# Role of post-transplant graft scintigraphy in kidney donation after circulatory death

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**Background:** There is no consensus on how to predict post-transplant function of donation after circulatory death (DCD) kidneys. Thus, we aimed to identify renal scintigraphy parameters that could predict 1-year kidney function.

**Methods:** In this single center study, we included all consecutive DCD kidney recipients between 2013 and 2021 ($n = 29$). Patients who did not have a scintigraphy within 10 days of transplantation ($n = 3$), recipients of multiple organs and less than 18 years old were excluded ($n = 1$). Primary endpoint was the estimated glomerular filtration rate (eGFR).

**Results:** Median eGFR and serum creatinine at 1 year were 67 μmol/L (56–81) and 111 ml/min (99–132), respectively. Among parameters tested, the 3RD/2ND-minute activity ratio had the best diagnostic performance (AUC: 0.74 and 0.71, for eGFR and creatinine) 1 year post transplantation. Using 1.21 as the best cut off, the 3RD/2ND-minute activity ratio specificity and sensitivity to predict eGFR >60 ml/min was 0.82 and 0.83. Renal function was significantly better at 1 week, 3, 6, and 12 months after transplantation in patients with 3RD/2ND-minute activity ratios above 1.21.

**Conclusion:** This study suggests that the 3RD/2ND-minute activity ratio can predict graft function at 1 year. The benefit of post-transplant scintigraphy should be further validated in a prospective cohort.

## Introduction

Organ transplants are meeting less than 10% of global demands. In the United States, 13 people die each day while waiting for a kidney transplant (1). This shortage has led to an interest in expanding the donor pool with donors after circulatory death (DCD) (2, 3). Compared with standard-criteria grafts, the use of DCD kidneys is associated with an increased rate of delayed graft function (DGF) (4), higher rates of

biopsy-proven acute rejection, and higher incidence of overall graft failure (5). Besides a higher risk of local immune activation and subsequent rejection (6), the presence of DGF is associated with an increased length of hospital stay, increasing patient's morbidity and transplantation-related costs (7). However, the relationship between DGF, or other early surrogates of kidney graft function, and long-term graft and patient survival remains uncertain. In addition, the reported incidence of DGF greatly varies from 18% to 55% (8, 9). Such variability results from ambiguity in the definition of the event, differences in reporting, as well as inconsistency in donors characteristics that are analyzed (9, 10). While persistent inflammation in protocol biopsies performed within the first 6 months post-transplantation correlates with decreased renal function at 1 and 2 years (11), the procedure may be associated with relevant complications (e.g., hemorrhage or arteriovenous fistula) (12). In this context, research has focused on identifying urinary and blood biomarkers, and non-invasive imaging modalities capable of predicting renal function (13).

Renal scintigraphy (RS) has a wide range of clinical applications such as the assessment of suspected obstructive nephropathy (14) and the evaluation of renal and urinary tract malformations (15). In the context of transplantation, RS accurately assesses the occurrence of tubular necrosis, as well as vascular and post-renal complications (16). Renogram grades from 0 to 5 were shown to correlate with 1- and 5-year graft survival in recipients of living and donated after brainstem death (DBD) kidneys (17). Despite the ability to predict survival of DBD kidney transplants in some studies, there is no consensus on the systematic use of RS after transplantation, the timing, and which parameters to rely on to predict kidney function.

Accurate post-operative estimation of graft function and survival is important since it impacts hospital stay, patient anxiety, the number of necessary tests and use of dialysis facilities. We recently analyzed the ability of standard and novel RS parameters to predict kidney function recovery in a cohort of patients with acute renal failure. In this setting, the most accurate parameters to predict recovery were the 3RD/2ND-minute activity ratio, and the 2ND/3RD-minute slope. Thus, in the present study we examined the ability of these newly developed RS parameters to predict kidney function and graft survival following DCD kidney transplantation.

## Materials and methods

### Study population, setting, and data collection

All consecutive patients who underwent renal transplantation from donation after circulatory death, between January 2013 and December 2021 in our institution (Lausanne University Hospital)

were retrospectively analyzed. Those who did not undergo renal scintigraphy (RS) within 10 days post-transplantation ($n = 3$) or underwent repeat kidney transplantation ($n = 1$) or were <18 years old ($n = 0$) were excluded. Hence, a total of 29 patients (16 males, 13 females) were included in this study. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (CER-VD #2021–00081). Demographics and clinical data were collected from each patient's electronic medical records. Donor characteristics were retrieved from donor information sheets, and included age, last serum creatinine level, cold and warm ischemia time. Warm ischemia was defined as the time of agonal phase onset to the time when core cooling is initiated. Vascular anastomosis time was the time between the end of the cooling period to successful renal artery anastomosis and perfusion of the donor kidney. All laboratory tests and radiologic assessments (including RS) were performed at the discretion of the treating physician.

### Outcome measures

Data were analyzed to determine the correlation between early post-operative RS and kidney function (primary outcome). Kidney function was assessed by serum creatinine levels (sCr) and estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation at 1 week, 3-, 6-, and 12-months post-transplantation.

