Effect of kidney replacement therapy modality after first kidney graft failure on second kidney transplantation outcomes

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ABSTRACT

Background. There is a lack of information regarding which is the best dialysis technique after kidney transplant (KT) failure. The aim of this study is to compare the effect of kidney replacement therapy modality-peritoneal dialysis (TX-PD-TX), haemodialysis (TX-HD-TX) and preemptive deceased donor retransplantation (TX-TX) on patient survival and second KT outcomes.

Methods. A retrospective observational study from the Catalan Renal Registry was carried out. We included adult patients with failing of their first KT from 2000 to 2018.

Results. Among 2045 patients, 1829 started on HD (89.4%), 168 on PD (8.2%) and 48 (2.4%) received a preemptive KT. Non-inclusion on the KT waiting list and HD were associated with worse patient survival. For patients included on the waiting list, the probability of human leucocyte antigens (HLA) sensitization and to receive a second KT was similar in HD and PD. A total of 776 patients received a second KT (38%), 656 in TX-HD-TX, 72 in TX-PD-TX and 48 in TX-TX groups. Adjusted mortality after second KT was higher in TX-HD-TX patients compared with TX-TX and TX-PD-TX groups, without differences between TX-TX and TX-PD-TX groups. Death-censored second graft survival was similar in all three groups.

Conclusions. Our results suggest that after first KT failure, PD is superior to HD in reducing mortality in candidates for a second KT without options for preemptive retransplantation.

Keywords: allograft failure, dialysis, kidney replacement therapy, kidney transplantation, transitional care
INTRODUCTION

Kidney graft failure is an increasingly common issue because of a greater pool of kidney transplant (KT) recipients. Failed KT's account for 13.1% of the incident dialysis population in Catalonia and represent 35.2% of the patients on the kidney transplant waiting list [1]. This population shows increased morbidity and mortality in comparison with non-pretreated end-stage kidney disease (ESKD) patients starting dialysis. However, little attention has been given to this period of kidney replacement therapy (KRT) transition, when patients suffer from higher rates of complications [2]. Therefore, there is a lack of data on most issues related to patient and graft management of the failing transplant.

Regarding the modality of KRT, preemptive kidney retransplantation provides the best outcomes, in view of larger survival and better quality of life [3]. However, this option is nearly exclusive for living donor transplants in most countries, and most patients return to dialysis. However, there are few studies comparing the outcomes depending on the preferred dialysis technique. In a recent review [4], Fiorentino et al. summarized five studies [5–9] comparing outcomes of peritoneal dialysis (PD) and haemodialysis (HD) patients with failed primary KT's and concluded that it is still a matter of debate. Most of the studies were published >10 years ago and did not find differences in survival [5, 6] or if found, they were attributed to patient comorbidities. Regarding PD, it seems that there was a trend to better survival during the first year but worse thereafter. Moreover, there are no data about the impact of the dialysis modality on second KT outcomes.

In the present study, we have analyzed data from the Catalan Registry of Renal Patients to determine whether the type of dialysis modality (HD or PD) after first kidney allograft failure, in comparison with those patients receiving a preemptive deceased donor second KT, has an impact on patient survival and second KT outcomes.

MATERIALS AND METHODS

After gaining the approval of the Institutional Review Board, we used data from the Registry of Renal Patients of Catalonia (RMRC). This is a mandatory population-based registry covering 7.5 million people that collects information on all patients with ESKD requiring KT in Catalonia. At the time of starting KT and at every change of treatment throughout KT, a registration form is filled in. Every year an update must be carried out and sent to the RMRC up to the finalization of KT, death of patient or loss of follow-up.

Study population

A retrospective observational study has been carried out with the analysis of data from patients with failing of their first kidney allograft in Catalonia from 2000 to 2018. Patients with multi-organ transplantation and patients that received a second living donor KT were excluded. Among the 2045 patients identified and selected for the study, 776 received a second KT from a deceased donor (Fig. 1). All cases were followed-up until December 2018.

