swiss medical weekly

ORIGINAL ARTICLE


# Risk factors of delayed kidney graft function following donation after circulatory death – a retrospective cohort study of Swiss kidney transplants

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**Published**
27 April 2026

**doi**
https://doi.org/10.57187/5007

**Cite this as**
Swiss Med Wkly. 2026;156:5007

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## Summary

AIMS OF THE STUDY: On 1 September 2011, donation after circulatory death (DCD) organ donation resumed in Switzerland after the DCD programme had been suspended for four years due to jurisdictional and medico-ethical discrepancies. DCD has gained relevance due to the worldwide scarcity of donor organs and now accounts for nearly half of all donations in the Swiss transplant setting. This study aimed to identify risk and protective factors for the occurrence of delayed graft function, which is a common early complication following kidney transplantation, especially in DCD transplants.

METHODS: This retrospective cohort study included all Swiss DCD kidney transplants performed between 1 September 2011 and 31 August 2024. The primary outcome was the occurrence of delayed graft function, defined as the need for dialysis within the first week following kidney transplantation. A complete-data, multivariable analysis using a logistic regression model for the event of delayed graft function was conducted for the following variables: donor age and donor comorbidity, cause of death, year of transplantation, functional warm and cold ischaemia time, use of abdominal normothermic regional perfusion, and use of hypothermic machine perfusion.

RESULTS: Of 499 controlled DCD donors, 351 were kidney donors. These donors enabled a total of 711 kidney transplants, including 7 double kidney transplants. Of the 650 recipients who qualified for analysis, 315 (48.5%) experienced delayed graft function. Odds ratios for delayed graft function were 0.18 (0.09–0.33) for procurement with abdominal normothermic regional perfusion, 0.55 (0.36–0.83) for preservation with hypothermic machine perfusion, 1.00 (0.73–1.36) for functional warm ischaemia time, and 1.33 (1.01–1.73) for cold ischaemia time.

CONCLUSIONS: A statistically significant decrease in delayed graft function risk was observed for the use of abdominal normothermic regional perfusion and hypothermic machine perfusion. No evidence was found for an association between functional warm ischaemia time and delayed graft function, and only weak evidence was found for cold ischaemia time. These findings underscore the effectiveness of modern procurement and preservation methods used in kidney transplantation and are consistent with current research findings.

## Introduction

In the context of the scarcity of donor organs worldwide, donation after circulatory death (DCD) has become a key pillar in increasing the donation rate within the Swiss transplant setting. In 2023, 21.3% of European donors were DCD donors and 78.7% were donation-after-brain-death donors, whereas in Switzerland, DCD accounted for 48.0% of donors [1, 2]. This reflects a slow and steady increase in the proportion since the reintroduction of the Swiss DCD programme in 2011.

On 1 July 2007, a new transplantation law was passed in Switzerland. At this time, DCD organ donation was routinely performed in the university hospitals of Zurich and Geneva. However, discrepancies between the new law and the national guidelines of the Swiss Academy of Medical Sciences led to the suspension of DCD donation in Switzerland, as it was unclear whether organ procurement from DCD donors was legally permissible under the revised legislation. A working group set up by Swisstransplant, the Swiss National Foundation for organ donation and transplantation, initiated efforts to harmonise the Transplantation Act with national ethical and clinical guidelines. On 1 September 2011, DCD donation was officially reintroduced in Switzerland, with additional procurement hospitals joining in the following years [3]. DCD organ donation in Switzerland has been almost exclusively performed in patients with poor neurological prognosis following severe brain injury, leading to a joint decision to withdraw life-sustaining therapy. This corresponds to controlled DCD, or Maastricht category III.

Although DCD organ donation has led to increased organ availability, it is associated with a higher risk of complications in liver and kidney transplantation, primarily because of the combined effects of functional warm ischaemia time (fWIT) and cold ischaemia time inherent to this type of organ donation. In particular, DCD kidney transplants are associated with higher rates of delayed graft function compared with kidney transplants from brain death donors, corroborating the importance of ischaemic injury in the heterogeneous pathogenesis of delayed graft function [4–9]. Broadly, two strategies have been explored to reduce the incidence of delayed graft function, focusing on the optimisation of organ procurement and preservation. While rapid procurement has long been considered the gold standard, the past decade has seen the implementation of normothermic regional perfusion (NRP) programmes in many European countries. These have been shown to decrease complication rates in both liver and kidney transplants [5–7, 10–12]. To mitigate the detrimental effects of prolonged cold ischaemia time after procurement, hypothermic machine perfusion has been increasingly adopted as a preservation method for kidney, liver, lung, and heart grafts. In Switzerland, the majority of DCD kidney transplants are now preserved using this method. As demonstrated in a meta-analysis by Tingle et al. [4], hypothermic machine perfusion significantly reduces the incidence of delayed graft function in kidney transplants, an effect that has not been previously demonstrated in the Swiss kidney transplant population.

