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Abbreviations

BMI, body mass index

BSA, body surface area

CI, confidence interval

CIT, cold ischemic time

CKD, chronic kidney disease

CMV, cytomegalovirus

CVA, cerebrovascular accident

CVD, cardiovascular disease

ESKD, end-stage kidney disease

HR, hazard ratio

KTR, kidney transplant receipt

NT-proBNP, N-terminal pro brain natriuretic peptide

Abstract

Background: End-stage kidney disease, and dialysis vintage is characterized by accelerated atherosclerosis, volume overload and progressive left ventricular hypertrophy, leading to elevated N-terminal pro brain natriuretic peptide (NT-proBNP) levels. Pretransplant dialysis vintage is associated with excess mortality after transplantation. We want to study whether pretransplant NT-proBNP is associated with posttransplantation mortality and if it explains the association of dialysis vintage with posttransplantation mortality in kidney transplant recipients (KTR).

Methods: We measured plasma NT-proBNP on arrival at the hospital before kidney transplantation in 658 KTR between January 1995 and December 2005 in our center. Multivariable Cox regression analyses, adjusted for potential confounders were used to prospectively study the associations of dialysis vintage and NT-proBNP with all-cause mortality.

Results: During median 12.7 (7.8-15.6) years of follow-up after transplantation, 248 (37.7%) KTR died. Dialysis vintage was associated with an increased risk of posttransplant mortality in the fully adjusted model (hazard ratio [HR], 1.22; 95% confidence interval [CI] 1.03-1.43; *P*=0.02), independent of potential confounders. The association weakened materially and lost significance after further adjustment for NT-proBNP (HR, 1.14; 0.96-1.34; *P*=0.14). NT-proBNP was independently associated with all-cause mortality in the fully adjusted model (HR, 1.34; 1.16-1.55; *P*<0.001). The association remained independent of adjustment for dialysis vintage (HR, 1.31; 1.13-1.52; *P*<0.001).

Conclusions: Our study shows that longer dialysis vintage is associated with a higher mortality risk in KTR, and this association might be explained for a considerable part by variation in pretransplant NT-proBNP at the time of transplantation.

Introduction

Kidney transplantation is the treatment of choice for end-stage kidney disease (ESKD) patients, as transplantation improves quality of life and life expectancy compared to dialysis.[1,2] Preemptive transplantation generally leads to better outcomes compared to transplantation after a period of dialysis.[3,4] Nevertheless, due to the generalized shortage in donor organs, patients with ESKD often need to start with dialysis.[5] Dialysis vintage is a significant and prognostic marker of mortality in ESKD patients and KTR with or without underlying cardiovascular disease.[6-8] Several mechanisms are proposed to underlie the detrimental effects derived from dialysis on the cardiovascular system. Dialysis causes significant stress on the cardiovascular system by accelerated atherosclerosis, intradialytic volume overload and subsequent progression of left ventricular hypertrophy.[9] Volume overload causes ventricular wall stress resulting in the release of N-terminal pro brain natriuretic peptide (NT-proBNP) by the ventricular cells.[10,11] High serum levels of NT-proBNP are strongly associated with volume overload and NT-proBNP is a well-established biomarker to diagnose and assess the severity of congestive heart failure.[12-14] High plasma NT-proBNP is also independently associated with mortality in general population, ESKD patients and KTR.[15-19] Moreover, It has been shown that NT-proBNP is independently associated with dialysis vintage.[20] However, it is not known if pretransplant NT-proBNP levels are associated with posttransplantation mortality and if NT-proBNP plays a role in the association of dialysis vintage and mortality in KTR.

The aim of this study is to assess whether dialysis vintage and pretransplant NT-proBNP are independently associated with mortality in KTR, and in this respect, we also aimed to investigate whether variation in pretransplant NT-proBNP influence the association between dialysis vintage and mortality in KTR.

Materials and Methods

Study population

This study was conducted in the Transplant Lines Genetics cohort, details of the cohort have been published previously.[21] From a total of 912 KTR who underwent transplantation between January 1995 and December 2005 in the University Medical Center Groningen, the Netherlands, we prospectively selected 686 KTR with available pretransplant serum NT-proBNP levels. We excluded 28 KTR who had a primary nonfunction graft, defined as graft function inadequate to prevent the need for dialysis in the absence of rejection or surgical etiologies of graft failure for 3 months post-transplantation. This results in 658 KTR available for analyses. The Institutional Review Board of the University Medical Center Groningen approved the study protocol (METc 2014/077). All KTR gave written informed consent. All procedures were conducted in accordance with the declarations of Helsinki and Istanbul.

