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Association Between Deceased Donor Acute Kidney Injury Assessed Using Baseline Serum Creatinine Back-Estimation and Graft Survival: Results From the French National CRISTAL Registry

Rémi Lenain¹ MD, Camille Prouteau¹ MD, Aghilès Hamroun¹ MD, Yohann Foucher^{2,3} PhD, Magali Giral⁴ PhD, Mehdi Maanaoui^{1,5} MD, and Marc Hazzan¹ PhD, on behalf of the Contributors to the CRISTAL National Registry

1. Department of Nephrology, Lille University Hospital, Lille, France
2. INSERM UMR 1246 - SPHERE, University of Nantes, Tours University, Nantes, France
3. Nantes University Hospital, Nantes, France
4. CRTI UMR 1064, Inserm, Université de Nantes; ITUN, CHU Nantes; RTRS Centaure, Nantes, France
5. University of Lille, INSERM U1190, Translational Research for Diabetes, Lille, France

Address for correspondence: Rémi Lenain, Department of Nephrology, Lille University Hospital, 59037 Lille, France

Email: remi.lenain@chru-lille.fr

ORCID ID: RL: 0000-0001-6317-9763; YF: 0000-0003-0330-7457

Abstract

Rationale & Objective: While deceased donor acute kidney injury (AKI) frequently leads to kidney discards, its impact on long-term graft survival in kidney transplant recipients remains unclear. We investigated the association between deceased donor AKI assessed using back-estimation of baseline serum creatinine (Scr) and graft survival.

Study Design: Observational cohort study.

Setting & Participants: Adult patients represented within the French CRISTAL registry who received a single kidney allograft from brain-dead deceased donors between January 2006 and December 2017.

Exposure: A back-estimated MDRD Study equation-derived Scr baseline value was derived for an assumed glomerular filtration rate at 75 mL/min/1.73 m². A refined classification system for donor AKI was implemented as follows: no AKI, undetermined AKI/chronic kidney disease (CKD), recovery from AKI, and ongoing AKI.

Outcome: Death-censored graft survival.

Analytical Approach: Multivariable Cox models using a robust variance estimator for paired kidneys from the same donor.

Results: 26,786 recipients were classified as follows: no-AKI (n=19,276); undetermined AKI/CKD (n=1745); recovery from AKI (n=2392); and ongoing AKI (n=3373). We observed 4458 kidney graft losses during a median follow-up of 5.7 years. Compared to no-AKI, deceased donor ongoing AKI was associated with an increased risk of graft failure (HR=1.24, 95%CI: 1.13–1.35). The HRs for graft failure in the undetermined AKI/CKD (HR=1.18,

95%CI: 1.06–1.31) and recovery from AKI (HR=1.18, 95%CI: 1.06–1.31) groups were similar to that observed in the ongoing AKI group. The adverse effect of deceased donor AKI was no longer evident when relying either on the admission or the lowest SCr level throughout the procurement procedure as baseline SCr value.

Limitations: No measurement of urine output in donors.

Conclusions: Deceased donor ongoing AKI, undetermined AKI/CKD, and recovery from AKI according to back-estimated baseline Scr are associated with decreased graft survival. The definition of baseline Scr as the first value measured on admission would have led to a misclassification bias and erroneous estimates.

Keywords: acute kidney injury, graft survival, kidney transplantation, clinical epidemiology, kidney failure, acute kidney failure

Plain language summary

Although deceased-donor acute kidney injury (AKI) portends an increased risk of delayed graft function in the short term, its impact on long-term graft survival is a matter of ongoing debate. Most of the existing studies did not show any association between donor AKI and graft survival. By refining donor AKI classification in accordance with international guidelines, we found that not only ongoing donor AKI but also the presence of at least one abnormal serum creatinine value during procurement were associated with lower graft survival in kidney transplant recipients.

1. Introduction

While the transplant community continues to be faced by an undeniable organ shortage, the discard of procured deceased donor kidneys has been growing steadily.¹ The discard rate of deceased donor kidneys in the USA has reached 19% in 2018, being twice as high as it is in France.²⁻⁴ Renal failure during organ procurement has a serious adverse impact on discard rates, with >30% of discarded organs being from donors with a last measured serum creatinine (SCr) value >1.5 mg/dL⁵. A recent study documented an independent association between deceased donor acute kidney injury (AKI) – defined in accordance with the AKI Network criteria⁶ – and an increased risk of kidney discard, which was noticeably AKI stage-dependent.⁷ Such increased discard rates are inconsistent with the recent literature that does not clearly support a deleterious effect of AKI on kidney allograft outcomes. Indeed, although deceased donor AKI portends an increased risk of delayed graft function in the short term,⁸ its impact on long-term graft survival remains a matter of ongoing debate. According to a registry study from the UK,⁹ donor AKI is associated with a reduced graft survival at one year post-transplantation. However, two recent studies based on data from USA registries showed that donor AKI did not give rise to any deleterious effect on long-term graft survival.^{10,11} Inconsistencies in defining AKI may have contributed to the seemingly conflicting literature. The Kidney Diseases Improving Global Outcomes (KDIGO) guidelines define AKI by an absolute increase of ≥ 0.3 mg/dL or a $\geq 50\%$ increase in SCr over baseline.¹² The baseline value is generally defined as the average of all SCr concentrations measured within the year before admission.¹³ During procurement, however, this information is frequently unavailable. Most published studies have therefore taken either admission SCr value⁹⁻¹¹ or the lowest SCr concentration measured throughout the procurement procedure as baseline.¹⁴ Unfortunately, both approaches are inherently limited by possible misclassification of donor AKI status.¹⁵ Indeed, consistently increased SCr values do not allow distinguishing between a community-acquired AKI and a preexisting chronic kidney disease (CKD). Moreover, donors who had recovered from AKI before organ procurement would be systematically ruled as AKI-free. It is

therefore plausible that misreporting of donor AKI status may have influenced risk estimates in published studies. In this scenario, a refined classification system for donor would be valuable to account for misclassification bias.

In the absence of a reliable baseline SCr concentration, the KDIGO guidelines recommend estimating a MDRD study-derived baseline SCr value¹² under the assumption of a baseline glomerular filtration rate (GFR) of 75 mL/min/1.73 m². Two studies in critically ill patients with AKI have independently validated the use of back-estimation for baseline SCr.^{16,17} Although unsuitable for patients with known or suspected CKD, backward estimation of baseline SCr would provide a way to overcome inconsistencies in donor AKI classification during the course of kidney procurement. This registry-based cohort study was undertaken to examine the association between deceased donor AKI assessed by back-estimation of baseline SCr and long-term graft survival rates in a large cohort of kidney transplant recipients.

2. Methods

2.1. Data source

The present study was conducted using data obtained from the French national CRISTAL Registry between January 1, 2006 and December 31, 2017.¹⁸ The registry has received approval from the French data protection authority as well as a waiver of obtaining written informed consent. The registry is administered by the *Agence de la Biomédecine* – a state agency that coordinates and administers organ procurement. In each center, data are collected on patients at the time of transplantation and annually thereafter until the patient's death. The registry conforms to the tenets of the Istanbul Declaration and the ethical guidelines set forth by the Helsinki Declaration. The use of organs obtained from prisoners is banned. Ethics approval for the registry was received from the French National Commission for Data Protection and Liberties.

