapy
SD	standard deviation
SEM	standard error of the mean
T	transplantable
TMA	thrombotic microangiopathy
Tx	transplantation

## ABSTRACT

Background: Among factors determining long-term kidney allograft outcome, pre-transplant renal replacement therapy (RRT) is the most easily modifiable. Previous studies analyzing RRT modality impact on patient and graft survival are conflicting. Studies on allograft function are scarce, lack sufficient size and follow-up.

Methods: We retrospectively studied patient and allograft survival together with allograft function and its decline in 2277 allograft recipients during 2000-2014. Pre-transplant RRT modality  $\geq 60$  days was grouped into ‘no RRT’ (n=136), ‘hemodialysis (HD)’ (n=1847), ‘peritoneal dialysis (PD)’ (n=159), and ‘HD+PD’ (n=135) was evaluated.

Results: Kaplan-Meier analysis demonstrated superior 5-/10-/15-yr 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-yr rejection-free graft survival (73.8 vs. 63.8%) in PD vs. 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-yr estimated glomerular filtration rate (eGFR) in ‘PD’ vs. ‘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’.

Conclusions: Allograft recipients on pre-transplant PD vs. HD demonstrated superior all-cause patient and rejection-free graft survival along with better allograft function (eGFR).

## INTRODUCTION

Chronic kidney disease (CKD) affects 1 in 10 people worldwide. In the US, 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 5-fold increased mortality<sup>1</sup> and ESRD survival rate is often worse than for many solid tumors, highlighting the importance and urgency of the problem.<sup>2</sup> Compared to dialysis, kidney allograft transplantation offers substantial survival<sup>3,4</sup> and quality of life<sup>5</sup> benefits for ESRD patients, and it is cost-effective in the long run.<sup>6</sup> However, organ shortage warrants optimal 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.<sup>7</sup>

Long-term allograft outcome is determined by factors (both modifiable and non-modifiable) 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 pre-transplant dialysis modality and patient and allograft outcomes.<sup>8-12</sup> A recent meta-analysis found that compared to HD, pre-transplant PD was associated with better post-transplant patient survival, decreased risk for delayed graft function (DGF) and similar graft survival.<sup>13</sup> However, most studies lacked sufficient sample size. While studies with large sample size do exist, due to the nature of large registry databases, analysis is focused on hard endpoints and functional allograft data is not available.<sup>8-12</sup> Published evidence suggests that a higher level of residual renal function (RRF) is independently associated with a better survival in dialysis patients.<sup>14-16</sup> While pre-transplant RRF does not impact on graft survival or function in preemptive renal transplants,<sup>17</sup> it is unclear whether this holds true for patients on dialysis and whether the higher RRF in PD vs. 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 pre-transplant dialysis modality<sup>18,19</sup>, both demonstrating similar graft function in recipients with pre-transplant HD vs. PD regimens. However, sample size was small<sup>18,19</sup>, functional graft data was available only up to 1 year<sup>18</sup> and generalizability might be impaired because only donors after cardiac death were studied.<sup>18</sup> We therefore analyzed patient and allograft outcome with respect to pre-transplant 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 January 1, 2000 to December 31, 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 due to the retrospective and non-invasive nature of the study. Only transplants in adults ( $\geq 18$  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 analyzed 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 **Figure 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.<sup>20</sup> Both outcomes were modeled by using continuous survival time variables. As analyses for graft survival (non-censored 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 analyzed 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<sup>21</sup>) 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  $\geq 60$  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 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  $\geq 60$  days”.

Other covariates included transplant, recipient, and donor variables. Transplant covariates included urgency status, number of mismatches for human leukocyte antigen (HLA)-A, HLA-B, and HLA-DR, respectively, AB0 incompatibility, full house match, and cold ischemia 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, 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 vs. living), gender, blood group, height, weight, BMI, BSA, and age.

#### *Statistical analysis*

Categorical variables in the subgroups were compared by using cross-tabulation, continuous variables are summarized by means  $\pm$  standard deviation unless stated otherwise. D’Agostino & Pearson omnibus test was used to test for normality. T tests, ordinary one-way ANOVA and non-parametric tests were used for comparison of means as applicable. Survival analyses comprised Kaplan-Meier graphs analyzed by log rank test and multivariable Cox regression models. Observations were censored for all-cause death, graft failure (dialysis initiation), or loss to follow-

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up, whichever came first. To avoid collinearity between the primary variables of interest separate Cox models were used. For covariates with non-proportional 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. Since variable selection does not improve model stability,<sup>22</sup> we conducted analyses without pre-selection (i.e. adjusting for all pre-RRT variables) to avoid over-adjustment bias.<sup>23</sup> 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 3 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 (**Figure 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 pre-transplant 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 **Figure 2**. Unadjusted 5-yr, 10-yr, and 15-yr survival rates were significantly better for allograft recipients on pre-transplant PD compared to those on pre-transplant 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  $\geq 60$  days for both HD and PD had similar 5-yr, 10-yr, and 15-yr 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  $\geq 60$  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%,  $p=0.001$ ).

**Supplementary Table 1** 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 (**Figure 3**) in transplant recipients with pre-transplant PD regimens compared to patients on pre-transplant 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 (**Figure 4**) were similar ( $HR=0.71$  [0.47-1.06],  $p=0.096$ ). Compared to patients with pre-transplant HD regimens, transplant recipients with no RRT for  $\geq 60$  days pre-transplant 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 pre-transplant dialysis modality, the full model showed that highly immunized (HI) and highly urgent (HU) urgency status, HLA-DR mismatches, higher cold ischemia time, higher recipient age, primary kidney disease, hemiplegia, ulcus disease, Charlson comorbidity index showed effects on all-cause patient death (**Supplementary Figure 1**). Similarly, HLA-DR mismatches, pre-emptive transplant, recipient BMI, previous kidney transplant, living donor type, and donor age showed effects on graft loss (**Supplementary Figure 2**). Cardiovascular diseases were predictive of patient death and graft loss in univariable (**Supplementary Table 1**) but not in multivariable analyses. Simultaneous pancreas transplant was neither a predictor in univariable nor in multivariable Cox proportional hazard models and results did not differ when patients were analyzed separately.