Recipient characteristics and follow-up

Relevant donor, recipient, and transplant characteristics were extracted from the Groningen Kidney Transplant Database, which contains information of all kidney transplantations that have been performed at our center since 1968. In addition, the database contains the outcomes of outpatient visits (e.g. cause of death, and other relevant variables) after transplantation. Missing patient characteristics, transplantation-related parameters, and pretransplantation clinical and laboratory data were complemented with data from medical records. These data included pretransplantation characteristics, dialysis vintage, and serum creatinine (sample was taken before transplantation and before a dialysis if this was necessary before the transplantation).

Pretransplant plasma samples were stored at −80°C until assessment of biochemical measures for this study. Plasma NT-proBNP levels were measured afterwards by immunoassay on an Elecsys 2010 analyzer instrument (ELECSYS proBNP, Roche Diagnostics, Germany).[22]

The body surface area (BSA) was calculated as: BSA = ($W^{0.425}$ (kg) × $H^{0.725}$ (cm)) × 0.007184^{23} and body mass index (BMI) as weight (kg) by height (m) squared. Smoking behavior was classified in 2 groups as never or former smoking and current smoking. History of cardiovascular disease was considered positive if there was an event of previous angina pectoris, myocardial infarction, objectified cardiac valve disease, coronary artery disease, left ventricular hypertrophy, congestive heart failure, peripheral artery disease including aortic aneurysms. History of cerebrovascular accident (CVA) was considered as a previous transient ischemic attack or CVA. Diabetes was defined as the use of antidiabetic medication or a fasting plasma glucose >7.0 mmol/L.

Standard immunosuppression consisted of cyclosporine micro emulsion (Neoral, Novartis, Pharma b.v., Arnhem, the Netherlands; 10 mg/kg; trough-levels idem) and prednisolone from 1993 until 1996. Mycophenolate mofetil (Cellcept, Roche, Nederland b.v., Woerden, the Netherlands; 2 g/d) was added from May 1997 to date. Since 1998, standard immunosuppression consisted of triple therapy with tacrolimus (Prograft or Advagraf, Astellas Pharma b.v. Leiden, the Netherlands; initial trough level 8-12 ng/mL, followed by 6-10 ng/mL (>2 months) and 4-6 ng/mL (>6 months) or cyclosporine micro emulsion (Neoral®, Novartis Pharma b.v. Arnhem, the Netherlands; 2 times 4 mg/kg daily; initial trough level 200-500 ug/L, 150-500 ug/L (>2 months) and 75-125 ug/L (>6 months), in combination with mycophenolate mofetil (Cellcept®, Roche b.v. Woerden, the Netherlands; 2g daily or Myfortic®, Novartis Pharma, b.v. Arnhem, the Netherlands; 1440 mg daily), and prednisolone. Current immunosuppressive medication was extracted from the medical records.

Study outcome

Primary outcome of this study was all-cause mortality censored for graft failure. Graft failure was defined as end stage kidney disease requiring dialysis or retransplantation. The outpatient program of the hospital uses a continuous surveillance systems by the municipal registration of death to ensure up-to-date information on patient status (alive or deceased). Secondary outcome was cardiovascular mortality censored for noncardiovascular mortality and graft failure. Information on the cause of death was derived from patients' medical records and was assessed by a nephrologist. Cardiovascular mortality was defined as death due to cerebrovascular disease, ischemic heart disease, heart failure, or sudden circulatory death, and coded according to a previously specified list of International Classification of Diseases, Ninth Revision (codes 410–447) as described previously.[24]

Statistical analyses

Normally distributed variables are presented as mean ± standard deviation, and skewed distributed variables as median [interquartile range]. Nonnormally distributed variables were transformed for subsequent analyses.

To identify independent correlations of NT-proBNP with relevant patient factors, univariable and subsequent multivariable linear regression analyses was performed. Multivariable linear regression models were constructed using backward selection ($P_{out} > 0.05$) including variables that were significantly associated with NT-proBNP in univariable analysis and clinical relevant variables. Kaplan-Meier survival analyses were performed to study the associations of tertiles of NT-proBNP and dialysis vintage with all-cause mortality and differences between tertiles were tested with the log-rank test.

