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Baseline kidney function following kidney transplantation is often used in research and clinical decision-making yet is not well defined. Here, a method to determine baseline function was proposed and validated on three single-center retrospective cohorts consisting of 922 patients from Belgium (main cohort) and two validation cohorts of 987 patients from the Netherlands and 519 patients from Germany. For each transplant, a segmented regression model was fitted on the estimated glomerular filtration rate (eGFR) evolution during the first-year post-transplantation. This yielded estimates for change point timing, rate of eGFR change before and after change point and eGFR value at change point, now considered the "baseline function". Associations of eGFR evolution with recipient/donor characteristics and the graft failure rate were assessed with linear regression and Cox regression respectively. The change point occurred on average at an eGFR value of 43.7±14.6 mL/min/1.73m^2, at a median time of 6.5 days post-transplantation. Despite significant associations with several baseline donor-recipient characteristics (particularly, donor type; living vs deceased), the predictive value of these characteristics for eGFR value and timing of the change point was limited. This followed from a large heterogeneity within eGFR trajectories, which in turn indicated that favorable levels of kidney function could be reached despite a suboptimal initial evolution. Segmented regression consistently provided a good fit to early eGFR evolution, and its estimate of the change point can be a useful reference value in future analyses. Thus, our study shows that baseline kidney function after transplantation is heterogeneous and partly related to pretransplant donor characteristics.

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KEYWORDS: change point; eGFR evolution; kidney transplant; nadir; segmented regression

Lay Summary

Decline of kidney function (quantified via the estimated glomerular filtration rate [eGFR]) is increasingly used as an alternative end point to graft failure, as it is observed earlier after transplantation and in more recipients. However, as "normal" kidney function differs widely between patients, this decline is defined as a relative decrease compared with the patient-specific "baseline kidney function." Currently, established methods to determine this baseline function are lacking. We propose to use segmented regression, which models the change point at which the initial, rapid eGFR increase following transplantation reaches a more stable eGFR level. This model showed an excellent fit to the eGFR evolutions of 922 recipients in the main cohort, and 1506 recipients in 2 validation cohorts. We conclude that the eGFR value at the change point is useful as a reference eGFR value, expressing the baseline kidney function, in future studies that use eGFR decline as an end point.

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The early evolution of kidney function following kidney transplantation is characterized by a steep increase, with the exception of cases with delayed graft function. After a couple of days to weeks, kidney function stabilizes, reaching a change point that can be considered the "baseline

kidney function." There is a need for an objective and robust method to define this baseline function, as kidney function decline (compared with such a reference value) is commonly part of the composite end point in clinical studies of kidney disease.[1] This trend is elicited by the decline in graft failure events, which can lead to issues with underpowered analyses when graft survival is the primary end point.

More generally, the clinical relevance of the early evolution of kidney transplant function is not clear. In research where the prognostic value of kidney function evolution following transplantation is evaluated, the early evolution is often disregarded because of the large variability in early estimated glomerular filtration rate (eGFR) values, rapid fluid shifts, and frequent adjustments of the immunosuppression.[2] Time series models,[3] latent class mixed models,[4] and deep learning models[5] have been used to analyze post-transplant kidney functional trajectories, but no attempts were made to model baseline kidney function. Furthermore, none of the studies on early kidney transplant function has assessed the importance of the change point between the first phase (steep increase) and the second phase (stabilization) of the evolution for post-transplant prognosis.

Because of the erratic evolution of eGFR in the early post-transplant period, it is challenging to define the timing and eGFR value of this change point consistently.[2] However, appropriate modeling could offer an objective way of defining this change point, compared with a determination purely based on clinical estimation. The transition between different stages of a disease or natural evolution has been studied extensively in other medical areas, such as disease progression in patients with HIV,[6] onset of cognitive decline in elderly individuals,[7,8] and lung function measurements in children with cystic fibrosis.[9] In these articles, the evolution was modeled with segmented regression models.

Once the appropriate method to determine the change point has been established, the prognostic value of this point and related factors can be assessed. Earlier studies regarding kidney function after transplantation have demonstrated associations between the rate of graft failure beyond the first year and eGFR values at certain time points within the first year after transplantation.[10–14] More recent studies have suggested that variables that describe the dynamics of the kidney function (such as slopes over particular time intervals) might be more informative than values at single time points.[10,15] However, neither the clinical determinants of the change point nor the prognostic importance of the change point has been established in kidney transplantation.

The goal of this study is to objectively define a change point in the early eGFR evolution to obtain a robust parameter of the baseline kidney function following kidney transplantation. Furthermore, we aim to relate the early evolution of kidney function following transplantation, described in terms of the change point of the kidney function evolution and related slopes, to baseline clinical characteristics and to graft failure after 1-year post-transplantation.

METHODS

Study population and data collection

Adults who received a kidney transplant at the University Hospitals Leuven between March 2004 and February 2013 were eligible for this observational cohort study. Patients had to be under follow-up at 1-year post-transplantation. Recipients of combined transplantation or kidney transplantation after another solid organ transplantation were excluded. Other reasons for exclusion were primary non-function (i.e., permanent dialysis treatment since transplantation), graft loss or death within the first transplant year, and too few eGFR measurements (i.e., <5 measurements during the first month post-transplantation). All transplants were crossmatch negative with the complement-dependent cytotoxicity assay. Clinical data were collected prospectively during routine follow-up and stored in electronic medical records that were linked to an SAS database (SAS Institute). The pre-transplant donor-specific antibody (DSA) status was determined as described in the study by Senev *et al.*[16] This study was approved by the ethical committee of the University Hospitals Leuven (S64006) and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Supplementary Table S1).

There were 2 validation cohorts. The first consisted of 987 transplantations, performed between February 2006 and July 2019 at Leiden University Medical Center in the Netherlands. The second consisted of 519 transplantations, performed between April 2003 and January 2008 at Hannover Medical School in Germany. Data collection and analysis were performed with informed consent of the patients and with approval of the institutional ethics board (Leiden: W2020.031; Hannover: number 2765). Exclusion criteria for the validation cohorts were identical to those for the main cohort.

Determination of kidney function

The level of kidney allograft function was quantified using the estimated glomerular filtration rate (eGFR; estimated using the Modification of Diet in Renal Disease Study equation[17]). These eGFR values were monitored frequently at irregular intervals, during either hospitalization or outpatient clinic visits. Only eGFR values collected during the first year after transplantation were included in this study. Delayed graft function (DGF) was defined as the need for dialysis within the first week after transplantation. Only eGFR values without dialysis reflect the actual kidney function following transplantation. Therefore, the timing and duration of this dialysis treatment were taken into account while assessing associations of the first-year eGFR evolution with recipient-donor characteristics and outcome.