### Dynamic renal scintigraphy

A 20 min dynamic acquisition using a $128 \times 128$ matrix ($30 \times 1s$ frame followed by $117 \times 10s$ frame) was performed after injection of 20–50 MBq of Tc99m-MAG3 ($n = 15$) or I123-HIPPURAN ($n = 14$) on a single head gamma-camera (Millennium MPR, General Electrics, Waukesha, WI). To calculate quantitative renal uptake, we measured a kidney phantom filled with a standardized activity after each scan. A correction for attenuation was systematically applied. The first 30 s were reconstructed in 1-s and 3-s images for optimal visual evaluation of the arterial phase. A delay between the vascular activity (defined as the time between blood arrival in the iliac artery and the renal graft) was reported when >3 s. In addition, visual grading of time activity curves was done as previously published (16). A rising curve (Grade 3–4) was considered due to acute tubular necrosis. The following parameters were considered and collected: cortical perfusion index (derived from the ratio of areas under the arterial and renal curves), time to maximal vascular uptake (vascular peak time), time to maximal renal uptake (renal graft peak time), the median bladder appearance time (time between injection and the appearance of radioactive urine in the bladder),

tracer's elimination half-life, accumulation index (percentage of total injected activity excreted by the kidney within one minute between 30 to 50 s and 90 to 110 s post-injection), elimination index [ratio of renal activity at peak time (max 3 min) to the renal activity at 20 min], accumulation slope (slope of the TAC during the one minute interval ). Serial one-minute renal absolute activity counts of the graft during the 2nd and 3rd minutes post-injection were extracted, and additional parameters were computed for the transplanted kidneys: renal activity ratio and activity slope between the 2nd and 3rd minutes (3rd/2nd-minute activity ratio, and 2nd/3rd-minute slope, respectively).

## Study definitions

Coexisting conditions were ascertained from physician documentation. DGF was defined as the need for at least one hemodialysis treatment in the first week after kidney transplantation or a failure of serum creatinine to fall by at least 10% on three consecutive days in the first week post-operatively (18).

## Statistical analysis

Descriptive statistics were used to report the data; results are reported as medians and interquartile ranges (IQR) or means and standard deviations, as appropriate. Categorical variables were summarized as numbers and percentages. A logistic regression analysis was used to analyze the association of single scintigraphy parameters, with kidney function. Sensitivity, specificity (with binomial 95% confidence intervals, CI), positive predictive value, negative predictive value (with bootstraps 95% confidence intervals) as well as the area under the Receiver operating characteristic (ROC) curve (AUC) were calculated using the (pROC) and (cutpointr) packages. The optimal cutpoint was set to maximize the sum of sensitivity and specificity. No imputation was made for missing data. Analysis were performed with R (RStudio v1.4.1717).

## Results

Twenty-nine patients fulfilled the inclusion criteria and were analyzed. Their baseline characteristics are shown in **Table 1**. Median recipient age was 53 (25–73) years and 45% were female. Median body mass index (BMI) prior to transplantation was 27.8 (21.6–43) kg/m$^2$. The median duration on dialysis prior to transplantation was 56 months (0–102). Two (7%) patients underwent a preemptive transplantation. Median donor age was 53 (14–65) years.

TABLE 1 Baseline patient characteristics.

| Characteristic and Clinical data | Patients (N = 29) |
|---|---|
| Recipient characteristics | |
| Age, year – (range) | 53 (25–73) |
| Sex – n (%) | |
| Male | 16 (55) |
| Female | 13 (45) |
| Coexisting disorders – n (%) | |
| Hypertension | 23 (79) |
| Cardiovascular disease[a] | 12 (41) |
| Diabetes mellitus | 8 (28) |
| Body mass index, kg/m$^2$ – Median (IQR) | 27.8 (21.6–43) |
| Pre-emptive transplantation – n (%) | 2 (7) |
| Pre-transplant dialysis duration, months – Median (IQR) | 56 (0–102) |
| Donor characteristics | |
| Age, yr – (range) | 52 (14–65) |
| Warm ischemia time, min – Median (IQR) | 33 (25–124) |
| Cold ischemia time, min – Median (IQR) | 459 (217–886) |
| Last serum creatinine, µmol/L – Median (IQR) | 71 (32–147) |
| Transplantation characteristics | |
| Anastomosis time, min – Median (IQR) | 30 (13–69) |
| Allograft with >1 renal artery – n (%) | 6 (21) |
| Renal function post transplantation | |
| Day of the renal scintigraphy | 2 (1–10) |
| Delayed graft function – n (%) | 18 (62) |
| Length of hospital stay, days – Median (IQR) | 22 (13–79) |
| Serum creatinine at 1 week, µmol/L – Median (IQR) | 475 (301–608) |
| Serum creatinine at 3 months[b], µmol/L – Median (IQR) | 122 (104–137) |
| Serum creatinine at 6 months[a], µmol/L – Median (IQR) | 113 (102–139) |
| Serum creatinine at 12 months[a], µmol/L – Median (IQR) | 111 (99–131) |
| eGFR at 1 week, ml/min – Median (IQR) | 15 (12–24) |
| eGFR at 3 months[b], ml/min – Median (IQR) | 65 (52–77) |
| eGFR at 6 months[a], ml/min – Median (IQR) | 66 (51–79) |
| eGFR at 12 months[a], ml/min – Median (IQR) | 67 (55–81) |
| Biopsy-proven acute rejection – n (%) | 1 (3) |

[a]Data were available for 27 of the 29 patients.
[b]Data were available for 28 of the 29 patients.