The impact of delayed graft function on long-term graft survival in DCD kidney transplants remains controversial [13–16]. Although some studies have suggested that delayed graft function does not significantly impair long-term graft survival or only does so when its duration exceeds 14 days, a recent meta-analysis by Li et al., including 38 publications from 2007 to 2020, reported increased rates of graft failure, acute rejection, and mortality within the first year after transplant [13–16]. These differences in long-term outcomes likely reflect the heterogeneity of delayed graft function, which is more of a syndromic phenotype impacted by the baseline functional tissue mass, the intensity and form of injury, the degree of repair capacity, and the variety of interventions [8, 17].

In the present study, the aim is to identify both risk and protective factors associated with the occurrence of delayed graft function following controlled DCD kidney transplantation.

## Materials and methods

### Study design and data source

This retrospective multicentre cohort study analysed all utilised, controlled DCD kidney transplants performed in Switzerland between 1 September 2011 and 31 August 2024. Donor characteristics and recipient data, including early outcome measures, were extracted from the Swiss Organ Allo-

**ABBREVIATIONS**

**ANRP** abdominal normothermic regional perfusion

**DCD** donation after circulatory death

**FWIT** functional warm ischaemia time

cation System, the national database for organ donation, allocation, and transplantation. Procurement reports were reviewed for timestamps from the procurement process, which were used to calculate relevant ischaemia times.

### Ethics statement

This study meets the criteria of a quality control project as per the guidance document of the ethics committee of the Canton of Bern, Switzerland, which is part of the Swiss Association of Ethics Committees. The study does not fall under the scope of the Human Research Act (Humanforschungsgesetz, Art. 2, Abs. 1) and thus did not require approval by the Bernese Ethics Committee before its implementation (BASEC no. Req-2024-01632).

### Definitions

Delayed graft function was defined as the need for dialysis within the first week following kidney transplantation, the standard definition used in many studies of delayed graft function [8, 9].

In Switzerland, both rapid procurement and aNRP are practised, although aNRP is performed exclusively at the University Hospital of Geneva. fWIT is defined as the interval from the onset of organ hypoperfusion during the agonal phase to the initiation of organ reperfusion with either a cold preservation solution in rapid procurement or normothermic reperfusion using extracorporeal membrane oxygenation in NRP. In the Swiss context, relevant organ hypoperfusion is defined as a mean arterial pressure below 50 mmHg sustained for at least 2 minutes [18]. Hypothermic machine perfusion is routinely employed for controlled DCD kidneys in Switzerland. The device currently in use for kidney graft perfusion in the Swiss transplant system is the LifePort kidney transporter (Organ Recovery Systems, Itasca, IL, USA). This system keeps kidney grafts at a constant temperature of 3-5°C until transplantation while perfusing them with a mean arterial pressure of 30 mmHg [19].

Patient characteristics, such as the medical history data of donors (e.g. history of hypertension), were exported from the Swiss Organ Allocation System, where they were entered according to the medical records of the donors. Diabetes was defined as a diabetic metabolic condition requiring treatment with either oral antidiabetic medications or insulin therapy.

### Statistical analysis

Continuous variables are presented as medians with interquartile ranges (IQRs). Categorical variables are presented as absolute counts and percentages. A complete case analysis was performed. Multivariable analysis was conducted using a logistic regression model to estimate odds ratios (OR) for the occurrence of delayed graft function. The variables included in the model were donor age and comorbidity (including a history of hypertension, cardiovascular comorbidities, and diabetes), out-of-hospital resuscitation, cause of death (anoxia, stroke, or other), year of transplantation, fWIT, cold ischaemia time, procurement technique (aNRP or rapid procurement), and preservation method (hypothermic machine perfusion or static cold storage). For continuous variables, donor age, ischaemia times (cold ischaemia time and fWIT), and calendrical year of transplantation, the assumption of linearity in relation to the occurrence of delayed graft function was relaxed using restricted cubic splines, allowing the model to capture both linear and nonlinear associations. With 315 events for the primary outcome, 20 coefficients were estimated in the model, yielding an events-per-parameter ratio of 15.8, which is considered sufficient to minimise the risk of overfitting. Because observations were not independent (some recipients received their kidney from the same donor), the donor identifier was included as a cluster term in the model, and robust covariance estimates were used. All statistical analyses were performed using R version 4.5.2 (https://www.r-project.org/, available as Free Software under the terms of the Free Software Foundation's GNU General Public License), and regression analyses were performed with the rms package version 8.1-0.