#### *Secondary outcome: 1-yr, 3-yr, 5-yr graft function and eGFR slope*

Allograft function after 1, 3, and 5 years post-transplant differed significantly between pre-transplant RRT modality groups (**Figure 5**). Lowest serum creatinine and highest eGFR was seen in recipients with no pre-transplant RRT, followed by pre-transplant 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 pre-transplant PD regimens than in those with HD regimens at 1 year (142.0 [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 pre-transplant RRT, who had the best allograft function, those with pre-transplant HD demonstrated significantly lower eGFR at 1 year (47.7 [46.7-48.8] vs. 52.5 [49.7-55.3] mL/min/1.73m<sup>2</sup>, p<0.001), 3 years (46.0 [45.0-47.0] vs. 52.5 [48.4-56.6] mL/min/1.73m<sup>2</sup>, p<0.001), and 5 years post-transplant (45.4 [44.2-46.5] vs. 50.0 [46.4-53.5] mL/min/1.73m<sup>2</sup>, p=0.008), respectively, whereas eGFR in patients on pre-transplant PD was similarly good at 1 year (49.9 [46.9-52.9] mL/min/1.73m<sup>2</sup>, p=0.134), 3 years (47.2 [43.9-50.5] mL/min/1.73m<sup>2</sup>, p=0.220), and 5 years post-transplant (48.9 [45.2-52.7] mL/min/1.73m<sup>2</sup>, p=0.397), respectively. We also analyzed 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-yr serum creatinine 147.6 [140.8-154.2] vs. 160.3 [155.9-164.8] µmol/L, p=0.027; 5-yr eGFR 48.8 [46.7-50.9] vs. 44.9 [43.7-45.9]

mL/min/1.73m<sup>2</sup>, p<0.001). Interestingly, as demonstrated by significant interaction between donor type and pre-transplant RRT (p=0.001), this benefit was particularly more pronounced in patients with either no RRT ( $\Delta=6.5$  mL/min/1.73m<sup>2</sup>) or on PD ( $\Delta=4.6$  mL/min/1.73m<sup>2</sup>) compared to a relatively small benefit for HD ( $\Delta=2.6$  mL/min/1.73m<sup>2</sup>) and HD+PD ( $\Delta=2.8$  mL/min/1.73m<sup>2</sup>) patients, respectively (p<0.001) (**Figure 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 pre-transplant dialysis, whereas 5-yr eGFR was not related to donor age in patients with no RRT prior to allograft transplantation (**Figure 6B**).

Allograft function decline measured by eGFR slope during post-transplant years 1-5 was slowest in recipients on pre-transplant PD (-0.56 mL/min/1.73m<sup>2</sup> per year), followed by HD (-0.86 mL/min/1.73m<sup>2</sup> per year), HD+PD (-0.97 mL/min/1.73m<sup>2</sup> per year), and patients with no pre-transplant RRT (-1.47 mL/min/1.73m<sup>2</sup> per year). However, differences between pre-transplant RRT groups were not statistically significant (p=0.283). Repeated measures linear mixed-effects modeling accounting for living vs. deceased donation status yielded similar results (data not shown). In addition to that, secondary analysis of eGFR slopes comparing subgroups of living vs. deceased donation allografts within the respective pre-transplant RRT groups revealed significant benefits only for recipients on pre-transplant 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 (**Figure 7**).

#### *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 pre-transplant 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’, ‘PD’, HD’, and ‘HD+PD’, respectively (p<0.001), demonstrating reduced DGF prevalence in ‘PD’ vs. ‘HD’ patients.

We recorded 771 patients who experienced  $\geq 1$  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’,

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HD', and 'HD+PD', respectively ( $p=0.019$ ). Kaplan-Meier survival estimates of cumulative AR-free graft survival are shown in **Figure 8A** and demonstrate similar survival for 'no RRT' and 'PD' patients. Unadjusted 3-months, 6-months, and 1-yr AR-free graft survival rates were significantly better for 'PD' vs. '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 (**Figure 8B**) in 'PD' compared to 'HD' patients ( $HR=0.700$  [95% CI 0.508-0.965],  $p=0.029$ ).

## DISCUSSION

In 2277 kidney allograft recipients who were followed for up to 18 years post-transplantation, pre-transplant treatment with PD was associated with superior patient survival (36% lower all-cause mortality risk) compared to pre-transplant HD, which is consistent with results from large registry studies.<sup>8-12</sup> Despite efforts to 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 vs. 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.<sup>12,13</sup>

Along those lines, we found an AR-free allograft survival benefit associated with pre-transplant PD vs. HD treatment, hinting at a RRT modality-related rather than patient characteristics-related effect. We confirm recent results from others<sup>9-11</sup> but contradicting older findings of still others who reported pre-transplant PD to be associated with either favorable<sup>8</sup> or deleterious<sup>12</sup> effects on allograft survival. However, the authors analyzing 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.<sup>8</sup> Moreover, some studies categorized pre-transplant RRT according to the modality used either for the longest period<sup>8</sup>, at the time of transplantation<sup>12</sup> or at study entry<sup>10</sup> and therefore did not further subgroup patients who had received both HD and PD in a sequential manner. When looking at pre-transplant RRT modality as the primary variable of interest one needs to consider the importance of stable long-term treatment with a single RRT modality vs. bias due 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  $\geq 60$  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 pre-millennial cohorts of 20-29 years ago<sup>8,12</sup> 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<sup>8,9,11,12</sup> and 6 years<sup>10</sup>, 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 pre-transplant 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 due to between-group differences regarding predictors of allograft 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<sup>24</sup> and development of interstitial fibrosis and atrophy may not be accurately represented in changes in serum creatinine,<sup>25</sup> compared to 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.<sup>26</sup> In addition, it has been shown that eGFR slope is a strong predictor of long-term kidney allograft outcome and may facilitate its prediction.<sup>27,28</sup> While the overwhelming number of studies analyzing pre-transplant RRT modality did not incorporate data on actual allograft function, there are only 2 reports taking into account creatinine or eGFR, both failing to demonstrate graft function differences in recipients with pre-transplant HD vs. PD regimens. However, sample size was small in both studies<sup>18,19</sup>. Moreover, functional graft data was available only up to 1 year<sup>18</sup> and solely donors after cardiac death were studied, impairing generalizability to a large extent.<sup>18</sup>

Finally, we analyzed long-term allograft function with respect to donor age as well as living vs. deceased donation status within pre-transplant RRT modality groups. Higher donor age was associated with decreased 5-yr 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 due 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-yr 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, both recipients of pre-emptive allografts and PD patients are known to have better preserved RRF.<sup>14,29</sup> 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.<sup>11</sup> 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 pre-transplant 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, due to the small sample size significant interaction between donor type and pre-transplant 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.<sup>26</sup> 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. Due to the retrospective nature of this study, we could not compare outcomes of ESRD patients with equal eligibility for HD vs. 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 vs. PD are therefore likely to be biased by the pre-transplant 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 by patients who either received a living donation graft early on, had preferential early allocation by chance due to 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. Due to the single-center nature, our results may not extrapolate to other centers, especially as donation after cardiac death is not performed in Germany. Also, most studies analyzing pre-transplant 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 to 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-center 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-yr post-transplant and of DGF and AR episodes in a comparatively large-size sample analyzing pre-transplant 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 pre-transplant PD vs. HD. Moreover, this is the first study to demonstrate in a considerable sample-size population a significant allograft function benefit of pre-transplant 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.