Median pre-transplant serum creatinine levels (sCr) in donors was 71 (32–147) µmol/L.

Median warm, cold ischemia and vascular anastomosis time were 33 (25–124), 459 (217–886) and 30 (13–69) minutes, respectively. Median follow-up duration was 27 months (3–96). DGF was observed in 18 (62%) patients. One patient (3%) experienced a biopsy-proven acute rejection. During the first year, one graft (3%) was explanted due to early recurrence of complement-mediated thrombotic microangiopathy. Median sCr and eGFR at 1 year were 111 (99–131) µmol/L and 67 (55–81) ml/min, respectively.

Dynamic RS was performed in all patients between day 1–10 (median: 2) post transplantation. Table 2 provides quantitative and qualitative scintigraphy data. First, we assessed the diagnostic ability of various RS parameters to discriminate between patients with sCr levels at 1 year above and below 80 μmol/L using ROC curves. As shown in Figure 1, the AUC of the accumulation index, accumulation slope, elimination index, renal flow index, 3RD/2ND-minute activity ratio, and 2ND/3RD-minute slope were: 0.67 (95% CI, 0.27–1.00), 0.74 (95% CI, 0.41–1.00), 0.71 (95% CI, 0.31–1.00), 0.54 (95% CI, 0.18–0.89), 0.74 (95% CI, 0.50–0.97), and 0.71 (95% CI, 0.29–1.00), respectively. Of note, renal grading scale, cortical perfusion index, vascular and renal peak time, median bladder appearance time, and tracer elimination half-time did not discriminate between high and low sCr or eGFR levels at 1 year (AUC ≤0.5, data not shown).

We similarly tested the ability of RS parameters to predicted eGFR above or below 60 ml/min at one year. The AUC of the accumulation index, accumulation slope, elimination index, renal flow index, 3RD/2ND-minute activity ratio, and 2ND/3RD-minute slope were: 0.55 (95% CI, 0.32–0.78), 0.59 (95% CI, 0.37–0.81), 0.55 (95% CI, 0.37–0.81), 0.61 (95% CI, 0.37–0.84), 0.71 (95% CI, 0.47–0.94), and 0.62 (95% CI, 0.40–0.86), respectively (Figure 2). Altogether, the 3RD/2ND-minute activity ratio appeared to have the strongest differentiating capacity between the two groups (high vs. sCr and eGFR at 1 year, Figures 1, 2).

Based on these findings, we established a RS score in attempt to improve the prediction of renal function at 1 year. The score combined the accumulation slope, slope counts and 3RD/2ND-minute activity ratio. A pre-established scale (1: low, 2: moderate, 3: high risk, 4: very high) was given to each RS parameter (total score 3–12, Supplementary Figure S1A). Using logistic regression and random forest model, the AUC to discriminate patients with sCr levels above and below 80 μmol/L were 0.79 and 0.74, respectively (Supplementary Figure S1B). When using eGFR above and below 60 ml/min, the AUC were 0.65 and 0.47, respectively (Supplementary Figure S1B). Thus, the score did not provide a better prediction model than the 3RD/2ND-minute activity ratio alone, which was considered for further analysis.

We then calculated the optimal cut-off value for the 3RD/2ND-minute activity ratio parameter, defined as the maximal sum of sensitivity and specificity (absolute maximum = 2). For sCr levels (80 μmol/L) and eGFR (60 ml/min), the best cut-off was 1.22 (1.22–1.24) and 1.21 (1.21–1.21), respectively (Table 3). Sensitivity and specificity were 1.0 (1.0–1.0) and 0.64 (0.55–0.75) for sCr, 0.83 (0.76–0.89) and 0.82 (0.71–0.90) for eGFR at 1 year.

Interestingly, renal function was significantly higher at 1 week, 3 months, 6 months and 1 year in patients with a 3RD/2ND-minute activity ratio above 1.21 (Figures 3A, B). On the other hand, the presence or absence of DGF did not correlate with kidney function beyond 1 week (Supplementary Figures S1A,B). In the presence or absence of DGF, median eGFR and sCr levels at 1 year were 60 ml/min/1·73 m$^2$ (55–76) and 102 μmol/L (90–123) vs. 50 ml/min (46–63) and 117 μmol/L (104–132), respectively (Supplementary Figures S2A,B).

