RESEARCH ARTICLE

Pre-transplant residual diuresis and oxalic acid concentration influence kidney graft survival

Gideon Post Hospers[1]*, Mirjam Laging[1], Wesley J. Visser[2], Pedro Miranda Afonso[3,4], Jeroen GHP Verhoeven[1], Ingrid RAM Mertens zur Borg[5], Dennis A. Hesselink[1], AnnekeM.E. de Mik-van Egmond[2], Michiel G.H. Betjes[1], Madelon van Agteren[1], David Severs[1], Jacqueline van de Wetering[1], Robert Zietse[1], Michel J. Vos[6], Ido P. Kema[6], Marcia M.L. Kho[1], Marlies E.J. Reinders[1], Joke I. Roodnat[1]

1 Department of Internal Medicine, Department of Nephrology and Transplantation, Transplant Institute, Erasmus Medical Center, Rotterdam, The Netherlands, **2** Department of Internal Medicine, Division of Dietetics, Erasmus Medical Center, Rotterdam, The Netherlands, **3** Department of Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands, **4** Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands, **5** Department of Anaesthesiology, Erasmus Medical Center, Rotterdam, The Netherlands, **6** Department of Clinical Chemistry Metabolic diseases, University Medical Center Groningen, The Netherlands

* gideon-posthospers@hetnet.nl

OPEN ACCESS

Citation: Post Hospers G, Laging M, Visser WJ, Miranda Afonso P, Verhoeven JG, Mertens zur Borg IR, et al. (2025) Pre-transplant residual diuresis and oxalic acid concentration influence kidney graft survival. PLoS One 20(5): e0322516. https://doi.org/10.1371/journal.pone.0322516

Editor: Mohamed E Elrggal, Kidney and Urology Center, EGYPT

Received: November 7, 2024

Accepted: March 21, 2025

Published: May 16, 2025

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0322516

Abstract

Background and hypothesis

Oxalic acid, a toxic metabolic end product, accumulates when kidney function deteriorates. Apart from its direct tubulotoxicity, it crystallizes at concentrations above 30–40 μmol/L. High oxalic acid concentrations at transplantation might negatively influence kidney transplant function. The influence of the concentrations of oxalic acid and its precursors and residual diuresis on kidney transplant outcomes was studied.

Methods

In this prospective cohort study, patients who received a kidney transplant between September 2018 and January 2022 participated. Concentrations of oxalic acid and precursors were determined in pre-transplant blood samples. Data on residual diuresis and other recipient, donor or transplant related variables were collected. Follow-up lasted until July 1st 2023.

Results

496 patients were included, 154 were not on dialysis. Median residual diuresis was 1000 mL/day (IQR 200; 2000 mL/day). There were 230 living donor transplantations. Oxalic acid concentrations exceeded the upper normal concentration in 99% of patients, glyoxylic acid in all patients. There were 52 (10%) graft failures. As the influence of oxalic acid on the risk of graft failure censored for death was non-linear, it was categorized into two groups: ≤ 60 and > 60 μmol/L. In multivariable Cox analysis

Data availability statement: Our data is pseudonymized data, which, in the Netherlands, falls under the General Data Protection Regulation (GDPR). The raw data can be made available on request, under the conditions of a Data Transfer Agreement (DTA). Data requests can be sent to the first (gideon-posthospers@hetnet.nl), the second (m.laging@erasmusmc.nl) and last author (j.roodnat@erasmusmc.nl), but also to a non-author institutional point of contact: data-managers.niertransplantatie@erasmusmc.nl.

Funding: Funding: Foundation "Stichting de Merel" The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

the graft failure censored for death risk was significantly influenced by residual diuresis, donor type (living versus deceased), donor age and oxalic acid. In 180 patients oxalic acid concentration shortly after transplantation was significantly lower than pre-transplant concentrations, suggesting excretion by the new graft. A better eGFR at day 7 was associated with lower oxalic acid concentration. Oxalic acid and residual diuresis did not influence patient survival.

Conclusion

Residual diuresis and oxalic acid concentration are important and independent predictors of graft survival censored for death. These results underline the importance of pre-emptive transplantation, or optimizing the pre-transplant patients' condition regarding waste product concentrations.

Introduction

Kidneys are superior to dialysis in removing various (non-urea) solutes and even clinically negligible residual kidney function has been shown to provide non-urea solute clearance [1–5]. Toxic waste products accumulate in patients with (end stage) kidney disease, especially when diuresis is reduced [6,7].

Oxalic acid is one of these toxic waste products that are primarily excreted via glomerular filtration and tubular secretion by the kidney [8,9]. It is the end product of many metabolic processes in the body. Elgstoen et al. showed a positive relationship between serum creatinine and plasma oxalic acid concentrations in patients without primary or enteric hyperoxaluria [10]. Although dialysis can remove oxalic acid, concentrations typically rebound to pre-dialysis concentrations within 48 hours [11,12].

The super saturation threshold concentration of oxalic acid is supposed to be 30–40 μmol/L [13]. When concentrations in urine are above the threshold, calcium oxalate precipitates in the kidney [14,15]. When plasma concentrations are above the threshold, calcium oxalate precipitates in other organs as well [16–21]. There is a high oxalate nephropathy (recurrence) rate after kidney transplantation in patients with primary or enteric hyperoxaluria [14,22,23]. Kidney patients without primary or enteric hyperoxaluria may also have high oxalic acid concentrations, caused by the failing excretion. Previous studies in this population have shown that calcium-oxalate deposition in kidney biopsies within three months after transplantation heralds a poor prognosis regarding graft function [24,25]. In addition to precipitation, oxalic acid also demonstrates tubulotoxicity and may cause inflammation contributing to progressive kidney injury, even in the absence of visible precipitates [26–29].

Two studies found an increased mortality risk in kidney patients with high oxalic acid concentrations: Diabetic dialysis patients with high plasma oxalic acid concentrations were found to have a significantly increased mortality risk [30]. In another study, transplant recipients with high oxalic acid concentration at ten weeks after transplantation exhibited increased mortality rates, while the graft failure risk barely missed significance [31].

Apart from oxalic acid, its precursors, such as glycoaldehyde, glycolic acid, glyoxylic acid and glyceric acid, may accumulate as well when kidney function deteriorates (Fig 1) [32]. Kidney toxicity of these precursors has been studied as they also are metabolites of ethylene glycol (Fig 1). Ethylene glycol poisoning is notorious for its toxicity after ingestion [29,33]. Ethylene glycol itself is not toxic, but it enters the endogenous oxalate synthesis pathway via breakdown to glycoaldehyde and eventually to oxalic acid. The metabolites oxalic acid, glyoxylic acid and glycoaldehyde were shown to be tubulotoxic [26,28] and may lead to acute kidney failure. Very high concentrations may also lead to neurotoxicity and death if untreated [34]. In the kidney transplant setting the graft is placed in an environment with high concentrations of all kinds of waste products.

Low residual kidney function is associated with an increased delayed graft function (DGF) risk after kidney transplantation [35–37]. It cannot be ruled out that the effect that is attributed to low residual diuresis, in reality is the effect of a whole collection of accumulated toxic waste products. Therefore, the influence of residual diuresis, and oxalic acid and its precursors was studied in the same model. This study aimed to examine the influence of waste products as oxalic acid and its precursors and residual diuresis on kidney transplant outcomes.

Materials and methods

All adult patients referred for kidney transplant work-up between September 1st 2018 and January 1st 2022 were invited to participate in this study. Follow-up lasted until July 1st 2023. The study conformed to the principles outlined in the Declaration of Helsinki, and was approved by the Medical Ethics Committee of Erasmus University Medical Center (EMC) Rotterdam [MEC 2018–044). All patients provided written informed consent before inclusion. Participation comprised transplantation in the period studied, and a ten mL blood sample taken in the operating room immediately before transplantation. Concentrations of oxalic acid and its precursors: glyoxylic acid, glycolic acid and glyceric acid were determined. The volume of residual diuresis per day was self-reported, and based on last 24 hour urine sample handed in for general renal care. Collection was during the 24 hour preceding a haemodialysis session or a visit to the outpatient department for peritoneal dialysis or, for pre-emptive patients, the nephrology outpatient clinic. Besides, patients were asked to complete a questionnaire about dietary habits. Results of this food frequency questionnaire are described separately.

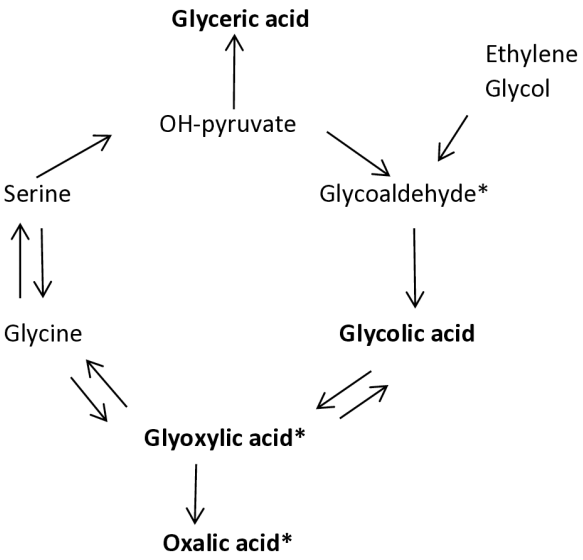

Fig 1. Endogenous oxalic acid synthesis pathway. In **bold** are the substances whose concentrations were determined. * Known to be nephrotoxic, tubulotoxic.

https://doi.org/10.1371/journal.pone.0322516.g001

All pre transplant survival and kidney function related recipient, donor and transplant characteristics supposed to influence transplant results were collected in the database and included in the analysis.