To investigate the association of NT-proBNP and dialysis vintage with the primary study outcome, Cox regression analyses were performed on both variables. NT-proBNP was $\log_2$-transformed to obtain the best-fitting model and a 2 base was used to allow for expression

of the HRs per doubling of NT-proBNP. Similarly, dialysis vintage was square root transformed to obtain the best-fitting model. Both transformed values of NT-proBNP and dialysis vintage were standardized to compare these 2 values with each other in the following Cox regression models. Model 1 shows crude hazard ratio (HR) for the standardized value of either standardized values of log_2-transformed NT-proBNP or square root-transformed dialysis vintage. In model 2, we first adjusted for age and sex. In model 3, we additionally adjusted for pretransplant plasma creatinine, history of cardiovascular disease and cerebrovascular accident, diastolic blood pressure, diabetic nephropathy, and BSA; in model 4 we additionally adjusted for transplantation variables such as cold ischemic time (CIT), living donor, delayed graft function, and cytomegalovirus (CMV) status of recipient; model 5 we additionally adjusted for dialysis modality (hemodialysis). Finally, in the last model we adjusted for standardized values of log_2-transformed NT-proBNP or standardized values of square root-transformed dialysis vintage dependent on the first model. We also tested the variables for hazard proportionality over time with the Schoenfeld residuals test. Similar analyses were performed for the secondary outcome. Because of lower numbers of events, these were restricted to analyses with continuous log_2-transformed NT-proBNP and square root-transformed dialysis vintage. To visualize the HR for the primary outcome for patients with elevated NT-proBNP, we plotted a linear spline, fitted on the fully adjusted Cox regression model in which the reference point of NT-proBNP 1200 ng/L was used as reference value as it was found to be the optimal diagnostic cut point for congestive heart failure in CKD patients with severe kidney insufficiency (eGFR of 44ml/min·1.73 m^2).[25] We compared the percentage change in the final model compared to the final model with addition of NT-proBNP or dialysis vintage. Percentage change in HR was calculated as: (HR before adjustment - HR after adjustment)/(HR before adjustment - 1) * 100. Effect moderation was analyzed using Cox regression with all-cause mortality as the end point,

and NT-proBNP as the condition, and their 2-way interaction as predictors. Effect moderators included in these analyzes were age, sex, BSA and, plasma creatinine.

Sensitivity analyses for the primary outcome were performed by excluding all preemptive transplantations.

All statistical analyses were performed with SPSS software, version 22.0 for Windows (IBM, Armonk, NY), R version 3.5.2 (Vienna, Austria) (http://cran.r-project.org/) and STATA 12.0 (STATA Corp.). In all analyses, a 2-sided *P-value* < 0.05 was considered significant.

Results

Baseline characteristics

We analyzed 658 KTR with a mean age of 46.8 ± 13.7 years, of which 59.4% of the recipients were males. Median dialysis vintage was 3.10 [1.76 – 4.59] years and median pretransplant NT-proBNP concentration was 2019 (787 – 5218) ng/L. Baseline characteristics according to tertiles of NT-proBNP are summarized in Table 1. KTR with higher concentrations of NT-proBNP were older, more often male, and were more likely to have diabetes, diabetic nephropathy, and cardiovascular diseases prior to transplantation. Moreover, KTR with higher levels of NT-proBNP had a longer dialysis vintage with hemodialysis being the most frequent used dialysis modality compared to peritoneal dialysis or no dialysis. Furthermore, KTR with higher NT-proBNP levels had a longer CIT, and experienced a higher incidence of delayed graft function and CMV seropositivity. In contrast, BMI, BSA, diastolic blood pressure, living donors, and preemptive transplantation, were inversely related to NT-proBNP. Pretransplant plasma creatinine and 1 year posttransplant eGFR were not associated with pretransplant NT-proBNP. Multivariable linear regression analyses showed that recipient age, history of cardiovascular disease, dialysis vintage, diabetic nephropathy, hemodialysis, CIT, CMV seropositivity in recipients, and living donors were positively associated with NT-proBNP.

BSA was inversely associated with NT-proBNP (Table S1, SDC, http://links.lww.com/TP/B868).

Dialysis vintage, all-cause mortality and cardiovascular mortality

During 12.7 (7.8 – 15.6) years of follow-up, 248 (37.7%) out of 658 KTR died before development of graft failure, with 68 (27.4%) deaths being classified as of cardiovascular origin. Of the patients that died, 45 (18.1%) had a history of known cardiovascular disease compared to 23 (5.6%) of patients that survived (P <0.001). Median pretransplant NT-proBNP concentrations of the patients that died during follow-up were higher (2913 [IQR 1394 – 8522] ng/L) compared to those of patients that survived (1594 [IQR 647 – 3985] ng/L) (P <0.001).