2.2. Data collection

Data were collected for all single kidney adult transplant recipients from brain-death deceased donors. Subjects were followed until they died or lost their graft, whichever occurred first. For subjects who were alive with their graft functioning at the end of the study, right-censoring was performed on September 30, 2019 (i.e., administrative censoring). Patients who received kidneys procured from donors aged less than 18 years were not eligible for inclusion. We excluded donors with either a single measurement or unknown SCr values.

2.3. Exposure

In accordance with the KDIGO guidelines, baseline SCr was initially back-estimated in all donors using the 4-variable MDRD study equation.¹² French laws prohibit collection of ethnicity in registries; therefore, each donor was considered as non-African American. According to the KDIGO guidelines, a SCr value was considered as increased for a ≥ 0.3 mg/dL or a $\geq 50\%$ increase over the back-estimated baseline SCr. Otherwise, the value was considered as normal. Irrespective of urine output (unavailable in the registry), the following refined classification system for donor AKI was implemented: 1) no AKI, donors with only normal SCr values throughout kidney procurement; 2) undetermined AKI/CKD, donors with only increased SCr values throughout kidney procurement; 3) recovery from AKI, donors showing at least one increased SCr value but a normal last measured SCr; 4) ongoing AKI, donors showing at least a normal SCr value but an increased last measured SCr. Patients with ongoing AKI were further subdivided according to the KDIGO AKI staging system upon considering changes from baseline to peak SCr values measured during kidney procurement as follows: stage I, increase by ≥ 0.3 mg/dL or 1.5 to < 2 -fold; stage II, 2 to < 3 -fold; and stage III, ≥ 3 -fold, or peak SCr value ≥ 4.0 mg/dL.¹² Finally, each recipient was classified according to the respective donor's status.

2.4. Outcomes

The primary outcome measure was death-censored graft survival defined as time from transplant to graft failure (i.e., return to dialysis or preemptive re-transplantation).

2.5. Robustness analyses

Considering that GFR varies with age and sex, we performed a sensitivity analysis by relaxing the assumption that each donor had a fixed value of 75 mL/min/1.73 m² as baseline GFR. Therefore, we refined the AKI categorization considering a back-estimated baseline SCr according to a median GFR relying on each donor's age and sex as described by van den Brand et al. (**Table S1**).¹⁹

In previous research, baseline SCr was defined^{9–11} or as the lowest SCr concentration measured throughout the procurement procedure.¹⁴ To ensure comparability across studies, we also applied the same methods of ascertainment and definitions to our dataset. Analogously to the main analysis, AKI was classified in accordance with the KDIGO guidelines although these classification approaches do not permit identification of the undetermined AKI/CKD and recovery from AKI categories.

2.6. Statistical analysis

Groups were compared on baseline variables by chi-square (categorical data) or Student's t-tests (continuous data). The Aalen-Johansen estimator was used to analyze the cumulative incidence of graft failure accounting for the competing risk of death.²⁰ The multiple imputations method was used to handle missing data on relevant covariates.²¹ The missingness rate was <10% for all covariates. Because our registry data had a multilevel structure (deceased donors can donate both kidneys), we separately imputed five complete data sets for donor risk factors and – subsequently – five complete data sets for recipient risk factors. We performed all analyses on each of the 25 (5 x 5) imputed data sets, and the results were combined using the Rubin rules²² to obtain average values. Hazard ratios (HRs) for graft survival according to deceased donor AKI assessed by back-estimation of baseline SCr were computed using Cox proportional hazards modeling with stratification for the recipient's region of residence. A multivariable backward selection procedure was implemented, with a univariate threshold $p < 0.20$ for inclusion and a $p < 0.05$ being defined as statistically significant in the final model. Transplantation era being a well-recognized risk factor has also been included in the multivariable analyses. Paired kidneys obtained from the same donor were treated as a cluster using a robust sandwich variance estimator for cluster-

correlated data in the Cox regression model.²³ Log-linearity and the proportional hazards assumption were tested using a graphical method. We also performed a complete case analysis without multiple imputation. All analyses were carried out in R, version 3.6.3.²⁴

3. Results

3.1. Cohort characteristics

Of the 16,117 deceased donors in the CRISTAL registry, 14,899 were included in the study. A total of 915 donors were excluded because of inadequate SCr data (i.e., single measurement or unknown SCr values). Most of these procurements were carried out between 2006 and 2008, partly accounting for the higher proportion of standard criteria donors among the excluded donors (**eTable S2**). The total number of transplanted kidneys was 26,786 (**Figure 1**). The median number of measured SCr values during procurement for each donor was 4 (minimum–maximum: 2–4), and the median delay between the admission and the last measurement value was 41 hours (first quartile: 22; third quartile: 84). Based on the proposed classification of AKI categories, kidneys were classified as follows: no-AKI (n=19,276); undetermined AKI/CKD (n=1745); recovery from AKI (n=2392); and ongoing AKI (n=3373). According to the AKI KDIGO staging system, the ongoing AKI group consisted of 2379, 734, and 260 donors with AKI stage I, II, and III, respectively. **Figure 2** depicts the temporal course of measured SCr values throughout kidney procurement in twenty randomly selected donors in each of the four AKI categories. **Table 1** summarizes the baseline donors and recipient characteristics, whereas **Table S3** shows the same variables according to AKI staging.

3.2. Follow-up and graft survival

A total of 4458 kidney graft losses occurred during a median follow-up was 5.7 years (first quartile: 3.0 years; third quartile: 8.9 years). The distribution according to AKI categories was as follows: undetermined AKI/CKD (n=297); recovery from AKI (n=411), and ongoing AKI (n=648). The distribution of graft losses according to the AKI stage in the ongoing AKI group

was as follows: stage I (n=460); stage II (n=148); and stage III (n=40). A total of 4115 recipients died, and their distribution according to AKI categories was as follows: undetermined AKI/CKD (n=257); recovery from AKI (n=321), and ongoing AKI (n=570). The distribution of deaths according to the AKI stage in the ongoing AKI group was as follows: stage I (n=407); stage II (n=121), and stage III (n=42).

Graft failure rates at 5 and 10 years after transplantation in the entire study cohort were 13.0% (95% confidence interval [CI]: 12.6–13.5%) and 23.7% (95% CI: 23.0–24.4%), respectively. According to the four AKI categories and KDIGO AKI staging in the ongoing AKI group, cumulative incidence curves are depicted in **Figure 3**. At 10 years post-transplantation, the graft failure rates according to AKI categories were: 23.1% (95% CI: 22.3–23.9%) for no-AKI; 23.0% (95% CI: 20.5–25.8%) for undetermined AKI/CKD, 25.8% (95% CI: 23.3–28.4%) for recovery from AKI; and 25.9% (95% CI: 24.0–28.0%) for ongoing AKI.

3.3. Confounder-adjusted effect of AKI categories on graft survival

Compared to no-AKI, ongoing AKI was associated with an increased risk of graft failure (HR=1.24, 95% CI: 1.13–1.35, **Table 2, Table S4 and S5**). The adverse significance of ongoing AKI was evident for both stage I (HR=1.21, 95% CI: 1.09–1.34) and stage II (HR=1.37, 95% CI: 1.16–1.63) but not for stage III (HR=1.20, 95% CI: 0.88–1.65). Notably, the HRs for graft failure in the undetermined AKI/CKD (HR=1.22, 95% CI: 1.07–1.38) and recovery from AKI (HR=1.18, 95% CI: 1.06–1.31) groups were similar to that observed in the ongoing AKI group. Complete case analysis before imputation produced similar results (**Table S6 and S7**), confirming that our conclusions were reliable.