There was no post transplantation protocol time for blood collection for determination of oxalic acid and precursor concentrations. In patients scheduled for a graft biopsy within 3 months after transplantation, blood was taken on the day of the biopsy for determination of serum concentrations of oxalic acid and its precursors. Almost all these blood collections were performed within 2 weeks after transplantation (median 7 (IQR 5–10 days).

Laboratory tests

To quantify the plasma organic acids (oxalic acid, glyoxylic acid, glycolic acid and glyceric acid), blood was taken and placed on ice followed by centrifugation at 4°C without delay. Heparinised plasma samples were de-proteinized by addition of 75 µL 37% hydrochloric acid to 0.5 mL plasma followed by centrifugation. The supernatant was stored at -70°C until analysis. For quantification, a gas chromatography mass spectrometry method (GC-MS) was used that was developed and validated according to the guidelines for bioanalytical method validation of the Dutch Scientific Association of Medical Laboratory Specialists in Clinical Chemistry and the ISO 15189:2012 standard describing requirements for quality and competence in medical laboratories. The current method is a further development of previous methods, as an in-house developed method and fulfils all requirements stated in Regulation (EU) 2017/746 of the European Parliament and of the Council on in vitro diagnostic medical devices for human use [38,39]. In short, the organic acids were derivatized using ethyl chloroformate combined with 1-propanol and pyridine followed by extraction with heptane. For separation a 15 meter ZB-FFAP column (Phenomenex) was used followed by quantification (Agilent 7890B GC) in positive chemical ionization mode using a gas reaction mixture of 5% ammonia in methane. Stable isotope labelled internal standards used were either 13C labelled (oxalic acid, glycolic acid, glyoxylic acid) or deuterium labelled (glyceric acid).

The precision of the assay was evaluated by measuring internal quality control (QC) samples at three concentration levels: low (L), medium (M), and high (H). The coefficients of variation (CV%) were determined for oxalate (oxalic acid), glycolate (glycolic acid), glycerate (glyceric acid), and glyoxylate (glyoxylic acid). The results are summarized as follows: oxalate CV% of 3.16 (L), 3.95 (M), and 4.24 (H); glycolate CV% of 2.52 (L), 1.87 (M), and 1.36 (H); glycerate CV% of 7.36 (L), 9.77 (M), and 5.98 (H); glyoxylate CV% of 6 (L), 4.14 (M), and 2.77 (H).

The sensitivity of the assay is reflected in the Lower Limit of Quantitation (LLOQ), which was determined to be 0.50 µmol/L for oxalic acid. The assay demonstrated excellent precision, with intra-assay, inter-assay, and repeatability coefficients of variation (CVs) all below 10%, meeting predefined acceptance criteria. The recovery of the method ranged between 88–113%, depending on matrix conditions, ensuring reliable quantification.

Regarding specificity, the GC-MS method provides high analytical specificity due to the use of selective ion monitoring, with oxalic acid quantified at m/z 191.9. The method validation confirmed no significant carry-over (<0.1%) and established a linear range up to 159 µmol/L, with a correlation coefficient (r^2) of 0.9997.

Data analysis

Statistical analysis was performed with IBM SPSS Statistics version 24 and R version 4.2.1 using the survival packages (v. 3.5.5). Baseline characteristics and outcomes were described as counts and percentages for categorical variables assessed using the Chi-square test. Continuous skewed variables were expressed as medians and interquartile ranges (IQR) and analysed via the Mann-Whitney U-test. A two sided p-value less than 0.05 was considered statistically significant.

Uni- and multivariable Cox proportional hazards analyses were performed to identify risk factors for death-censored graft survival and patient mortality using preselected variables (Table 1). Graft failure is defined as need to resume dialysis and/or a non-functioning graft on a nuclear scan. Natural cubic splines and polynomial functions were used to evaluate nonlinear effects of oxalic acid, residual diuresis, and donor age [40]. To determine the maximum number of degrees of

Table 1. Recipient, donor and transplantation characteristics from the entire population, the population of recipients with a living donor and the population with a deceased donor kidney. PD: peritoneal dialysis; DBD: donation after brain death; DCD: donation after cardiac death; HD: hemodialysis; HLA: human leukocyte antigen; IQR: interquartile range; vPRA: virtual Panel Reactive Antibodies.

	Total population N=496	Living donor n=230	Deceased donor n=266	p-value living versus deceased donor
Recipient characteristics:				
Gender (male) n *(%)*	300 (60.5)	131 (57)	169 (64)	0.08
Age (years) *median (IQR)*	62 (51; 69)	58 (46; 66)	65 (55; 71)	<0.001
BMI (kg/m2) *median (IQR)*	27 (24; 31)	26 (23; 29)	28 (24;33)	<0.001
CRP (mg/L) *median (IQR)*	3 (1; 8)	2 (1;5)	5 (2;11)	<0.001
Medical history:				
Cardiac event n *(%)*	89 (17.9)	30 (13)	59 (22)	0.005
Cerebrovascular accident n *(%)*	60 (12.1)	24 (10)	36 (14)	0.18
Vascular event n *(%)*	43 (8.7)	12 (5)	31 (12)	0.008
Diabetes mellitus n *(%)*	167 (33.7)	49 (21)	118 (44)	<0.001
Residual diuresis (mL/day) *median (IQR)*	1000 (200; 2000)	1550 (737; 2000)	500 (29; 1500)	<0.001
Use of diuretics, yes n *(%)*	184 (37.1)	83 (36)	100 (38)	0.499
Dialysis n *(%)*				<0.001
No	154 (31.0)	126 (55)	28 (11)	
PD	105 (21.2)	43 (19)	62 (23)	
HD	237 (47.8)	61 (27)	176 (66)	
Time on dialysis (months) *median (IQR)*	15(0; 30)	0 (0; 15)	23 (14; 40)	<0.001
Time between last dialysis and transplantation (days)				
PD only *median (IQR)*	0.39 (0.21; 0.71)	0.42 (0.25;1.1)	0.34 (0.18; 0.62)	0.027
HD only *median (IQR)*	1.34 (0.80; 1.95)	1.2 (1.0; 1.9)	1.14 (0.66; 1.98)	0.909
Hyperoxaluria, non-renal cause n *(%)*	20 (4.0)	10 (4)	10 (4)	0.457
Oxalic acid (µmol/L) *median (IQR)*	33.2 (18.0; 56.6)	22 (13; 42)	42 (26;62)	<0.001
Oxalic acid >60 µmol/L n (%)	113 (22.8)	36 (16)	77 (29)	<0.001
Glycolic acid (µmol/L) *median (IQR)*	5.7 (5.0; 6.7)	5.3 (4.7; 6.1)	6 (5.2; 7.0)	<0.001
Glyoxylic acid (µmol/L) *median (IQR)*	2.0 (1.4; 2.8)	1.7 (1.1; 2.5)	2.1 (1.5; 3.0)	<0.001
Glyceric acid (µmol/L) *median (IQR)*	2.6 (2.2; 3.1)	2.4 (2.0; 2.7)	2.8 (2.4; 3.3)	<0.001
vPRA *median (IQR)*	4 (0; 5)	4 (0; 5)	4 (0; 13.5)	0.692
vPRA n *(%)*				0.967
<4	229 (46.2)	106 (46)	123 (46)	
4-84	231 (46.4)	108 (47)	123 (46)	
≥85	36 (7.5)	16 (7)	20 (8)	
First kidney transplantation n *(%)*	421 (84.9)	203 (88)	218 (82)	0.033
Donor characteristics				
Donortype				<0.001
Living donor *n (%)*	230 (46.4)	230 (100)		
DBD n *(%)*	88 (17.7)		88 (33)	
DCD n *(%)*	178 (35.9)		178 (67)	
Age donor (years) *median (IQR)*	58 (48; 67)	56 (47; 64)	60 (50; 68)	<0.001
Donor gender (male) n *(%)*	253 (51.0)	114 (50)	139 (52)	0.306
Donor BMI (kg/m^2) median (IQR)	26 (23; 29)	26 (24; 29)	26 (23; 28)	0.262

(Continued)

Table 1. (Continued)

	Total population N=496	Living donor n=230	Deceased donor n=266	p-value living versus deceased donor
Donor comorbidity:				
hypertension n (%)	155 (31.3)	56 (24)	99 (37)	<0.001
Diabetes mellitus n (%)	23 (4.6)	0 (0)	23 (9)	<0.001
Donor creatinine (μmol/L) median (IQR)	72 (59; 83)	77 (69; 84)	65 (53; 80)	<0.001
Transplantation characteristics				
HLA A, B, DR mismatches				0.145
0-3	296 (59)	131 (57)	165 (62)	
4-6	200 (40.3)	99 (43)	101 (38)	
HLA mismatches median (IQR)	3 (3; 6)	3 (2;5)	3 (2; 4)	0.073
Cold ischemia time (min)	389 (120; 707)	118 (105;136)	695 (524; 808)	<0.001

https://doi.org/10.1371/journal.pone.0322516.t001

freedom in the multivariable model, we used 10% of the number of events. Covariates were removed using backward elimination. With log minus log plots, violations of the proportional hazards assumption were evaluated. Patients were censored at the date of the last clinical follow-up. Survival probability curves were then obtained using the Breslow estimator. To detect multicollinearity between residual diuresis and oxalic acid the variance inflation factor (VIF) was tested in linear regression analysis.