Statistical analysis

The demographics of recipients/donors were summarized by the mean value (with SD), median value and interquartile range (IQR) in case of continuous variables, and frequencies

and proportions in case of categorical variables. The occurrence of graft failure and recipient death (with functioning graft) was described using Aalen-Johansen estimates, to account for competing risks.[18]

To describe the eGFR trajectory in the first year after transplantation, we applied segmented regression for each patient individually.[19] The early, nonlinear evolution of kidney function was modeled by considering 2 distinct phases: an initial period of rapid eGFR increase (starting at eGFR = 0 ml/min per 1.73 m^2) and a stabilizing period (with gradual positive or negative trend). Our model included parameters for the steepness of the initial increase, the timing of the transition to the stabilizing phase (i.e., the change point), and the steepness of the further evolution. The eGFR value at the change point (i.e., the baseline kidney function) was derived from the initial slope and the timing of the change point. In addition, the evolution was modeled using a model with 2 change points, to assess possible benefits of using multiple change points. Model fit was assessed on the basis of a histogram of the subject-specific R^2 values (note that *R* software uses an alternative formula for R^2 for models where the intercept is fixed at 0). Furthermore, segmented regression was applied to simulated eGFR data with a similar trend, spread, and identical timings to the real observations. The estimates for the real and simulated data were compared to assess the sensitivity of the model fit to eGFR fluctuations. More details on this simulation study and on the segmented regression model and its application in *R* software are available in the Supplementary Methods.

For subjects without post-transplant dialysis (or only a single treatment on the first day), all estimates from the segmented regression model were included in further analyses. In case of >1 post-transplant dialysis treatment, the estimate for initial slope did not represent the functioning of the graft itself and was excluded from further analyses. Similarly, the estimates for timing and eGFR value at change point and slope after change point were only included in further analyses if the estimated change point occurred after the last dialysis.

Multiple linear regression was used to describe the association between the early evolution of eGFR (described by natural log of the initial slope, natural log of the timing of change point, eGFR value at change point, and slope after change point) and clinical characteristics: recipient biological sex and age, donor biological sex and age, donor type (living donation, donation after brain death [DBD], and donation after circulatory death [DCD]), repeat transplantation, pretransplant DSA status, number of human leukocyte antigen mismatches on locus A, B, and DR, and cold ischemia time. The most influential variables were identified with a standardized multiple linear regression analysis. The predictive accuracy of these clinical characteristics for the early evolution was assessed using R^2 and mean absolute error values, after the estimates for ($\log_e$-transformed) initial slope and timing of change point were converted to the original scale using the Smearing retransformation method.[20]

Associations of clinical characteristics with the cause-specific graft failure rate were examined using a Cox proportional hazard model (censoring at loss to follow-up or death). Although death with a functioning graft is a competing event for graft failure, competing event models are not appropriate, as this study is not intended to establish a prediction model but the interest is with etiology.[18,21,22] Similarly, we analyzed the association of the initial slope, timing of change point, eGFR value at change point, and slope after change point with the cause-specific rate of graft failure following 1-year post-transplantation, corrected for the occurrence of T cell–mediated rejection (excluding borderline) or antibody-mediated rejection and rejection treatment (i.e., corticosteroids, thymoglobulin, plasmapheresis, and rituximab) during the first year after transplantation. The eGFR value at 1-year post-transplantation was added as a confounder in additional analyses, to examine the prognostic value of the early evolution parameters.

All analyses were performed using R software version 4.3.1. We used 2-sided hypotheses tests and considered $P < 0.05$ as significant.

RESULTS

Cohort characteristics

The main cohort for this study included 922 transplantations, with a median of 8.2 person years of follow-up (IQR, 5.8–10.7 person years). Full details about the cohort characteristics are presented in Figure 1 and Table 1. There was no missingness in the demographic data for the main cohort. Most allografts were DBD (715 of 922, 77.5%), whereas DCD (151 of 922, 16.4%) or donation by a living donor (56 of 922, 6.1%) occurred less frequently. There were 563 male (61.1%) and 359 female (38.9%) recipients, with an average age of 53.3 ± 13.2 years.

Model evaluation

The R^2 of the individual fits of the segmented regression model were consistently high, ranging from 0.84 to 1.00 (median, 0.98; IQR, 0.97–0.99; Figure 2a). The distribution of R^2 values was similar in cases with and without DGF (Supplementary Figure S1). Several examples of observed eGFR evolutions and the corresponding fits from the segmented regression model are presented in Figure 2b through d. Fitting the segmented regression model on simulated data with the same underlying trend and spread as the observed eGFR values resulted in highly similar estimates for the early evolution parameters (Supplementary Figure S2).

With the model with 2 change points, the R^2 values were even higher (median, 0.99; IQR, 0.98–0.99), as expected when using a more flexible model. However, the improvement in model fit was minimal in most cases (median, 0.004; IQR, 0.002–0.009; Supplementary Figure S3). The timing of the second change point proved to be highly heterogeneous, compared with the first change point. In most cases (76.4%), the first change point represented baseline kidney function,