## Discussion

In this retrospective study including 29 DCD kidney transplant recipients, we found that early post-operative 3RD/2ND-minute activity ratio on RS alone could predict kidney function at one year. We found that this new index, calculated based on renal counts in the first 3 min had better prognostic abilities, than conventional RS parameters such as the accumulation index, accumulation slope, elimination index and renal flow index or even a complex score.

Beyond RS, several clinical scores such as donor risk score index (19), or scores that include cold ischemia time, recipient BMI, donor age, last donor sCr, and administration of anti-thymocyte globulin are used to predict kidney function (20). DGF is an outcome of interest in an era where renal allografts increasingly originate from marginal donors, such as extended criteria and DCD donors. In this cohort, the occurrence of DGF did not significantly affect graft function beyond 1 week post-operatively. While DGF is a well-described risk factor for long-term graft survival in DBD donor kidney transplantation (4, 21), in particular in the presence of acute rejection (6, 22, 23), this association is much less clear with controlled DCD donor kidney transplantation (24–26). Interestingly, this form of resilience of DCD kidneys following DGF was attributed to a downregulation of intra-graft pro-inflammatory pathways, as well as upregulation of cell proliferation suppressor pathways in a cohort comparing DBD and DCD kidney transplants (27). The lack of association between early DGF and long-term graft function in DCD donor kidney transplantation may also be because of the subjectivity of using DGF as an outcome measure, as well as differences in definitions and early post-transplant dialysis prescriptions between clinicians and centers (28, 29).

TABLE 2 Quantitative and qualitative post-transplant scintigraphy data.

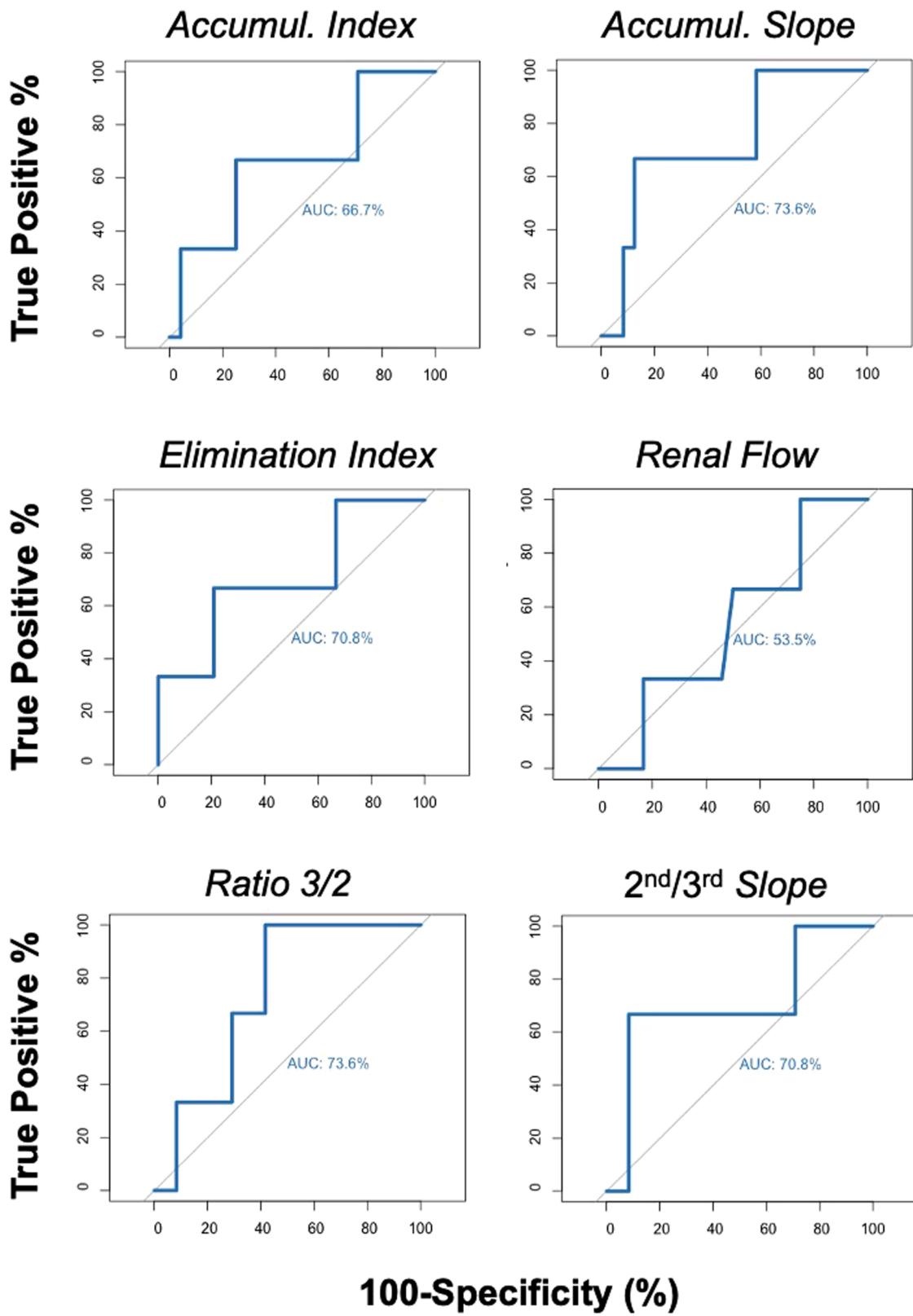| Quantitative and qualitative scintigraphy data | Patients (N = 29) |
|---|---|
| Accumulation index – Median (IQR) | 4.18 (3.65–4.94) |
| Accumulation slope – Median (IQR) | 0.55 (0.38–0.71) |
| Elimination index – Median (IQR) | 0.55 (0.49–0.69) |
| Renal flow index – Median (IQR) | 0.68 (0.20–1.18) |
| 3RD/2ND-minute activity ratio – Median (IQR) | 1.21 (1.17–1.24) |
| 2ND/3RD Slope counts – Median (IQR) | 1658.0 (1259.0–2131.0) |