3.5. Robustness analyses

When baseline SCr was back-estimated under the assumption of a baseline GFR depending on donor's age and sex, the patient distribution between the four groups was similar except for 2,159/19,276 no-AKI recipients who were re-allocated in the recovery from AKI (1316/2159) and ongoing AKI (843/2159) groups (**Figure S1**). Their mean donor age was 44.4 ± 15.1 years. The group's overall characteristics and the corresponding cumulative

incidence curves are summarized in **Table S8 and Figure S2**. The observed effect of ongoing AKI on graft failure was confirmed (HR=1.23, 95%CI: 1.13-1.34; **Table 2, Table S9 and S10**). Similar results were observed in the undetermined AKI/CKD group (HR=1.28, 95% CI: 1.15-1.42). Conversely, recovery from AKI was no longer associated with graft failure (HR=1.10, 95% CI: 0.99-1.21).

When baseline SCr was defined as the first SCr value at admission or the lowest SCr value during organ procurement, 28.3% and 57.7% of kidneys were considered with AKI respectively versus 28% in our classification and 24.8% when adapted to gender and age. 49% (848/1745) of recipients classified as undetermined AKI/CKD and 90% (2162/2392) of those with recovery from AKI (2162/2392) would have been labeled as no AKI. Furthermore, 29% (5598/19,276) of no-AKI recipients would have been misclassified as AKI when baseline SCr was defined as the lowest SCr concentration measured as shown by alluvial diagrams (**Figure 4**). Importantly, the adverse effect of deceased donor AKI on graft survival was no longer evident when relying either on admission SCr values or the lowest SCr concentration measured throughout the procurement procedure as baseline. In the former case, HRs for graft failure for AKI stage I, II, and III were 1.05 (95% CI: 0.96–1.14), 0.99 (95% CI: 0.85–1.15), and 1.14 (95% CI: 0.88–1.48), respectively (**Table S11, S12 and Figure S3**). In the latter case, HRs for graft failure for AKI stage I, II, and III were 1.06 (95% CI: 0.99–1.13), 1.02 (95% CI: 0.91–1.14), and 1.05 (95% CI: 0.85–1.30), respectively (**Table S13, S14 and Figure S4**).

4. Discussion

The primary novelty of this registry-based study lies in the standardized classification of deceased donor AKI obtained through back-estimation of baseline SCr. Interestingly, such an approach appears suitable for organ procurement conditions. Furthermore, we found that not only donor AKI – but also two novel at-risk categories (i.e., recovery from AKI and

undetermined AKI/CKD) – were associated with lower long-term graft survival rates in renal transplant recipients.

Although AKI of the native kidneys is associated with an increased risk of CKD and end-stage renal disease,^{25,26} whether the same applies to kidney transplant recipients is unclear. A review that evaluated the impact of donor AKI on graft survival failed to identify a significant association between the two events in 25 of the 29 reviewed studies.²⁷ However, conclusions should be drawn cautiously since the criteria to define baseline SCr were inconsistent. Using the peak-to-nadir difference for SCr measurements, Heilman et al.¹⁴ did not show that AKI exert detrimental effects. In a large propensity score-matched study of 6722 donor/recipient pairs either with or without AKI (based on the admission SCr value and the highest SCr value at procurement), Liu et al.¹⁰ failed to identify an association between donor AKI and graft loss. However, Boffa et al.⁹ demonstrated that donor AKI – defined as the difference in SCr between procurement and admission – is associated with a 1.2-fold increased risk of graft loss at one year. All of these studies defined baseline SCr according to the first value on admission or the lowest value during the organ procurement; unfortunately, these approaches may lead to a misclassification bias for the detection of AKI in critically ill patients.^{15,17} This problem may be circumvented by back-estimation of baseline SCr according to the KDIGO guidelines, as previously validated in patients who needed intensive care.¹⁶

With the application of the back-estimation method to categorize deceased donor AKI, we identified undetermined AKI/CKD, recovery from AKI, and ongoing AKI as being significantly and similarly associated with less favorable long-term graft survival rates. Specifically, the risk of graft loss in each of these categories was 1.2-fold higher than that observed in the no AKI group. These results suggest that not only ongoing AKI, but also more nuanced forms of deceased donor AKI (e.g., recovery from AKI – which may be characterized by a normal last SCr value), may exert a detrimental impact on graft survival. Additionally, our data validate the findings from previous studies on native kidneys^{28,29} reporting an impaired renal survival after an AKI episode, even after a complete recovery, which may reflect a decline in

functional reserve that may lead to AKI.³⁰ It is noteworthy that this effect was also found according to the KDIGO staging and tended to increase with AKI severity apart from stage III. This could be explained by a lack of statistical power given the small sample size of the stage III AKI subgroup, thereby reflecting clinicians' reluctance to accept those grafts.⁷ In the current study, the definition of baseline SCr as the first value measured on admission would have resulted in a misclassification bias of numerous patients in two risk categories (undetermined AKI/CKD and recovery from AKI) as no AKI – leading to erroneous risk estimates. While it can be argued that most deceased donors in the undetermined AKI/CKD actually had AKI (because the effect size was similar to that observed for the ongoing AKI group), our robustness analysis revealed that patients in this category were previously misclassified as either AKI or no AKI in a similar proportion, ultimately blunting the association between AKI and less favorable graft survival rates.

While the baseline SCr back-estimation method described in the KDIGO guidelines might seem coarse upon assigning a baseline eGFR value of 75 mL/min/1.73 m² to all donors, the deleterious effects of ongoing AKI and undetermined AKI/CKD were consistent using reference GFR values according to donor's age and sex. The re-allocation of young patients from the no-AKI to the recovery from AKI group could partly explain the reduction of the observed effect, suggesting a possible age-modifier on the ability to recover after an AKI episode.

Importantly, our findings do not constitute evidence that donor kidneys with AKI should be discarded. First, compared with AKI classifications based on admission or lowest Scr, the back-estimation method is meant to overcome misclassification and decrease the proportion of donor kidneys that are considered to have AKI, thereby reducing the number of discarded kidneys. Indeed, donor AKI is an important cause of discard in the European allocation system and even more in the U.S where it accounts for 64% of discarded kidneys³¹. Second, we would like to emphasize that the adverse impact of AKI on graft survival in our findings is of limited magnitude with regard to the 10% death cumulative incidence at two years post-registration on the waiting list³. Practices in kidney transplantation are constantly evolving,

especially toward a personalized medicine, and prediction tools of graft failure are becoming more and more accurate. Assessing an unambiguous effect of donor AKI may be useful to evaluate the potential benefit of innovative preservation techniques^{32,33}. New methodological implementations such as time-dependent propensity score could help to estimate the life expectancy gain resulting from transplantation with an AKI donor when compared to similar patients awaiting for a better graft proposal³⁴. Such methodological implementation in this donor AKI context could provide an answer to discourage discard policies based on expected graft survival rates.

