ORIGINAL ARTICLE

Regression of left atrial diameter after kidney transplantation is associated with prolonged survival: an observational study

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SUMMARY

Renal transplantation reduces the dramatically elevated risk of cardiovascular death in dialysis patients. We previously showed that left atrial diameter before transplantation predicts cardiovascular and overall mortality. Now, we investigated the association of changes in cardiac morphology after transplantation and mortality. We retrospectively analyzed data from the Austrian transplant repository using multivariable Cox and competing risk models and multivariable logistic regression for the prediction of changes in cardiac morphology. We identified 414 patients with a median follow-up of 8 years and observed a significant progression of mean diameter of left atrium (LA), right atrium and right ventricle and a significant regression of left ventricle. Complete case analysis of 243 patients with a regression of initially enlarged LA diameter had a significantly lower risk of adjusted overall and cardiovascular mortality; hazard ratio (HR 0.45, 95% CI 0.30–0.69, $P < 0.001$, 124 deaths), and HR of 0.43 [95% CI 0.21–0.92, $P = 0.029$, 48 cardiovascular (CV) deaths], respectively. Only age at transplantation was significantly associated with regression of LA (OR 0.75, 95% CI 0.60–0.93, $P = 0.007$). Patients with regression of LA after kidney transplantation exhibited a lower overall and CV mortality risk. Besides age, peritoneal dialysis and antihypertensive therapy were mediators of LA regression.

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Introduction

Cardiovascular disease is highly prevalent among patients with CKD, and cardiovascular events are the leading cause of death in patients with end-stage renal disease. The risk of cardiovascular death of patients on dialysis is ten to twenty times higher compared to the general population, even after stratification by age, gender, race, and the presence of diabetes [1].

In contrast to the general population where cardiovascular mortality is mainly conferred by atherosclerotic coronary artery disease, dialysis patients show a higher proportion of sudden, presumably arrhythmic cardiac death. Cardiovascular mortality in dialysis patients is not only driven by conventional risk factors such as hypertension, hyperlipidemia, and diabetes, but also uremia, electrolyte abnormalities, and hemodynamic factors causing changes in cardiac morphology and

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function [2,3]. Common echocardiographic findings in dialysis patients are left ventricular hypertrophy (LVH), left ventricular dilatation, and left ventricular systolic dysfunction, as well as dilation of the left atrium as a result of fluid overload and impaired left ventricular diastolic relaxation [4].

Successful renal transplantation dramatically reduces the highly increased cardiovascular mortality of dialysis patients [1,5,6]. This decrease in cardiovascular mortality in renal transplant recipients compared to dialysis patients is partly due to the selection bias in those being wait-listed for transplantation, but also caused by the reduction in uremic and hemodynamic abnormalities potentially leading to regression of abnormal cardiac morphology after successful transplantation.

In an earlier study including 553 renal transplant recipients, we showed that left atrial diameter at the time of transplantation independently predicted overall and cardiac mortality, whereas right atrial diameter predicted functional graft loss [7].

Similarly, a cardiac MRI study by Patel *et al.* [8] showed an independent association of pretransplant left atrial volume with mortality after transplantation.

It remains unclear to which extent the enlargement of the left atrium is reversible by successful transplantation and whether or not a regression of left atrial dilatation impacts survival. An understanding of the changes in cardiac morphology after renal transplantation could have implications for the timing and interpretation of post-transplant follow-up echocardiograms and help to identify a potential risk population.

The aim of this study was to examine the changes in echocardiographic abnormalities after transplantation, in particular left atrial enlargement, and its association with survival. Another aspect investigated by the study is potentially modifiable factors influencing the progression or regression of pathological cardiac morphology.

Patients and methods

Study population

We retrospectively analyzed data from the Austrian dialysis and transplant repository OEDTR (Österreichisches Dialysis- and Transplantation Registry), which were merged with echocardiography data repositories from the transplant centres [9].

We included all patients who received a first kidney-only transplant between the beginning of 1994 and the end of 2014 with an echocardiographic examination performed within 3 years before transplantation and at least one follow-up examination after transplantation. A flow diagram showing the included and excluded patients is provided in Fig. 1. The study period starts with the introduction of mandatory echo evaluation in 1994. The end of observation was chosen to allow for at least 2 years of follow-up. Four hundred and fourteen patients with a median follow-up of 8.0 years were available for analysis. Twenty-six patients were lost to follow-up at a median of 1.2 years (IQR 0.25–4.14 years).