Results

There were 512 patients that consented and underwent a kidney transplantation. In 16 patients concentrations of oxalic acid and/or its precursors were missing. Results of 496 patients were available for analysis. Table 1 shows baseline recipient, donor and transplant related characteristics, there were no missing values in these 496 patients. Characteristics of the recipient population of a living donor versus recipients of a deceased donor kidney are shown in Table 1. Supplementary table 1 shows characteristics of the population of pre-emptive patients versus the population on dialysis. There are significant differences; mostly unfavorable for the latter (supplementary Table 1). There were 19 patients with enteric hyperoxaluria, one patient with primary hyperoxaluria was included. The latter patient was diagnosed with kidney insufficiency and type 1 primary hyperoxaluria at the age of 63 years. He had an excellent response to pyridoxine treatment and at the age of 65, he received a kidney only transplantation with excellent results.

Fig 2 illustrates the concentrations of oxalic acid, glyoxylic acid, glycolic acid and glyceric acid in the total patient population, in the sub-population not on dialysis and in the sub-population on dialysis. Only 1.2% of the patients had pre-transplant oxalic acid concentrations within the normal range. Glycolic acid and glyceric acid concentrations were within normal values in 87% and 22% of cases, respectively. In all patients glyoxylic acid concentrations were above the normal range. Concentrations of oxalic acid and all precursors were significantly higher in the dialysis population compared to the patients not on dialysis.

Graft survival censored for death

Until July 2023, there were 52 (10.5%) patients with graft failure and 48 (9.7%) patients died. The cubic spline Cox regression model showed a linear relationship between residual diuresis and the log-hazard ratio of graft failure censored for death (supplementary Figs 1 and 2). Residual diuresis was included as a linear continuous variable. However, the effect of oxalic acid on graft survival turned out to be non-linear, as shown in Figs 3 and 4. The influence was not significant at low values, but became significant when the lower band of the 95% confidence interval exceeds zero. This pattern was observed for both deceased and living donor kidney transplantation. Although the exact super saturation threshold of

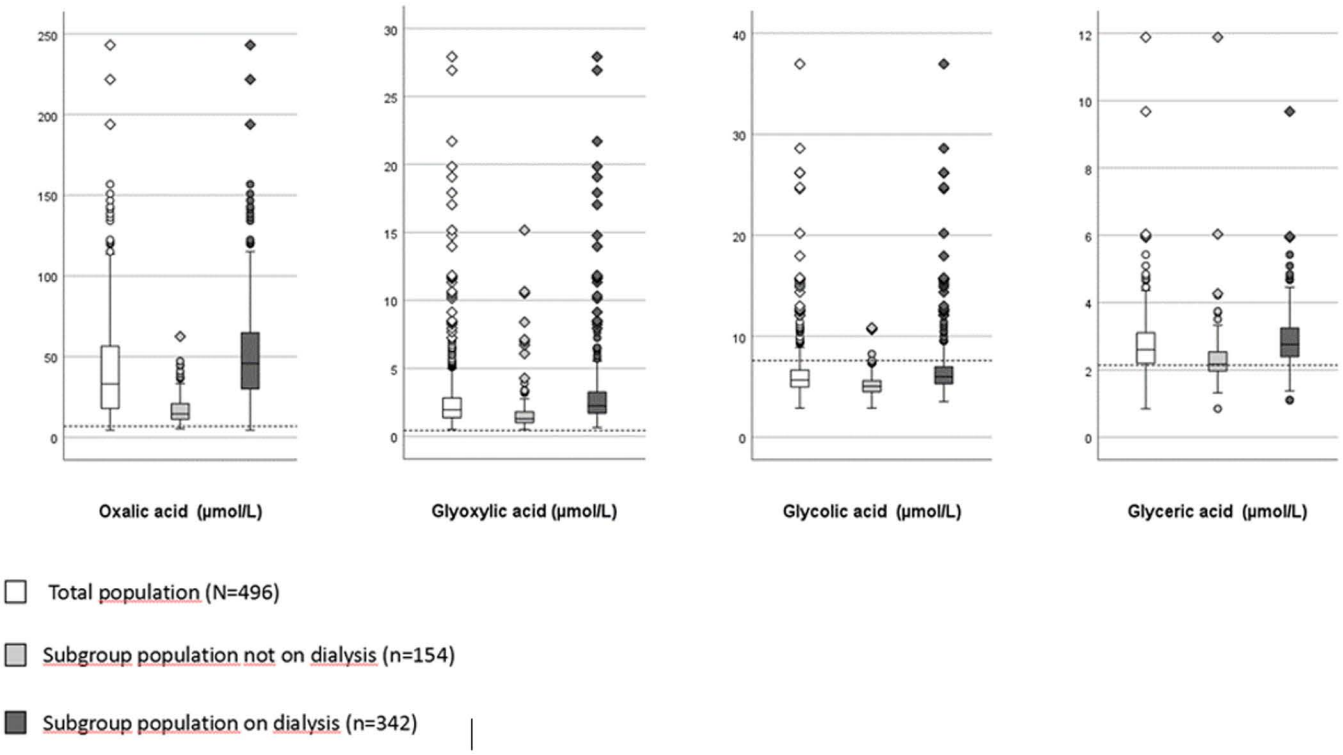

Fig 2. Distribution of oxalic acid, glyoxylic acid, glycolic acid and glyceric acid concentrations in the population studied. Dashed lines (-----) denote upper limits of normal concentration (oxalic acid 7.0 µmol/L; glyoxylic acid 0.4 µmol/L; glycolic acid 7.6 µmol/L; glyceric acid 2.1 µmol/L). The differences in concentrations between the subgroups on dialysis or preemptive were significant for oxalic acid and all precursors ($p < 0.001$).

https://doi.org/10.1371/journal.pone.0322516.g002

oxalic acid remains uncertain, it is generally presumed to be within the range of 30–40 µmol/L [13,14]. Above this threshold crystallisation/deposition occurs. In our population, the estimated threshold for the influence on graft survival censored for death is at 60 µmol/L in the recipient population with a living donor and at 70 µmol/L, in the recipient population with a deceased donor kidney (Figs 3 and 4). Based on Figs 3 and 4, oxalic acid concentration was categorized as ≤ 60 and > 60 µmol/L. There were 113 patients with oxalic acid concentration>60 µmol/L; 112 of them were dialysis patients, one was pre-emptive (supplementary table 1). Consistent with previous findings, the influence of donor age followed a J-shaped curve modelled with a quadratic effect ($p = 0.015$) [41]. Supplementary table 2 shows the results of those variables with a p-value <0.1 in univariable analysis. Though dialysis type (none, hemodialysis or peritoneal dialysis) and time between last dialysis and transplantation were significantly associated with graft failure in univariable analysis, there was no interaction between them.

All variables present in Table 1 were tested in multivariable Cox analysis. Results of the multivariable analyses with backward elimination on graft failure censored for death are shown in Table 2. Residual diuresis, donor age, donor type (living versus deceased donor kidney transplantation), and oxalic acid concentration remained in the model and significantly influenced the graft failure risk; there was no significant interaction between these variables. The proportional hazards assumption was not violated.

To detect multicollinearity between residual diuresis and oxalic acid the VIF was tested in linear regression analysis. There was no collinearity, the VIF was 1,13.

Figs 5 and 6 depict the influence of residual diuresis and oxalic acid on graft survival. For Fig 5 donor age is set to 58 years (median age) and donor type to living donor. For Fig 6 donor age is set to 58 years and donor type is set to