**FIGURE 1**
ROC curves illustrating the diagnostic ability of RS parameters to discriminate patients with serum creatinine levels above or below 80 µmol/L at 1 year.
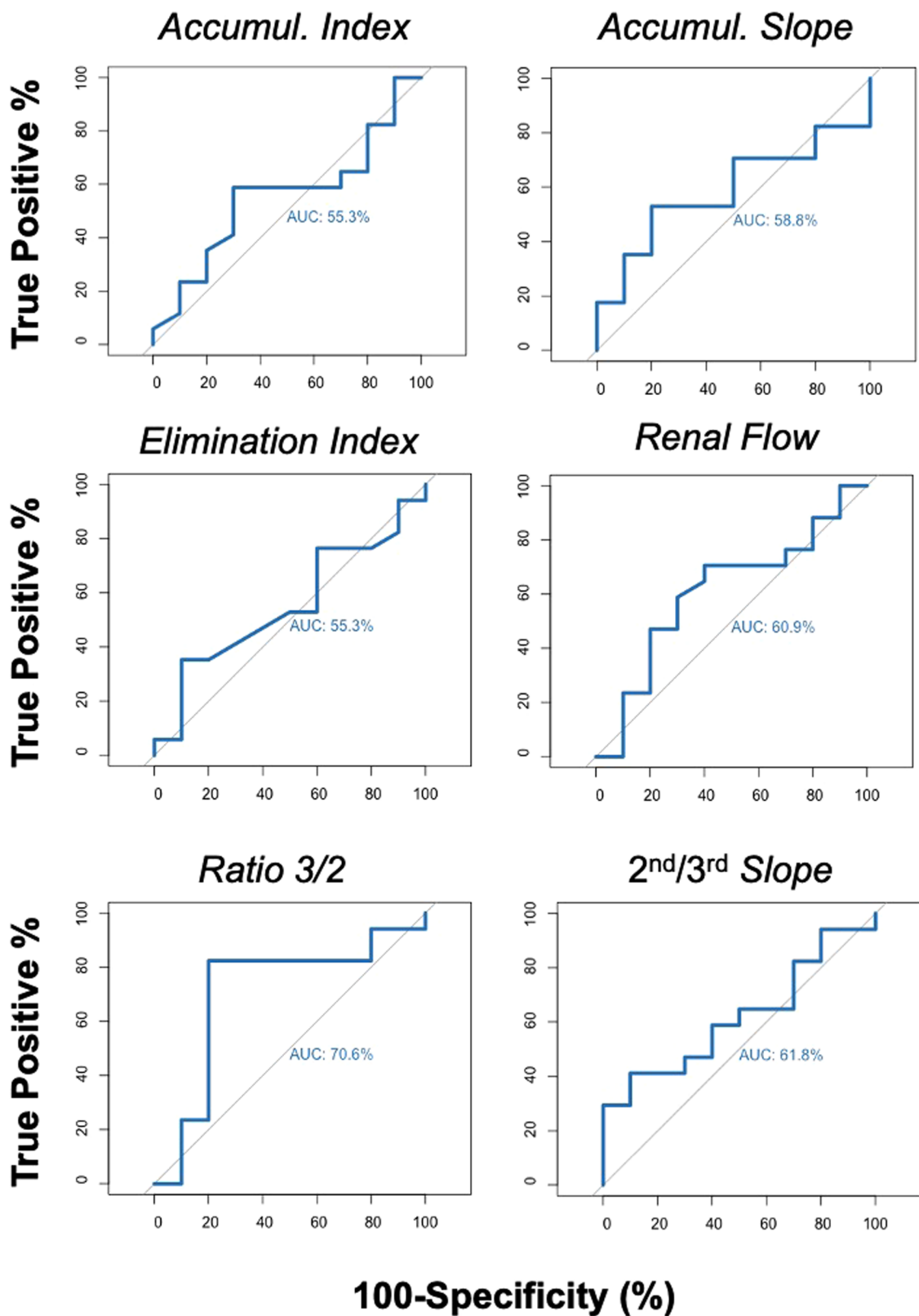