To test for a potential selection bias, we compared the baseline demographics of patients with echocardiograms with all other patients transplanted within the same period. This comparison revealed that our study population was older and had a higher number of antihypertensive medication (Table S1).

All clinical investigations were conducted in accordance with the guidelines of the 2013 Declaration of Helsinki. The requirement for informed consent from the patients was waived because of the study's retrospective design.

Echocardiography

Of the 414 patients, 52% had one follow-up echocardiogram, 19% had two, 12% had three, and 16% had four or more follow-up echocardiograms. The median time to first echocardiogram was 1.3 years (IQR 0.38; 5.19). The distribution of the first post-transplant echocardiograms over time is plotted in Fig. S1.

The following echocardiographic parameters were extracted from the above-mentioned databases: length of left atrial diameter (LA), left ventricular end diastolic diameter (LV), length of right atrial diameter (RA), and length of right ventricular diameter (RV). In 46% of patients, the left ventricular function (LVF) was quantified by ejection fraction (EF) or reported qualitatively as normal, mildly, moderately, or severely reduced LVF. For the remaining patients, LVF was not reported. In patients with available LVF measurements, 88% had a normal or mildly reduced left ventricular function (defined as an EF >41% [10]). Left ventricular hypertrophy was not included in our analysis as echocardiography is not sensitive enough to assess expected discrete changes in left ventricular mass, compared to cardiac MRI [11,12]. Other parameters were not included in the analysis due to low numbers of reported morphological values. It is of note that some parameters were only semi-quantitatively reported, which explains the deviating numbers of analyzed echocardiograms for different parameters in Table 1. The majority of measurements

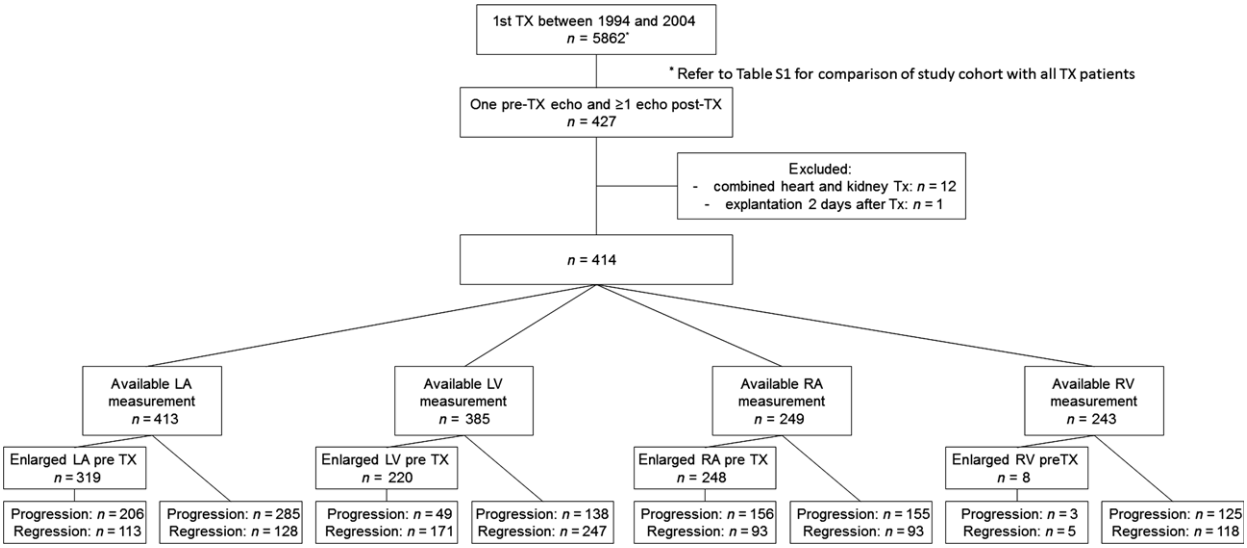

Figure 1 Flow diagram of included and excluded patients, as well as proportion of enlarged measurements in the pretransplant echocardiogram and the distribution of progression and regression for each echocardiographic parameter. Progression and regression were defined as numeric increase and decrease, respectively, of the respective post-transplant echocardiographic parameter. LA, diameter of left atrium; RA, diameter of right atrium; LV, diameter of left ventricle; RV, diameter of right ventricle; TX, transplantation.

were taken in two-dimensional mode. The reference values for each parameter were defined as suggested by the European Association of Cardiovascular Imaging [10].