Dialysis vintage was associated with all-cause mortality (HR: 1.33; 95% confidence interval (CI) [1.18 – 1.51]; P <0.001 per SD increase, Table 2). This association remained independent of adjustment for age, sex, pretransplant serum creatinine, BSA, history of CVD and diabetes, CIT, living donor, delayed graft function, CMV status of recipient, and dialysis modality (hemodialysis) (Table 2, model 5: HR [95% CI]: 1.22 [1.03 – 1.43]; P = 0.02). When standardized values of log_2NT-proBNP were added to the model, the HR of dialysis vintage with all-cause mortality decreased by 40% and this association became nonsignificant (Table 2, model 6: HR [95% CI]: 1.14 [0.96 – 1.34], P = 0.14). Furthermore, dialysis vintage was associated with cardiovascular mortality as secondary outcome, however, this association did not remain significant in the adjusted models (Table S2, SDC, http://links.lww.com/TP/B868).

All-cause mortality according to tertiles of NT-proBNP

The mortality rates in NT-proBNP tertiles were as follow: 53 (24.2%) in the first, 87 (39.5%) in the second and 108 (49.3%) in the third tertile (Figure 1: log-rank P <0.001). In univariable Cox regression analysis of NT-proBNP as a continuous variable, NT-proBNP was significantly associated with all-cause mortality (Table 2: HR [95% CI]: 1.67 [1.48 – 1.89]; P<0.001 per SD increase). This association remained significant after adjustment for the same variables as done

with in the dialysis vintage models (Table 2, model 5: HR [95% CI]: 1.34 [1.16 – 1.55]; *P* <0.001). When standardized value of square root transformed dialysis vintage was added to the model, the HR of NT-proBNP with all-cause mortality was reduced by 9% (Table 2, model 6: HR [95% CI]: 1.31 [1.13 – 1.52], *P* <0.001), but the strong association remained significant. Similar results, albeit with a slightly stronger point estimate of the HR, were found in analyses with cardiovascular mortality as secondary outcome (Table S2, SDC, http://links.lww.com/TP/B868). When analyzed according to tertiles of NT-proBNP, patients in the highest tertile had the highest mortality risk (Table 2, model 6: HR [95% CI]: 1.60 [1.10 – 2.33], *P* = 0.02) compared to patients in the first tertile. A fully adjusted linear spline for the association between NT-proBNP and risk of mortality is shown in Figure 2. Furthermore, we found no significant effect modification by age, sex, BSA or plasma creatinine for the association between NT-proBNP levels and all-cause mortality. Schoenfeld residuals test revealed proportional hazards.

Sensitivity analyses

In sensitivity analyses, when excluding preemptive transplantations, the HRs for analyses with the primary outcome remained similar: NT-proBNP in the fully adjusted model: HR [95% CI]: 1.30 [1.13 – 1.50]; *P* <0.001 was associated with all-cause mortality. When adding NT-proBNP in in the fully adjusted model of dialysis vintage, the association with all-cause mortality also weakened and became nonsignificant (HR [95% CI]: 1.13 [0.98 – 1.32]; *P* = 0.10) (Table S3, SDC, http://links.lww.com/TP/B868).

Discussion

In this study, we found that dialysis vintage and pretransplant NT-proBNP are independent associated with all-cause mortality in KTR during a median follow-up of 12.7 (7.8 – 15.6) years. Moreover, the association of dialysis vintage with all-cause mortality was strongly dependent upon adjustment for NT-proBNP, with a 40% reduction in HR after adjustment. Results for

analyses with cardiovascular mortality as outcome were not materially different for NT-proBNP. However, dialysis vintage was not associated with cardiovascular mortality.

Cardiovascular disease is the leading cause of morbidity and mortality in KTR patients. The majority of the KTR patients have 1 or more cardiovascular risk factors which put them at a 50-fold higher risk of experiencing a cardiac event compared to general population.[26] Pretransplant dialysis vintage has earlier been found to be significantly associated with survival rate in KTR.[6,8] Dialysis patients are more susceptible to cardiac events and mortality due to specific comorbidities through which patients have resulted in ESKD in the first place (e.g. diabetes and hypertension).[27] Dialysis by itself can put stress on the heart while it is associated with accelerated coronary atherosclerosis, cardiac arrhythmias, acute heart failure, and sudden circulatory death.[9,28,29] Dialysis exerts significant stress especially on the cardiovascular system through progression of cardiac dilation, left ventricular hypertrophy and left ventricular dysfunction which are caused by intradialytic volume overload, hypertension, and subclinical ischemia.[9,28] Dialysis patients who are ineligible for transplantation have in general more comorbidities and are in worse physical condition compared to dialysis patients who are put on the transplantation waiting list. It is well known that dialysis vintage is positively associated with mortality in ESKD patients and, accordingly, preemptive transplantation leads to a considerable improvement in graft and patient survival compared to dialyzed transplantation recipients.[3,4]