## ACKNOWLEDGEMENTS

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**TABLES***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
<i>Transplantation</i>						
Urgency status, n (%)						
T	1959 (86.0)	116 (85.3)	1590 (86.1)	141 (88.7)	112 (83.0)	
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	<b>0.003</b>
HLA-B	0.99±0.74	1.16±0.66	1.00±0.74	0.94±0.75	0.86±0.67	<b>0.006</b>
HLA-DR	0.77±0.73	0.51±0.71	0.81±0.73	0.66±0.75	0.71±0.70	<b>&lt;0.001</b>
Full house match, n (%)	372 (16.3)	8 (5.9)	301 (16.3)	41 (25.8)	22 (16.4)	<b>&lt;0.001</b>
AB0 incompatibility, n (%)	69 (3.0)	19 (14.0)	36 (1.9)	7 (4.4)	7 (5.2)	<b>&lt;0.001</b>
Cold ischemia time, hours (mean±SD)	12.6±7.3	4.1±4.1	13.3±7.1	10.6±7.2	12.8±7.5	<b>&lt;0.001</b>
<i>Recipient</i>						
Gender, n (%)						
f	896 (39.4)	54 (39.7)	692 (37.5)	79 (49.7)	71 (52.6)	
m	1381 (60.6)	82 (60.3)	1155 (62.5)	80 (50.3)	64 (47.4)	

Blood group, n (%)						0.185
A	980 (43.0)	60 (44.1)	785 (42.5)	67 (42.1)	68 (50.4)	
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 <sup>2</sup> (mean±SD)	24.9±4.0	24.3±3.7	25.0±3.9	24.7±3.8	24.3±4.3	<b>0.019</b>
BSA, m <sup>2</sup> (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 (%)						<0.001
Glomerulonephritis	610 (26.8)	38 (27.9)	481 (26.0)	45 (28.3)	46 (34.1)	
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	<b>&lt;0.001</b>
Previous kidney Tx, n (%)	321 (14.1)	13 (9.6)	266 (14.4)	13 (8.2)	29 (21.5)	<b>0.004</b>
Simultaneous pancreas Tx, n (%)	184 (8.1)	17 (12.5)	136 (7.4)	25 (15.7)	6 (4.4)	<b>&lt;0.001</b>
Coronary artery disease, n (%)	516 (22.7)	21 (15.4)	443 (24.0)	25 (15.7)	27 (20.0)	<b>0.013</b>
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)	<b>0.023</b>
Charlson comorbidity score	4.1±1.9	3.6±1.8	4.2±1.9	3.7±1.6	3.7±2.0	<b>&lt;0.001</b>
<hr/>						
<i>Donor</i>						
Donor type, n (%)						<b>&lt;0.001</b>
Cadaveric	1829 (80.3)	24 (17.6)	1580 (85.5)	113 (71.1)	112 (83.0)	
Living	448 (19.7)	112 (82.4)	267 (14.5)	46 (28.9)	23 (17.0)	
Gender, n (%)						0.057
f	1167 (51.3)	83 (61.0)	924 (50.0)	87 (54.7)	73 (54.1)	
m	1110 (48.7)	53 (39.0)	923 (50.0)	72 (45.3)	62 (45.9)	
Blood group, n (%)						0.247
A	931 (40.9)	57 (41.9)	743 (40.2)	64 (40.3)	67 (49.6)	
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)	
O	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	<b>0.001</b>
BMI, kg/m <sup>2</sup> (mean±SD)	25.8±4.1	25.1±3.5	25.9±4.1	25.5±4.6	25.2±3.8	<b>0.016</b>
BSA, m <sup>2</sup> (mean±SD)	1.91±0.22	1.87±0.19	1.92±0.22	1.89±0.25	1.89±0.21	<b>0.001</b>
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

P is given for statistical differences between pre-transplant RRT modality groups. BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CKD, chronic kidney disease; HD, hemodialysis; HI, highly immunized; HLA, human leukocyte 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.

## FIGURE LEGENDS

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

*Figure 2:* Unadjusted (Kaplan-Meier) primary outcomes comparing allograft recipients according to pre-transplant 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, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy.

*Figure 3:* Multivariable Cox proportional hazard (reduced) model analyzing 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, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis; RRT, renal replacement therapy; TMA, thrombotic microangiopathy; Tx, transplantation.

*Figure 4:* Multivariable Cox proportional hazard (reduced) model analyzing 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, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis; RRT, renal replacement therapy; Tx, transplantation.

*Supplementary Figure 1:* Multivariable Cox proportional hazard (full) model analyzing all-cause patient death. The model accounts for transplant, recipient, and donor variables. \*Continuous variables cold ischemia time, dialysis vintage prior to Tx, recipient BMI, and Charlson comorbidity index were dichotomized using the median. BMI, body mass index; CI, confidence interval; HD, hemodialysis; HI, highly immunized; HLA, human leukocyte antigen; HR, hazard ratio; HU, highly urgent; I, immunized; PD, peritoneal dialysis; RRT, renal replacement therapy; T, transplantable; TMA, thrombotic microangiopathy; Tx, transplantation.

*Supplementary Figure 2:* Multivariable Cox proportional hazard (full) model analyzing death-censored graft loss. The model accounts for transplant, recipient, and donor variables.

\*Continuous variables cold ischemia time, dialysis vintage prior to Tx, recipient BMI, Charlson comorbidity index, and donor BMI were dichotomized using the median. BMI, body mass index; CI, confidence interval; HD, hemodialysis; HI, highly immunized; HLA, human leukocyte antigen; HR, hazard ratio; HU, highly urgent; I, immunized; PD, peritoneal dialysis; RRT, renal replacement therapy; T, transplantable; Tx, transplantation.

*Figure 5:* 1-yr, 3-yr, and 5-yr post-transplant allograft function. Mean eGFR $\pm$ SD is shown for pre-transplant RRT groups. ANOVA p for log-transformed variables; eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SD, standard deviation.