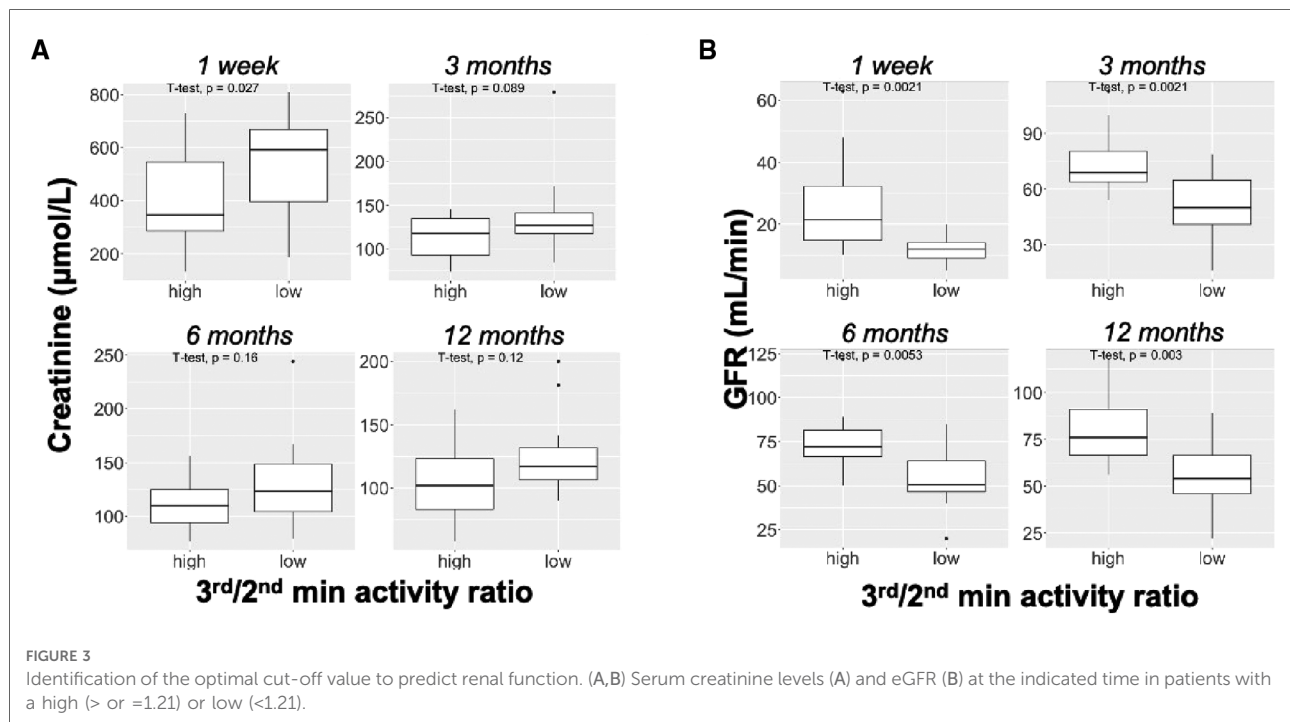
FIGURE 2
ROC curves illustrating the diagnostic ability of RS parameters to discriminate patients with eGFR above or below 60 ml/min at 1 year.