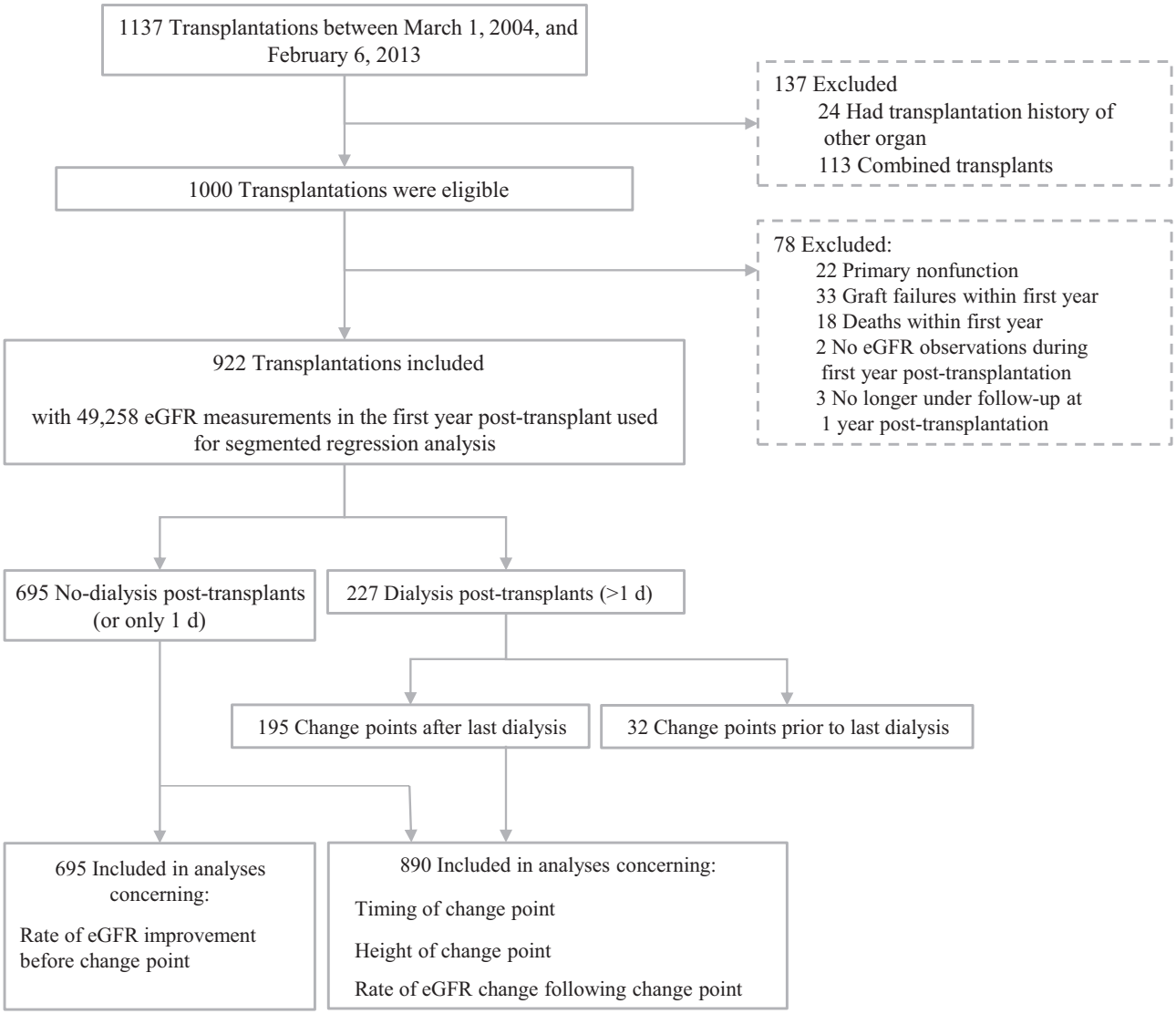

Figure 1 | Flowchart. eGFR, estimated glomerular filtration rate.

and only in few cases (4.9%), it was expressed by the second change point. In 8.4% of cases, both the first and second change point occurred within 7 days of the change point estimated by the single change point model, such that each could represent baseline kidney function. In the remaining 10.3% of cases, neither the first nor the second change point occurred within this time frame. The ambiguous link between these change points and the stabilization of kidney function, and the minimal improvement in model fit, motivated our decision to proceed using the single change point model in further analyses.

Early evolution of kidney function

DGF occurred after 239 of 922 (26.0%) transplants. The median duration of dialysis following transplantation in these recipients was 4 days, and it ranged from a single dialysis session to 7.9 months of treatment (IQR, 2–13 days). Among 227 recipients who received >1 day of dialysis, treatment was ceased before the estimated change point in 195 cases, and after the change point in the remaining 32 cases. The baseline characteristics for the recipients who experienced DGF are described in more detail in Supplementary Table 2.

The median time until change point was 6.5 days (IQR, 3.5–15.8 days; N = 890), and the mean eGFR value at that point was 43.7 ± 14.6 ml/min per 1.73 m^2 (N = 890; Figure 3a–d). Before the change point, the eGFR increased at a median rate of 41.8 ml/min per 1.73 m^2 per week (IQR, 16.8–84.7 ml/min per 1.73 m^2; N = 695). After the change point, the mean change in eGFR was 0.1 ± 0.4 ml/min per 1.73 m^2 per week (N = 890) until 1-year post-transplantation, which indicates stabilization of the kidney function. The relatively broad IQRs and high SDs demonstrate the heterogeneity of eGFR evolutions during the first-year post-transplantation.

Table 1 | Cohort characteristics: demographic and clinical characteristics of the main cohort from Leuven and the validation cohorts from Leiden and Hannover

Characteristics	Leuven cohort (N = 922)	Leiden cohort (N = 987)	Hannover cohort (N = 519)
Recipients			
Sex, n (%)			
Male	563 (61.1)	627 (63.5)	299 (57.6)
Female	359 (38.9)	360 (36.5)	220 (42.4)
Age, yr, mean ± SD	53.3 ± 13.2	53.3 ± 13.5	49.9 ± 12.9
Repeat transplantation, n (%)	137 (14.9)	120 (12.2)	64 (12.3)
Body mass index, kg/m^2, mean ± SD	25.4 ± 4.5	26.6 ± 4.7	24.4 ± 3.6
Cold ischemia time, h, mean ± SD	14.2 ± 5.7	8.3 ± 6.0	13.6 ± 7.2
A-B-DR mismatches, mean ± SD	2.7 ± 1.3	3.1 ± 1.5	2.4 ± 1.8
Delayed graft function, n (%)	239 (25.9)	267 (27.1)	143 (27.6)
Dialysis pre-transplant, n (%)	895 (97.1)	718 (72.7)	499 (96.1)
Dialysis post-transplant, n (%)			
Yes, started during first week	239 (25.9)	–	143 (27.6)
Yes, started after first week	2 (0.2)	–	0 (0)
No	681 (73.9)	–	376 (72.4)
Pretransplant DSA, n (%)			
Positive	96 (10.4)	47 (4.8)	–
Negative	826 (89.6)	940 (95.2)	–
Ethnicity			
Caucasian	906 (98.3)	–	–
African	12 (1.3)	–	–
Asian	3 (0.3)	–	–
Hispanic	1 (0.1)	–	–
Donors			
Sex, n (%)			
Male	493 (53.5)	488 (49.4)	278 (53.6)
Female	429 (46.5)	499 (50.6)	241 (46.4)
Age, yr, mean ± SD	47.5 ± 14.7	53.4 ± 13.2	49.1 ± 14.8
Type, n (%)			
Living donor	56 (6.1)	479 (48.5)	86 (16.6)
Donation after brain death	715 (77.5)	232 (23.5)	433 (83.4)
Donation after circulatory death	151 (16.4)	276 (28.0)	0 (0)
Graft failure, %[a]			
At 2 yr	1.2	1.0	3.5
At 3 yr	2.7	2.2	5.4
At 6 yr	7.3	5.8	9.0
Death with functioning graft, %[a]			
At 2 yr	1.6	1.5	1.9
At 3 yr	3.7	2.8	4.5
At 6 yr	11.8	8.2	6.5
Follow-up after transplantation			
No. of eGFR measurements within the first-year post-transplant			
Total	49,258	35,857	21,447
Minimum	25	16	10
Median	49	32	36
p25–p75	41–61	27–41	29–48
Maximum	202	177	147

–, not available; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; p25, 25th percentile; p75, 75th percentile.
[a]Aalen-Johansen estimate of the proportion of recipients who experienced the event of interest, up to selected time points.

Effect of recipient/donor demographics on early evolution

Next, we evaluated the clinical determinants of the parameters of the change point (Tables 2 and 3; Supplementary Figures S4 and S5). The change point occurred later in male recipients (male: 14.4 ± 18.7 days; female: 11.8 ± 16.5 days; $P = 0.001$; Table 2), whereas in female donors, it