### Missing data

Cases with missing data were as follows: 24 (3.4%) without information about fWIT, 18 (2.5%) without information about cardiovascular comorbidities, 15 (2.1%) without information about resuscitation, 8 without information about hypertension, 4 without information about diabetes, and 2 without information about aNRP. For several recipients, data for more than one variable were missing. Demographic and clinical characteristics were compared, and substantial differences between excluded and included recipients were identified. Missing data were likely due to documentation

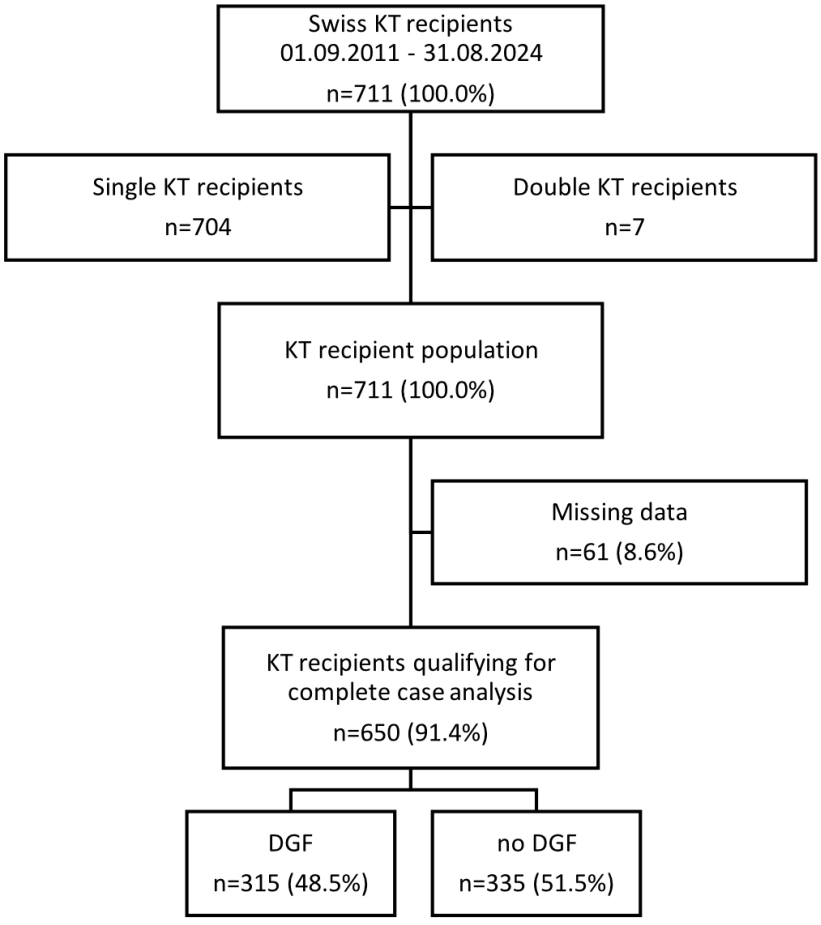
failures or illegible records. Thus, data were assumed to be missing at random. Given the low proportion of missingness in the individual variables, multiple imputation was not performed, and a complete case analysis was carried out.

## Results

### Study population

Over the 13-year period, 499 controlled DCD donors were identified and 384 were utilised, resulting in a total of 711 kidney transplantations. Seven transplants were dual transplants in which both kidneys from a single donor were allocated to the same recipient. A total of 61 kidney transplants (8.6%) were excluded because of missing data, and 650 kidney transplants (91.4%) derived from 351 donors qualified for a complete case analysis (figure 1). Among the 650 kidney transplants included in the analysis, 315 recipients (48.5%) developed delayed graft function, while 335 (51.5%) did not.