Several caveats of our study need to be considered. First, the burden of comorbidities in donors may vary across countries. This poses a limitation regarding the ability to generalize our conclusions, and replication in independent samples is paramount for ensuring external validity. Second, the prevalence of donor AKI might have been underestimated because our registry lacked data about urine output. This could lead to a potential blunting of the association between donor AKI and graft survival. Third, the ethnic correction factor was not applied when back-estimating the SCr baseline value. We acknowledge that the consequences of such an omission were impossible to identify, given that it would increase the prevalence of AKI among African Americans. However, we believe that it had only a small impact on our results. Indeed, the 1.212 ethnic correction factor was calculated for African American CKD patients in the MDRD study and might not be accurate for high GFR values³⁵ as well as for African non-American people, where GFR estimations were less biased without ethnic correction factor in many countries.³⁶⁻³⁹ Furthermore, in France, Flamant et al. estimated a 1.08 ethnic correction factor in a CKD stage III African European sample⁴⁰, which implies that the actual 1.212 ethnic correction factor would overestimate GFR levels in this subpopulation. Another limitation is that the number of AKI events depends on the quantity of SCr measurements. Consequently, a more thorough monitoring of SCr evolution can further improve accuracy in the identification of donor AKI. Finally, registry-based studies are prone to unavoidable confounding or residual confounding on unmeasured variables.

In summary, we demonstrate that deceased donor AKI is associated with lower long-term graft survival. Similarly, recovery from AKI and undetermined AKI/CKD were associated with less favorable graft survival. As such, the presence of at least one increased SCr value before kidney procurement – independent of the last SCr value – resulted in a 1.2-fold increased risk of graft failure. Finally, SCr baseline back estimation is a reliable method to overcome misclassification bias and should be considered when investigating donor AKI. A better appreciation of donor AKI is a critical step to further develop appropriate conservative strategies.

Article information

Contributors to the CRISTAL National Registry : ALEZRA Eric (CHU Bordeaux); AMMI Myriam (Chirurgie Vasculaire - CHU Angers); BERTRAND Dominique (Néphrologie - CHU Rouen); BESNARD Thierry (Coordination de prélèvements - CHU Poitiers); BRANCHEREAU Julien (CHU Nantes); BRUYERE Franck (Urologie - CHU Tours); BUCHLER Matthias (Néphrologie - CHU Tours); CHEMOUNY M Jonathan (Néphrologie - CHRU Rennes); CORNUAULT Mathieu (Coordination Prélèvements Organes et Tissus - CHU Nantes); COUZI Lionel (CHU Bordeaux); DEFORTESCU Guillaume (Urologie - CHU Rouen); DEL BELLO Arnaud (CHU Toulouse); DUBE Laurent (Coordination Hospitalière des Prélèvement d'Organes et de Tissus - CHU Angers); DUCOS Guillaume (CHU Toulouse); DUVEAU Agnès (Néphrologie Dialyse et transplantation - CHU Angers); ESCHWEGE Pascal (Urologie - CHRU Nancy); ESPOSITO Laure (CHU Toulouse); ETIENNE Isabelle (Néphrologie - CHU Rouen); FOURDINIER Ophélie (Néphrologie - CHU Amiens); GAME Xavier (CHU Toulouse); GARANDEAU Claire (Néphrologie - CHU Nantes); GARROUSTE Cyril (CHU Clermont-Ferrand); GATAULT Philippe (Néphrologie - CHU Tours); GIRERD Sophie (Néphrologie - CHRU Nancy); GRALL-JESEQUEL Anne (CHU Brest); GREGOIRE Hélène (Unité de Prélèvement d'Organes et de Tissus - CHRU Nancy); GUY Laurent (CHU

Clermont-Ferrand); HENG Anne-Elisabeth (CHU Clermont-Ferrand); HOURMANT Maryvonne (Néphrologie - CHU Nantes); KAMAR Nassim (CHU Toulouse); KAMINSKI Hannah (CHU Bordeaux); KARAM Georges (Urologie - CHU Nantes); KERFORNE Thomas (Anesthésie-Réanimation, INSERM U1082 - CHU Poitiers); LADRIERE Marc (Néphrologie - CHRU Nancy); LAMBERT Dominique (Coordination Hospitalière des Prélèvement d'Organes et de Tissus - AP-HM); LANFRANCO Luca (CHU Brest); LE MEUR Yannick (CHU Brest); LECHEVALLIER Eric (Urologie - AP-HM); LEGRIS Tristan (Néphrologie - AP-HM); MARTIN-LEFEVRE Laurent (Coordination Prélèvements Organes et Tissus - CHU Nantes); MERCIER Emmanuelle (Médecine intensive réanimation - CHU Tours); MERVILLE Pierre (CHU Bordeaux); MOAL Valérie (Néphrologie - AP-HM); OUENDO Martial (Anesthésie-Réanimation - CHU Amiens); PESTEIL Francis (CHU Limoges); PFISTER Christian (Urologie - CHU Rouen); POULAIN Coralie (Néphrologie - CHU Amiens); PRADERE Benjamin (Urologie - CHU Tours); PRUDHOMME Thomas (CHU Toulouse); REROLLE Jean-Pierre (CHU Limoges); ROGIER Julien (CHU Bordeaux); SAINT Fabien (Urologie Transplantation – EPROAD 4669 - CHU Amiens); SALLUSTO Fédécio (CHU Toulouse); TATON Benjamin (CHU Bordeaux); THIERRY Antoine (Néphrologie, Hémodialyse et Transplantation Rénale, INSERM U1082 - CHU Poitiers); THURET Rodolphe (Urologie - CHU Montpellier); VACHIERY LAHAYE Florence (Coordination Hospitalière des Dons pour la Greffe - CHU Montpellier); VALLEE Maxime (CHU Poitiers); VARDON-BOUNES Fanny (CHU Toulouse); VENHARD Jean-Christophe (Coordination PMO Réanimation - CHU Tours); VIGNEAU Cécile (Néphrologie - CHRU Rennes); WOLF Philippe (CHU Strasbourg). Contributors are listed in alphabetical order.