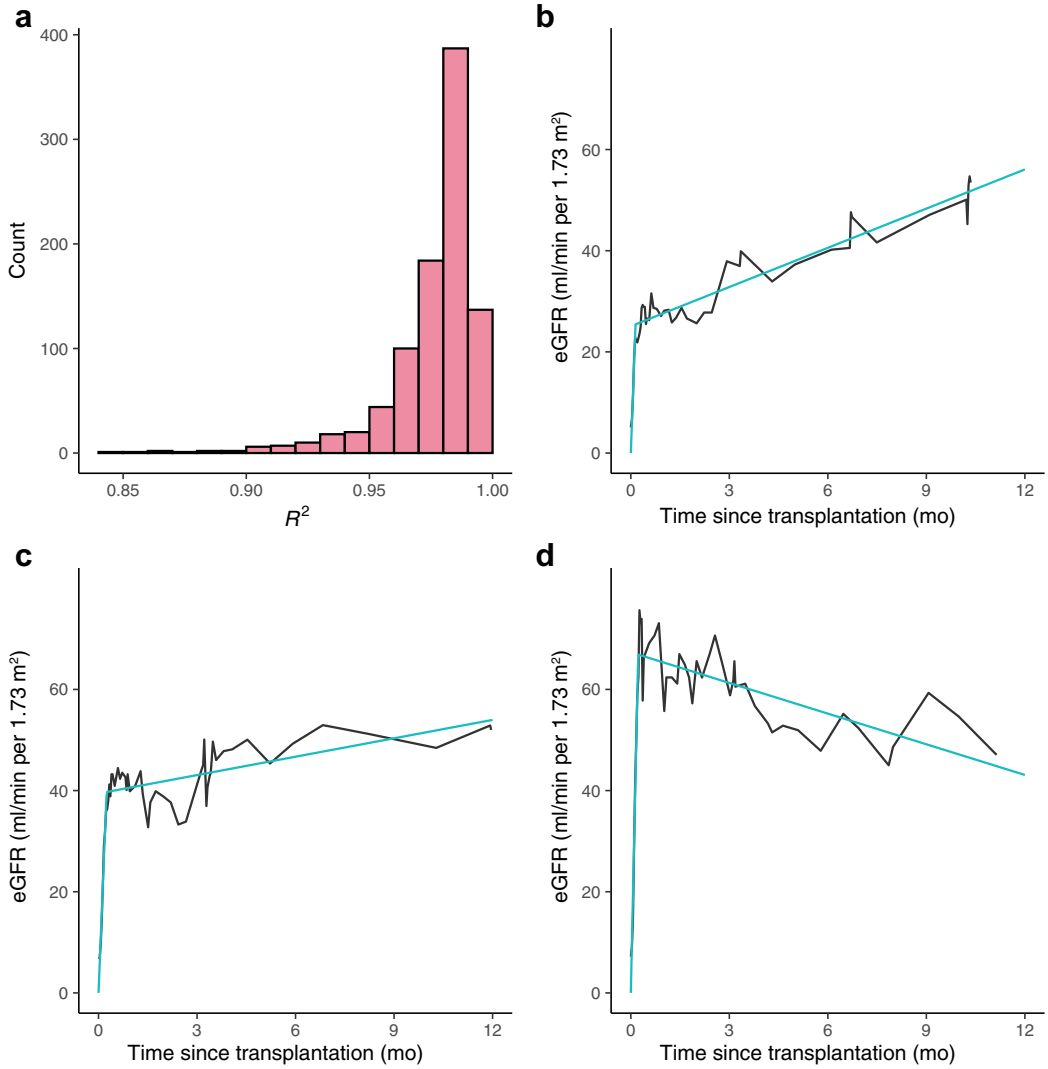

Figure 2 | Goodness of fit for segmented regression models. (a) Histogram of the R^2 values corresponding to the fits of the segmented regression models on the individual estimated glomerular filtration rate (eGFR) evolutions ($N_{total} = 922$). (**b–d**) Examples of the eGFR evolution (black curve) observed in a recipient were randomly selected from the data set. The fitted curves from the segmented regression model (blue curves) capture the general shape of the eGFR evolutions: the initial, strong rise, followed by a phase with fluctuating, but overall more stable, eGFR values.

occurred at a lower eGFR value (male: 45.8 ± 15.1 ml/min per 1.73 m^2; female: 41.7 ± 13.6 ml/min per 1.73 m^2; $P <$ 0.001). Increasing donor and recipient age had a negative effect on the initial increase of eGFR, and on the eGFR value at the time of the change point (donor age: –3.4 ml/min per 1.73 m^2 per 10 years; 95% confidence interval [CI], –4.0 to –2.8 ml/min per 1.73 m^2 per 10 years; $P < 0.001$; recipient age: –1.8 ml/min per 1.73 m^2 per 10 years; 95% CI, –2.6 to –1.1 ml/min per 1.73 m^2 per 10 years; $P < 0.001$). After the change point, older recipients tended to have a positive effect on the eGFR change (0.04 ml/min per 1.73 m^2 per week, per 10 years; 95% CI, 0.02–0.06 ml/min per 1.73 m^2 per week, per 10 years; $P < 0.001$), whereas older donors tended to have a negative effect on the eGFR change (–0.02 ml/min per 1.73 m^2 per week, per 10 years; 95% CI, 0.04 to –0.01 ml/min per 1.73 m^2 per week, per 10 years; $P = 0.012$).

Different aspects of early evolution were affected by donor type. The initial rate of eGFR improvement was markedly higher in cases with a living donor, compared with donation after brain death (living: 146.4 ± 67.6 ml/min per 1.73 m^2 per week; DBD: 61.3 ± 45.1 ml/min per 1.73 m^2 per week; $P < 0.001$). Hence, the change point occurred earlier (living: 5.5 ± 10.3 days; DBD: 12.7 ± 16.6 days; $P < 0.001$) and at a higher eGFR value (living: 54.3 ± 14.7 ml/min per 1.73 m^2; DBD: 43.4 ± 14.4 ml/min per 1.73 m^2; $P < 0.001$) in case of a living donor. In contrast, the change point occurred later in case of DCD (19.3 ± 23.7 days; $P = 0.002$) compared with DBD. After the change point, the rate of change tended to be more negative with a living donor (–0.3 ml/min per 1.73 m^2 per month; 95% CI, –0.4 to –0.2 ml/min per 1.73 m^2 per month; $P < 0.001$). Living donation (compared with donation after brain death) proved to have