**Figure 1:** Flow diagram showing DCD kidney recipient inclusion and exclusion criteria. Abbreviations: KT = kidney transplant; DGF = delayed graft function.




Donor and recipient characteristics are summarised in table 1.

**Table 1:** Donor characteristics, graft storage and recipient characteristics.

| | | | |
|---|---|---|---|
| Donor characteristics (n = 351) | Age in years, median (IQR) | | 59.0 (48.0–65.0) |
| | Male sex, n (%) | | 237 (67.5) |
| | Hypertension, n (%) | | 114 (32.5) |
| | Cardiovascular comorbidities, n (%) | | 84 (23.9) |
| | Diabetes, n (%) | | 15 (4.3) |
| | Cause of death | Anoxia, n (%) | 178 (50.7) |
| | | Stroke, n (%) | 77 (21.9) |
| | | Other, n (%) | 96 (27.4) |
| | fWIT in minutes, median (IQR) | | 25.0 (20.0–31.0) |
| | aNRP, n (%) | | 59 (16.8) |
| | Out-of-hospital reanimation, n (%) | | 174 (49.6) |
| Graft storage (n = 650) | Hypothermic machine perfusion, n (%) | | 479 (73.7) |
| | Cold ischaemia time in hours, median (IQR) | | 9.1 (7.4–11.3) |
| Recipient characteristics (n = 650) | Age in years, median (IQR) | | 58.0 (49.0–66.0) |
| | Male sex, n (%) | | 409 (62.9) |

Abbreviations: fWIT = functional warm ischaemia time; aNRP = abdominal normothermic regional perfusion

### Modelling delayed graft function

Multivariable logistic regression analysis (table 2) demonstrated that procurement with aNRP significantly decreased the risk of delayed graft function (OR 0.18, 95% CI 0.09–0.33, p <0.001). Hypothermic machine perfusion also significantly reduced the risk of delayed graft function (OR 0.55, 95% CI 0.36–0.83, p = 0.004). Longer cold ischaemia time was associated with a higher rate of delayed graft function (OR 1.33, 95% CI 1.01–1.73, p = 0.110), but the association did not reach conventional levels of statistical significance. fWIT showed no evidence of an effect on the occurrence of delayed graft function (OR 1.00, 95% CI 0.73–1.36, p = 0.420). No significant associations were observed for the remaining variables in the model, as detailed in table 2.

**Table 2:** Risk and protective factors for delayed graft function. For the three continuous variables (donor age, fWIT, and cold ischaemia time), the odds ratios represent the effect of a change from the lower to the upper limit of the interquartile range (IQR).

| | Interquartile difference (IQR) | Odds ratio (95%-CI) | Chi-square | d.f. | p-value |
|---|---|---|---|---|---|
| **Donor characteristics** | | | | | |
| Age, in years | 17.0 (48.0–65.0) | 1.14 (0.87–1.50) | 2.16 | 2 | 0.34 |
| *... nonlinear* | – | – | 0.174 | 1 | 0.68 |
| Hypertension | – | 1.34 (0.87–2.07) | 1.78 | 1 | 0.18 |
| Cardiovascular comorbidities | – | 0.79 (0.50–1.26) | 0.969 | 1 | 0.32 |
| Diabetes | – | 1.32 (0.48–3.61) | 0.282 | 1 | 0.60 |
| Out-of-hospital resuscitation | – | 1.02 (0.56–1.83) | 0.003 | 1 | 0.96 |
| Cause of death | – | – | 2.67 | 2 | 0.26 |
| -Anoxia | – | 0.61 (0.33–1.12) | – | – | – |
| -Stroke | – | 0.82 (0.47–1.43) | – | – | – |
| fWIT, in minutes | 11.0 (20.0–31.0) | 1.00 (0.73–1.36) | 1.74 | 2 | 0.42 |
| *... nonlinear* | – | – | 0.436 | 1 | 0.51 |
| aNRP | – | 0.18 (0.09–0.33) | 28.5 | 1 | <0.001 |
| Transplantation year | 5.0 (2018–2023) | 1.03 (0.67–1.58) | 0.032 | 2 | 0.98 |
| **Graft storage** | | | | | |
| Cold ischaemia time, in hours | 4.0 (7.3–11.3) | 1.33 (1.01–1.73) | 4.38 | 2 | 0.11 |
| *... nonlinear* | – | – | 2.16 | 1 | 0.14 |
| Hypothermic machine perfusion | – | 0.55 (0.36–0.83) | 8.12 | 1 | 0.004 |

Abbreviations: IQR = interquartile range; CI = confidence interval; fWIT = functional warm ischaemia time; aNRP = abdominal normothermic regional perfusion

## Discussion

We observed a reduction of approximately 80% in the likelihood of delayed graft function with the use of aNRP and a reduction of approximately 50% with the use of hypothermic machine perfusion, after adjusting for other risk factors, such as donor age, comorbidities, cause of death, and warm and cold ischaemia times.