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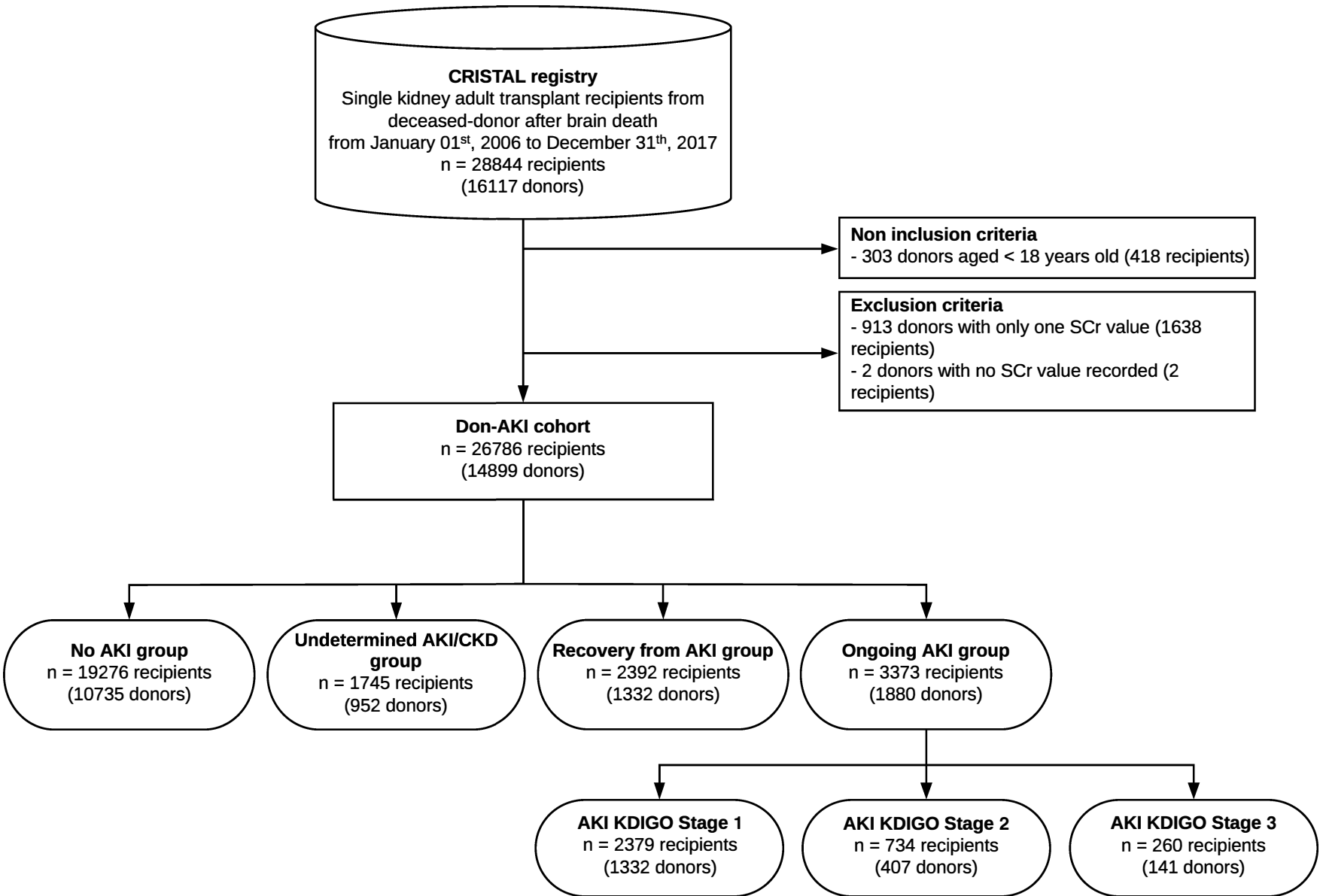
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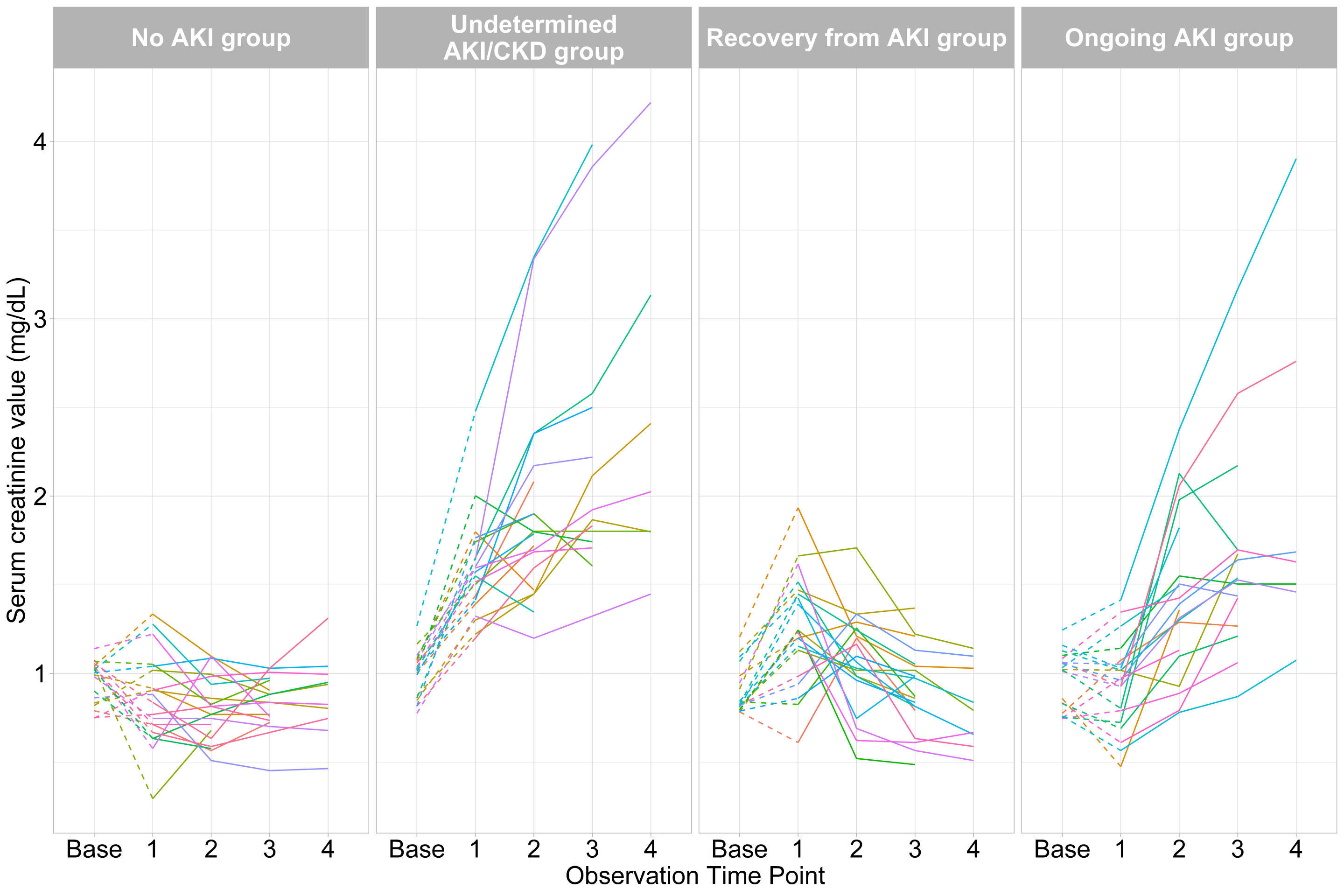
Figure 1. Flow of patients through the study