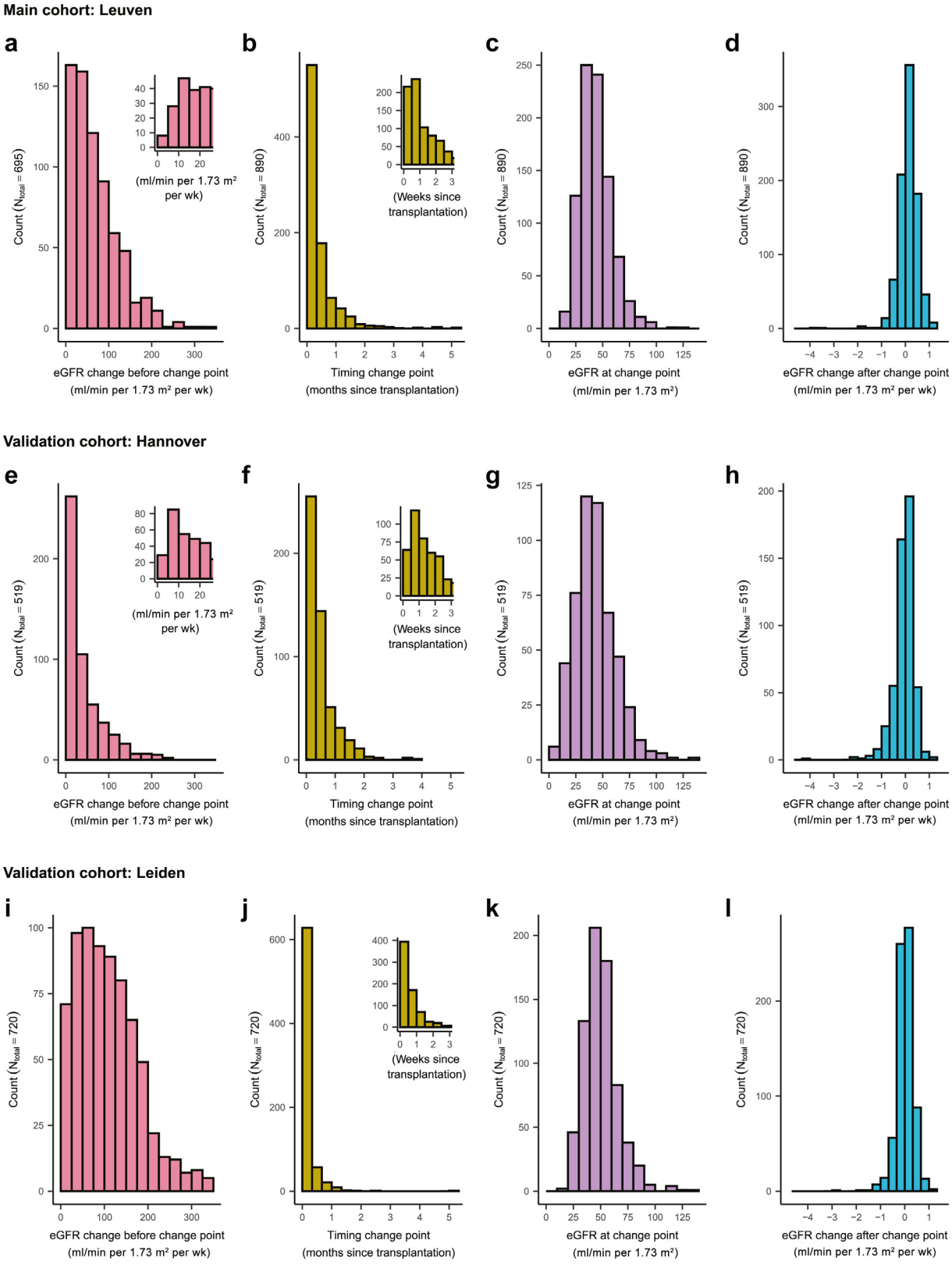

Figure 3 | Estimated values for first-year estimated glomerular filtration rate (eGFR) evolution descriptors. Distributions of estimated values for each of the early evolution descriptors. For the main cohort from Leuven: (**a**) timing of the change point, (**b**) eGFR value at change point, (**c**) slope before change point, and (**d**) slope after change point. For the validation cohort from Hannover: (**e**) timing change point, (**f**) eGFR value at change point, (**g**) slope before change point, and (**h**) slope after change point. For the validation cohort from Leiden: (**i**) timing change point, (**j**) eGFR value at change point, (**k**) slope before change point, and (**l**) slope after change point. These estimates are based on individual fits of the segmented regression model.

Table 2 | Clinical determinants of the first-year eGFR evolution after kidney transplantation (univariate)

	Timing change point, mo since transplantation (N = 890)[a]		eGFR at change point, ml/min per 1.73 m^2 (N = 890)		eGFR change before change point, ml/min per 1.73 m^2 per wk (N = 695)[a]		eGFR change after change point, ml/min per 1.73 m^2 per wk (N = 890)	
Parameter	**Estimate β (95% CI)**	***P***	**Estimate β (95% CI)**	***P***	**Estimate β (95% CI)**	***P***	**Estimate β (95% CI)**	***P***
Demographics								
Sex recipient (male = 1)	0.21 (0.08 to 0.34)	0.001	0.92 (−1.05 to 2.89)	0.361	−0.10 (−0.24 to 0.04)	0.155	0.02 (−0.04 to 0.08)	0.483
Sex donor (male = 1)	0.05 (−0.08 to 0.17)	0.478	4.07 (2.17 to 5.98)	<0.001	0.11 (−0.03 to 0.24)	0.111	0.05 (−0.00 to 0.11)	0.053
Age recipient (decades)	0.05 (−0.00 to 0.10)	0.053	−1.85 (−2.56 to −1.13)	<0.001	−0.08 (−0.13 to −0.03)	0.002	0.04 (0.02 to 0.06)	<0.001
Age donor (decades)	0.03 (−0.02 to 0.07)	0.247	−3.39 (−4.01 to −2.78)	<0.001	−0.10 (−0.15 to −0.06)	<0.001	−0.02 (−0.04 to −0.01)	0.012
Compared with donation after brain death:								
Donation after circulatory death	0.26 (0.09 to 0.42)	0.002	−0.79 (−3.34 to 1.76)	0.544	−0.11 (−0.28 to 0.07)	0.246	0.02 (−0.05 to 0.09)	0.606
Living donor	−0.91 (−1.17 to −0.65)	<0.001	10.99 (6.98 to 15.00)	<0.001	1.00 (0.75 to 1.25)	<0.001	−0.32 (−0.43 to −0.21)	<0.001
Cold ischemia time (per 5 h)	0.16 (0.09 to 0.23)	<0.001	−1.16 (−2.20 to −0.12)	0.030	−0.13 (−0.20 to −0.06)	<0.001	0.03 (−0.00 to 0.06)	0.073
Repeated transplantation	0.10 (−0.08 to 0.28)	0.279	3.07 (0.36 to 5.78)	0.026	0.14 (−0.07 to 0.34)	0.191	−0.09 (−0.16 to −0.01)	0.031
Pre-transplant DSA status	0.37 (0.16 to 0.57)	0.001	−0.73 (−3.89 to 2.44)	0.651	−0.20 (−0.44 to 0.04)	0.096	−0.06 (−0.15 to 0.03)	0.171
A-B-DR antigen mismatches	−0.02 (−0.06 to 0.03)	0.542	−0.64 (−1.38 to 0.10)	0.091	0.03 (−0.02 to 0.08)	0.200	−0.01 (−0.03 to 0.01)	0.513

CI, confidence interval; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate.
[a]Log_e transformed.
Effect of baseline donor/recipient characteristics on the early evolution descriptors was calculated using simple linear regression models.