Data analysis

Patients were classified in the following groups depending on the KRT strategy for the second transplant: from failed first KT to HD and then second KT (TX-HD-TX); from failed first KT to PD and then second KT (TX-PD-TX) and from failed KT directly to second KT (TX-TX). Details on group assignments are shown in Supplementary data, Table S1. We also analysed the patients who did not receive a second KT and remained on dialysis (HD or PD) depending on their KT waiting list situation (included or not included). The collected variables were gender, age, diabetes mellitus, cardiovascular disease, panel reactive antibody (PRA) by cellular cytotoxicity (CDC), functional autonomy defined by the Karnofsky scale adapted for dialysis patients [10], inclusion on the waiting list and time in dialysis before second KT. We collected and also calculated PRA (Luminex) in patients who lost their graft between 2014 and 2018.

Comparisons between groups were performed by Chi-squared test for categorical data and analysis of variance or Kruskal–Wallis equality-of-populations rank test for continuous data (P < .05 was considered significant). Baseline characteristics of the study cohort were expressed as a number and a proportion, mean ± standard deviation (SD) or median and interquartile range.
Table 1. Baseline characteristics of patients after first kidney graft failure depending on kidney replacement therapy

| Variable                          | Total (n = 2045) | HD (n = 1829) | PD (n = 168) | TX (n = 48) | P-value | Missing (%) |
|-----------------------------------|-----------------|---------------|-------------|------------|---------|-------------|
| Gender (n, %)                     |                 |               |             |            |         |             |
| Male                              | 1244 (60.8)     | 1122 (61.3)   | 93 (55.4)   | 29 (60.4)  | .314    | 0           |
| Female                            | 801 (39.2)      | 707 (38.7)    | 75 (44.6)   | 19 (39.6)  |         |             |
| Age at first TX (n, %)            |                 |               |             |            |         |             |
| 0–44 years                        | 737 (36.0)      | 636 (34.8)    | 81 (48.2)   | 20 (41.7)  |         |             |
| 45–64 years                       | 932 (45.6)      | 837 (45.8)    | 74 (44.0)   | 21 (43.7)  |         |             |
| >65 years                         | 376 (18.4)      | 356 (19.4)    | 13 (7.8)    | 7 (14.6)   | <.001   | 0           |
| Diabetes                          |                 |               |             |            |         |             |
| No                                | 1412 (69.0)     | 1241 (67.9)   | 137 (81.5)  | 34 (70.8)  | .001    | 0           |
| Yes                               | 633 (31.0)      | 588 (32.1)    | 31 (18.5)   | 14 (29.2)  | .001    | 0           |
| Cardiovascular disease (n, %)     |                 |               |             |            |         |             |
| No                                | 988 (48.9)      | 851 (47.1)    | 109 (65.2)  | 28 (56.2)  | <.001   | 1           |
| Yes                               | 1030 (51.1)     | 955 (52.9)    | 58 (34.8)   | 17 (37.8)  | <.001   | 1           |
| First TX type (n, %)              |                 |               |             |            |         |             |
| Deceased                          | 1919 (93.8)     | 1719 (94.0)   | 158 (94.0)  | 42 (87.5)  |         |             |
| Live                              | 126 (6.2)       | 110 (6.0)     | 10 (6.0)    | 6 (12.5)   | .181    | 0           |
| %PRA (n, %)                       |                 |               |             |            |         |             |
| 0–10%                             | 1666 (95.4)     | 1500 (95.5)   | 127 (93.4)  | 29 (93.5)  |         |             |
| 11–50%                            | 66 (3.8)        | 57 (3.7)      | 7 (5.1)     | 2 (6.5)    |         |             |
| >50%                              | 15 (0.8)        | 13 (0.8)      | 2 (1.5)     | 0 (0)      | .548    | 15          |
| Cause of first TX failure (n, %)  |                 |               |             |            |         |             |
| PNF                               | 60 (3.4)        | 59 (3.7)      | 1 (0.7)     | 0 (0)      |         |             |
| Surgical complications            | 199 (11.1)      | 176 (10.9)    | 16 (10.5)   | 7 (33.3)   |         |             |
| Chronic damage                    | 1177 (65.9)     | 1062 (65.8)   | 102 (67.1)  | 13 (61.9)  |         |             |
| Acute rejection                   | 102 (5.7)       | 93 (5.8)      | 9 (5.9)     | 0 (0)      |         |             |
| Other                             | 249 (13.9)      | 224 (13.8)    | 24 (15.8)   | 1 (4.8)    | .084    | 13          |
| First TX survival (median month, P25-P75) | 81 (23–148)   | 83 (23–147)   | 86 (37–155) | 58 (12–159) | .359    | 0           |
| Age at first graft failure (Years (SD)) | 56.9 (15.1) | 57.6 (14.9) | 51.5 (15.6) | 51.9 (18.2) | <.001   | 0           |
| Functional autonomy (n, %)        |                 |               |             |            |         |             |
| Normal/nearly normal              | 1357 (80.9)     | 1212 (79.8)   | 127 (92.0)  | 18 (85.7)  |         |             |
| Limited                           | 244 (14.6)      | 232 (15.3)    | 10 (7.2)    | 2 (9.5)    |         |             |
| Dependent/hospitalized            | 76 (4.5)        | 74 (4.9)      | 1 (0.8)     | 1 (4.8)    | .004    | 18          |