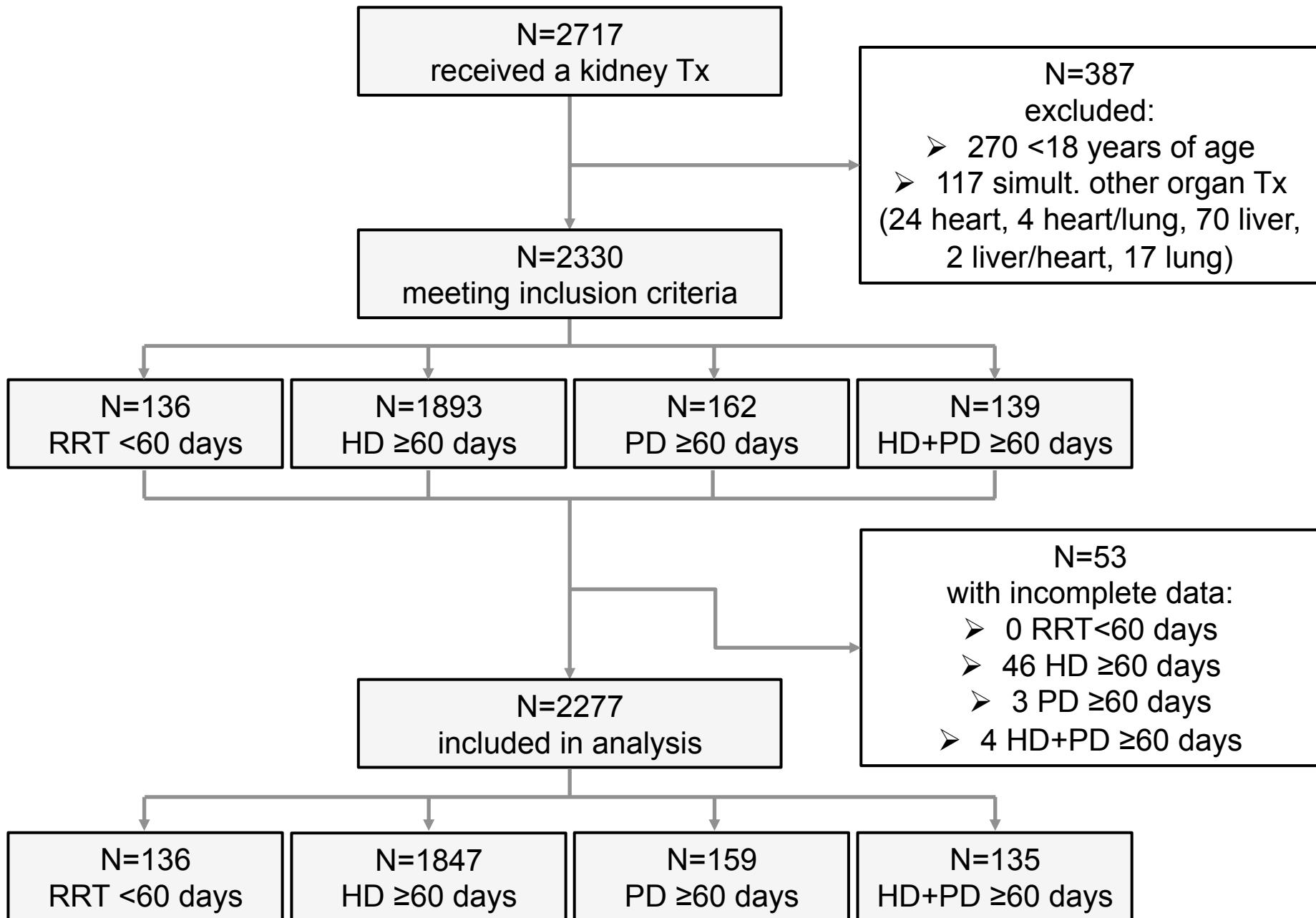
*Figure 6:* Influence of donor factors on allograft outcomes. **A** Benefit of living vs. deceased donation type for 5-yr allograft function given as  $\Delta$  eGFR (shadowed area); 5-yr post-transplant eGFR is given as means $\pm$ SEM, open symbols ○ denote living donation (liv.), closed symbols ● denote deceased (dec.) donation. P<0.001 for living vs. deceased donation comparison. **B** Relationship of donor age and 5-yr eGFR. R<sup>2</sup>, regression coefficient B, and p values are given for linear regression across individual pre-transplant RRT groups. eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SEM, standard error of the mean.

*Figure 7:* Allograft function decline during post-transplant years 1-5. Mean eGFR slope $\pm$ SEM is shown and statistically compared between living vs. cadaveric donation within pre-transplant RRT groups. eGFR, estimated glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy; SEM, standard error of the mean.

*Figure 8:* Acute rejection episodes within 1 year post-transplant according to pre-transplant RRT modality. (A) Unadjusted (Kaplan-Meier) cumulative AR-free graft survival according to pre-transplant RRT modality. Maximum follow-up was 12 months, log rank (Mantel-Cox) p=0.018 (B) Multivariable Cox proportional hazard (reduced) model analyzing 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

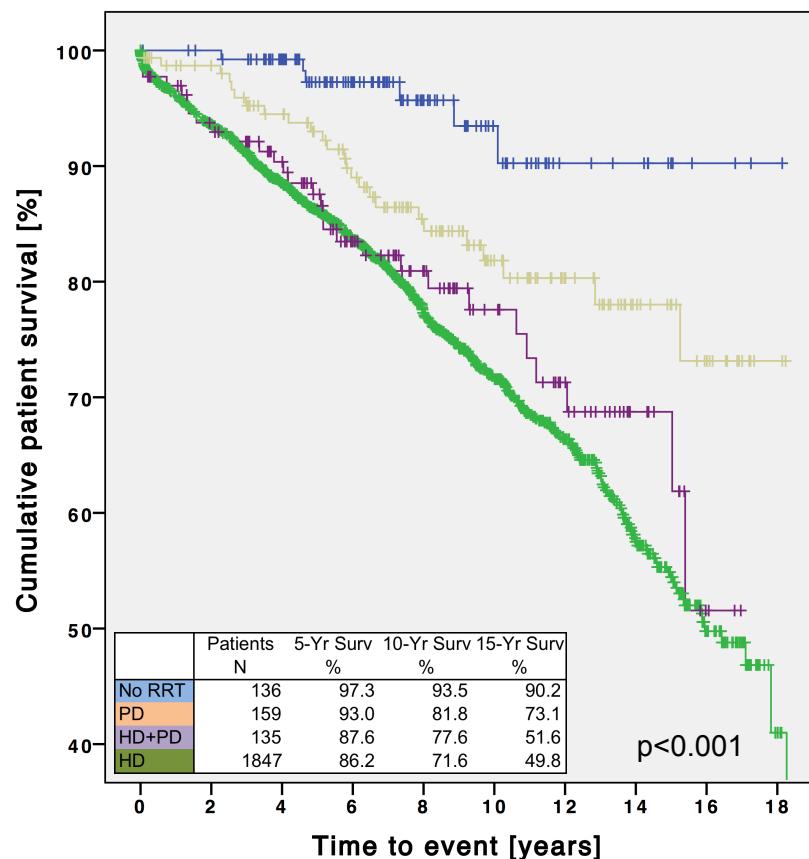
mass index; CI, confidence interval; HD, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis; RRT, renal replacement therapy; Tx, transplantation.