The beneficial effect of modern organ procurement and preservation strategies, specifically aNRP and hypothermic machine perfusion, on early transplant outcomes has been well documented over the past decade. During this time, an increasing number of transplant centres in Europe have adopted aNRP and hypothermic machine perfusion for recipients considered high-risk, in high-volume centres, or even as standard practice [4–7, 11, 20, 21].

The significant reduction in delayed graft function risk associated with the use of aNRP as an independent factor is striking, yet consistent with current literature. Padilla et al. compared two Spanish cohorts (RP, n = 1437; aNRP, n = 865) with respect to short- and long-term outcomes after kidney transplantation. Following propensity score matching, the RP group exhibited a significantly higher risk of delayed graft function compared with the aNRP group. Donor age, prevalence of donor arterial hypertension, fWIT, and recipient age of the matched Spanish study population (n = 335 for both RP and NRP) were largely comparable with those in the present Swiss cohort. Cold ischaemia time in the Spanish study was notably longer, with a median of 14.4 and 14.8 hours for RP and aNRP, respectively, compared with 9.1 hours in the Swiss cohort [6]. Oniscu et al. [5] evaluated two British DCD cohorts (rapid procurement, n = 5744; NRP, n = 210) for post-transplant outcomes. Here, the overall incidence of delayed graft function was lower than in the groups from Switzerland and Spain because of the younger donor age. However, again, the NRP group demonstrated a significantly lower incidence of delayed graft function compared with the rapid procurement group [5].

Increased functional warm and cold ischaemia times have been associated with a higher risk of delayed graft function in DCD kidney transplants, and most importantly, they are risk factors for the discarding of recovered kidneys [22, 23]. Our analysis found no or only weak evidence supporting ischaemia times as independent risk factors for delayed graft function. Prolonged fWIT may not significantly affect delayed graft function risk as long as it remains below 40 minutes [20]. In our cohort, the median fWIT was 25 minutes. In a previous analysis, based on data that included the current study population, we found no significant difference in fWIT between rapid procurement and NRP cohorts [24]. The extent to which fWIT can be reduced through NRP depends heavily on the timing and nature of pre-mortem interventions such as heparin administration and early cannulation. In Switzerland, heparin administration and guide-wire placement are performed before brain death diagnosis, whereas cannulation is carried out after confirmation of death following a mandatory no-touch period of 5 minutes. By contrast, in Spain, both heparin administration and cannulation are practised pre-mortem. This procedural difference, despite overall comparable cut-offs for observation and ischaemia times, may explain the findings reported by Padilla et al. [6], who observed a longer fWIT in rapid procurement (18 minutes) compared with the NRP group (13 minutes). Conversely, Oniscu et al. [5] reported a shorter fWIT in the rapid procurement group (18 minutes) compared with the NRP group (23 minutes) in a British cohort, in which no pre-mortem cannulation was performed.

The beneficial effect of hypothermic machine perfusion on delayed graft function observed in DCD kidney transplants is consistent with current evidence. In two meta-analyses, Tingle et al. [4, 21] reported a relative risk of 0.77 and 0.78, respectively, for delayed graft function in kidneys preserved with hypothermic machine perfusion compared with static cold storage. They concluded that hypothermic machine perfusion significantly reduced the risk of delayed graft function and improved long-term graft survival, making it a cost-effective intervention overall. Whereas Tingle et al. presented their results using relative risk, we used odds ratios, which are not directly comparable. Nevertheless, despite differences in study design and statistical methodology, our findings support and align with the conclusions of Tingle et al., reinforcing the effectiveness of hypothermic machine perfusion in reducing the incidence of delayed graft function.