Outcomes

The outcome parameters were overall and cardiovascular mortality and graft loss.

Statistical analysis

Continuous demographic variables are reported as mean and standard deviation, or median and interquartile range if not normally distributed.

Overall survival time was visualized by Kaplan–Meier plots. We conducted time-to-event analyses using uni- and multivariable Cox proportional hazard models, as well as a Fine and Gray model to account for competing risks (cardiovascular and noncardiovascular death) [13]. The echocardiographic parameters were dichotomized based on their progression/regression in the time course after transplantation. Progression and regression were defined as numeric increase and decrease, respectively, of the respective post-transplant echocardiographic parameter. To avoid misclassification of patients with few echocardiograms and/or exhibiting only small changes of the respective parameter, we applied two additional models: One including only patients with large changes of the respective parameter and one including only patients with their first echocardiogram within the first year after transplantation and patients with three or more sequential echocardiograms. We included only patients with enlarged measurements at the time of transplantation in the respective models. The proportional hazards assumption was tested by inspection of the Schoenfeld residuals (Fig. S2). Estimates of effect size showed that inclusion of 206 subjects exhibiting a progression and 113 patients exhibiting a regression of enlarged LA with a median observation time of 15.3 years and an annual mortality rate of 3% would yield a detectable hazard ratio of smaller than 0.62 or greater than 1.72 with a power of 0.8 at an alpha error of 0.05. For the analysis of factors associated with the progression or regression of echocardiographic parameters, we used multivariable logistic regression models. Initial covariable selection was based on clinical expertise: age at transplantation, dialysis vintage, mode of dialysis, antihypertensive therapy, the presence of diabetes, and renal function. Only variables with an unadjusted $P < 0.15$ were selected for the multivariable Cox model. For renal function, we used the slope of eGFR calculated by the MDRD equation. We only used measurements from 6 months after transplantation onwards when allograft function had stabilized. Analyses were carried out in complete cases only. A two-sided P-value below 0.05 was considered statistically significant. For all statistical analysis, we used SAS 9.4 for Windows (Cary, NC, USA).

Table 1. Demographic data and echocardiographic parameters of patients at time of transplantation.

Variable	*n*	Value
Age (years)	414	56 ± 13
Sex (% male)	414	60%
Dialysis vintage (years)	374	2.51(1.24;3.92)
Dialysis modality (%)		
HD	302	80.75%
PD	57	15.24%
Preemptive	15	4.01%
Number of antihypertensive medications	329	2.60 (±1.8)
0	58	17.6%
1–2	104	31.6%
3–4	113	34.4%
>4	54	16.4%
Diabetes (%)	337	
No DM	272	80.7%
DM I	7	2.1%
DM II	58	17.2%
Donor age (years)	360	51 (±14)
Donor type (%)	374	
Deceased	330	88.2%
Living	44	11.8%
HLA mismatch		
MMA	317	1 (0;1)
MMB	323	1 (1;2)
MMDR	320	1 (0;1)
Sum of HLA MM	309	3 (2;4)
LA (mm) [Ref. <40 mm (m), <38 mm (w)]	413*	48 ± 10
RA (mm) [Ref. <25 mm]	249*	48 ± 10
LV (mm) [Ref. <50 mm (m), <45 mm (w)]	385*	50 ± 7
RV (mm) [Ref. <41 mm]	243*	30 ± 5

LA, diameter of left atrium; RA, diameter of right atrium; LV, diameter of left ventricle; RV, diameter of right ventricle; MMA, MMB, MMDR, HLA mismatch in locus A, B, DR; HD, hemodialysis; PD, peritoneal dialysis.

Values are expressed as percentage, mean and standard deviation or median and IQR (25th percentile; 75th percentile).

*Only patients with follow-up for respective echocardiographic parameter are indicated.

Results

Baseline data

The baseline characteristics of the study cohort are summarized in Table 1. In the pretransplant echocardiograms, 77% of patients had an enlarged left atrium of >40 mm and >38 mm for men and women, respectively. Seventy-nine percent of patients had an enlarged right atrium of >25 mm. Fifty-five percent of patients had an enlarged left ventricle of >50 and >45 mm for men and women, respectively. Only 2% had an enlarged right ventricle of >41 mm.