HD, haemodialysis; PD, peritoneal dialysis; PNF, primary non function; PRA, panel reactive antibody; SD, standard deviation; TX, transplant.

For the multivariable analysis, all models were initially adjusted by gender, age, diabetes mellitus, previous cardiovascular event (ischaemic heart disease, heart failure, peripheral vascular disease and cerebrovascular disease), type of first KT (living or deceased donor), CDC before first KT, functional status and dialysis duration before second KT. Finally, only statically significant variables ($P < .05$) and gender, age and type of KRT after first graft failure were considered in the chosen models.

We analysed patient survival after the first graft loss and after the second KT. Also, survival of the second graft was determined for each group. Survival analysis was performed by using the Kaplan–Meier in the univariate and the Cox regression in the multivariable analysis. All statistical tests were considered significant if $P < .05$ for two-tailed tests. Analyses were performed using STATA software version 13.

**RESULTS**

**Failing kidney allograft population outcomes**

Overall, there were 2045 patients with failing kidney allografts during the study period. Among them, 1829 started on in-centre HD (89.4%), 168 started on PD (8.2%) and 48 (2.4%) received a preemptive deceased donor kidney allograft. Baseline characteristics of this population are shown in Table 1. The mean follow-up was 5.3 years. After the first graft loss, the probability of receiving a second KT was similar to deceased (Fig. 2A). Patients returning to HD were older, had a higher prevalence of diabetes and cardiovascular disease and showed lower functional autonomy. Therefore, the proportion of patients reincluded in the KT waiting list was higher in PD than in HD ($P = .002$). However, for patients included on the waiting list, the probability of receiving a second KT was similar in HD and PD (Fig. 2B). For patients included on the waiting list the meantime to receive a second KT is 18.4 ± 11 and 18.1 ± 13 months for TX-HD-TX and TX-PD-TX, respectively. Human leucocyte antigens (HLA) sensitization determined by Luminex was available after first kidney failure in patients who lost their graft between 2014 and 2018 without showing differences between HD and PD (data not shown).

We then compared patient survival between patients remaining on HD, PD and patients receiving a second KT (Fig. 3A). Survival was similar either in patients remaining on PD or HD and both significantly lower than survival in patients that received a second deceased donor KT. Patients on dialysis, waitlisted and not retransplanted had better survival than...
Effect of KRT after graft failure

FIGURE 2: (A) Death and second kidney transplantation probability after first kidney graft failure. (B) Probability of receiving a second kidney transplant in waitlisted patients, comparing haemodialysis (HD) with peritoneal dialysis (PD). Once included on the waiting list, probability of receiving a second transplant is similar in both HD and PD groups ($p = 0.735$).