**Figure 1.** Flow chart of study population.

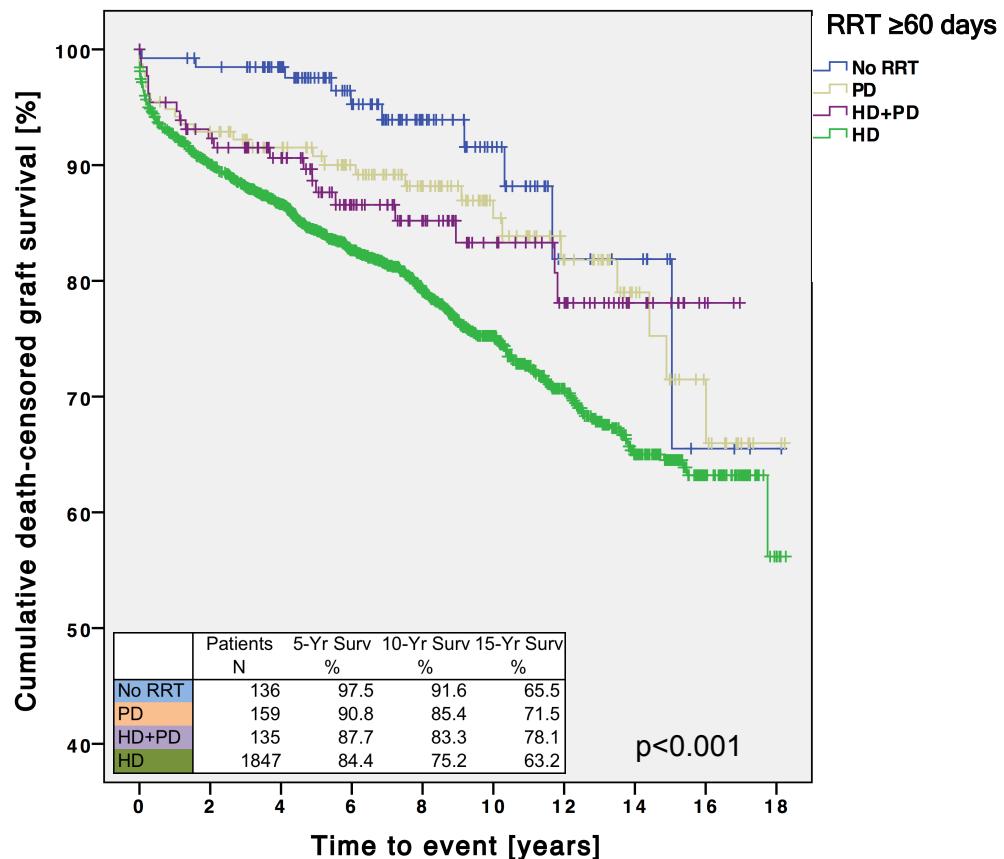


**Figure 2.** Unadjusted (Kaplan-Meier) primary outcomes comparing patients according to pre-transplant RRT modality.

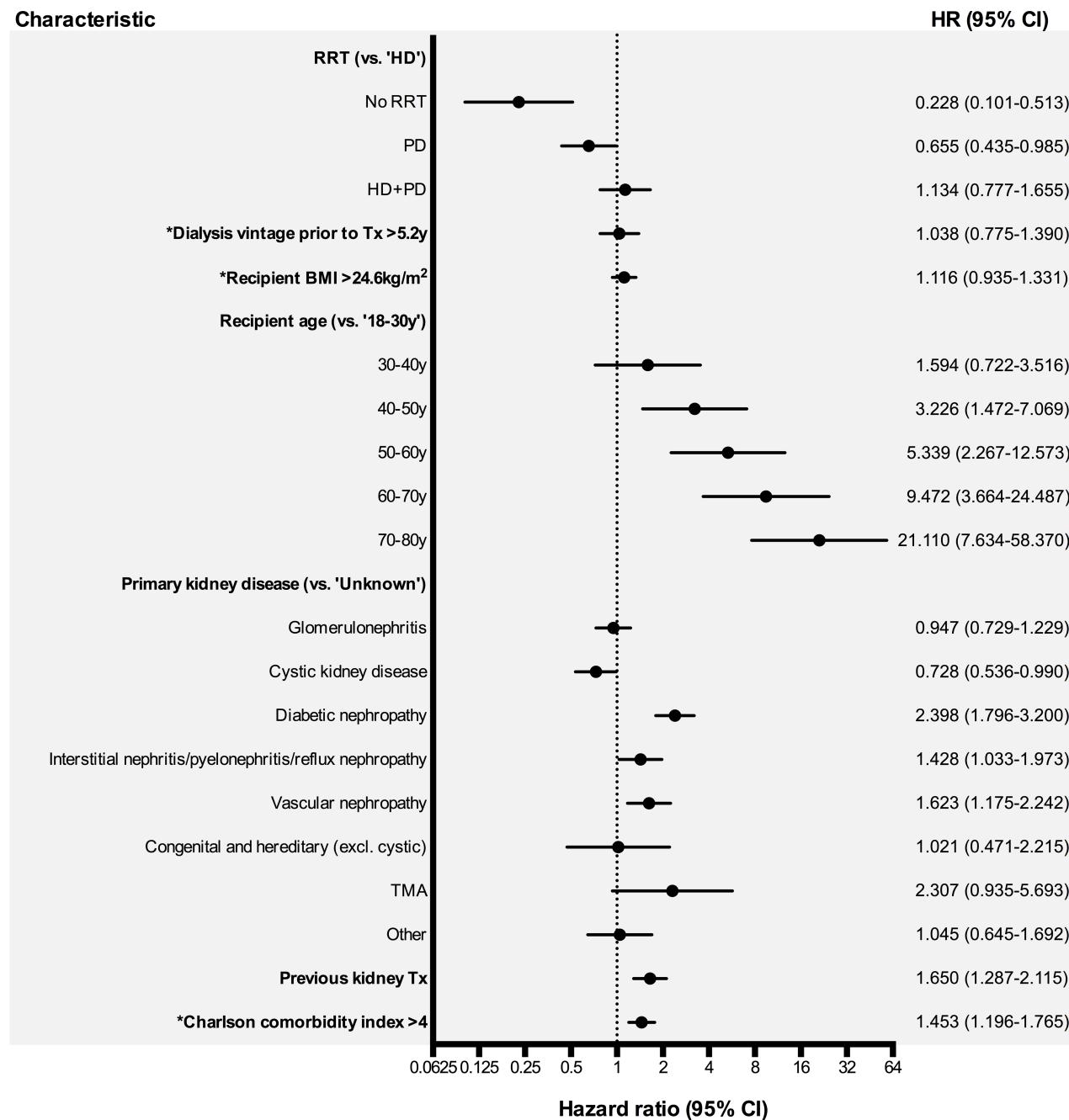