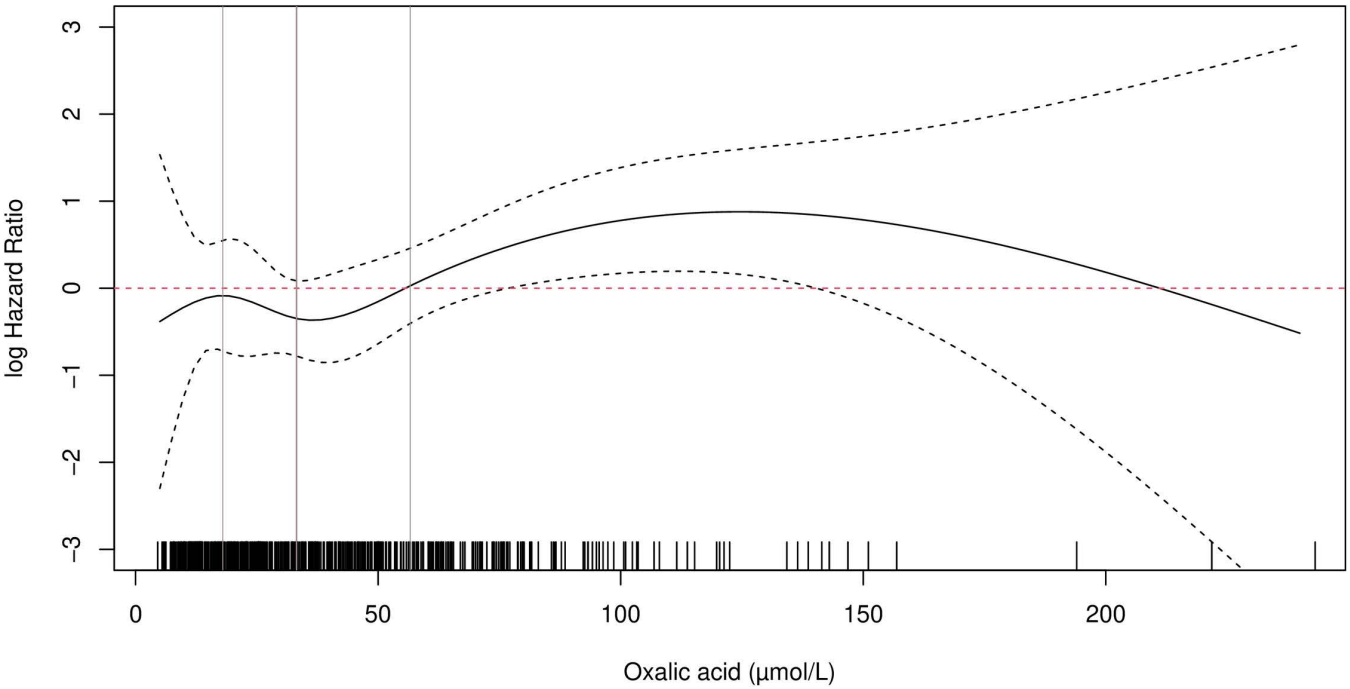

Fig 3. The influence of oxalic acid modelled using a natural cubic spline function. Recipients of a living donor kidney. Donor age is set to 58 years (median age), residual diuresis set to 1000mL/day (median). Median and IQR of oxalic acid concentration are shown as vertical lines. The small vertical lines above the X-axis represent the observed oxalic acid concentrations. The influence of oxalic acid on graft failure risk censored for death becomes significant when the confidence interval exceed zero.

https://doi.org/10.1371/journal.pone.0322516.g003

deceased donor. Survival curves are shown for combinations of oxalic acid categories and residual diuresis volumes at the 25th and 75th percentiles.

Patient survival

In the follow up period, 48 patients died. Oxalic acid concentration did not significantly influence the mortality risk. Variables with significant influence in univariable analysis are shown in supplementary table 3. In multivariable analysis the variables included in the final model were: recipient age, recipient CRP, glyceric acid concentration on day of transplantation, and type of kidney replacement therapy (none, hemodialysis or peritoneal dialysis) (Table 3).

Post Transplant follow-up

From 180 patients that underwent a graft biopsy, post-transplant oxalic acid plasma concentrations were available. Almost all concentrations were obtained within 2 weeks after transplantation (median 7 (IQR 5–10) days after transplantation). In this population post-transplant plasma oxalic acid concentrations were significantly lower compared to pre transplant concentrations: mean 24 ± 25 versus 43 ± 29 µmol/L (median (IQR): 14 (7-14) versus 36 (19–59) µmol/L ($p < 0.001$)). In most patients with an eGFR > 20 ml/min, oxalic acid concentrations were below the upper limit of normal. Oxalic acid concentrations were still high in most patients with an eGFR < 20 ml/min (Fig 7). At 1 year after transplantation eGFR (estimated Glomerular Filtration Rate) was not significantly different between the patients with a functioning transplant with pre-transplant oxalic acid concentration ≤60 or > 60 µmol/L; respectively, 47 ± 19 and 43 ± 23 ml/min ($p = 0.079$). However, there had been more graft losses at year 1 in the population >60 (19/113; 17%) compared to the population ≤60 (16/383; 4%; $p < 0.001$).

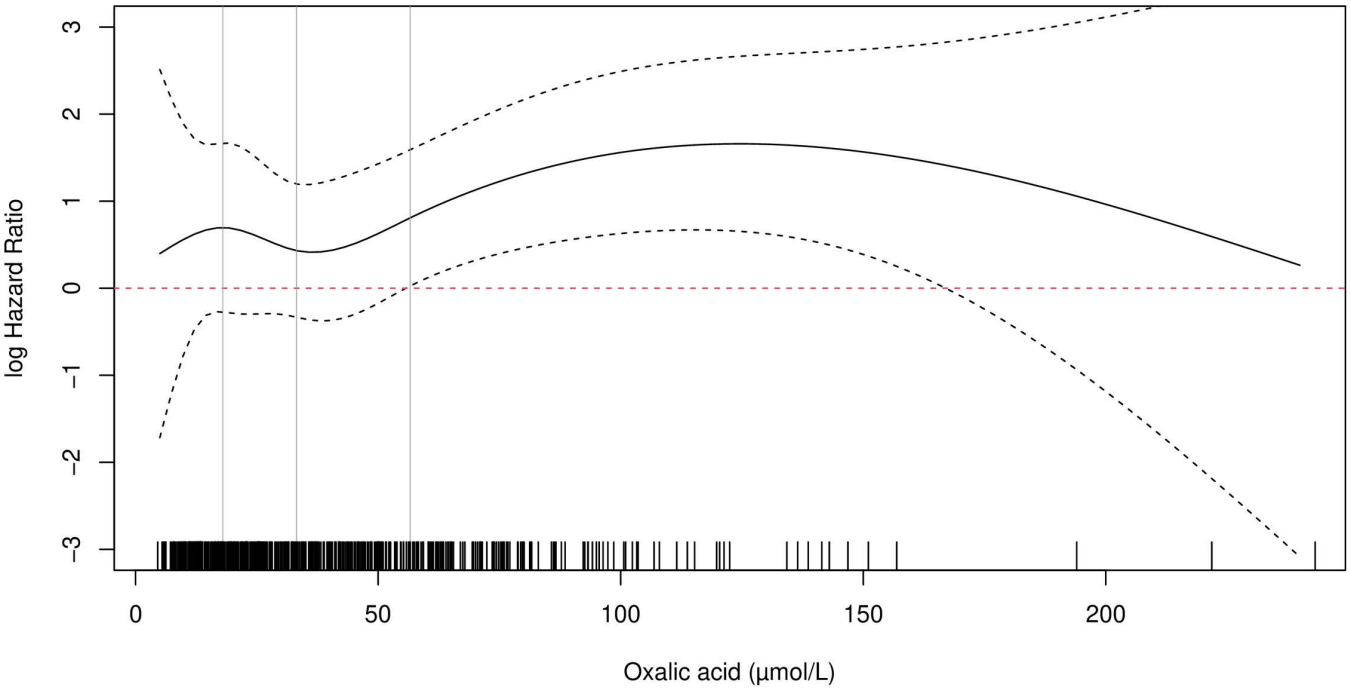

Fig 4. The influence of oxalic acid modelled using a natural cubic spline function. Recipients of a deceased donor kidney. Donor age is set to 58 years (median age), residual diuresis set to 1000mL/day (median). Median and IQR of oxalic acid concentration are shown as vertical lines. The small vertical lines above the X-axis represent the observed oxalic acid concentrations. The influence of oxalic acid on graft failure risk censored for death becomes significant when the confidence interval exceed zero.

https://doi.org/10.1371/journal.pone.0322516.g004

Table 2. Final model of multivariable Cox Proportional Hazards analysis on graft failure censored for death. Total population N = 496 Events N = 52. All variables listed in Table 1 were included, exclusion was performed via backward elimination.

	Hazard ratio	95% CI		
		Lower	Upper	Sig.
Residual diuresis (per 100ml)	0.991	0.987	0.996	<0.001
Oxalic acid category (≤60 µmol/L)	2.082	1.154	3.753	0.015
Donor type (living)	2.127	1.070	4.227	0.031
Donor age (years)	0.918	0.833	1.013	0.089
Donor age^2 (years)	1.001	1.000	1.002	0.024

For categorical variables reference values are shown in brackets. For continuous variables units are in brackets.

https://doi.org/10.1371/journal.pone.0322516.t002

Discussion

This is the first study that describes a significant effect of residual diuresis and oxalic acid concentration on the graft failure risk after kidney transplantation. We show that patients with low or absent residual diuresis, have high concentrations of more or less toxic waste products, such as glyoxylic acid and oxalic acid. It is conceivable that excretion of large amounts of these products by the newly transplanted kidney may cause toxicity and damage impairing kidney function. Even in the selected population of patients that underwent a for cause graft biopsy, post-transplant oxalic acid concentrations were significantly decreased, suggesting excretion through the graft. Figs 5 and 6 show the combined effects of residual diuresis and oxalic acid concentration on graft survival. It is remarkable that the trajectories of the lines diverge, indicating that