TABLE 3 Diagnostic performance of the 3rd/2nd-minute activity ratio.

| 3rd/2nd minute activity ratio median (IQR) | Area under curve | Best cut-off | Sensitivity | Specificity |
|---|---|---|---|---|
| Serum creatinine level at 1 years[a] | 0.74 (0.66–0.82) | 1.22 (1.22–1.24) | 1.0 (1.0–1.0) | 0.64 (0.55–0.75) |
| eGFR at 1 year[a] | 0.71 (0.64–0.80) | 1.21 (1.21–1-21) | 0.83 (0.76–0.89) | 0.82 (0.71–0.90) |

[a]Data were available for 27 of the 29 patients.



FIGURE 3
Identification of the optimal cut-off value to predict renal function. (A,B) Serum creatinine levels (A) and eGFR (B) at the indicated time in patients with a high (> or =1.21) or low (<1.21).

Kidney graft function in this cohort was similar to other studies, which was reported between 43 and 53 ml/min at 1 year for DCD grafts (30, 31). In our cohort, cold ischemia time was 459 min (217–886), which appears to be few hours shorter than most studies (32, 33), possibly having an impact on the incidence of DGF (34, 35). In a previous study, the tubular function slope (defined as the slope of the graft TAC using a linear fit between 30 and 60) was shown to be lower in patients with DGF, and predicted graft failure at 1 year (AUC 0.70) (36). Benjamins et al. described a similar parameter, the average upslope that was defined by the formula: (counts at 3 min—counts at 20 s)/160 s, which had high specificity and sensitivity to detect DGF one week after transplantation (37). Both these parameters are similar to our 3RD/2ND-minute activity ratio as they focus on the extraction/uptake phase occurring in the first minutes of RS. Our findings are thus consistent with others and confirm that this phase has the best predictive value for renal graft outcome. Our data suggest that RS may identify patients who will have adequate graft function at one year. Such knowledge could help selecting patients to undergo closer follow-up. It could

be relevant for clinical decision making in several clinical settings (for instance hospital discharge, choice of immunosuppressive therapy). In addition, qualitative interpretation of RS is hindered by larger inter-observer variability. Although the use of a specific program to calculate these parameters may also have a learning curve (38), the 3RD/2ND-minute activity ratio seems to be a promising tool to improve inter-observer agreement as it is a simple ratio of activity counts with no further processing.

This study has several strengths. It is the first to evaluate the ability of RS to predict renal function specifically in patients undergoing DCD kidney transplantation. All RS were reviewed by two nuclear medicine specialists blinded to the outcome. Additional parameters, based on renal absolute counts, were calculated. Our findings appear robust, as they were confirmed by several sensitivity analyses. However, limitations need to be acknowledged. First, our cohort included only a small number of patients, thus with low power increasing the risk of type II errors and with potential confounding risk factors. In addition, this was a retrospective single-center study, which may affect statistical analysis.

Finally, patients who did not have a RS after surgery were excluded, potentially excluding patients with superior renal function post-operatively. However, most DCD patients had a post-operative RS, regardless of their eGFR, and as part of our standardized clinical protocol.

## Conclusion

In conclusion, the RS parameter 3RD/2ND-minute activity ratio has a good specificity and sensitivity to predict DCD kidney graft function at one year post transplantation. The benefit of post-transplant RS should be further evaluated in larger prospective studies.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

## Ethics statement

The studies involving human participants were reviewed and approved by Commission cantonale d'éthique de la recherche sur l'être humain (CER-VD). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

Study design: MB, GA, TA, MNL, AL. Acquisition of data: MB, GA, TA, JPV, JMC, AS, MNL, AL. Interpretation and analysis: MB, GA; TA, RPM, AS, DG, JOP, SD, MNL, AL. Drafting and revising critically: MB, GA, TA, RPM, JPV, JMC, AS, DG, JOP, SD, MNL, AL. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frtra.2022.1065415/full#supplementary-material.

## References

1. Israni AK, Zaun D, Gauntt K, Schaffhausen C, McKinney W, Snyder JJ. OPTN/SRTR 2020 annual data report: dOD. *Am J Transplant*. (2022) 22(Suppl 2):519–52. doi: 10.1111/ajt.16976

2. Assis-Borba L, Cristelli MP, Paula MI, Franco MF, Tedesco-Silva H, Medina-Pestana JO. Expanding the use of expanded criteria donors in kidney transplantation. *Int Urol Nephrol*. (2014) 46(8):1663–71. doi: 10.1007/s11255-014-0695-0

3. Summers DM, Watson CJ, Pettigrew GJ, Johnson RJ, Collett D, Neuberger JM, et al. Kidney donation after circulatory death (DCD): state of the art. *Kidney Int*. (2015) 88(2):241–9. doi: 10.1038/ki.2015.88

4. Yarlagadda SG, Coca SG, Formica RN, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. *Nephrol Dial Transplant*. (2009) 24(3):1039–47. doi: 10.1093/ndt/gfn667

5. Tennankore KK, Kim SJ, Alwayn IP, Kiberd BA. Prolonged warm ischemia time is associated with graft failure and mortality after kidney transplantation. *Kidney Int*. (2016) 89(3):648–58. doi: 10.1016/j.kint.2015.09.002

6. Wu WK, Famure O, Li Y, Kim SJ. Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation. *Kidney Int*. (2015) 88 (4):851–8. doi: 10.1038/ki.2015.190

7. Machnicki G, Lentine KL, Salvalaggio PR, Burroughs TE, Brennan DC, Schnitzler MA. Kidney transplant Medicare payments and length of stay: associations with comorbidities and organ quality. *Arch Med Sci*. (2011) 7 (2):278–86. doi: 10.5114/aoms.2011.22079

8. Zens TJ, Danobeitia JS, Leverson G, Chlebeck PJ, Zitur LJ, Redfield RR, et al. The impact of kidney donor profile index on delayed graft function and transplant outcomes: a single-center analysis. *Clin Transplant*. (2018) 32(3):e13190. doi: 10.1111/ctr.13190

9. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. *Lancet.* (2004) 364(9447):1814–27. doi: 10.1016/S0140-6736(04)17406-0

10. Koning OH, Ploeg RJ, van Bockel JH, Groenewegen M, van der Woude FJ, Persijn GG, et al. Risk factors for delayed graft function in cadaveric kidney transplantation: a prospective study of renal function and graft survival after preservation with University of Wisconsin solution in multi-organ donors. European Multicenter Study Group. *Transplantation.* (1997) 63(11):1620–8. doi: 10.1097/00007890-199706150-00015