Changes in echocardiographic characteristics after transplantation

In the course after transplantation, the mean diameter of LA, RA, and RV increased significantly, whereas there was significant decrease in LV diameter. The median increase in left atrial diameter was 1.3 mm/year (IQR 2.8 mm/year), the median increase in right atrial diameter was 0.5 mm/year (IQR 1.3 mm/year), the median increase in right ventricular diameter was 0.2 mm/year (IQR 1.2 mm/year), and the median decrease in left ventricular diameter was 1.1 mm/year (IQR 1.2 mm/year). Thirty-six percent of patients, who had an enlarged left atrium at the time of transplantation, showed a regression of left atrial diameter in the time after transplantation. A summary of the changes in echocardiographic parameters over time can be seen in Table S2.

Outcomes after transplantation

During a median follow-up of 8.0 years, 183 patients (44.2%) died and 77 patients (18.6%) experienced functional graft loss. The median survival time was 12.4 years, which is longer than the median follow-up because for the latter include censored patients who were counted as having an event. The 10-year functional graft survival rate was 79%. The distribution of causes of death may be found in Table S3.

In the univariable Cox model containing only complete cases with an enlarged LA at the time of transplantation ($n = 243$, 124 deaths), there was a significantly decreased hazard ratio for those who showed a regression of left atrial diameter compared to those who showed a progression (HR 0.45, 95% CI 0.30–0.69, $P < 0.001$). We found a similar reduction in a multivariable model including dialysis vintage, dialysis modality, donor age, the presence of diabetes, and renal function (HR 0.48, 95% CI 0.31–0.75, $P = 0.001$) (Table 2). For visualization purposes, Kaplan–Meier plots of mortality and functional graft survival are provided in Figs 2 and S3 acknowledging an immortal time bias.

In a similar multivariable Cox model for graft failure, there was no significant difference between the two groups. For the RA, there was no difference in survival or functional graft survival between patients who

Table 2. Univariable and multivariable Cox model for mortality in patients with an enlarged left atrium pretransplantation (complete case analysis), $n = 243$, number of events 124, Regression was defined as numeric decrease in diameter of left atrium after transplantation.

	Univariable			Multivariable		
Parameter	HR	Lower and upper 95% Confidence Interval	*P*-value	HR	Lower and upper 95% Confidence Interval	*P*-value
Regression of left atrial diameter (versus progression)	0.45	0.30–0.69	<0.001	0.48	0.31–0.75	0.001
eGFR slope (ml/min/year/1.73 m^2)	0.93	0.91–0.95	<0.001	0.92	0.90–0.95	<0.001
Age at transplantation (decade)	2.23	1.82–2.73	<0.001	Not included*		
Dialysis vintage (year)	1.13	1.02–1.25	0.023	1.10	0.99–1.23	0.086
Dialysis modality (PD versus HD)	0.44	0.25–0.78	0.005	0.41	0.23–0.75	0.004
Dialysis modality (preemptive versus HD)	0.00†	0.00	0.977	0.00†	0.00	0.978
Donor age (year)	1.02	1.01–1.04	0.001	1.02	1.01–1.04	0.001
Diabetes (yes versus no)	1.69	1.09–2.63	0.019	1.76	1.12–2.77	0.015
Antihypertensive Therapy (yes versus no)	0.82	0.51–1.31	0.409			

LA, diameter of left atrium; HD, hemodialysis; PD, peritoneal dialysis.

*Age was excluded from the multivariable model as a confounder as it is associated with both death and progression of LA.

†$n = 6$, cv events = 0, CI not computable, actual HR = 9.3×10^{-7}.

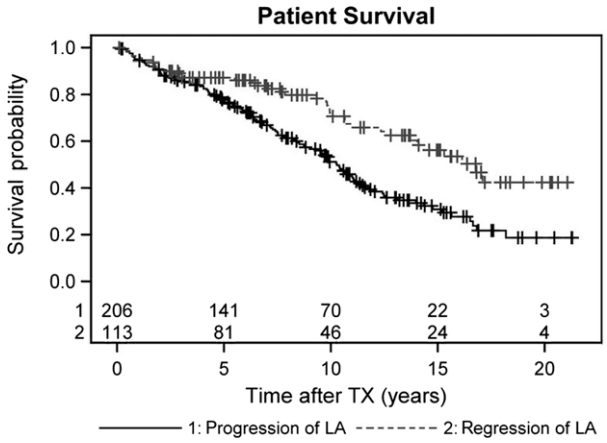

Figure 2 Kaplan–Meier plot with number of subjects at risk stratified by progression or regression of left atrial diameter after transplantation in patients with an enlarged left atrium pretransplantation (log rank $P < 0.001$). Progression and regression were defined as numeric increase and decrease, respectively, of the respective post-transplant echocardiographic parameter. TX, transplantation.