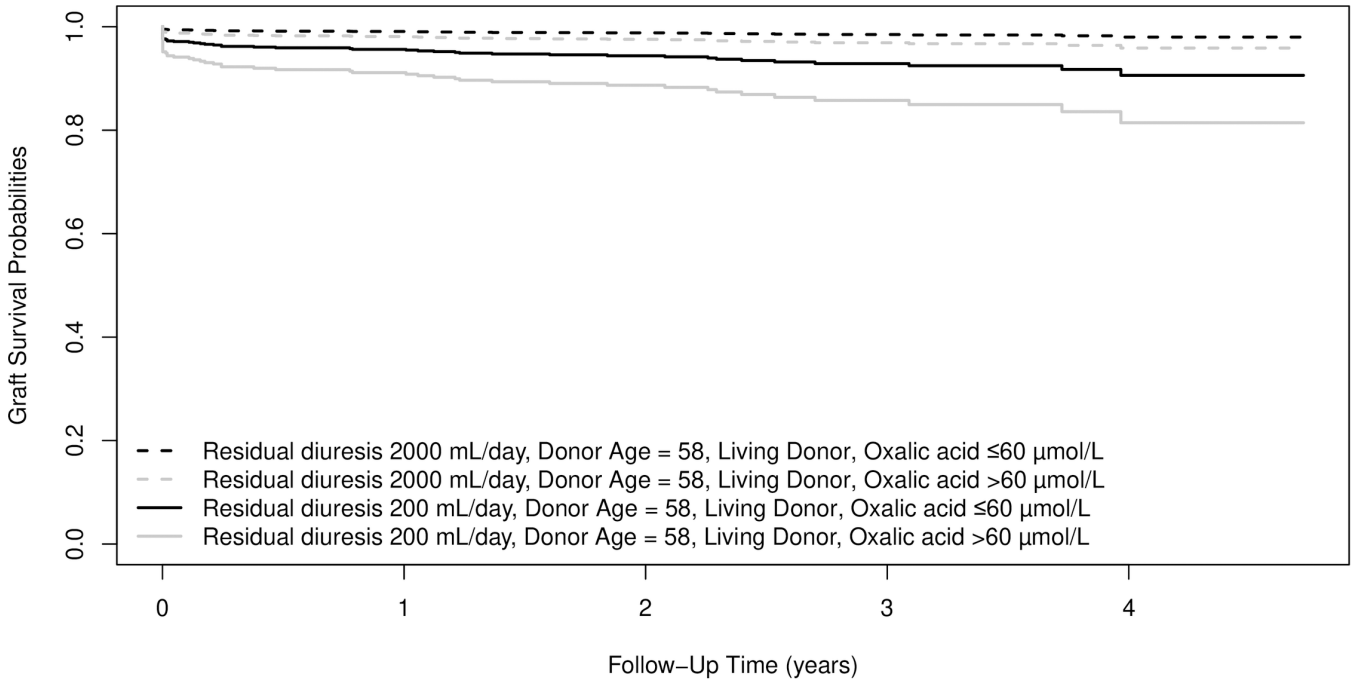

Fig 5. Based on the results in table 2. Expected survival probabilities for four individuals who share donor age of 58 years (median donor age). Individuals also share living donor type, but differ in residual diuresis volume (25th and 75th percentile) and in oxalic acid concentration category.

https://doi.org/10.1371/journal.pone.0322516.g005

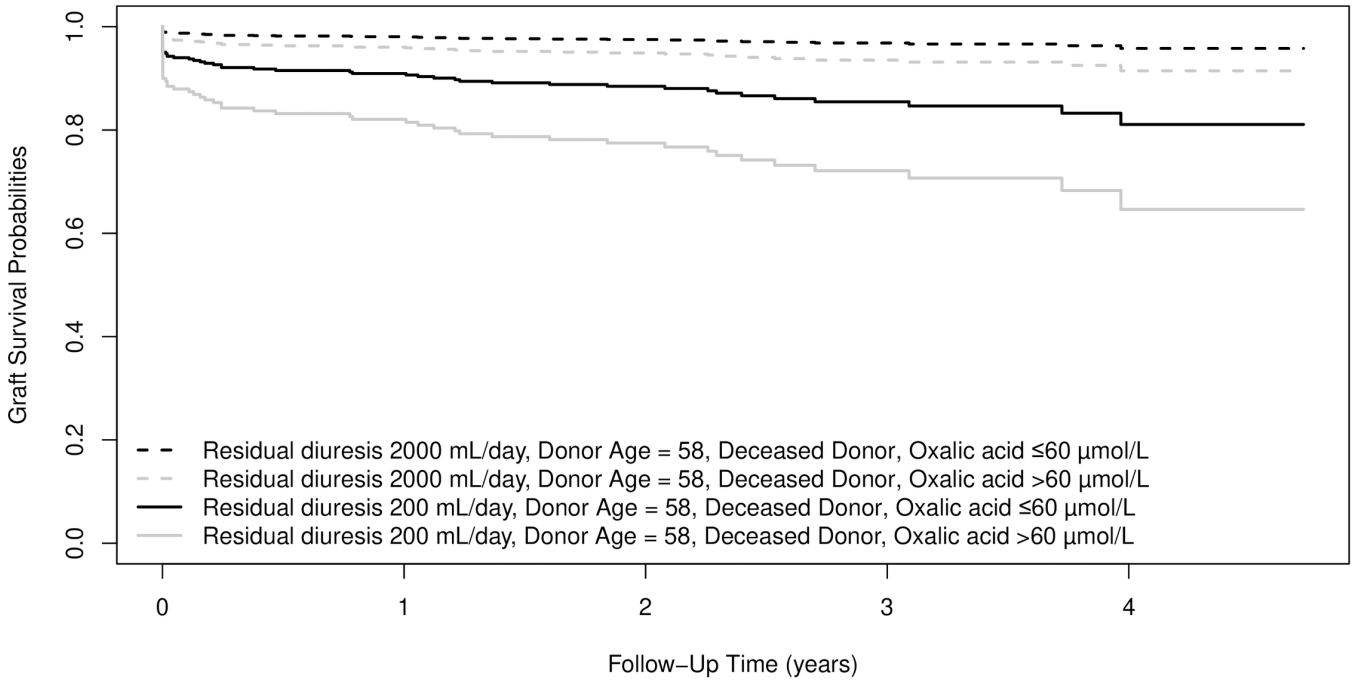

Fig 6. Based on the results in table 2. Expected survival probabilities for four individuals who share donor age of 58 years (median donor age). Individuals also share deceased donor type, but differ in residual diuresis volume (25th and 75th percentile) and in oxalic acid concentration category.

https://doi.org/10.1371/journal.pone.0322516.g006

Table 3. Final model of multivariable Cox Proportional Hazards analysis on patient death (N = 496, events = 48); All variables listed in Table 1 were included, exclusion was performed via backward elimination. The over-all effect of dialysis type as a categorical variable was tested comparing a model with and a model without dialysis type using chi-square test (P = 0.024).

	Hazard ratio	95.0% CI		Sig.
		Lower	Upper	
Recipient age (years)	1.093	1.057	1.13	<0.001
Recipient CRP (day 0)	1.027	1.007	1.049	0.01
Glyceric acid concentration (µmol/L)	1.347	1.061	1.71	0.014
Dialysis (no)				
Hemodialysis	2.641	1.146	6.089	0.023
Peritoneal dialysis	2.994	1.17	7.677	0.022

For categorical variables reference values are shown in brackets. For continuous variables units are in brackets.

https://doi.org/10.1371/journal.pone.0322516.t003

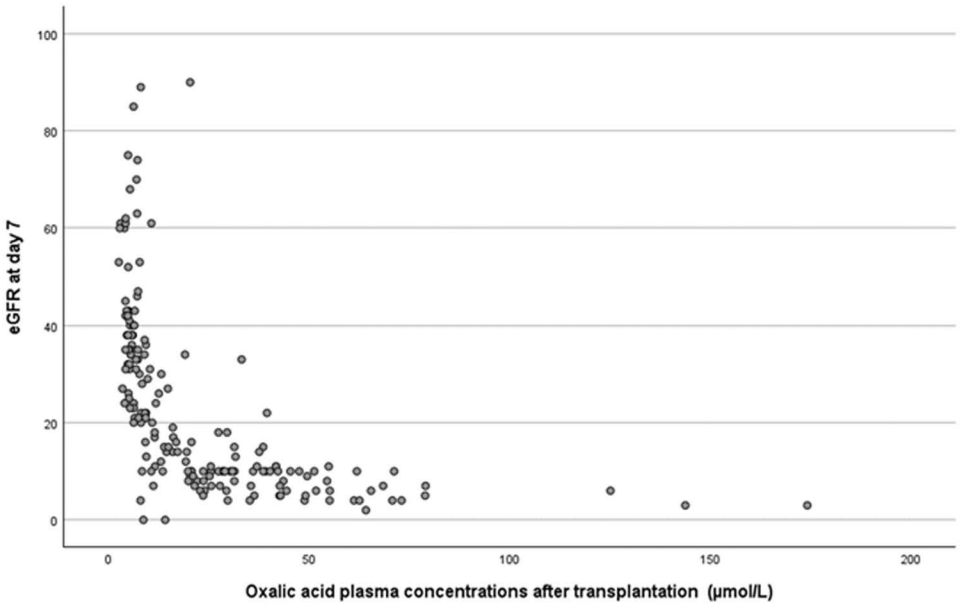

Fig 7. Post-transplantation oxalic acid plasma concentrations, in relation to kidney function at day 7 after transplantation (n = 180).

https://doi.org/10.1371/journal.pone.0322516.g007

the damage from the peri-transplantation period e.g. inflammation, toxicity and/or deposition of waste products, is only partially reversible. Figs 5 and 6 further underscore the vulnerability of recipients with low diuresis, exacerbated by high oxalic acid concentrations.