Table 3 | Clinical determinants of the first-year eGFR evolution after kidney transplantation (multivariable)

	Timing change point, mo since transplantation (N = 890)[a]		eGFR at change point, ml/min per 1.73 m^2 (N = 890)		eGFR change before change point, ml/min per 1.73 m^2 per wk (N = 695)[a]		eGFR change after change point, ml/min per 1.73 m^2 per wk (N = 890)	
Parameter	**Estimate β (95% CI)**	***P***	**Estimate β (95% CI)**	***P***	**Estimate β (95% CI)**	***P***	**Estimate β (95% CI)**	***P***
Demographics								
Sex recipient (male = 1)	0.27 (0.14 to 0.39)	<0.001	0.60 (−1.23 to 2.42)	0.522	−0.15 (−0.28 to −0.02)	0.023	0.02 (−0.04 to 0.07)	0.548
Sex donor (male = 1)	−0.01 (−0.13 to 0.12)	0.903	3.23 (1.43 to 5.03)	<0.001	0.13 (0.00 to 0.26)	0.045	0.03 (−0.03 to 0.09)	0.281
Age recipient (decades)	−0.01 (−0.06 to 0.04)	0.761	−0.26 (−0.99 to 0.46)	0.481	0.02 (−0.04 to 0.07)	0.536	0.04 (0.01 to 0.06)	0.001
Age donor (decades)	0.04 (−0.01 to 0.08)	0.089	−3.20 (−3.84 to −2.56)	<0.001	−0.11 (−0.16 to −0.07)	<0.001	−0.03 (−0.05 to −0.01)	0.002
Compared with donation after brain death:								
Donation after circulatory death	0.30 (0.13 to 0.46)	<0.001	−2.30 (−4.70 to 0.11)	0.061	−0.18 (−0.36 to −0.01)	0.041	0.01 (−0.06 to 0.08)	0.806
Living donor	−0.94 (−1.21 to −0.67)	<0.001	11.68 (7.75 to 15.60)	<0.001	1.06 (0.80 to 1.32)	<0.001	−0.26 (−0.38 to −0.14)	<0.001
Repeated transplantation	−0.02 (−0.21 to 0.17)	0.843	2.23 (−0.51 to 4.97)	0.110	0.17 (−0.03 to 0.38)	0.097	−0.07 (−0.15 to 0.01)	0.101
Pre-transplant DSA status	0.45 (0.23 to 0.66)	<0.001	−1.53 (−4.71 to 1.65)	0.345	−0.33 (−0.57 to −0.09)	0.007	−0.03 (−0.12 to 0.07)	0.610
A-B-DR antigen mismatches	−0.01 (−0.06 to 0.04)	0.735	−0.09 (−0.79 to 0.61)	0.800	0.04 (−0.01 to 0.09)	0.103	0.00 (−0.02 to 0.02)	0.850
R^2	0.10		0.17		0.14		0.06	
Adjusted R^2	0.09		0.16		0.13		0.05	
Mean absolute error[b]	0.34		10.27		37.36		0.27	
Median absolute error[b]	0.25		8.44		31.53		0.20	

CI, confidence interval; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate.
[a]Log_e transformed.
[b]The residuals were defined as the difference between the observed value and the predicted value, both on the original scale. In case of log_e-transformed outcomes, this predicted value was derived from the predicted value on the log_e scale, using the Smearing retransformation.[20]
Effect of baseline donor/recipient on the early evolution descriptors was calculated using multiple linear regression models.

the most influential effect in the association between clinical characteristics and each of the early evolution parameters (Supplementary Table S3).

Longer cold ischemia time was associated with slower initial improvement of kidney function, later change point, and lower eGFR value at the change point (–1.2 ml/min per 1.73 m^2 per 5 hours; 95% CI, –2.2 to –0.1 ml/min per 1.73 m^2 per 5 hours; $P = 0.030$). The change point also occurred later in recipients with positive pre-transplant DSA status (DSA positive: 18.2 ± 20.3 days; DSA negative: 12.9 ± 17.5 days; $P < 0.001$) and after delayed graft function (DGF: 33.0 ± 25.9 days; no DGF: 9.7 ± 13.0 days; $P < 0.001$), which was also associated with a lower eGFR at change point (DGF: 38.0 ± 13.6 ml/min per 1.73 m^2; no DGF: 45.0 ± 14.5 ml/min per 1.73 m^2; $P < 0.001$). After repeat transplantation, higher eGFR values were observed at the change point (repeat transplant: 46.5 ± 16.1 ml/min per 1.73 m^2; no repeat transplant: 43.4 ± 14.3 ml/min per 1.73 m^2; $P = 0.026$), whereas subsequent eGFR values tended to increase less (repeat transplant: 0.05 ± 0.40 ml/min per 1.73 m^2 per week; no repeat transplant: 0.13 ± 0.42 ml/min per 1.73 m^2 per week; $P = 0.031$).

We performed sensitivity analyses, where the segmented regression models were fitted on eGFR observations up to 6 months post-transplantation. The results of these analyses were highly similar to the main results (Supplementary Tables S4 and S5).

Prediction of change point from baseline donor-recipient characteristics

When predicting the expected values for the early evolution parameters based on baseline donor-recipient characteristics, the R^2 values were low, ranging from 0.06 to 0.17 (Table 3). The mean absolute error for the timing of the change point was 10.5 days (Supplementary Figure S6), which is relatively large, considering its median of 6.5 days (IQR, 3.5–15.8 days). The mean absolute error for the initial rate of eGFR improvement was 37.4 ml/min per 1.73 m^2 per week; for the eGFR value at change point, 10.3 ml/min per 1.73 m^2; and for eGFR change after the change point, 0.3 ml/min per 1.73 m^2 per week. Despite the significant associations described in the previous subsection, the different aspects of the early evolution could not be predicted with high precision, based on the baseline donor-recipient characteristics. For example, there was much more heterogeneity among the values estimated by the segmented regression model, compared with the values predicted by the multiple linear regression model (Supplementary Figure S7).

Effect of early evolution on graft failure

At 6 years post-transplantation, 7.3% of recipients were estimated to have experienced graft failure (Table 1; Supplementary Figure S8). Associations of graft failure with clinical characteristics of recipient and donor are described in Supplementary Table S6. A higher eGFR value at the change point (hazard ratio, 0.72 per 10 ml/min per 1.73 m^2 increase; 95% CI, 0.62–0.84 per 10 ml/min per 1.73 m^2 increase; $P < 0.001$) related to a lower rate of graft failure. A more rapid increase of kidney function after the change point related to a lower rate of graft failure (hazard ratio, 0.36 per ml/min per 1.73 m^2 increase per week; 95% CI, 0.25–0.52 per ml/min per 1.73 m^2 increase per week; $P < 0.001$). In addition, the rate of graft failure was higher when the change point was reached later (hazard ratio, 1.08 per additional week until change point; 95% CI, 1.03–1.14 per additional week until change point; $P = 0.004$; Table 4). When included as a confounding variable, eGFR at 1-year post-transplantation was significant, whereas the early evolution parameters were no longer significant (Supplementary Table S7). Within the recipients with an eGFR <60 ml/min per 1.73 m^2 at the change point, further change in eGFR by 1-year post-transplantation was heterogeneous, ranging from –29.9 to 57.6 ml/min per 1.73 m^2 (median, 6.3 ml/min per 1.73 m^2; IQR, –0.5 to 13.1 ml/min per 1.73 m^2). Although the exclusion of recipients who experienced graft failure within the first year biased these results toward cases with a more beneficial eGFR evolution, this suggests that a slower initial eGFR increase did not necessarily result in a worse prognosis.

Similar results were found in a sensitivity analysis, where the segmented regression models were fitted on eGFR observations up to 6 months post-transplantation (Supplementary Table S8).