progressed compared to those who regressed in RA diameter. The same was true for LV diameter and RV diameter (Figs S4–S9).

To exclude potential misclassification as progression/regression due to inaccuracy of measurements in patients with only small changes in parameters, we repeated the analysis for LA including only in patients, who exhibited an increase of >4 mm or a decrease of >4 mm ($n = 42$, 29 deaths). The results were similar as in the analysis containing all patients with a HR of 0.18 (95% CI 0.04–0.81, $P = 0.025$) in the multivariable model (Table S4).

We repeated the analysis including only patients with their first echocardiogram within the first year after transplantation and patients, who had three or more follow-up echocardiograms, assuming that in this group of patients, the progression/regression of echocardiographic parameters was assessed most accurately. This model, including 158 patients with 80 events, resulted in a similar HR of 0.39 (95% CI 0.22–0.68, $P = 0.001$) for regression of LA in the multivariable model for mortality (Table S5).

In a multivariable Fine and Gray model for only cardiovascular mortality and complete cases, patients with a regression of previously enlarged left atrium had a significantly decreased HR of 0.43 (95% CI 0.21–0.92, $P = 0.029$, $n = 243$, 48 CV deaths) (Table S6). The Kaplan–Meier analysis for cardiovascular mortality only is provided in Fig. S10. The results of the different models for regression of LA and mortality are summarized in a forest plot in Fig. 3.

Younger age at transplantation (OR 0.75 per decade, CI 0.60–0.93, $P = 0.008$) was the only significant independent predictor of LA regression (Fig. 4; Table S7). Pretransplant peritoneal dialysis (OR 1.81, CI 0.95–3.45, $P = 0.07$) and the number of blood pressure medication (OR 1.15, CI 0.99–1.32, $P = 0.06$) exhibited a trend toward LA regression suggesting that blood pressure control might be an important interventional approach. For both the regression of left ventricular diameter and

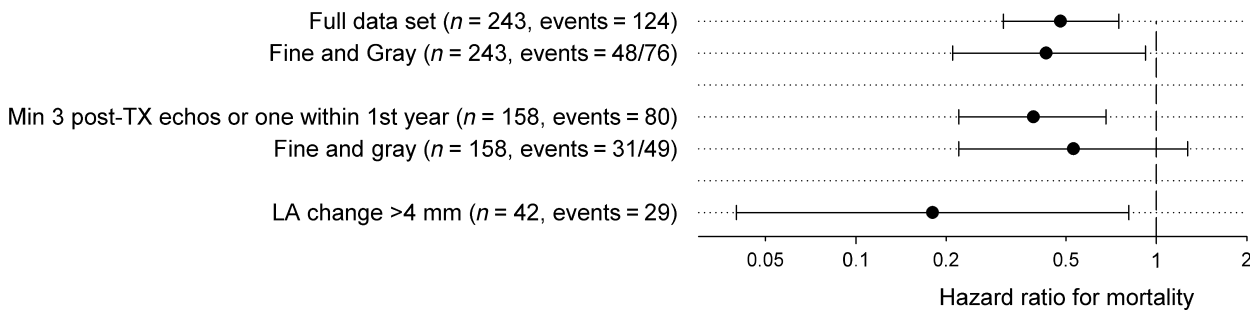

Figure 3 Forest plot summarizing the results of different multivariable models for the association of diameter of left atrium (LA) regression and mortality. Regression was defined as numeric decrease of LA after transplantation. The full data set includes all patients with an enlarged LA pre-TX; the respective Fine and Gray model is displayed below. The second model includes all patients with their first echocardiogram within the first year after TX and patients with three or more follow-up echocardiograms, with the respective Fine and Gray model below. The third model includes all patients exhibiting a change of >4 mm in LA. All models include complete cases only. The full models are provided in table 2 and S4–S6 of the Supplement.