There are no studies on the influence of residual diuresis or on residual kidney function on the graft failure risk after kidney transplantation. However, we recently found that the DGF risk is significantly influenced by residual diuresis [37]. There are two other studies on the incidence of DGF, that also describe a significant influence of residual diuresis [35,36].

In patients on peritoneal dialysis [3,42] and in patients on hemodialysis [43] low residual diuresis has been shown to have a significantly negative influence on patient survival. Besides, in dialysis patients, low residual kidney function is associated with serious comorbidities e.g.: anemia, cardiovascular disease, hypertension, left ventricular hypertrophy, vascular calcifications and early atherosclerosis, inflammation and under-nutrition [27,43–49]. This means that the pre-transplant patients with low or absent residual diuresis, are less vital than those with significant residual diuresis volume. The cause

of their comorbidities is probably associated with the toxicity of waste products, left behind as a result of failing diuresis [1,4,5,50]. Sudden excretion of these products by the newly transplanted kidney may cause damage to the kidney transplant.

Our study showed that oxalic acid concentrations were above the upper normal concentration in 98.8% of pre-transplant patients. Highest concentrations of oxalic acid, glyoxylic acid, glycolic acid and glyceric acid were found in pre transplant patients on dialysis (versus not yet) and in patients with the lowest residual diuresis volume.

The influence of oxalic acid on the graft failure risk censored for death was not linear. Above a concentration of 60 μmol/L oxalic acid exerts a significant and negative effect in univariable and in multivariable analysis. Although there is no unanimity on the exact super saturation threshold of oxalic acid, it is presumed to be within the range of 30–40 μmol/L [13,14,30]. Evidently, measurable damage to the transplanted kidney occurs at concentrations higher than this threshold. The influence remained unaffected by all other variables with significant influence. This means that, although the effect of residual diuresis on graft failure probably stands for the effect of many toxic waste products, oxalic acid, on top of that, independently exerts a significant effect on the graft failure risk. Krogstad et al. studied graft and patient survival in 167 kidney transplant patients from whom an oxalic acid concentration was determined at ten weeks after transplantation [31]. Patient survival was significantly worse in patients in the highest oxalic acid quartile, while its influence on graft survival censored for death barely failed significance ($p = 0.053$). The oxalic acid concentrations were relatively low in their study, most probably as a result of the dramatic drop in concentrations that happens after successful transplantation.

Oxalic acid is a small molecule, that can effectively be removed by hemodialysis. Increased net secretion (in the proximal tubule) becomes apparent with high oxalic acid intake [51]. Though concentrations decrease during dialysis, normalization of concentration depends on pre dialysis values but is seldom reached. Probably these concentrations reflect oxalic acid stores in the body. In patients with primary hyperoxaluria, even current dialysis programs are not able to prevent progressive oxalate accumulation in the majority of patients [52,53]. However, also in our pre transplant population, high oxalic acid, glyoxylic acid and glyceric acid concentrations are found in the vast majority of patients, while highest concentrations are found in those on dialysis.

Finally, there was no significant association between the incidence of patient mortality and oxalic acid concentrations, but high concentrations of its precursor glyceric acid were unfavourably associated with patient survival. Two rare, autosomal recessive metabolic disorders can result in significant excretion of urinary glycerate: primary hyperoxaluria type II and D-glyceric aciduria. There are no publications on toxicity of glyceric acid in the concentrations we found in our population. A limitation of our study is that residual function (residual eGFR), in dialysis patients with residual diuresis, was not available. Residual urine volume was included instead.

In conclusion: Residual diuresis and oxalic acid concentration are important and independent predictors of kidney graft survival censored for death. Preservation of residual diuresis, even after starting dialysis, is useful and gained attention nowadays [50]. Preservation can be achieved by using incremental hemodialysis, avoiding nephrotoxic events and treatments, and blood pressure control [54]. Dietary, lifestyle and pharmacological interventions are defined to ensure optimal native kidney function preserving care [55]. However, in addition to urea clearance (Kt/V) [56], more attention should be paid to removal of other substances that may not be sufficiently cleared by dialysis treatment. Examples are oxalic acid and glyoxylic acid: both recognized as tubulotoxic agents [26,28]. Our complementary study on dietary habits in the population studied, showed a significant relationship between dietary intake of oxalic acid and plasma oxalic acid concentration in this population of patients with end stage kidney disease [57]. In our center, efforts to reduce oxalic acid concentrations in patients with enteric hyperoxaluria led to the development of the successful hyperoxaluria treatment guideline to prevent early recurrence after transplantation [58]. In this guideline oxalic acid concentrations are reduced through dietary restrictions and intensified dialysis in the period before transplantation.

Our present study adds an argument to stimulate pre-emptive transplantation in patients who still have adequate diuresis and relatively low concentrations of oxalic acid and its precursors.

Supporting information

S1 Table. Recipient, donor and transplantation characteristics from the entire population, the pre-emptive recipient population and the population on dialysis.
(XLSX)

S2 Table. Univariable Cox Proportional Hazards analysis on graft failure censored for death (N = 496). (All variables listed in Table 1 were tested. Only those characteristics with a p-value <0.1 in univariable analysis are shown in this table).
(XLSX)

S3 Table. Univariable Cox Proportional Hazards analysis on patient death (N = 496). (All variables listed in Table 1 were tested. Only those characteristics with a p-value <0.1 in univariable analysis are shown in this table).
(XLSX)

S1 Fig. The influence of residual diuresis modelled using a natural cubic spline function. Recipients of a living donor kidney. Donor age is set to 58 years (median age), oxalic acid concentration is set to 33.2 μmol/l (median). Median and IQR of residual diuresis concentration are shown as vertical lines. The small vertical lines above the X-axis represent the observed residual diuresis volumes. The influence of residual diuresis on graft failure risk censored for death becomes significant when the confidence interval exceeds zero (dotted lines).
(TIF)

S2 Fig. The influence of residual diuresis modelled using a natural cubic spline function. Recipients of a deceased donor kidney. Donor age is set to 58 years (median age), oxalic acid concentration is set to 33.2 μmol/l (median). Median and IQR of residual diuresis concentration are shown as vertical lines. The small vertical lines above the X-axis represent the observed residual diuresis volumes. The influence of residual diuresis on graft failure risk censored for death becomes significant when the confidence interval exceeds zero (dotted lines).
(TIF)

Acknowledgments

We would like to thank Mrs Judith Kal-van Gestel MSc and Mrs Tessa Royaards for their updates of regular recipient and living donor data, Mrs Ineke Tieken, MSc for providing Eurotransplant deceased donor data, Mr Chris Ramakers, MSc for sample processing and storage and Mrs Sara J Baart, PhD for her statistical advice.

Author contributions

Conceptualization: Mirjam Laging, Wesley J. Visser, Anneke ME de Mik-van Egmond, Madelon van Agteren, Jacqueline van de Wetering, Marcia ML Kho, Joke I Roodnat.

Data curation: Gideon Post Hospers, Mirjam Laging, Wesley J. Visser, Pedro Miranda Afonso, Jeroen GHP Verhoeven, Ingrid RAM Mertens zur Borg, Anneke ME de Mik-van Egmond, Michiel GH Betjes, Madelon van Agteren, Ido P Kema, Marcia ML Kho, Joke I Roodnat.

Formal analysis: Gideon Post Hospers, Mirjam Laging, Pedro Miranda Afonso, Jeroen GHP Verhoeven, Ingrid RAM Mertens zur Borg, Michiel GH Betjes, Madelon van Agteren, Jacqueline van de Wetering, Robert Zietse, Ido P Kema, Marcia ML Kho, Joke I Roodnat.

Funding acquisition: Michiel GH Betjes, Robert Zietse, Joke I Roodnat.

Investigation: Gideon Post Hospers, Mirjam Laging, Wesley J. Visser, Pedro Miranda Afonso, Jeroen GHP Verhoeven, Ingrid RAM Mertens zur Borg, Dennis A Hesselink, Michiel GH Betjes, Madelon van Agteren, David Severs, Jacqueline van de Wetering, Robert Zietse, Michel J Vos, Ido P Kema, Marcia ML Kho, Joke I Roodnat.

Methodology: Gideon Post Hospers, Mirjam Laging, Wesley J. Visser, Pedro Miranda Afonso, Jeroen GHP Verhoeven, Ingrid RAM Mertens zur Borg, Dennis A Hesselink, Anneke ME de Mik-van Egmond, Michiel GH Betjes, Madelon van Agteren, David Severs, Jacqueline van de Wetering, Michel J Vos, Ido P Kema, Marcia ML Kho, Joke I Roodnat.

Project administration: Gideon Post Hospers, Mirjam Laging, Wesley J. Visser, Jeroen GHP Verhoeven, Dennis A Hesselink, Michel J Vos, Marlies EJ Reinders, Joke I Roodnat.

Resources: Dennis A Hesselink, Anneke ME de Mik-van Egmond, Madelon van Agteren, Jacqueline van de Wetering, Michel J Vos, Marcia ML Kho, Marlies EJ Reinders, Joke I Roodnat.