In the Swiss transplant setting, where procurement and transplant centres are located in relatively close geographical proximity, cold ischaemia time for kidney grafts can be kept relatively short. This is reflected in the median cold ischaemia time of 9.1 hours. Most studies included in the meta-analyses by Tingle et al. [4, 21] reported median cold ischaemia times exceeding 10.0 hours, and Padilla et al. [6] and Brennan et al. [22] reported even longer median cold ischaemia times, over 12.0 and 18.0 hours, respectively, depending on procurement methods and fWIT groupings.

Therefore, it is plausible that the relatively short cold ischaemia time in the Swiss DCD kidney transplant cohort is below the threshold at which a significant impact on delayed graft function would be expected. This interpretation is supported by the findings of Savoye et al. [20], who reported a median cold ischaemia time of 8.8 (IQR 7.1–12.1) hours in a cohort of 905 French kidney transplants and identified a cold ischaemia time of 10.0 hours or more as a significant risk factor for delayed graft function (OR 1.59, 95% CI 1.08–2.34, p = 0.017).

One limitation of our study is the known inadequacy of delayed graft function as a prognostic outcome marker [8, 9, 14, 17]. However, because of the lack of a robust early predictor of long-term kidney function, almost all studies use delayed graft function, defined as dialysis treatment during the first 7 postoperative days, as a primary outcome [4–6, 9, 13–16, 21]. The near-universal use of this simple and pragmatic delayed graft function definition facilitates the comparability of studies but does not capture the complexity of factors impacting organ quality, injury, and regenerative capacity [8, 9, 17]. Further studies are warranted to identify reliable predictive markers to investigate the effects of aNRP and hypothermic machine perfusion on mid- to long-term outcomes [8, 25].

A critical but ubiquitous weakness of studies on risk factors and outcomes is the lack of standardised processes in DCD donors and recipients [26–28]. The Swiss DCD policies and protocols are relatively standardised [18]. However, the specific geography facilitating short cold ischaemia times and the major variability in donor and recipient selection and allocation criteria, donor management, pre-procurement interventions, procurement techniques, and postoperative care across and within countries impact representativeness and comparability of findings in DCD studies [26–28]. The homogeneity of our large DCD cohort and the overall lower cold ischaemic organ damage seem to uncover otherwise attenuated effects such as fWIT or perfusion techniques. Another limitation concerns the nature of clinical data entry into the Swiss Organ Allocation System. Data are recorded based on clinical records and medical findings. Conditions such as hypertension or diabetes are documented as binary variables, without information on the time of diagnosis, disease stage, treatment, or clinical course, which limits the granularity of the statistical analysis.

The study represents the largest cohort of kidney transplants in Switzerland since the reintroduction of the DCD programme on 1 September 2011. We collected robust data on an increasingly relevant modality of kidney transplantation in the Swiss context, comparing standardised modern procurement and preservation techniques across ten different procurement centres.

In total, this observational study included 351 kidney donors, resulting in 650 kidney transplants over a 13-year period. To our knowledge, this constitutes the largest dataset of DCD kidney transplants reported in Switzerland. The findings of our study are consistent with those of other European research and reinforce the effectiveness of contemporary procurement and preservation strategies in kidney transplantation. Notably, we found no evidence of an association between fWIT and delayed graft function and only weak evidence for cold ischaemia time as a risk factor, which may be explained by the comparatively short ischaemia times observed in our cohort. Donor age and comorbidity also showed no significant association with the occurrence of delayed graft function. Given the strong beneficial effect of aNRP on early post-transplant outcomes, our results support the further extension of aNRP programmes in the Swiss transplant system.

## Data availability statement

Access to Swiss Organ Allocation System (SOAS) data requires permission from the Federal Office of Public Health. The website https://www.gate.bag.admin.ch/artx/ui/home contains information on research data access to SOAS.

**Acknowledgments**

The authors thank the Swiss transplant centres, the Federal Office of Public Health (FOPH), and Swisstransplant for their contributions to collecting, managing, and exporting data. The data included in this study were originally exported and analysed within the scope of the first author's dissertation at the University of Bern, Switzerland [24]. The main findings of the study were presented in an oral presentation at the 2025 ESOT Congress in London.

**Author contributions:** FI, JW, and MB participated in the research design, as well as the interpretation of the results and the preparation of the draft manuscript. SS participated in data analysis and FB in data extraction. All authors critically revised the manuscript and approved the submitted version.

## Financial disclosure

This study received no funding.

## Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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