**A**



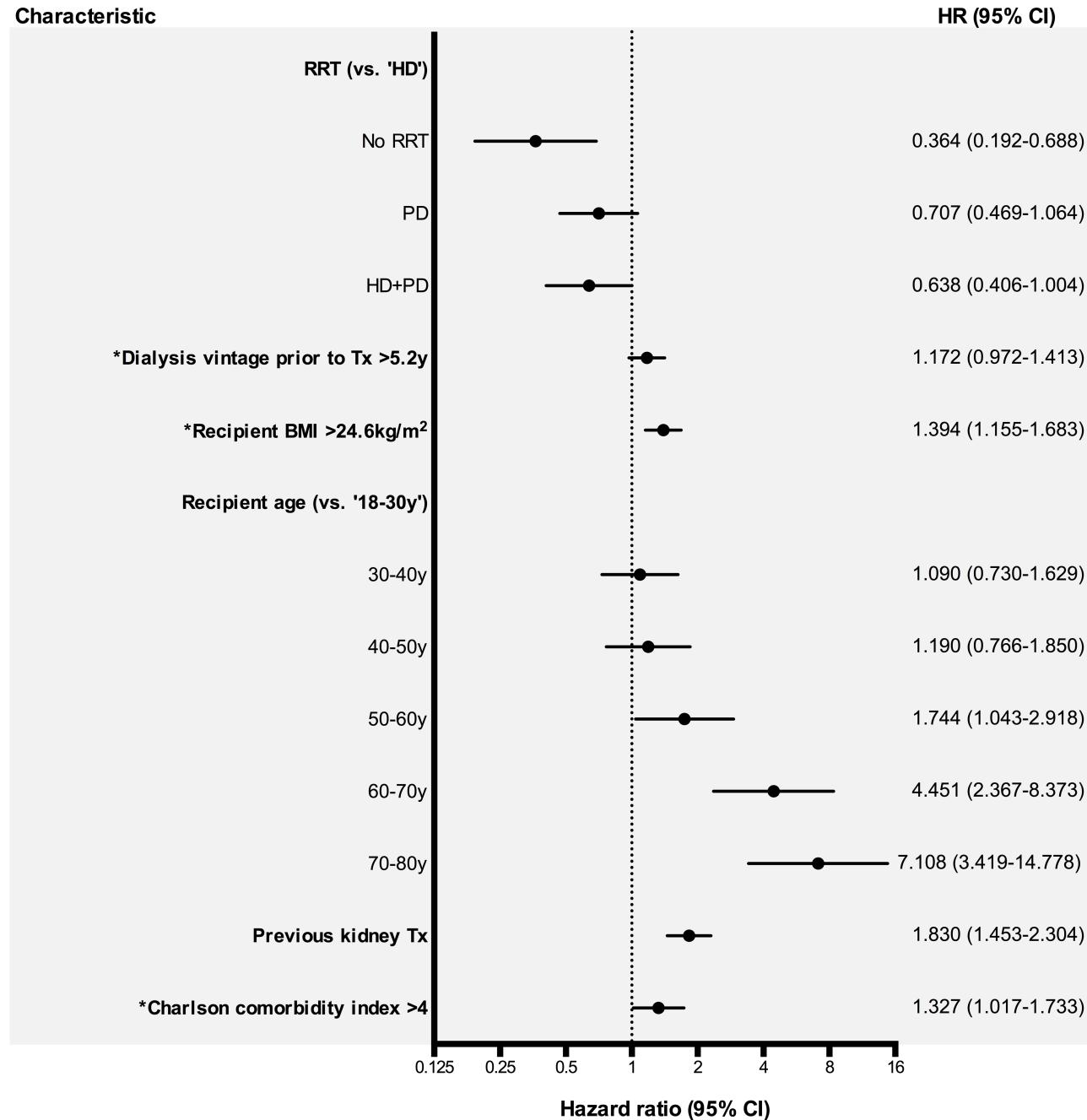
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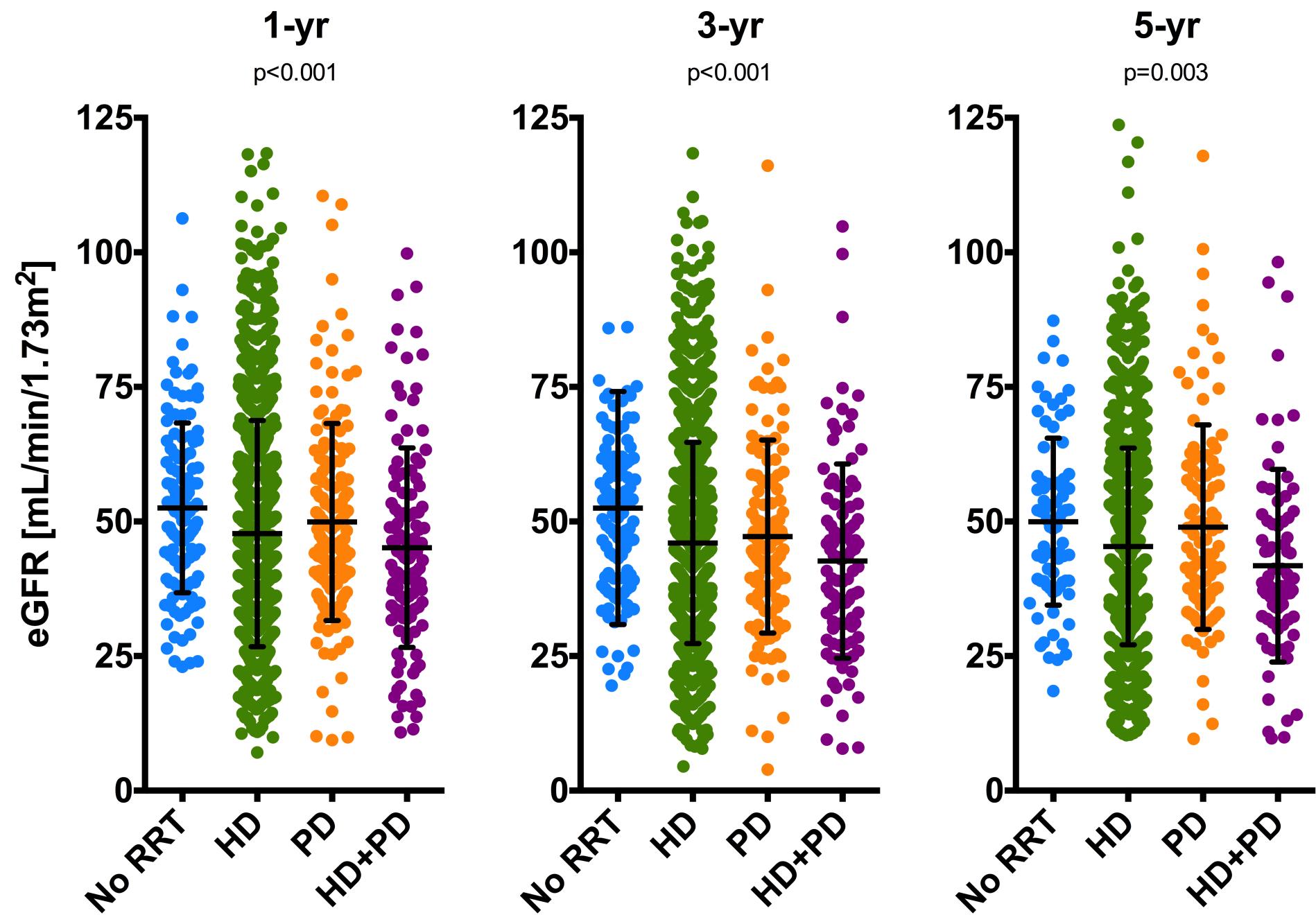
**Figure 3.** Multivariable Cox proportional hazard (reduced) model analyzing all-cause patient death.