Software: Gideon Post Hospers, Mirjam Laging, Dennis A Hesselink, Robert Zietse, Marcia ML Kho, Joke I Roodnat.

Supervision: Dennis A Hesselink, Marlies EJ Reinders, Joke I Roodnat.

Validation: Dennis A Hesselink, Anneke ME de Mik-van Egmond, David Severs, Joke I Roodnat.

Visualization: Ingrid RAM Mertens zur Borg, David Severs, Joke I Roodnat.

Writing – original draft: Gideon Post Hospers, Wesley J. Visser, Jeroen GHP Verhoeven, Ingrid RAM Mertens zur Borg, Anneke ME de Mik-van Egmond, Michiel GH Betjes, Madelon van Agteren, David Severs, Robert Zietse, Marcia ML Kho, Marlies EJ Reinders, Joke I Roodnat.

Writing – review & editing: Gideon Post Hospers, Mirjam Laging, Wesley J. Visser, Jeroen GHP Verhoeven, Ingrid RAM Mertens zur Borg, Dennis A Hesselink, Anneke ME de Mik-van Egmond, Michiel GH Betjes, Madelon van Agteren, David Severs, Jacqueline van de Wetering, Robert Zietse, Michel J Vos, Ido P Kema, Marcia ML Kho, Marlies EJ Reinders, Joke I Roodnat.

References

1. Toth-Manikowski SM, Sirich TL, Meyer TW, Hostetter TH, Hwang S, Plummer NS, et al. Contribution of "clinically negligible" residual kidney function to clearance of uremic solutes. Nephrol Dial Transplant. 2020;35(5):846–53. https://doi.org/10.1093/ndt/gfz042 PMID: 30879076
2. Snauwaert E, Holvoet E, Van Biesen W, Raes A, Glorieux G, Vande Walle J, et al. Uremic Toxin Concentrations are Related to Residual Kidney Function in the Pediatric Hemodialysis Population. Toxins (Basel). 2019;11(4):235. https://doi.org/10.3390/toxins11040235 PMID: 31022857
3. Termorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT, et al. The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. Am J Kidney Dis. 2003;41(6):1293–302. https://doi.org/10.1016/s0272-6386(03)00362-7 PMID: 12776283
4. Marquez IO, Tambra S, Luo FY, Li Y, Plummer NS, Hostetter TH, et al. Contribution of residual function to removal of protein-bound solutes in hemodialysis. Clin J Am Soc Nephrol. 2011;6(2):290–6. https://doi.org/10.2215/CJN.06100710 PMID: 21030575
5. Fry AC, Singh DK, Chandna SM, Farrington K. Relative importance of residual renal function and convection in determining beta-2-microglobulin levels in high-flux haemodialysis and on-line haemodiafiltration. Blood Purif. 2007;25(3):295–302. https://doi.org/10.1159/000104870 PMID: 17622712
6. Tanaka H, Sirich TL, Plummer NS, Weaver DS, Meyer TW. An Enlarged Profile of Uremic Solutes. PLoS One. 2015;10(8):e0135657. https://doi.org/10.1371/journal.pone.0135657 PMID: 26317986
7. Mair RD, Sirich TL, Plummer NS, Meyer TW. Characteristics of Colon-Derived Uremic Solutes. Clin J Am Soc Nephrol. 2018;13(9):1398–404. https://doi.org/10.2215/CJN.03150318 PMID: 30087103
8. Tomson CR, Channon SM, Ward MK, Laker MF. Oxalate retention in chronic renal failure: tubular vs glomerular diseases. Clin Nephrol. 1989;32(2):87–95. PMID: 2788548
9. Morgan SH, Purkiss P, Watts RW, Mansell MA. Oxalate dynamics in chronic renal failure. Comparison with normal subjects and patients with primary hyperoxaluria. Nephron. 1987;46(3):253–7. https://doi.org/10.1159/000184364 PMID: 3306417
10. Elgstoen KBP, Johnsen LF, Woldseth B, Morkrid L, Hartmann A. Plasma oxalate following kidney transplantation in patients without primary hyperoxaluria. Nephrol Dial Transplant. 2010;25(7):2341–5. https://doi.org/10.1093/ndt/gfq065 PMID: 20167571

11. Marangella M, Petrarulo M, Mandolfo S, Vitale C, Cosseddu D, Linari F. Plasma profiles and dialysis kinetics of oxalate in patients receiving hemodialysis. Nephron. 1992;60(1):74–80. https://doi.org/10.1159/000186708 PMID: 1738418
12. Tomson CR, Channon SM, Ward MK, Laker MF. Plasma oxalate concentration, oxalate clearance and cardiac function in patients receiving haemodialysis. Nephrol Dial Transplant. 1989;4(9):792–9. PMID: 2516611
13. Marangella M, Cosseddu D, Petrarulo M, Vitale C, Linari F. Thresholds of serum calcium oxalate supersaturation in relation to renal function in patients with or without primary hyperoxaluria. Nephrol Dial Transplant. 1993;8(12):1333–7. PMID: 8159301
14. Demoulin N, Aydin S, Gillion V, Morelle J, Jadoul M. Pathophysiology and Management of Hyperoxaluria and Oxalate Nephropathy: A Review. Am J Kidney Dis. 2022;79(5):717–27. https://doi.org/10.1053/j.ajkd.2021.07.018 PMID: 34508834
15. Cochat P, Rumsby G. Primary hyperoxaluria. N Engl J Med. 2013;369(7):649–58. https://doi.org/10.1056/NEJMra1301564 PMID: 23944302
16. Ben-Shalom E, Cytter-Kuint R, Rinat C, Becker-Cohen R, Tzvi-Behr S, Goichberg J, et al. Long-term complications of systemic oxalosis in children-a retrospective single-center cohort study. Pediatr Nephrol. 2021;36(10):3123–32. https://doi.org/10.1007/s00467-021-05002-1 PMID: 33651179
17. Prenen JA, Dorhout Mees EJ, Boer P. Plasma oxalate concentration and oxalate distribution volume in patients with normal and decreased renal function. Eur J Clin Invest. 1985;15(1):45–9. https://doi.org/10.1111/j.1365-2362.1985.tb00142.x PMID: 3921382
18. Bernhardt WM, Schefold JC, Weichert W, Rudolph B, Frei U, Groneberg DA, et al. Amelioration of anemia after kidney transplantation in severe secondary oxalosis. Clin Nephrol. 2006;65(3):216–21. https://doi.org/10.5414/cnp65216 PMID: 16550754
19. Lapointe HJ, Listrom R. Oral manifestations of oxalosis secondary to ileojejunal intestinal bypass. Oral Surg Oral Med Oral Pathol. 1988;65(1):76–80. https://doi.org/10.1016/0030-4220(88)90196-x PMID: 3422399
20. Mookadam F, Smith T, Jiamsripong P, Moustafa SE, Monico CG, Lieske JC, et al. Cardiac abnormalities in primary hyperoxaluria. Circ J. 2010;74(11):2403–9. https://doi.org/10.1253/circj.cj-10-0107 PMID: 20921818
21. Solmos GR, Ali A, Rodby RA, Fordham EW. Rapid reversal of bone scan abnormalities in a patient with type 1 primary hyperoxaluria and oxalosis. Clin Nucl Med. 1994;19(9):769–72. https://doi.org/10.1097/00003072-199409000-00004 PMID: 7982308
22. Karaolanis G, Lionaki S, Moris D, Palla V-V, Vernadakis S. Secondary hyperoxaluria: a risk factor for kidney stone formation and renal failure in native kidneys and renal grafts. Transplant Rev (Orlando). 2014;28(4):182–7. https://doi.org/10.1016/j.trre.2014.05.004 PMID: 24999029
23. Witting C, Langman CB, Assimos D, Baum MA, Kausz A, Milliner D, et al. Pathophysiology and Treatment of Enteric Hyperoxaluria. Clin J Am Soc Nephrol. 2021;16(3):487-95. Epub 2020/09/10. https://doi.org/01277230-202103000-00026
24. Palsson R, Chandraker AK, Curhan GC, Rennke HG, McMahon GM, Waikar SS. The association of calcium oxalate deposition in kidney allografts with graft and patient survival. Nephrol Dial Transplant. 2020;35(5):888–94. https://doi.org/10.1093/ndt/gfy271 PMID: 30165691
25. Snijders MLH, Hesselink DA, Clahsen-van Groningen MC, Roodnat JI. Oxalate deposition in renal allograft biopsies within 3 months after transplantation is associated with allograft dysfunction. PLoS One. 2019;14(4):e0214940. https://doi.org/10.1371/journal.pone.0214940 PMID: 30990835
26. Knauf F, Asplin JR, Granja I, Schmidt IM, Moeckel GW, David RJ, et al. NALP3-mediated inflammation is a principal cause of progressive renal failure in oxalate nephropathy. Kidney Int. 2013;84(5):895–901. https://doi.org/10.1038/ki.2013.207 PMID: 23739234
27. Cao Y, Liu W, Hui L, Zhao J, Yang X, Wang Y, et al. Renal tubular injury induced by ischemia promotes the formation of calcium oxalate crystals in rats with hyperoxaluria. Urolithiasis. 2016;44(5):389–97. https://doi.org/10.1007/s00240-016-0876-7 PMID: 27040948
28. Poldelski V, Johnson A, Wright S, Rosa VD, Zager RA. Ethylene glycol-mediated tubular injury: identification of critical metabolites and injury pathways. Am J Kidney Dis. 2001;38(2):339–48. https://doi.org/10.1053/ajkd.2001.26099 PMID: 11479160
29. Munro KM, Adams JH. Acute ethylene glycol poisoning: report of a fatal case. Med Sci Law. 1967;7(4):181–4. https://doi.org/10.1177/002580246700700404 PMID: 5587714
30. Pfau A, Ermer T, Coca SG, Tio MC, Genser B, Reichel M, et al. High Oxalate Concentrations Correlate with Increased Risk for Sudden Cardiac Death in Dialysis Patients. J Am Soc Nephrol. 2021;32(9):2375–85. https://doi.org/10.1681/ASN.2020121793 PMID: 34281958
31. Krogstad V, Elgstøen KBP, Johnsen LF, Hartmann A, Mørkrid L, Åsberg A. High Plasma Oxalate Levels Early After Kidney Transplantation Are Associated With Impaired Long-Term Outcomes. Transpl Int. 2022;35:10240. https://doi.org/10.3389/ti.2022.10240 PMID: 35368646
32. Robijn S, Hoppe B, Vervaet BA, D'Haese PC, Verhulst A. Hyperoxaluria: a gut-kidney axis? Kidney Int. 2011;80(11):1146–58. https://doi.org/10.1038/ki.2011.287 PMID: 21866092
33. Kruse JA. Methanol and ethylene glycol intoxication. Crit Care Clin. 2012;28(4):661–711. https://doi.org/10.1016/j.ccc.2012.07.002 PMID: 22998995
34. Ghannoum M, Gosselin S, Hoffman RS, Lavergne V, Mégarbane B, Hassanian-Moghaddam H, et al. Extracorporeal treatment for ethylene glycol poisoning: systematic review and recommendations from the EXTRIP workgroup. Crit Care. 2023;27(1):56. https://doi.org/10.1186/s13054-022-04227-2 PMID: 36765419
35. Jahn L, Rüster C, Schlosser M, Winkler Y, Foller S, Grimm M-O, et al. Rate, Factors, and Outcome of Delayed Graft Function After Kidney Transplantation of Deceased Donors. Transplant Proc. 2021;53(5):1454–61. https://doi.org/10.1016/j.transproceed.2021.01.006 PMID: 33612277