Table 4 | Association between first-year eGFR evolution and graft failure rate after 1-year post-transplant

	Univariate		Multivariable (corrected for baseline variables[a])	
Parameter	HR (95% CI)	*P*	HR (95% CI)	*P*
Timing change point (wk)	1.08 (1.03–1.14)	0.003	1.08 (1.02–1.14)	0.006
eGFR value at change point (per 10-ml/min per 1.73 m^2 increase)	0.74 (0.63–0.86)	<0.001	0.76 (0.64–0.89)	0.001
eGFR change before change point (per 10-ml/min per 1.73 m^2 increase per wk)	0.96 (0.92–1.01)	0.090	0.96 (0.91–1.01)	0.138
eGFR change after change point (per ml/min per 1.73 m^2 increase per wk)	0.36 (0.25–0.52)	<0.001	0.36 (0.24–0.53)	<0.001

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]Multivariable models were corrected for donor and recipient sex, donor and recipient age, donor type (donation after brain death, donation after circulatory death, or living donor), repeat transplantation, pretransplant donor-specific antibody status, and number of human leukocyte antigen-A-B-DR mismatches.
The effect of change point characteristics on the rate of graft failure was assessed using univariate and multivariate Cox regression models. Only graft failure events that occurred later than 1 year after transplantation were considered. These estimates were all corrected for the effects of acute rejection (T cell–mediated rejection, antibody-mediated rejection) and treatment (corticosteroids, thymoglobulin, plasmapheresis, and rituximab) during the first-year post-transplantation. On the basis of visual inspection of the scaled Schoenfeld residuals and formal proportional hazards checks (not reported), the proportional hazards assumption was not violated in any of these models.

Validation of results

Cohort characteristics of the validation cohorts were mostly similar to those of the main cohort (Table 1). There was no missingness in the data regarding the validation cohorts, except for pre-transplantation DSA status (unavailable for the Hannover cohort), data regarding post-transplant dialysis (unavailable for the Leiden cohort), and rejection and rejection treatment (unavailable for both validation cohorts). There was a notable difference regarding donor type, with more living donors in Leiden (48.5%; compared with 16.6% in Hannover and 6.1% in Leuven). Because of legal restrictions, donation after circulatory death is not performed in Germany.

In the Hannover cohort, 143 of 519 recipients experienced DGF. In case of post-transplant dialysis, selected estimates for initial slope, timing of change point, eGFR value at change point, and slope after change point were excluded from further analyses, as described in the Methods section. In the Leiden cohort, 267 of 987 recipients experienced DGF. As data regarding post-transplant dialysis were unavailable for this cohort, all recipients with DGF were excluded when assessing the associations with baseline donor-recipient characteristics and graft outcome. The baseline characteristics for the recipients who experienced DGF are described in more detail in Supplementary Table S2.

The R^2 values for the segmented regression models, fitted on the eGFR evolutions, were consistently high for both validation cohorts (Leiden: median, 0.98; IQR, 0.97–0.99; Hannover: median, 0.98; IQR, 0.96–0.99; Supplementary Figure S9). The estimates for the early evolution parameters showed a similar distribution, compared with the estimates in the main cohort (Figure 3), especially after stratification based on donor type (Figure 4). Furthermore, regarding the associations of the early evolution parameters with recipient/donor characteristics (Supplementary Figure S10) and graft failure rate (Supplementary Figure S11), the results for the main cohort and the validation cohorts were similar.

DISCUSSION

In this article, we modeled the initial increase and subsequent stabilization of eGFR following transplantation using segmented regression. The eGFR value at the change point determined with this method could serve as "baseline eGFR," a useful reference value when gauging changes in eGFR following kidney transplantation. The aptness of the segmented regression model was exemplified by R^2 values, which were consistently high across all individual model fits (ranging from 0.84 to 1.00). Furthermore, a simulation study showed that the parameter estimates were robust, despite (in some cases strong) eGFR fluctuations around the general trajectory. The timing of the transition between these 2 phases showed a highly skewed distribution. This change point occurred at a median of 6.5 days, with a range between 3.5 and 15.8 days (IQR) for most patients. The distribution of the initial rates of eGFR increase was similarly skewed, ranging from 2.8 to 348.1 ml/min per 1.73 m^2 increase per week, with the most common increase being 25.1 ml/min per 1.73 m^2 increase per week. Note that cases with DGF (whose initial eGFR increase was affected by dialysis treatment) were not included in this calculation of the initial eGFR slopes. Stabilization of eGFR happened at a wide range of values, symmetrically distributed around 43.7 ml/min per 1.73 m^2. Changes ranging from –0.5 to 0.7 ml/min per 1.73 m^2 per week (at the 5th and 95th percentile, respectively) were observed afterwards. These aspects of early eGFR evolution were associated with several recipient/donor characteristics, and the immunologic risk assessed by pretransplant DSA status. Although these associations were highly statistically significant, the high variability in eGFR evolution within patients with similar characteristics resulted in a poor prediction of the early evolution based on baseline demographics. Change point timing, eGFR at the change point, and eGFR change following the change point were associated with the graft failure rate following 1-year post-transplantation. However, these significant associations did not hold after correcting for eGFR at 1-year post-transplantation, indicating that the most recently observed eGFR values had the most prognostic value for (short-term) graft failure.

Our segmented regression model is a tool for objective calculation of baseline kidney function, of potential relevance for other studies. The segmented regression models describing the early eGFR evolution showed excellent goodness of fit in multiple cohorts, with easily interpretable output. Note that the model assumption of eGFR $= 0$ at time of transplantation did not hold in case of preemptive transplantation (27/922 recipients in the main cohort). However, we found that models with a freely estimated intercept mistakenly recognized strong fluctuations later during eGFR evolution as the change point. Hence, we recommend using the model with intercept fixed at 0 after preemptive transplantation as well.

The initial evolution of eGFR did not necessarily imply a change in the functioning of the kidney allograft. The initial increase of eGFR might have reflected the removal of a surplus of creatinine, built up before transplantation. Longer cold ischemia times were related to a slower and smaller initial improvement of eGFR, suggesting involvement of perioperative damage. Our study indicates, however, that this initial evolution of eGFR was also related to donor characteristics, as indicated by the association with donor type, sex, and age, factors that reflect the kidney function before donation. These associations provide explanations for cases where eGFR values increased slower than expected. For example, higher donor age was related to a slower eGFR improvement before stabilization, and a tendency toward a decline in eGFR afterwards. This is reminiscent of earlier studies, which showed a negative effect of higher donor age (in living donors) on recipient baseline eGFR[23,24] and risk of graft failure.[25,26] The more beneficial early evolution after donation from a male donor could be expected, as the larger size of the allograft corresponds to a greater filtering capacity. Early eGFR evolution was most favorable in case of a living donor (which proved to be the most influential factor affecting early eGFR evolution), and