In keeping with previous studies, we reproduced the association between dialysis vintage and higher risk of mortality after transplantation, independent of adjustment for important potential confounders. However, we identified for the first time that this association is largely dependent on pretransplant NT-proBNP levels. NT-proBNP is a peptide normally released in response of cardiac stretch, and is clinically used as a biomarker for diagnosing heart failure and for screening of volume overload and left ventricular dysfunction.[12,14] Elevated

levels of NT-proBNP are often seen in dialysis patients, which is caused by volume overload and interdialytic weight gain.[30] Moreover, high NT-proBNP levels are associated with several other factors, such as diminished kidney function, female gender and increasing age.[16,31] Previously, it has been shown that NT-proBNP during dialysis or posttransplantation is a prognostic marker for cardiovascular morbidity and mortality in dialysis patients and KTR.[16,17,19] In the current study, NT-proBNP is found to be independently associated with mortality in KTR. In addition, when NT-proBNP was added to the final model of dialysis vintage the HR of the association of dialysis vintage and all-cause mortality risk was reduced by 40% and lost significance. Thus, making NT-proBNP to be a potential biomarker for the impact of dialysis on the cardiovascular condition of ESKD patients.

The susceptibility for chronic fluid overload and fluid retention as result of dialysis can differ among patients. One study found that patients with low BMI and low serum albumin levels are more susceptible to chronic fluid overloading.[30] Other study showed that younger patients, males, and diabetic patients are more prone to intradialytic volume changes while undergoing hemodialysis.[32] Explanation for these differences are not yet known. Different hemodialysis frequency can also have an different impact on the cardiovascular status; a few studies have shown that frequent intensive daily dialysis and nocturnal home hemodialysis might improve blood pressure control and reduce left ventricular mass.[33,34] Therefore, dialysis vintage alone might not be a usable prognostic predictor for mortality in ESKD patients and KTR. We suggest that NT-proBNP, as an indirect assessment of the cardiovascular status, could be used as an additional predictor variable for mortality in KTR.

To date, no clear guidelines for cardiovascular screening and surveillance exist for kidney transplant candidates without cardiac symptoms.[35] The aim of preoperative cardiac risk evaluation in kidney transplant candidates is to reduce morbidity and mortality of cardiovascular disease and to determine if the transplant candidate has an active cardiac disease,

defined as unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular heart disease.[35] Potential transplantation recipients who exert cardiac symptoms are referred to a cardiologist for further examination, but different guidelines offer different recommendations regarding to the approach of asymptomatic patients.[35] Although, our study was initially not designed to test the predictive value of NT-proBNP regarding mortality in KTR, the current study does, however, prove the significance association of pretransplant NT-proBNP in KTR and their risk of mortality after transplantation.

One of the strengths of this study is the long follow-up time and a relatively large cohort. Some limitations need to be addressed. First, data on serum NT-proBNP of 226 patients (24.7%) is missing. Because of these missing values, these cases were not included in the main analyses resulting in 658 cases with NT-proBNP values instead of potential 884 cases. It is unknown why these samples were missing.

Another limitation is that we do not have multiple measurements of NT-proBNP samples. It would be interesting in future studies to assess whether NT-proBNP is usable as a biomarker by following the trend of NT-proBNP from pretransplant evaluation to the actual transplantation and posttransplantation. Previous studies showed a high between-person coefficient of variation of NT-proBNP**,** which suggests that the use of a single value of NT-proBNP comparing to a reference value may be limited.[36,37] Instead, series of NT-proBNP measurements may show large relative change, which may suggest for worsening of the volume status or cardiovascular condition in a patient.[37] Furthermore, the lack of other cardiac measurements, such as an electrocardiography, and concentrations of high-sensitive troponin T limit full assessment of the cardiac condition. While we have data about dialysis vintage, we do not have other dialysis factors, such as arteriovenous vascular access, fluctuations in volume status, dialysis frequency, prevalence of anemia, and left ventricular abnormalities, which all might influence the NT-proBNP levels and the cardiovascular system.[33,34]

For future studies it would be interesting to include information on the cardiac evaluation of the patient. NT-proBNP could be compared with an evaluation tool for heart function, e.g. echocardiography, since it has already been shown that transplantation improves left ventricular ejection fraction and heart failure condition.[38] Also, it remains an important issue whether patients with elevated NT-proBNP will still benefit from transplantation compared with staying on dialysis and that our results ask for such studies to be performed.