**Figure 4.** Multivariable Cox proportional hazard (reduced) model analyzing death-censored graft loss.

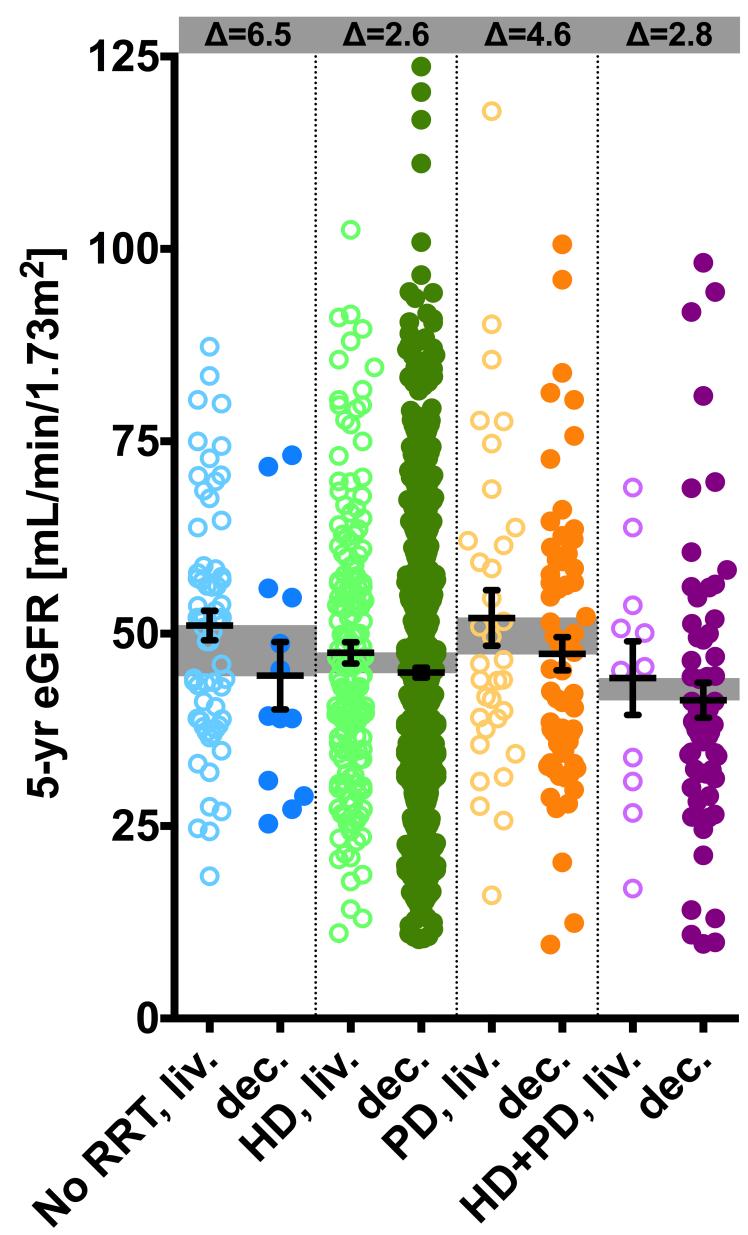


**Figure 5.** 1-yr, 3-yr, and 5-yr post-transplant allograft function.

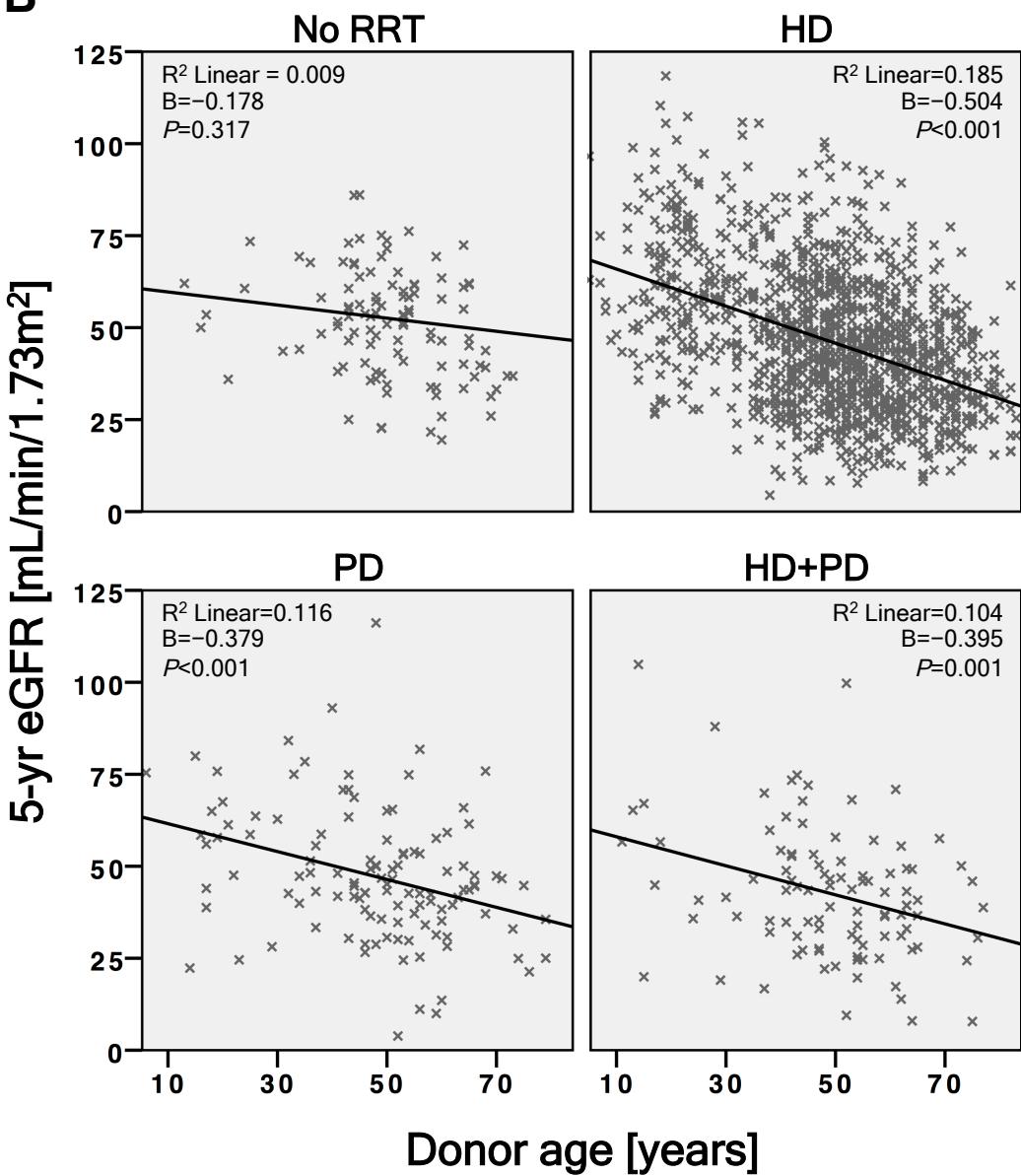


**Figure 6.** Influence of donor factors on allograft outcomes.