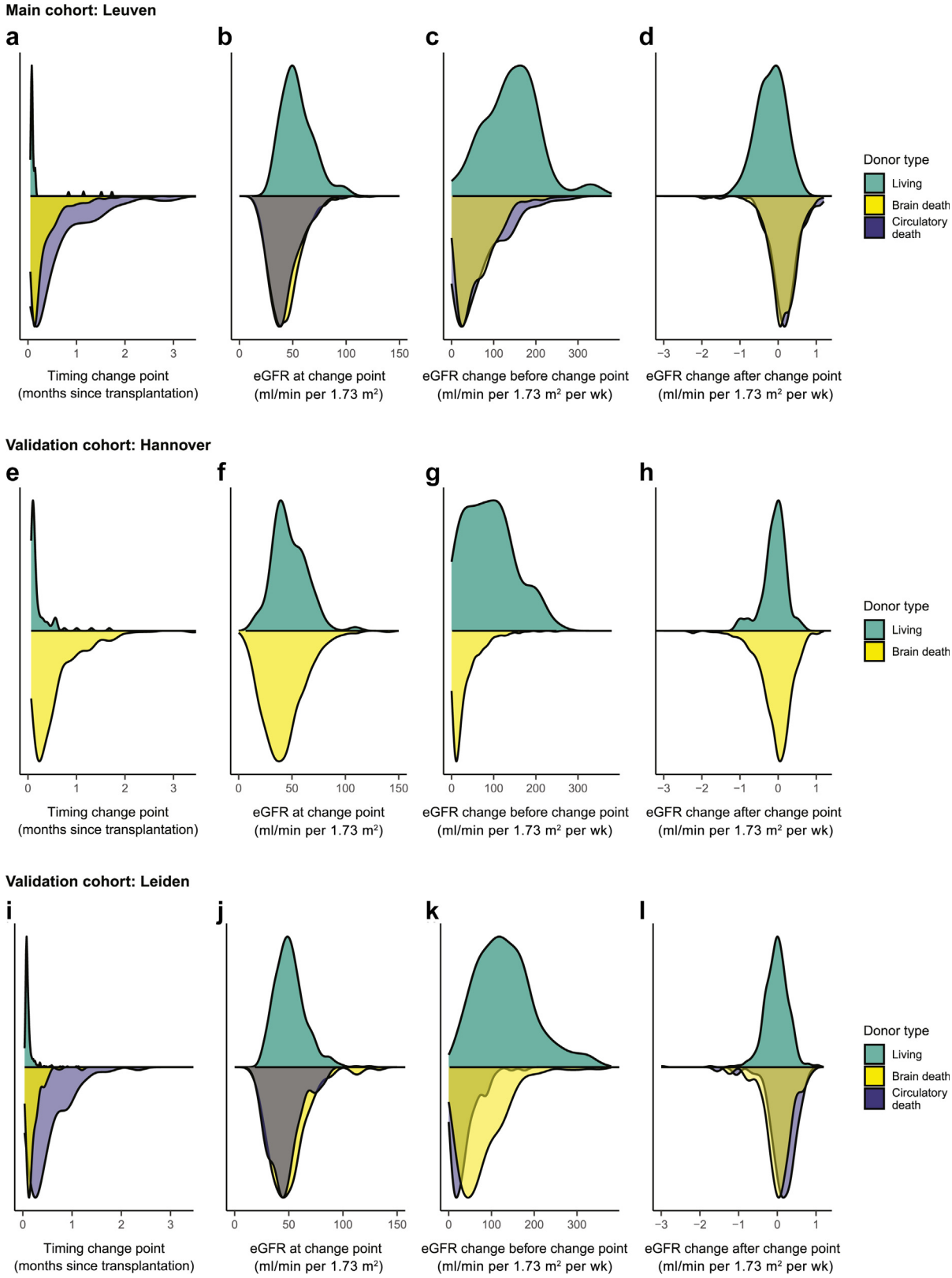

Figure 4 | Associations between donor type and first-year estimated glomerular filtration rate (eGFR) evolution in different cohorts. Densities of estimated values for early evolution descriptors, stratified by donor type. For the main cohort from Leuven: (**a**) timing of the change point, (**b**) eGFR value at change point, (**c**) slope before change point, and (**d**) slope after change point. For the validation cohort from Hannover: (**e**) timing change point, (**f**) eGFR value at change point, (**g**) slope before change point, and (**h**) slope after change point. For the validation cohort from Leiden: (**i**) timing change point, (**j**) eGFR value at change point, (**k**) slope before change point, and (**l**) slope after change point. These plots show the similarities between the different cohorts, with regard to the distributions of the early evolution descriptors.

least in case of a DCD donor. Earlier studies have reported about this less favorable early evolution with a DCD donor compared with a DBD donor.[27]

Despite statistically significant associations between demographics and the different aspects of early eGFR evolution, this early evolution could not be predicted accurately. The variation in eGFR trajectories within groups of patients with similar demographics was larger than the variation between groups, such that there were no "defining features" that permitted accurate prediction. These baseline characteristics cannot account for all possible scenarios of the post-transplantation eGFR evolution, as other factors, like rejection, concomitant drugs (e.g., calcineurin inhibitors, cotrimoxazole), infections, and urological and surgical complications, can affect serum creatinine and graft function.

This large heterogeneity in eGFR trajectories during the first-year post-transplantation has important implications for the prognosis of kidney transplant function. The early evolution parameters showed less prognostic value for graft failure (occurring after 1-year post-transplantation) than the eGFR value at 1-year post-transplantation. However, changes between eGFR at the change point and at 1-year post-transplantation were heterogeneous, in particular when the change point was reached within the first month after transplantation. This suggests that a suboptimal initial eGFR evolution does not necessarily imply a worse outcome, which is an important message to share with kidney recipients.

Our study has some limitations. In our analyses, we used a 2-stage approach, where estimates from segmented regression models were considered fixed in subsequent analyses. This resulted in a minor underestimation of the SEs in the linear and Cox regression models. Bayesian methods allow for propagation of the uncertainty around the segmented regression estimates into subsequent analyses but would have required proper specification of the prior information on the change point. In addition, we had to exclude cases of graft failure or recipient death within the first year after transplantation. The applied methods required a sufficient duration of follow-up, such that the characteristic increase-stabilization pattern of the eGFR observations could be perceived and modeled. A shorter period of follow-up was applied as a sensitivity analysis, but this did not affect our conclusions, indicating their robustness. The cohorts included in this study were highly homogeneous with regard to ethnicity. Further validation in more diverse populations is required to support the general use of this method.

In conclusion, we defined and independently validated the timing and height of the change point in the early eGFR evolution, along with the rates of eGFR change before and after this change point during the first-year post-transplantation. All were related to recipient/donor demographics (in particular donor type), immunologic risk, and graft outcome. Although the characteristics of the change point significantly associated with pretransplant factors and can help explain clinical cases, the change point could not be predicted accurately from these pretransplant factors. Considerable heterogeneity within the observed eGFR trajectories indicated that favorable levels of kidney function could be reached despite a suboptimal initial evolution. Primarily, the segmented regression model to calculate the change point and the eGFR at the change point (baseline kidney function) could serve as a useful reference in future research.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

The code for the segmented regression model is documented in the Supplementary Methods. The Clinical Trial Center and the Ethics Committee Research of University Hospitals Leuven restrict sharing of clinical data, as these are confidential and are subject to General Data Protection Regulation. A request for access to the data used in this study can be sent to the corresponding author, MN.

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AUTHOR CONTRIBUTIONS

EC, MC, and MN designed the study. EC, MC, JC, M-PE, DK, AS, EVL, KW, MN, WG, IS, APJdV, SM, and JK were involved in data collection and curation. EC performed all analysis with input from MC, GV, and MN. EC and MN wrote the manuscript, which was revised by all coauthors.

Supplementary material is available online at www.kidney-international.org.

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