Lastly, other strong markers associated with cardiovascular outcomes in KTR were not available in this study. It would be interesting if NT-proBNP is still an independent prognostic predictor if it was corrected for other known strong prognostic markers, such as fibroblast growth factor 23,[39] high-sensitivity troponin T,[40] central wave reflection and aortic stiffness.[41]

Conclusion

In conclusion, our study shows that dialysis vintage is a predictor of mortality in KTR and this association might be explained for a considerable part by variation in pretransplant NT-proBNP at the time of transplantation. Future studies are needed to evaluate the potential value of NT-proBNP screening as check of cardiac patency of patients on the waiting list of kidney transplantation.

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Figure Legends

Figure 1 Kaplan-Meier curve for all-cause mortality censored for graft failure among 658 kidney transplant recipients according to tertiles of baseline NT-proBNP (ng/L). Tertile I = 588 (361 – 786), tertile II = 2019 (1571 – 2756), tertile III = 8429 (5224 – 22 112).

Figure 2 Associations between NT-proBNP and all-cause mortality in 658 KTR. Data were fit by a Cox proportional hazards regression model based on restricted cubic splines and adjusted for age, sex, pretransplant serum creatinine, history of CVD and CVA, diastolic blood pressure, diabetic nephropathy, BSA, cold ischemic time, living donor, delayed graft function, CMV status of recipient, dialysis modality (hemodialysis), and square root of dialysis vintage (yrs.). Data are shown on a standardized $\log_2$ scale. Reference standard was 1200 ng/L defined as an optimal cut-off for diagnosis of heart failure in patients with GFR <44ml/min/1.73 m^2. The grey area represents the 95% CI. KTR, kidney transplant recipient. Z-scores on the x-axis corresponds with the following NT-proBNP values (ng/L): -2 = 125; -1 = 535; 0 = 2290; 1 = 9797; 2 = 42 055; 3 = 180 295.

Table 1. Baseline characteristics according to tertiles of NT-proBNP in 658 kidney transplant recipients

	Tertiles of (NT-pro)BNP (ng/L)					
	Overall	**I**	**II**	**III**	**NT-proBNP (St. β)**	**P**
NT-proBNP, (ng/L)	2019 (787 – 5218)	588 (361 – 786)	2019 (1571 – 2756)	8429 (5224 – 22 112)		
Recipient demographics						
Age (yrs.)	46.8 ± 13.7	43.3 ± 13.4	47.9 ± 13.4	49.1 ± 13.6	0.22	**<0.001**
Male, n (%)	391 (59.4)	138 (63.0)	136 (61.8)	117 (53.4)	0.10	**0.01**
BMI (kg/m^2)	24.1 (21.6 – 27.0)	24.4 (21.9 – 27.3)	24.9 (21.8 – 27.4)	23.6 (21.2 – 25.7)	-0.12	**0.003**
BSA (m^2)	1.88 ± 0.19	1.91 ± 0.19	1.91 ± 0.20	1.83 ± 0.17	-0.17	**<0.001**
Systolic blood pressure (mmHg)	142.9 ± 17.3	142.5 ± 16.7	143.9 ± 17.7	142.3 ± 17.6	-0.01	0.72
Diastolic blood pressure (mmHg)	83.8 ± 10.9	85.0 ± 11.8	83.7 ± 10.5	82.9 ± 10.3	-0.09	**0.02**
Pretransplant plasma creatinine (umol/L)	916 ± 284	896 ± 295	952 ± 291	900 ± 265	0.02	0.63
1 year posttransplant eGFR (ml/min/1.73m^2)	48.4 ± 15.6	48.4 ± 15.1	47.8 ± 15.1	48.9 ± 16.6	-0.03	0.40
Diabetes, n (%)	28 (4.3)	6 (2.7)	8 (3.6)	14 (6.4)	0.09	**0.02**
History of cardiovascular disease, n (%)	68 (10.3)	9 (4.1)	20 (9.1)	39 (17.8)	0.18	**<0.001**
History of cerebrovascular accident, n (%)	12 (1.8)	3 (1.4)	5 (2.3)	4 (1.8)	0.01	0.72
Smoking at transplantation, n (%)	29 (4.4)	8 (3.7) (n = 154)	14 (6.4) (n = 138)	7 (3.2) (n = 117)	0.17	**<0.001**
Dialysis vintage before transplantation (yrs.)	3.10 (1.76 – 4.59)	1.92 (0.94 – 3.37)	3.28 (2.03 – 4.43)	4.09 (2.55 – 5.28)	0.38	**<0.001**
Dialysis modality, n (%)						
Hemodialysis	359 (54.6)	72 (32.9)	126 (57.3)	161 (73.5)	0.35	**<0.001**
Peritoneal dialysis	267 (40.6)	118 (53.9)	91 (41.4)	58 (26.5)	-0.22	**<0.001**
No dialysis/Preemptive transplantation	32 (4.9)	29 (13.2)	3 (1.4)	0 (0)	-0.30	**<0.001**
Primary kidney disease, n (%)						
Primary glomerular disease	176 (26.7)	64 (29.2)	60 (27.3)	52 (23.7)	-0.05	0.25
Glomerulonephritis	42 (6.4)	13 (5.9)	15 (6.8)	14 (6.4)	-0.01	0.75
Tubular interstitial disease	82 (12.5)	34 (15.5)	20 (9.1)	28 (12.8)	-0.02	0.70
Polycystic kidney disease	109 (16.6)	39 (17.8)	39 (17.7)	31 (14.2)	-0.03	0.49