Among the 2045 patients included, 776 received a second KT (38%): 656 TX-HD-TX (84.5%), 72 TX-PD-TX (9.3%) and 48 TX-TX (6.2%). Baseline characteristics are shown in Table 3. TX-HD-TX patients on dialysis not waitlisted, yet lower than those retransplanted (Fig. 3B). Comparing PD versus HD, the beneficial effect of PD on survival was only observed in the cohort of patients that received a second kidney allograft (Fig. 3B). Multivariable adjusted models for patient survival after the first KT showed that variables associated with survival were age, diabetes, cardiovascular disease, non-inclusion on the waiting list, HD as KRT and functional status (Table 2). Interestingly, better survival was associated with TX-TX and TX-PD transition. Major causes of death in HD were cardiovascular (39.3%), infection (24.6%) and cancer (9.2%) and in PD were cardiovascular (46.6%), infection (15.6%) and cancer (2.2%). Causes of death after first kidney allograft failure are detailed in Supplementary data, Table S2.

Recipients of a second KT

Among the 2045 patients included, 776 received a second KT (38%): 656 TX-HD-TX (84.5%), 72 TX-PD-TX (9.3%) and 48 TX-TX (6.2%). Baseline characteristics are shown in Table 3. TX-HD-TX
patients were older and had a higher prevalence of diabetes and cardiovascular disease. The period on dialysis was similar in TX-HD-TX and TX-PD-TX. Early graft loss (<90 days after kidney transplantation), acute rejection as the cause of graft failure and renal function during the first year after retransplantation were similar among all the three groups, as shown in Table 4.

We then compared patient survival (Fig. 4A) and death-censored graft survival (Fig. 4B) between TX-TX, TX-HD-TX and TX-PD-TX groups. Multivariable adjusted models for patient and graft survival after a second KT are shown in Table 5. Variables associated with mortality were age, diabetes, cardiovascular disease, limited functional status and HD-TX transition. Variables associated with death-censored second graft survival were female gender and age. Major causes of death in TX-HD-TX were cardiovascular (31.9%), infection (27.9%), and cancer (11.7%), and in TX-PD-TX were cardiovascular (40%) and infection (20%). All
evolution between both groups may be caused by the proinflammatory state in which these patients are, causing anaemia and malnutrition and making them more susceptible to infections [18, 19].

When living donor KT is not feasible, preemptive deceased-donor kidney retransplantation represents the optimal therapy for patients who lose kidney allograft, exhibiting greater patient and graft survival, thanks to avoiding the morbidity and mortality associated with dialysis initiation [3, 15, 20]. However, this option is not always possible due to patient comorbidities or limited because of HLA sensitization, or by the fact that time on dialysis is a relevant criterion in our allocation score. Thus, only 2.4% of patients from our cohort received a preemptive second KT and therefore, most patients needed to start dialysis. A comparable preemptive retransplantation rate is shown in a US study [13].

In our cohort, most patients were on HD rather than PD. Regarding inclusion on the waiting list for a second KT, patients on PD were more frequently included than patients on HD. This observation is consistent with the fact that HD patients were older, showed more cardiovascular comorbidities and had inferior functional status. However, once included in the waiting list, the probability and the waiting time for receiving a second KT were similar among HD and PD patients. Likewise, in a registry-based study from the US Renal Data System, the median time to retransplantation was ~2 years, and when comparing time to retransplantation between PD and HD groups in a multivariable propensity score analysis, no differences were observed [8].

Management of immunosuppressant in patients with failing allograft is subjective because of the lack of clinical evidence. Practice for tapering immunosuppression may be critical for preventing HLA sensitization and it could be different between HD and PD. Unfortunately, in our registry, we do not have data on immunosuppression tapering. However, our observation that HLA sensitization determined by Luminess was similar in patients on HD and PD indirectly suggests that the management of immunosuppression was comparable. This similar HLA sensitization after graft failure in patients on HD and PD may explain the similar probability of transplantation in both groups. Comparable HLA sensitization between HD and PD groups after allograft loss is found in other studies [8].