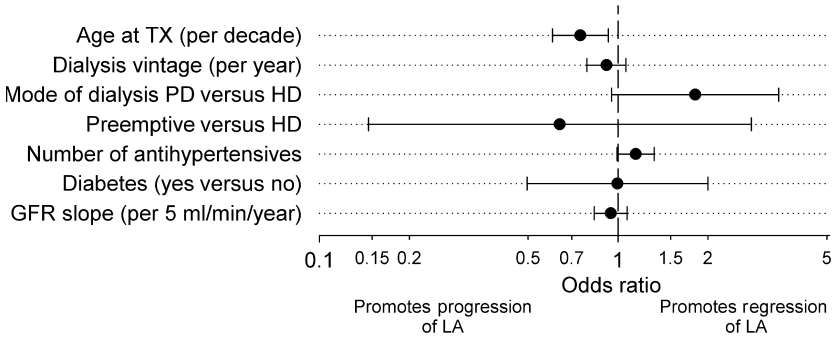

Figure 4 Predictors of regression of left atrial diameter in patients with an enlarged left atrium pretransplant. Regression was defined as numeric decrease of diameter of left atrium after TX. TX, transplantation; pre, preemptive; PD, peritoneal dialysis; HD, hemodialysis.

the regression of right ventricular diameter, only antihypertensive therapy proved to be significantly associated with regression. None of the above-mentioned parameters were associated with the progression or regression of right atrial diameter (Figs S11–S13).

Additional pretransplant parameters stratified for LA regression and progression are provided in Table S8.

Discussion

Our main finding was that the majority of patients, who had an enlarged atrium at the time of transplantation, showed a progression of left atrial diameter and that those patients had a significantly higher risk of mortality compared to patients that exhibited a regression of left atrial diameter after transplantation.

Earlier studies showed that the left atrial diameter at the time of transplantation was an independent predictor for survival after transplantation [7,8]. Left atrial dilatation in dialysis patients is mainly a result of fluid overload and impaired diastolic relaxation, which would be expected to improve after successful renal transplantation and normalization of fluid homeostasis. This hypothesis, however, was not supported by our findings, which showed an overall progression of left atrial diameter over the median follow-up time of almost 8 years. When looking at factors influencing the progression of left atrial diameter, only the age at transplantation was significantly associated with a progression. The number of antihypertensive drugs was the only modifiable factor associated with regression of LA, although not statistically significant. Also, peritoneal dialysis before transplantation was associated with a trend toward regression of LA. Other plausible factors, such as dialysis vintage, did not influence the change in left atrial diameter. Another interesting aspect potentially explaining the reduced cardiac mortality after renal transplantation was investigated by Lai *et al.* [14], who found a rapid and persisting QTc interval shortening after renal transplantation. This could explain a decrease in the incidence of arrhythmias after transplantation.

Kensinger *et al.* [15] found a significant regression of left atrial volume index in 143 kidney transplant recipients with a follow-up time of 24 months after transplantation. However, this study did not report outcomes and had a high proportion of patients with incomplete follow-up, as only 60% and 33% had a follow-up echocardiogram at 12 and 24 months, respectively.

We observed that patients who had a progression of left atrial diameter after transplantation showed a significantly increased risk of overall mortality. This association of regression of LA and post-transplant survival has not been demonstrated before and has potential implications for the prognostic value of follow-up echocardiographic examinations after transplantation.

The present analysis uncovered an overall decrease in left ventricular diameter after transplantation. In contrast to left atrial diameter, there was no difference in survival depending on progression or regression of left ventricular diameter. The change in left ventricular parameters after renal transplantation has been subject of several studies with differing results and conclusions. Patel *et al.* [12] investigated fifty renal transplant recipients and fifty wait-listed patients with two sequential cardiac MRIs, which were on average 2.6 years apart. They found no change in any of the measured cardiac parameters between patients that were transplanted compared to those who remained on the waiting list. This study, however, was subject to immortal time bias due to the time between wait-list entry and transplantation not being accounted for. In contrary, several studies did find a regression of LVH and left atrial diameter after transplantation [16–19]. Fewer studies have investigated the association of changes in echocardiographic parameters with outcome after transplantation. Paoletti *et al.* [20] showed that regression of left ventricular hypertrophy was a significant predictor of cardiac event-free survival.