36. Chaumont M, Racapé J, Broeders N, El Mountahi F, Massart A, Baudoux T, et al. Delayed Graft Function in Kidney Transplants: Time Evolution, Role of Acute Rejection, Risk Factors, and Impact on Patient and Graft Outcome. J Transplant. 2015;2015:163757. https://doi.org/10.1155/2015/163757 PMID: 26448870

37. Post Hospers GV, Verhoeven WJ, Laging JGHP, Baart MSJ, Mertens zur Borg IRAM, Hesselink DA, et al. Delayed graft function after kidney transplantation: The role of residual diuresis and accumulated waste products, as oxalic acid and its precursors. Transpl Int 2024 Jul 19:37:13218 https://doi.org/10.103389/ti202413218

38. Koolstra W, Wolthers BG, Hayer M, Elzinga H. Development of a reference method for determining urinary oxalate by means of isotope dilution-mass spectrometry (ID-MS) and its usefulness in testing existing assays for urinary oxalate. Clin Chim Acta. 1987;170(2–3):227–35. https://doi.org/10.1016/0009-8981(87)90132-x PMID: 3436057

39. Koolstra W, Wolthers BG, Hayer M, Rutgers HM. An improved high performance liquid chromatographic method for determining urinary oxalate, making use of an ID-MS reference method. Clin Chim Acta. 1987;170(2–3):237–43. https://doi.org/10.1016/0009-8981(87)90133-1 PMID: 3436058

40. Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. Bone Marrow Transplant. 2020;55(4):675–80. https://doi.org/10.1038/s41409-019-0679-x PMID: 31576022

41. Laging M, Kal-van Gestel JA, van de Wetering J, Ijzermans JNM, Weimar W, Roodnat JI. The relative importance of donor age in deceased and living donor kidney transplantation. Transpl Int. 2012;25(11):1150–7. https://doi.org/10.1111/j.1432-2277.2012.01539.x PMID: 22860760

42. Liao CT, Chen YM, Shiao CC, Hu FC, Huang JW, Kao TW, et al. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis. Nephrol Dial Transplant. 2009;24(9):2909–14. Epub 2009/02/20. https://doi.org/10.1093/ndt/gfp056 PMID: 19225016

43. Kong J, Davies M, Mount P. The importance of residual kidney function in haemodialysis patients. Nephrology (Carlton). 2018;23(12):1073–80. https://doi.org/10.1111/nep.13427 PMID: 29920874

44. Virzì GM, Milan Manani S, Clementi A, Castegnaro S, Brocca A, Riello C, et al. Eryptosis Is Altered in Peritoneal Dialysis Patients. Blood Purif. 2019;48(4):351–7. https://doi.org/10.1159/000501541 PMID: 31291616

45. Menon MK, Naimark DM, Bargman JM, Vas SI, Oreopoulos DG. Long-term blood pressure control in a cohort of peritoneal dialysis patients and its association with residual renal function. Nephrol Dial Transplant. 2001;16(11):2207–13. https://doi.org/10.1093/ndt/16.11.2207 PMID: 11682669

46. de Sequera P, Corchete E, Bohorquez L, Albalate M, Perez-Garcia R, Alique M, et al. Residual Renal Function in Hemodialysis and Inflammation. Ther Apher Dial. 2017;21(6):592–8. https://doi.org/10.1111/1744-9987.12576 PMID: 28971592

47. Wang AY-M, Wang M, Woo J, Law M-C, Chow K-M, Li PK-T, et al. A novel association between residual renal function and left ventricular hypertrophy in peritoneal dialysis patients. Kidney Int. 2002;62(2):639–47. https://doi.org/10.1046/j.1523-1755.2002.00471.x PMID: 12110029

48. Iwasawa H, Nakao T, Matsumoto H, Okada T, Nagaoka Y, Wada T. Phosphate handling by end-stage kidneys and benefits of residual renal function on phosphate removal in patients on haemodialysis. Nephrology (Carlton). 2013;18(4):285–91. https://doi.org/10.1111/nep.12039 PMID: 23432763

49. Chen H-C, Chou C-Y, Jheng J-S, Chen I-R, Liang C-C, Wang S-M, et al. Loss of Residual Renal Function is Associated With Vascular Calcification in Hemodialysis Patients. Ther Apher Dial. 2016;20(1):27–30. https://doi.org/10.1111/1744-9987.12376 PMID: 26637989

50. Koppe L, Soulage CO. Preservation of residual kidney function to reduce non-urea solutes toxicity in haemodialysis. Nephrol Dial Transplant. 2020;35(5):733–6. https://doi.org/10.1093/ndt/gfz224 PMID: 31711183

51. Holmes RP, Ambrosius WT, Assimos DG. Dietary oxalate loads and renal oxalate handling. J Urol. 2005;174(3):943–7; discussion 947. https://doi.org/10.1097/01.ju.0000169476.85935.e2 PMID: 16094002

52. Marangella M, Petrarulo M, Cosseddu D, Vitale C, Linari F. Oxalate balance studies in patients on hemodialysis for type I primary hyperoxaluria. Am J Kidney Dis. 1992;19(6):546–53. https://doi.org/10.1016/s0272-6386(12)80833-x PMID: 1595703

53. Hoppe B, Graf D, Offner G, Latta K, Byrd DJ, Michalk D, et al. Oxalate elimination via hemodialysis or peritoneal dialysis in children with chronic renal failure. Pediatr Nephrol. 1996;10(4):488–92. https://doi.org/10.1007/s004670050145 PMID: 8865249

54. Liu Y, Zou W, Wu J, Liu L, He Q. Comparison between incremental and thrice-weekly haemodialysis: Systematic review and meta-analysis. Nephrology (Carlton). 2019;24(4):438–44. https://doi.org/10.1111/nep.13252 PMID: 29532551

55. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet. 2021;398(10302):786–802. https://doi.org/10.1016/S0140-6736(21)00519-5 PMID: 34175022

56. Tattersall J, Martin-Malo A, Pedrini L, Basci A, Canaud B, Fouque D, et al. EBPG guideline on dialysis strategies. Nephrol Dial Transplant. 2007;22 Suppl 2:ii5-21. https://doi.org/10.1093/ndt/gfm022 PMID: 17507427

57. Visser WJ, Hospers GP, van Egmond AME, Laging M, Verhoeven JGHP, Baart SJ, et al. Dietary intake of oxalic acid affects plasma oxalic acid concentration in patients with kidney failure. Clin Nutr ESPEN. 2025;67:303–10. https://doi.org/10.1016/j.clnesp.2025.03.030 PMID: 40127762

58. Roodnat JI, de Mik-van Egmond AME, Visser WJ, Berger SP, van der Meijden WAG, Knauf F, et al. A Successful Approach to Kidney Transplantation in Patients With Enteric (Secondary) Hyperoxaluria. Transplant Direct. 2017;3(12):e331. https://doi.org/10.1097/TXD.0000000000000748 PMID: 29536032