Evidence to determine whether HD or PD after allograft failure is better in terms of survival are scarce and sometimes contradictory. The main studies in the field comparing HD with PD were summarized in a recent review [4] which concluded that the choice of dialysis modality after graft failure should be based on clinical characteristics due to a lack of definitive evidence in the scientific literature. Regarding PD, some studies find a temporary benefit in the first period of the technique (approximately the first year) either in transplant-naïve patients [21] or those suffering from allograft loss [8], which is lost afterward.

Our study underscores the beneficial impact of receiving a second KT in patients on dialysis after first graft failure. Patient survival was higher in both HD and PD patients comparing transplantation versus no transplantation, and even when comparing transplantation versus waitlisted but not transplanted. Beyond the well-known KT benefit, we tried to ascertain whether the dialysis modality may also influence patient survival after the first graft failure. Our results suggest that PD is superior to HD in terms of patient survival, particularly in patients that received a second KT, and provides similar outcomes to preemptive second KT. In spite of this, for patients that are not retransplanted, the increased survival associated with PD seems to have vanished. The different impact of dialysis modality on survival, depending on whether the patient is suitable for a second KT or not, may explain some discrepancies in previous studies, as only

Table 2. Multivariable model of patient survival after first kidney transplant

| Gender              | Ref | HR   | 95% CI       |
|---------------------|-----|------|-------------|
| Male                |     | 0.90 | 0.78–1.04   |
| Female              |     |      |             |

| Age                 | Ref | HR   | 95% CI       |
|---------------------|-----|------|-------------|
| 0–44 years          |     | 3.70 | 3.02–4.52   |
| 45–64 years         |     | 10.86| 8.38–14.07  |
| >64 years           |     |      |             |

| Diabetes            | Ref | HR   | 95% CI       |
|---------------------|-----|------|-------------|
| No                  |     | 1.21 | 1.05–1.41   |
| Yes                 |     |      |             |

| Cardiovascular disease | Ref | HR   | 95% CI       |
|------------------------|-----|------|-------------|
| No                     |     | 1.23 | 1.06–1.43   |
| Yes                    |     |      |             |

| KRT transition after first graft failure | Ref | HR   | 95% CI       |
|------------------------------------------|-----|------|-------------|
| TX-PD-TX                                |     | 2.80 | 0.79–9.93   |
| TX-TX                                   |     | 9.28 | 3.45–25.00  |
| TX-HD (no WL)                           |     | 7.08 | 2.62–19.08  |
| TX-HD (WL)                              |     | 3.71 | 1.37–10.01  |
| TX-TX-TX                               |     | 13.32 | 4.56–38.94 |
| TX-PD-TX (no WL)                        |     | 5.39 | 1.77–16.41  |
| TX-PD (WL)                              |     |      |             |

| Functional autonomy | Ref | HR   | 95% CI       |
|---------------------|-----|------|-------------|
| Normal/nearly normal|     | 1.48 | 1.17–1.87   |
| Limited              |     |      |             |
| Dependent/hospitalized|   | 4.34 | 2.89–6.53   |

CI, confidence interval; KRT, kidney replacement therapy; HR, hazard ratio; WL, waiting list.

causes of death after the second KT are detailed in Supplementary data, Table S3.

DISCUSSION

Management of kidney allograft failure is guided by poor evidence and stands as a current clinical issue. Patients with a failed allograft have increased in the last decade, representing ~3% of the incident dialysis population in the USA [11] or even as much as 15% in some European regions like Catalonia [1]. Moreover, this group of patients represents an important proportion of waitlisted people for KT [11].