Our study exhibits all limitations of an observational analysis. The retrospective inclusion of patients with existing echocardiograms resulted in a selection of older patients receiving a higher number of blood pressure medication, as shown in the comparison of our study population with all transplant recipients in our registry. The findings in the investigated population may not be representative for younger allograft recipients with less arterial hypertension.

Furthermore, we did not have information on the pretransplant echocardiographic examination's timing in respect to the dialysis treatment and therefore differences in patients' volume status may have influenced the result of the exam. The analysis of several echocardiographic parameters such as left ventricular mass or left ventricular diastolic dysfunction was not possible due to the incompleteness of parameters in our echo database. Strengths of our study are the large number of patients with sequential echocardiograms with long-term follow-up and modelling of hard outcomes such as mortality and graft survival. Annual updates of the registry ensured a complete record of outcomes.

We addressed potential limitations by applying and comparing different models, including a Fine and Gray competing risk analysis and repeated analysis including only patients with the most reliable data, which each reduced the number of analyzed patients, but all confirmed the result of the original model, suggesting robustness of our findings.

In conclusion, our data showed that renal transplantation did not result in a regression of left atrial diameter in the majority of patients who had an enlarged atrial diameter at time of transplantation. Patients who experienced a regression of left atrial diameter, however, exhibited a significantly longer adjusted overall survival. Predictors of regression of left atrial diameter were age at transplantation, number of antihypertensives, and peritoneal dialysis prior to transplantation.

Authorship

FR and AK: involved in interpretation and analysis of data and wrote the manuscript. MK: analyzed data and involved in revision of manuscript. AB, RS-M, TB: involved in collection of data and revision of manuscript. RO: involved in conception and design and revision and final approval of manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Comparison of baseline characteristics of study cohort ($n = 414$) and all transplant patients ($n = 5488$).

Table S2. Distribution of causes of death.

Table S3. Changes of echocardiographic parameters over time.

Table S4. Univariable and multivariable Cox model for mortality in patients with an enlarged left atrium pre-transplantation (complete case analysis) and a progression or regression >4 mm.

Table S5. Univariable and multivariable Cox model for mortality in patients with an enlarged left atrium pre-transplantation (complete case analysis) including only patients with their first echocardiogram within the first year after transplantation or patients with 3 or more follow-up echocardiograms.

Table S6. Univariable and multivariable Fine and Gray model for cardiovascular mortality in patients with an enlarged left atrium pre-transplantation (complete case analysis) containing all patients.

Table S7. Predictors of regression of left atrial diameter in all patients.

Table S8. Demographic characteristics and baseline echocardiographic parameters stratified by progression and regression of left atrial diameter.

Figure S1. Distribution of first echo after transplantation over time.

Figure S2. Schoenfeld residuals of the Cox model for mortality in patients with an increased left atrium.

Figure S3. Kaplan-Meier-Plot for graft survival stratified by progression or regression of left atrial diameter after transplantation in patients with an enlarged left atrium pre-transplantation.

Figure S4. Kaplan-Meier-Plot for patient survival stratified by progression or regression of left ventricular diameter after transplantation in patients with an enlarged left ventricle pre-transplantation.

Figure S5. Kaplan-Meier-Plot for graft survival stratified by progression or regression of left ventricular diameter after transplantation in patients with an enlarged left ventricle pre-transplantation.

Figure S6. Kaplan-Meier-Plot for patient survival stratified by progression or regression of right atrial diameter after transplantation in patients with an enlarged right atrium pre-transplantation.

Figure S7. Kaplan-Meier-Plot for graft survival stratified by progression or regression of right atrial diameter after transplantation in patients with an enlarged right atrium pre-transplantation.

Figure S8. Kaplan-Meier-Plot for patient survival stratified by progression or regression of right ventricular diameter after transplantation in all patients.

Figure S9. Kaplan-Meier-Plot for graft survival stratified by progression or regression of right ventricular diameter after transplantation in all patients.

Figure S10. Kaplan-Meier-Plot for cardiovascular death only with number of subjects at risk stratified by progression or regression of left atrial diameter after transplantation in patients with an enlarged left atrium pre-transplantation.

Figure S11. Forest plot of predictors for regression of left ventricular diameter.

Figure S12. Forest plot of predictors for regression of right atrial diameter.

Figure S13. Forest plot of predictors for regression of right ventricular diameter.

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