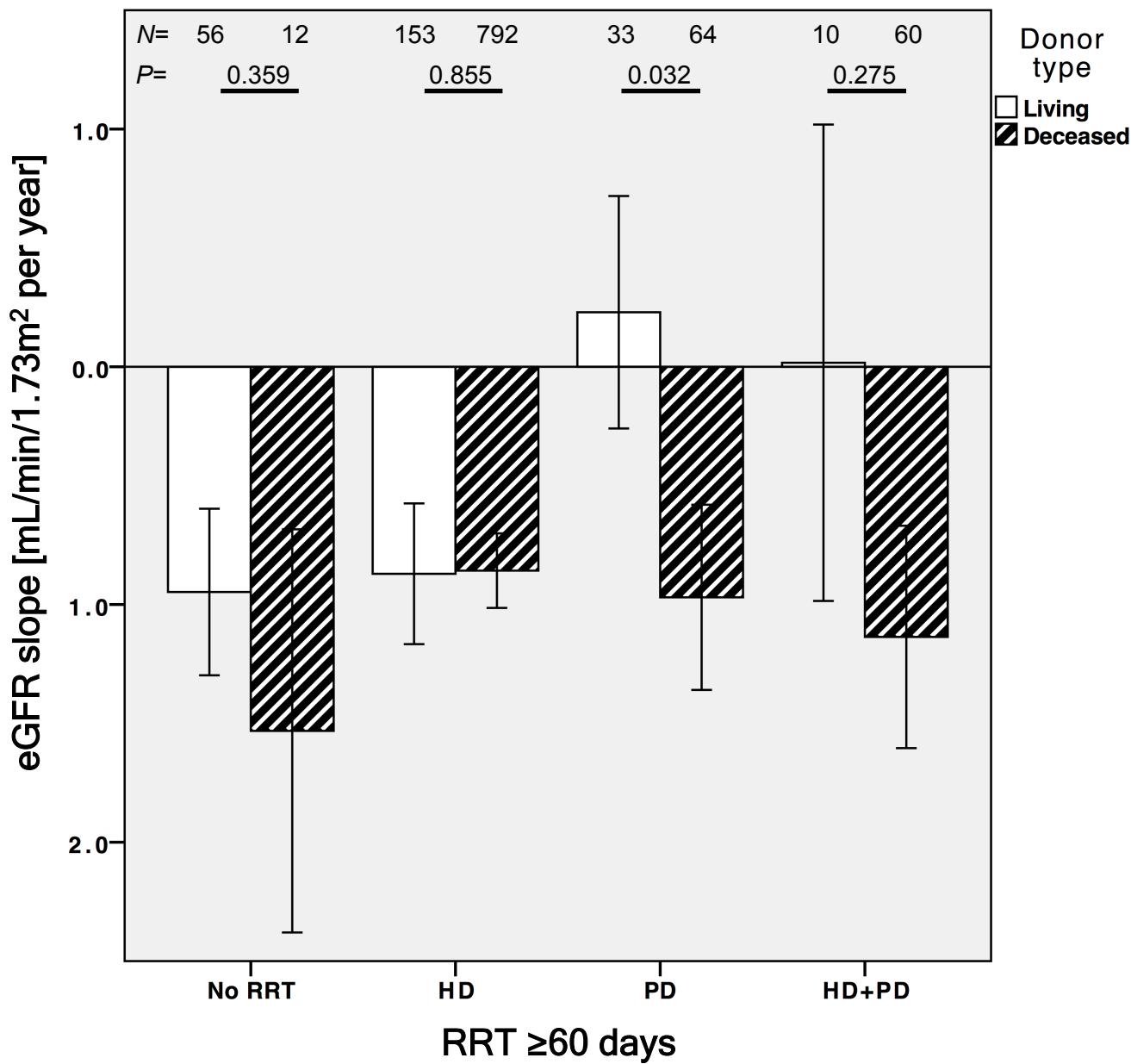
**A**



**B**

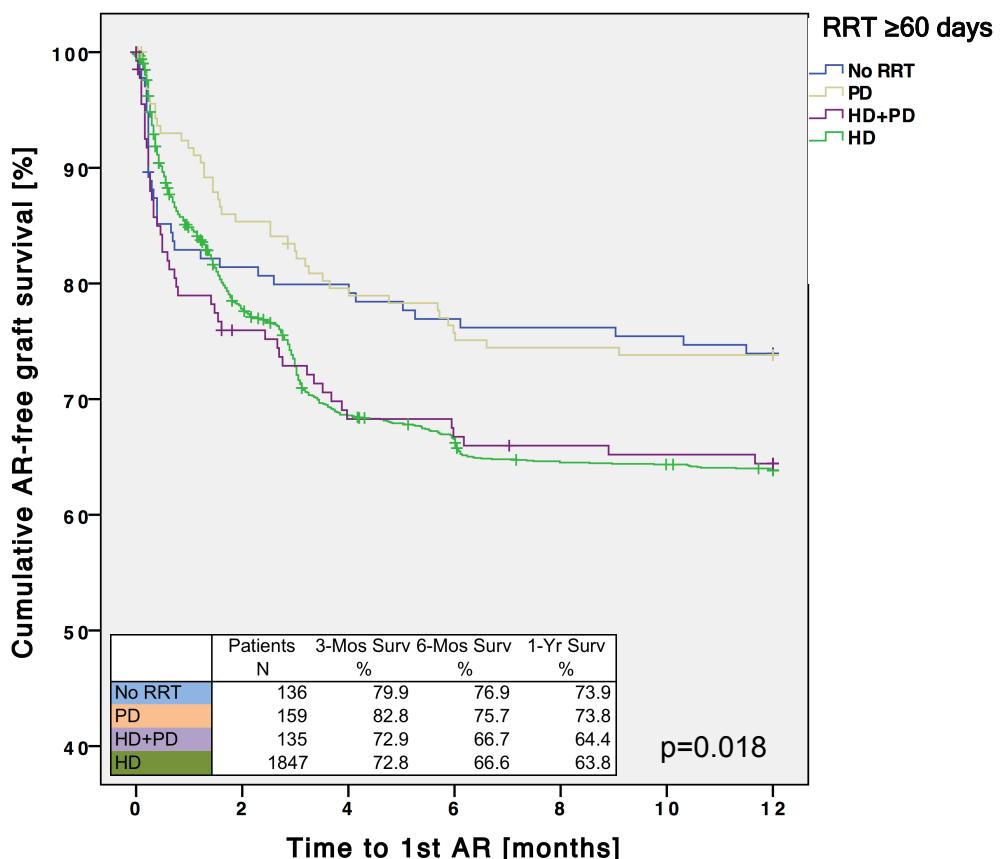


**Figure 7.** Allograft function decline during post-transplant years 1-5.



**Figure 8.** Acute rejection episodes within 1 year post-transplant according to pre-transplant RRT modality.

**A**



**B**