Following graft failure, living donor repeated transplantation is the best option [12]. However, in Spain this path is uncommon, and most patients are evaluated for a second deceased donor KT. Thus, to minimize transplantation bias, we excluded recipients of second KT from a living donor. The Spanish health system guarantees to chronic kidney disease population universal evaluation for KT feasibility as demonstrated by the fact that almost 60% of patients are relisted for second transplantation in our cohort. Similar [13] or lower [14] overall relisting in patients with allograft failure are depicted in other studies. Despite this fact, after the first kidney graft failure, we observed that the probability to receive a second KT is similar to dying. Patients from our cohort were quite older (~10 years) compared with other studies [7, 15]. It is well-known that mortality in patients requiring dialysis after kidney graft loss is higher than in transplant-naïve peers [16, 17]. This difference in the evolution between both groups may be caused by the proinflammatory state in which these patients are, causing anaemia and...
Table 3. Second kidney transplant recipient baseline characteristics depending on previous kidney replacement therapy

| Variable, n (%) | Total (n = 776) | TX-TX (n = 48) | TX-HD-TX (n = 656) | TX-PD-TX (n = 72) | P-value | Missing (%) |
|----------------|----------------|----------------|-------------------|-------------------|---------|-------------|
| Gender         |                |                |                   |                   |         |             |
| Male           | 471 (60.7)     | 29 (60.4)      | 401 (61.1)        | 41 (56.9)         | .788    | 0           |
| Female         | 305 (39.3)     | 19 (39.6)      | 255 (38.9)        | 19 (43.1)         |         |             |
| Age at first TX|                |                |                   |                   |         |             |
| 0–44 years     | 254 (32.7)     | 12 (25)        | 208 (31.7)        | 34 (47.2)         |         |             |
| 45–64 years    | 380 (49.0)     | 25 (52.1)      | 323 (49.2)        | 32 (44.4)         |         |             |
| >64 years      | 142 (18.3)     | 11 (22.9)      | 125 (19.1)        | 6 (8.3)           | .029    | 0           |
| Diabetes       |                |                |                   |                   |         |             |
| No             | 652 (84.6)     | 41 (89.1)      | 541 (82.9)        | 70 (97.2)         | .004    | 1           |
| Yes            | 119 (15.4)     | 5 (10.9)       | 112 (17.1)        | 2 (2.8)           | .004    | 1           |
| Cardiovascular disease |    |                |                   |                   |         |             |
| No             | 336 (44.1)     | 26 (62.2)      | 267 (41.1)        | 43 (59.7)         | .788    | 0           |
| Yes            | 429 (55.9)     | 17 (37.8)      | 383 (58.9)        | 29 (40.3)         | .482    | 0           |
| First TX type  |                |                |                   |                   |         |             |
| Deceased       | 714 (92)       | 42 (87.5)      | 606 (92.4)        | 66 (91.7)         | <.001   | 1           |
| Live           | 62 (8)         | 6 (12.5)       | 50 (7.6)          | 6 (8.3)           | .482    | 0           |
| %PRA           |                |                |                   |                   |         |             |
| 0–10%          | 637 (95.5)     | 39 (95.1)      | 541 (95.6)        | 57 (95.0)         |         |             |
| 11–50%         | 25 (3.8)       | 2 (4.9)        | 21 (3.7)          | 2 (3.3)           |         |             |
| >50%           | 5 (0.8)        | 0 (0)          | 4 (0.7)           | 1 (1.7)           | .741    | 14          |
| Functional autonomy |       |                |                   |                   |         |             |
| Normal/nearly normal | 618 (92.1)    | 18 (85.7)      | 546 (91.8)        | 618 (92.1)        |         |             |
| Limited        | 47 (7)         | 2 (9.5)        | 44 (7.4)          | 47 (7.0)          |         |             |
| Dependent/hospitalized | 6 (0.9)       | 1 (4.8)        | 5 (0.8)           | 6 (0.9)           | .132    | 14          |
| Time until second transplant |        |                |                   |                   |         |             |
| <1 year        | 158 (21.7)     | 42 (87.5)      | 141 (21.5)        | 17 (23.6)         | .679    | 0           |
| >1 year        | 570 (78.3)     | 17 (37.8)      | 515 (78.5)        | 55 (76.4)         | .679    | 0           |
| Death          |                |                |                   |                   |         |             |
| No             | 590 (76)       | 40 (83.3)      | 482 (73.5)        | 68 (94.4)         | <.001   | 0           |
| Yes            | 186 (24)       | 8 (16.7)       | 174 (26.5)        | 4 (5.6)           | .376    | 0           |
| Second kidney graft failure |        |                |                   |                   |         |             |
| No             | 603 (77.7)     | 39 (81.2)      | 504 (76.8)        | 60 (83.3)         |         |             |
| Yes            | 173 (22.3)     | 9 (18.8)       | 152 (23.2)        | 12 (16.7)         |         |             |

HD, haemodialysis; PD, peritoneal dialysis; PRA, panel reactive antibodies; TX, transplant.