Dysplasia and Hypoplasia	16 (2.4)	6 (2.7)	6 (2.7)	4 (1.8)	-0.07	0.09
Renovascular disease	51 (7.8)	18 (8.2)	13 (5.9)	20 (9.1)	-0.01	0.73
Diabetic nephropathy	17 (2.6)	4 (1.8)	3 (1.4)	10 (4.6)	0.11	**0.004**
Other or unknown cause	165 (25.1)	41 (18.7)	64 (29.1)	60 (27.4)	0.08	**0.05**
Donor demographics						
Donor age (yrs.)	43.1 ± 14.1	44.2 ± 12.8	42.6 ± 14.5	42.6 ± 14.9	-0.02	0.56
Male, n (%)	333 (50.6)	105 (47.9)	107 (48.6)	113 (51.6)	-0.008	0.84
Transplantation details						
Living donor, n (%)	150 (22.8)	70 (32.0)	47 (21.4)	33 (15.1)	-0.21	**<0.001**
Acute rejection, n (%)	234 (35.6)	69 (31.5)	83 (37.7)	82 (37.4)	0.04	0.37
Delayed graft function, n (%)	169 (25.7)	43 (19.6)	63 (28.6)	63 (28.8)	0.10	**0.01**
CIT (hrs.)	18.0 (10.4 – 23.0)	15.6 (3.0 – 21.0)	19.0 (11.1 – 23.1)	19.9 (14.0 – 24.0)	0.24	**<0.001**
CIT excluding living donors (hrs.)	20.0 (16.0 – 24.0)	18.0 (15.5 – 23.0)	20.5 (16.0 – 25.0)	21.0 (17.0 – 25.7)	0.13	**0.003**
Warm ischemic time (min.)	35 (30 – 44)	36.0 (30 – 45)	35 (30 – 43)	36 (30 – 43)	-0.02	0.57
CMV status						
CMV seropositivity recipient, n (%)	292 (44.4)	78 (35.6)	96 (43.6)	118 (53.9)	0.14	**<0.001**
CMV seropositivity donor, n (%)	320 (48.6)	100 (45.7)	111 (50.5)	110 (50.2)	0.01	0.80
Retransplantation						
2nd transplantation, n (%)	43 (6.5)	12 (5.5)	14 (6.4)	17 (7.8)	0.03	0.42
3rd transplantation, n (%)	3 (0.5)	0 (0)	1 (0.5)	2 (0.9)	0.06	0.15
Immunosuppressant						
Use of corticosteroids, n (%)	653 (99.2)	219 (100)	216 (98.2)	218 (99.5)	-0.01	0.78
Use of calcineurin inhibitor, n (%)	642 (97.6)	215 (98.2)	212 (96.4)	215 (98.2)	0.02	0.70
Use of proliferation inhibitor, n (%)	544 (82.7)	182 (83.1)	174 (79.1)	188 (85.8)	0.03	0.38
Use of mTOR, n (%)	35 (5.3)	12 (5.5)	16 (7.3)	7 (3.2)	-0.05	0.24
Other immunosuppressants, n (%)	207 (31.5)	69 (31.5)	72 (32.7)	66 (30.1)	0.006	0.89

Data are presented as n (%), mean ± SD, or median [interquartile range] for nominal, normally distributed, and nonnormally distributed data, respectively.

The *P*-value represents the p for trend in univariable linear regression analysis. Abbreviations: NT-proBNP, N-terminal prohormone of brain natriuretic peptide; BMI, body mass index; BSA, body surface area; eGFR (CKD-EPI), estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); CIT, cold ischemic time; CMV, cytomegalovirus; mTOR, mammalian target of rapamycin;

Table 2 Associations of continuous standardized Log_2 NT-proBNP (ng/L), standardized square root dialysis vintage (yrs.), and NT-proBNP in tertiles with all-cause mortality in 658 stable kidney transplant recipients