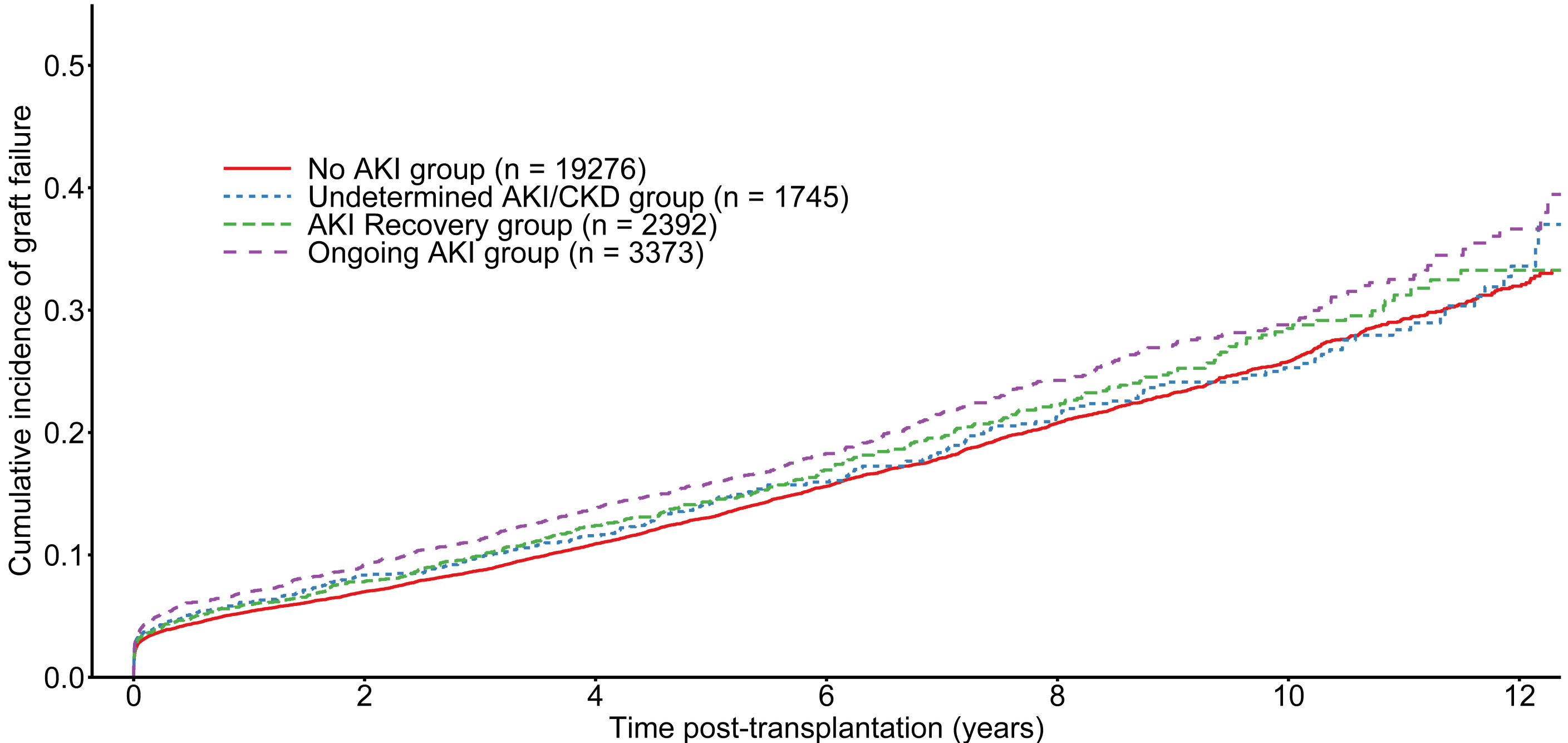
Figure 2. Temporal course of serum creatinine values in the four different acute kidney injury categories (20 randomly selected donors in each category). Base corresponds to the back-estimated baseline SCr value.

Figure 3. Cumulative incidence curves of graft failure in the four different acute kidney injury categories (A) and according to KDIGO stages of acute kidney injury (B).

Figure 4. Alluvial diagram depicting allocation of patients to different acute kidney injury categories according to different definitions of baseline serum creatinine. Panel A, first serum creatinine value on admission; Panel B, lowest serum creatinine value measured throughout the procedure.