Table 4. Second kidney graft evolution depending on previous kidney replacement therapy

| Variable, n, % | Total (n = 776) | TX-TX (n = 48) | TX-HD-TX (n = 656) | TX-PD-TX (n = 72) | P-value | Missing (%) |
|----------------|----------------|----------------|-------------------|-------------------|---------|-------------|
| Early graft failure | 48 (6.2)      | 4 (8.3)        | 41 (6.3)          | 3 (4.2)           | .603    | 0           |
| Rejection as cause of graft failure | 14 (1.8)      | 0 (0)          | 13 (1.98)         | 1 (1.39)          | 1.000   | 12          |
| First eGFR       |                |                |                   |                   |         |             |
| 0–29            | 169 (24.5)     | 13 (29.6)      | 147 (25.4)        | 9 (13.6)          | .152    | 11          |
| 30–59           | 327 (47.5)     | 19 (43.2)      | 268 (46.3)        | 40 (60.6)         |         |             |
| >59             | 193 (28)       | 12 (27.3)      | 164 (28.3)        | 17 (25.8)         |         |             |
| Second eGFR     |                |                |                   |                   |         |             |
| 0–29            | 92 (16.1)      | 5 (15.2)       | 83 (17.18)        | 4 (7.0)           | .150    | 26          |
| 30–59           | 292 (51.0)     | 13 (39.4)      | 248 (41.35)       | 31 (54.4)         |         |             |
| >59             | 189 (33.0)     | 15 (45.5)      | 152 (31.47)       | 22 (38.6)         |         |             |

eGFR, estimated glomerular filtration rate (measured in mL/min/1.73 m²); HD, haemodialysis; PD, peritoneal dialysis; TX, transplant.
lack of fistula has been established as a risk factor for mortality in this population [23]. However, this finding deserves further investigation. In addition to dialysis modality and transplantation, we found that other determinants of patient survival after first KT are age, diabetes mellitus, cardiovascular disease and functional status. Previous publications also report a detrimental effect of these comorbidities [7, 24].

Our study also analysed the outcome after receiving a second KT. As far as we know, this is the first study in the literature reporting the influence of dialysis modality in this setting. Our results show that early and late immunological and non-immunological graft outcomes were comparable between HD and PD and similar to those with preemptive second KT. Thus, it seems that neither the dialysis modality nor preemptive KT may have a significant impact on death-censored second graft survival. In agreement with these results, several studies have shown that the impact of pretransplant dialysis time on second graft survival is related to an increase in the risk of mortality.
Table 5. Multivariable models of patient and graft survival after second kidney transplant