	Log_2 NT-proBNP in Z-score	**Square root dialysis vintage in Z-score**	**NT-proBNP I**	**NT-proBNP II**	**NT-proBNP III**
Model	**HR (95% CI)**	**HR (95% CI)**	586 (358 – 781)	1998 (1558 – 2663)	8303 (5189 – 21 900)
1	1.67 (1.48 – 1.89)****	1.33 (1.18 – 1.51)****	1.0 (ref)	1.93 (1.37 – 2.72)****	2.91 (2.09 – 4.04)****
2	1.49 (1.31 – 1.68)****	1.28 (1.11 – 1.47)****	1.0 (ref)	1.47 (1.04 – 2.08)*	2.26 (1.62 – 3.15)****
3	1.44 (1.27 – 1.64)****	1.35 (1.17 – 1.55)****	1.0 (ref)	1.49 (1.05 – 2.11)*	2.14 (1.51 – 3.02)****
4	1.41 (1.23 – 1.61)****	1.30 (1.10 – 1.52)***	1.0 (ref)	1.45 (1.02 – 2.05)*	2.00 (1.40 – 2.84)****
5	1.34 (1.16 – 1.55)****	1.22 (1.03 – 1.43)*	1.0 (ref)	1.32 (0.93 – 1.89)	1.73 (1.19 – 2.50)**
6	1.31 (1.13 – 1.52)****	1.14 (0.96 – 1.34)	1.0 (ref)	1.28 (0.89 – 1.82)	1.60 (1.10 – 2.33)*

Data are presented as HR, hazard ratio; 95% CI, confidence interval; NT-proBNP, N-terminal pro-B-Type Natriuretic Peptide; Z-score, standardized score; P-value is shown as: * ≤0.05, ** ≤ 0.01, *** 0.001, **** <0.001 .

Model 1 = Crude standardized values of log_2 NT-proBNP / square root of dialysis days.
Model 2 = as model 1 and additionally adjusted for age and sex.
Model 3 = as model 2 and additionally adjusted for pretransplant serum creatinine, history of CVD and CVA, diastolic blood pressure, diabetic nephropathy, and BSA.
Model 4 = as model 3 and additionally adjusted for cold ischemic time, living donor, delayed graft function, and CMV status of recipient.
Model 5 = as model 4 and additionally adjusted for dialysis modality (hemodialysis).
Model 6 = as model 5 and additionally adjusted for crude standardized values of log_2 NT-proBNP / square root of dialysis year

Figure 1

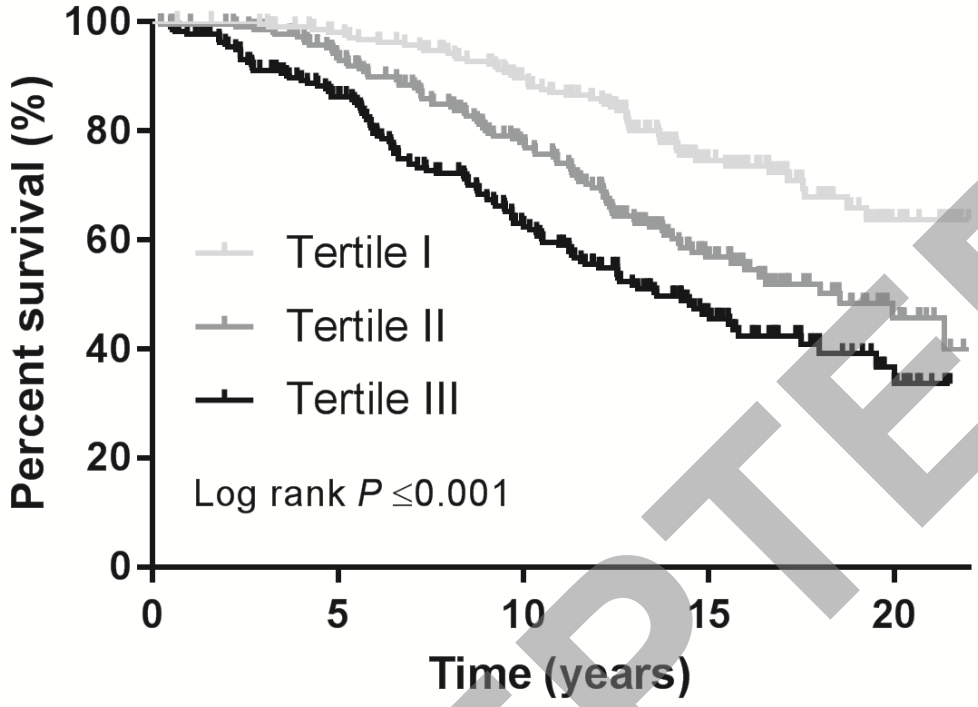

Figure 2