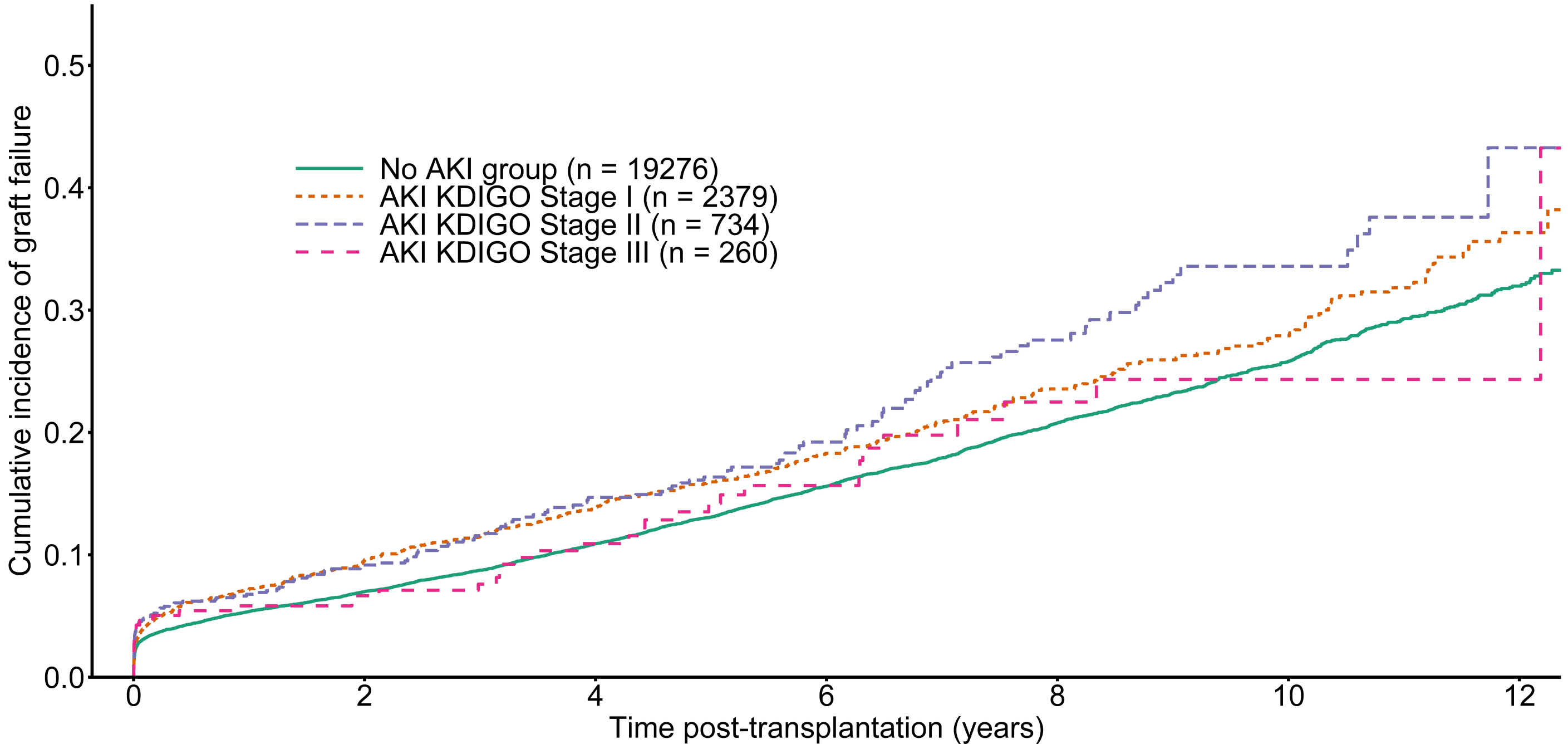






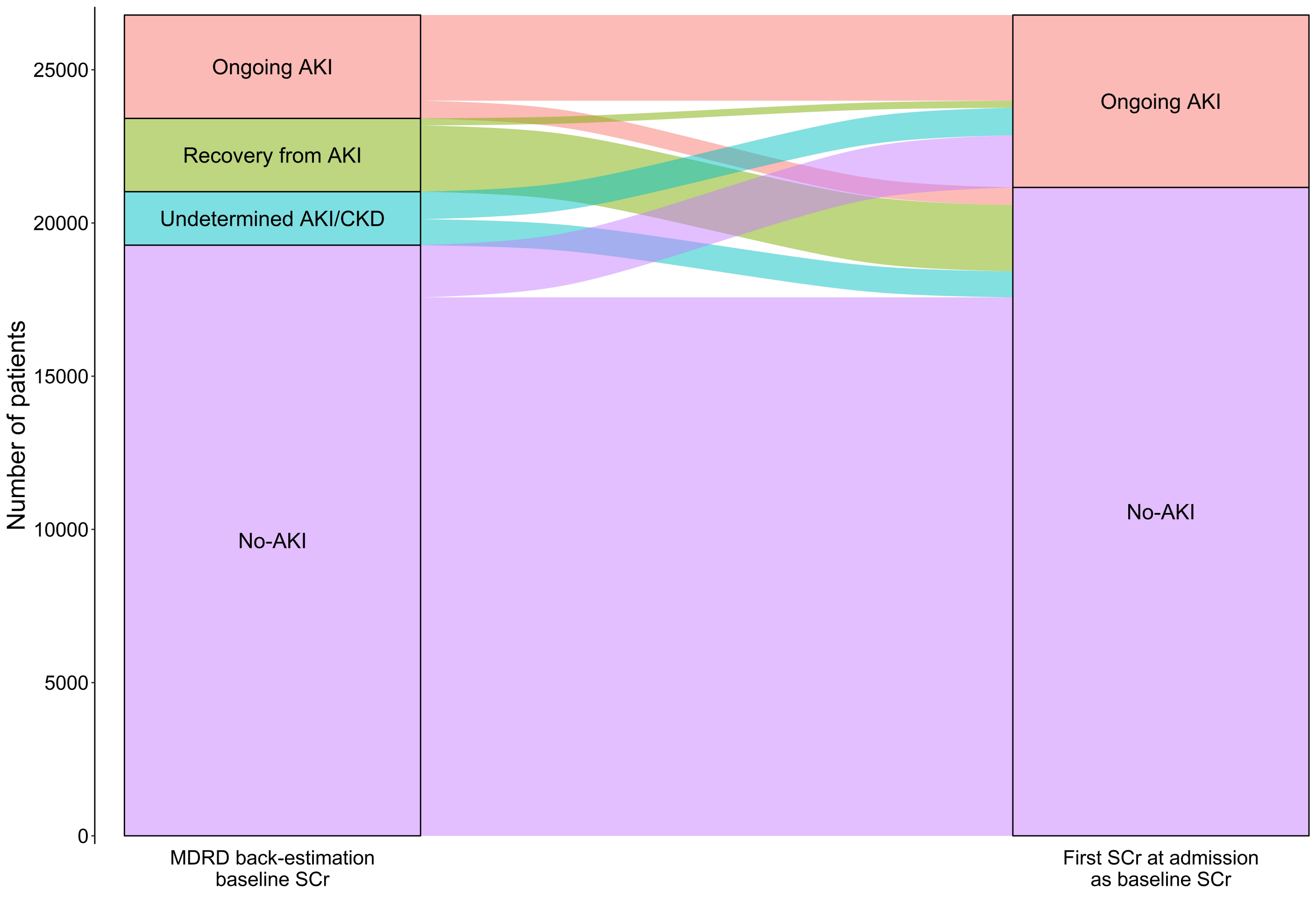
Number of at-risk patients

—	19276	15418	11259	7673	4699	2325	559
—	1745	1364	1018	694	440	241	61
—	2392	1896	1334	925	578	254	59
—	3373	2678	1919	1303	796	399	80



Number of at-risk patients

—	19276	15418	11259	7673	4699	2325	559
- -	2379	1884	1370	948	605	306	67
- -	734	577	402	261	144	69	7
- -	260	217	147	94	47	24	6



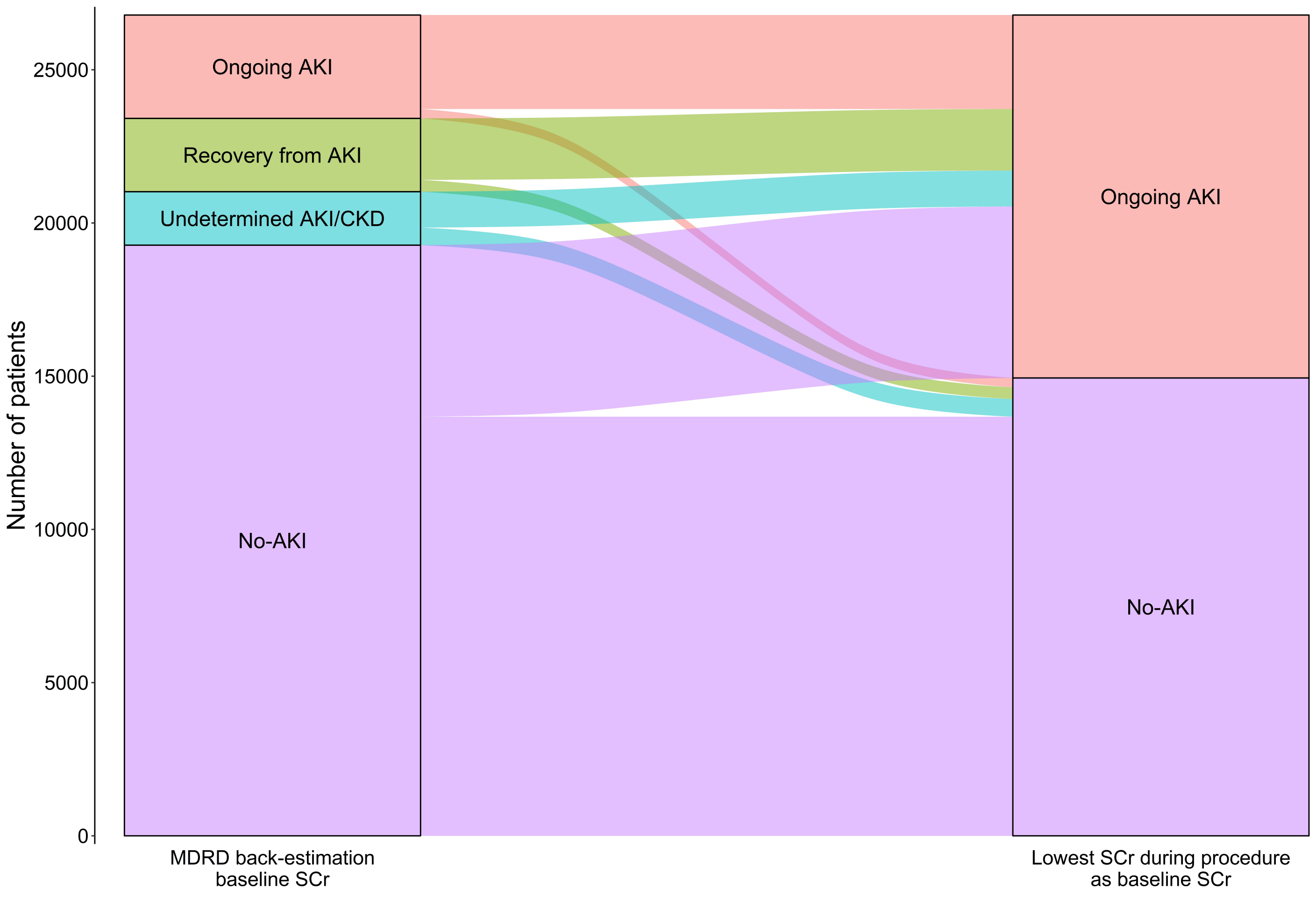


Table 1. Baseline characteristics of recipients and donors according to different acute kidney injury categories