|                                | Patient survival since first graft failure | Patient survival after second kidney transplant | Death-censored second graft survival |
|--------------------------------|------------------------------------------|-----------------------------------------------|-------------------------------------|
|                                | HR 95% CI | HR 95% CI | HR 95% CI |
| Gender                         |           |           |           |
| Male                           | Ref       | Ref       | Ref       |
| Female                         | 0.85 0.62–1.16 | 0.94 0.69–1.29 | 1.40 1.03–1.89 |
| Age                            |           |           |           |
| 0–44 years                     | Ref       | Ref       | Ref       |
| 45–64 years                    | 4.19 2.64–6.66 | 3.84 2.40–6.14 | 1.06 0.76–1.49 |
| >64 years                      | 12.07 7.28–20.01 | 8.75 5.18–14.79 | 1.92 1.25–2.95 |
| Diabetes                       |           |           |           |
| No                             | Ref       | Ref       | Ref       |
| Yes                            | 1.57 1.07–2.29 | 1.01 0.57–1.79 | 1.81 1.28–2.57 |
| CV disease                     |           |           |           |
| No                             | Ref       | Ref       | Ref       |
| Yes                            | 1.81 1.28–2.57 | 1.19 0.76–1.86 | 1.19 0.76–1.86 |
| KRT transition after first graft failure |           |           |           |
| TX-PD-TX                       | Ref       | Ref       | Ref       |
| TX-TX                          | 3.93 0.55–26.11 | 1.03 0.09–11.44 | 4.84 1.19–19.61 |
| TX-HD-TX                       | 4.57 1.13–18.51 | 4.84 1.19–19.61 | 4.84 1.19–19.61 |
| Functional autonomy            |           |           |           |
| Normal/nearly                  | Ref       | Ref       | Ref       |
| Limited                        | 1.32 0.76–2.30 | 1.01 0.57–1.79 | 5.59 1.69–18.50 |
| Dependent/hospitalized         | 7.00 2.16–22.72 | 5.59 1.69–18.50 | 5.59 1.69–18.50 |

CI, confidence interval; CV, cardiovascular; HD, haemodialysis; KRT, kidney replacement therapy; PD, peritoneal dialysis; HR, hazard ratio; TX, transplant. Statistically significant values are shown in bold.

rather than an independent impact on the graft [12, 25]. Related to the preemptive effect, a registry-based study from the Austrian cohort observed that superior graft survival of preemptive versus non-preemptive primary KT recipients was lost when excluding living donors and KTs performed before the year 2000, yet only when dialysis time was <1.5 years [26]. An unexpected observation was that the female gender appeared to be a risk factor for death-censored second allograft survival, as it has not been identified as so in other studies [25, 27, 28]. However, in a study specifically aiming at sex as a possible risk factor for primary allograft failure, female KT recipients were at higher risk of death-censored allograft survival in case of receiving a male donor, and only in the 15–24 years range when receiving a female donor [29].

Despite the absence of any effect on graft survival, the dialysis modality was relevant to patient survival. Again, we found that patients on HD after first graft failure and then transplanted (TX-HD-TX transition) exhibited lower patient survival than patients on PD and then transplanted (TX-PD-TX transition). The decrease in cancer as a death cause in patients on pretransplant PD deserves further investigation. Retrospective studies from different cohorts have shown no impact of dialysis modality on cancer incidence either during dialysis [30] or after primary transplantation [31]. However, no data on mortality are specified in these studies. Other risk factors associated with mortality were similar to those after first KT: age, diabetes, cardiovascular disease and functional autonomy.

Our study has some limitations. Like other registry-based studies, our work is limited by the retrospective nature of the data and, therefore, no causal relationship can be established. As previously mentioned, we have no information regarding the tapering of immunosuppression, graft intolerance, embolization or transplantectomy. Analysis of patient survival could be better based on replacement modality included as time-dependent covariates and not as baseline covariates representing ‘future exposure’ to kidney replacement therapy/ waiting list over the follow-up. Finally, regarding the impact of KRT on second KT outcomes, there could be other unmeasured clinical factors related to the choice of the technique that affected patient selection. But it has also some strengths. This is a national registry including all patients transplanted in the six Catalan kidney transplant centres, as well as a national registry of KRT, so it gathers all the follow-up in dialysis and transplantation. Last but not the least, we have data on HLA sensitization after the first KT failure.

In conclusion, our study suggests that after the first KT failure, PD is superior to HD in reducing mortality in candidates for a second KT without options for preemptive retransplantation.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

J.M.C is member of the CKJ editorial board. The other authors of this manuscript have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.
AUTHORS’ CONTRIBUTIONS
C.C., I.R., J.C., M.Q. and J.M.C. helped conceive the study. J.C. performed the statistical analysis. C.C. and J.M.C. prepared the draft manuscript. N.M., A.M., S.C., A.F., E.M., A.C. and J.T. revised critically the article.

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