Variable	Entire cohort n=26,786	No AKI n=19,276	Undetermined AKI/CKD n=1745	Recovery from AKI n=2392	Ongoing AKI n=3373
Donor age, years	54.3 ± 15.7	54.8 ± 15.8	50.2 ± 13.5	52.8 ± 15.5	54.7 ± 15.9
Male donor	15417 (57.6%)	10680 (55.4%)	1045 (59.9%)	1433 (59.9%)	2259 (67.0%)
Donor BMI, kg/m ²	25.9 ± 5.1	25.5 ± 4.9	27.4 ± 5.4	26.6 ± 5.2	26.6 ± 5.4
Donor SCr value at admission, mg/dL	0.9 ± 0.4	0.8 ± 0.2	1.7 ± 0.6	1.3 ± 0.5	1.0 ± 0.3
Last donor SCr value, mg/dL	1.0 ± 0.6	0.7 ± 0.2	2.2 ± 1.1	1.0 ± 0.2	1.8 ± 0.8
Donor death due to cerebrovascular disease	15502 (57.9%)	12056 (62.5%)	586 (33.6%)	1110 (46.4%)	1750 (51.9%)
Donor history of diabetes	2174 (8.5%)	1484 (8.0%)	149 (9.0%)	204 (9.0%)	337 (10.5%)
Donor history of smoking	11504 (43.0%)	8384 (43.5%)	752 (43.1%)	1007 (42.1%)	1361 (40.4%)
Donor history of hypertension	8977 (33.6%)	6441 (33.5%)	486 (27.9%)	787 (33.1%)	1263 (37.6%)
Expanded criteria donor	12607 (47.1%)	9100 (47.2%)	696 (39.9%)	1028 (43.0%)	1783 (52.9%)
Recipient age, years	53.3 ± 13.4	53.5 ± 13.5	50.9 ± 12.2	52.4 ± 13.3	54.0 ± 13.5
Male recipient	16720 (62.4%)	11987 (62.2%)	1101 (63.1%)	1549 (64.8%)	2083 (61.8%)
Recipient BMI, kg/m ²	25.0 ± 4.6	25.0 ± 4.6	24.8 ± 4.5	24.9 ± 4.6	25.0 ± 4.6
First kidney transplantation	21528 (83.0%)	15478 (82.9%)	1418 (83.9%)	1890 (81.6%)	2742 (84.0%)
Pre-transplant renal replacement therapy					
- Peritoneal dialysis	2455 (9.3%)	1762 (9.3%)	186 (10.9%)	212 (9.0%)	295 (8.9%)
- Hemodialysis	20716 (78.8%)	14877 (78.7%)	1339 (78.2%)	1857 (79.0%)	2643 (79.9%)
- Pre-emptive transplantation	3111 (11.8%)	2272 (12.0%)	188 (11.0%)	282 (12.0%)	369 (11.2%)
Primary kidney disease					
- Other	4227 (15.8%)	3048 (15.8%)	276 (15.8%)	361 (15.1%)	542 (16.1%)
- Glomerulonephritis	6444 (24.1%)	4630 (24.0%)	436 (25.0%)	601 (25.1%)	777 (23.0%)
- Vascular	2496 (9.3%)	1798 (9.3%)	141 (8.1%)	228 (9.5%)	329 (9.8%)
- Unknown	4827 (18.0%)	3458 (17.9%)	326 (18.7%)	434 (18.1%)	609 (18.1%)
- Diabetic nephropathy	2465 (9.2%)	1792 (9.3%)	134 (7.7%)	210 (8.8%)	329 (9.8%)
- Polycystic kidney disease	4109 (15.3%)	2958 (15.3%)	268 (15.4%)	366 (15.3%)	517 (15.3%)
- Pyelonephritis	2218 (8.3%)	1592 (8.3%)	164 (9.4%)	192 (8.0%)	270 (8.0%)
Positive anti-HLA class I antibodies	8036 (30.0%)	5853 (30.4%)	482 (27.6%)	747 (31.2%)	954 (28.3%)
Positive anti-HLA class II antibodies	6442 (24.0%)	4698 (24.4%)	375 (21.5%)	625 (26.1%)	744 (22.1%)
Time spent on dialysis, years	3.4 ± 4.1	3.4 ± 4.0	3.6 ± 4.3	3.5 ± 4.1	3.5 ± 4.0
Recipient history of diabetes	4433 (17.1%)	3245 (17.4%)	253 (15.0%)	369 (15.9%)	566 (17.5%)
Recipient history of cancer	2238 (8.5%)	1634 (8.6%)	130 (7.5%)	194 (8.2%)	280 (8.4%)
Recipient history of smoking	10824 (43.8%)	7817 (44.0%)	683 (42.5%)	975 (43.6%)	1349 (43.7%)
Recipient history of cardiovascular disease	5327 (20.8%)	3862 (21.0%)	322 (19.3%)	451 (19.5%)	692 (21.6%)

Cold ischemia time, h	17.5 ± 6.4	17.5 ± 6.4	17.7 ± 6.3	17.4 ± 6.3	17.5 ± 6.2
Hypothermic machine perfusion	3907 (14.7%)	2766 (14.4%)	280 (16.3%)	338 (14.2%)	523 (15.7%)
HLA-A-B-DR incompatibilities > 4	13738 (51.3%)	9885 (51.3%)	874 (50.1%)	1230 (51.4%)	1749 (51.9%)

Data are given as mean ± standard deviation or count (percentage). Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; BMI, body mass index; SCr, serum creatinine; HLA, human leukocyte antigen.

Table 2. Cox regression analysis of the association between donor acute kidney injury and risk of graft failure

	MDRD back-estimated baseline SCr assuming that GFR is 75 mL/min/1.73m ²			MDRD back-estimated baseline SCr assuming a reference GFR for age and sex		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Donor acute kidney failure (model 1)						
- No AKI	Reference	-	-	Reference	-	-
- Undetermined AKI/CKD	1.22	[1.07–1.38]	0.003	1.28	[1.15–1.42]	< 0.001
- Recovery from AKI	1.18	[1.06–1.31]	0.003	1.10	[0.99–1.21]	0.08
- Ongoing AKI (all stages)	1.24	[1.13–1.35]	< 0.001	1.23	[1.13–1.34]	< 0.001
Donor AKI according to KDIGO stage (model 2)						
- No AKI	Reference	-	-	Reference	-	-
- AKI KDIGO stage I	1.21	[1.09–1.34]	< 0.001	1.23	[1.11–1.36]	< 0.001
- AKI KDIGO stage II	1.37	[1.16–1.63]	< 0.001	1.27	[1.07–1.51]	0.006
- AKI KDIGO stage III	1.20	[0.88–1.65]	0.3	1.19	[0.90–1.58]	0.2

All models were adjusted for numerous donor (age, sex, cerebrovascular cause of death, diabetes, and hypertension), recipient (age, BMI, previous kidney transplant, pre-transplant renal replacement therapy, primary kidney disease, positive anti HLA class II antibodies, time spent on dialysis, HIV status, cardiovascular disease, diabetes, smoking), and transplantation (cold ischemia time, year of transplantation and number of HLA A-B-DR incompatibilities) covariates.

Abbreviations: CI, confidence interval; AKI, acute kidney injury; CKD, chronic kidney disease; KDIGO, Kidney Diseases Improving Global Outcomes; BMI, body mass index; HLA, human leukocyte antigen; HIV, human immunodeficiency virus.