11. Mengel M, Gwinner W, Schwarz A, Bajeski R, Franz I, Bröcker V, et al. Infiltrates in protocol biopsies from renal allografts. *Am J Transplant.* (2007) 7 (2):356–65. doi: 10.1111/j.1600-6143.2006.01635.x

12. Ahmad I. Biopsy of the transplanted kidney. *Semin Intervent Radiol.* (2004) 21(4):275–81. doi: 10.1055/s-2004-861562

13. Yazici B, Gunay E, Akgün A, Sen S, Ozbek SS. Scintigraphic and sonographic findings of subcapsular cortical necrosis in a transplanted kidney. *Clin Nucl Med.* (2018) 43(7):542–5. doi: 10.1097/RLU.0000000000002106

14. Taylor AT, Brandon DC, de Palma D, Blaufox MD, Durand E, Erbas B, et al. SNMMI procedure standard/EANM practice guideline for diuretic renal scintigraphy in adults with suspected upper urinary tract obstruction 1.0. *Semin Nucl Med.* (2018) 48(4):377–90. doi: 10.1053/j.semnuclmed.2018.02.010

15. Blaufox MD, De Palma D, Taylor A, Szabo Z, Prigent A, Samal M, et al. The SNMMI and EANM practice guideline for renal scintigraphy in adults. *Eur J Nucl Med Mol Imaging.* (2018) 45(12):2218–28. doi: 10.1007/s00259-018-4129-6

16. Benjamens S, Berger SP, Glaudemans AWJM, Sanders JSF, Pol RA, Slart RHJA. Renal scintigraphy for post-transplant monitoring after kidney transplantation. *Transplant Rev (Orlando).* (2018) 32(2):102–9. doi: 10.1016/j.trre.2017.12.002

17. Heaf JG, Iversen J. Uses and limitations of renal scintigraphy in renal transplantation monitoring. *Eur J Nucl Med.* (2000) 27(7):871–9. doi: 10.1007/s002590000281

18. Lim MA, Bloom RD. Medical therapies to reduce delayed graft function and improve long-term graft survival: are we making progress? *Clin J Am Soc Nephrol.* (2020) 15(1):13–5. doi: 10.2215/CJN.13961119

19. Gourishankar S, Grebe SO, Mueller TF. Prediction of kidney graft failure using clinical scoring tools. *Clin Transplant.* (2013) 27(4):517–22. doi: 10.1111/ctr.12135

20. Chapal M, Le Borgne F, Legendre C, Kreis H, Mourad G, Garrigue V, et al. A useful scoring system for the prediction and management of delayed graft function following kidney transplantation from cadaveric donors. *Kidney Int.* (2014) 86 (6):1130–9. doi: 10.1038/ki.2014.188

21. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. *Am J Transplant.* (2011) 11(11):2279–96. doi: 10.1111/j.1600-6143.2011.03754.x

22. Gill J, Dong J, Rose C, Gill JS. The risk of allograft failure and the survival benefit of kidney transplantation are complicated by delayed graft function. *Kidney Int.* (2016) 89(6):1331–6. doi: 10.1016/j.kint.2016.01.028

23. Troppmann C, Gillingham KJ, Gruessner RW, Dunn DL, Payne WD, Najarian JS, et al. Delayed graft function in the absence of rejection has no long-term impact. A study of cadaver kidney recipients with good graft function at 1 year after transplantation. *Transplantation.* (1996) 61(9):1331–7. doi: 10.1097/00007890-199605150-00008

24. Lim WH, McDonald SP, Russ GR, Chapman JR, Ma MK, Pleass H, et al. Association between delayed graft function and graft loss in donation after cardiac death kidney transplants-A paired kidney registry analysis. *Transplantation.* (2017) 101(6):1139–43. doi: 10.1097/TP.0000000000001323

25. Summers DM, Johnson RJ, Allen J, Fuggle SV, Collett D, Watson CJ, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet.* (2010) 376 (9749):1303–11. doi: 10.1016/S0140-6736(10)60827-6

26. Summers DM, Johnson RJ, Hudson A, Collett D, Watson CJ, Bradley JA. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. *Lancet.* (2013) 381 (9868):727–34. doi: 10.1016/S0140-6736(12)61685-7

27. de Kok MJ, McGuinness D, Shiels PG, de Vries DK, Nolthenius JBT, Wijermars LG, et al. The neglectable impact of delayed graft function on long-term graft survival in kidneys donated after circulatory death associates with superior organ resilience. *Ann Surg.* (2019) 270(5):877–83. doi: 10.1097/SLA.0000000000003515

28. Li Y, Jin Y, Kapke A, Pearson J, Saran R, Port FK, et al. Explaining trends and variation in timing of dialysis initiation in the United States. *Medicine (Baltimore).* (2017) 96(20):e6911. doi: 10.1097/MD.0000000000006911

29. Akkina SK, Connaire JJ, Israni AK, Snyder JJ, Matas AJ, Kasiske BL. Similar outcomes with different rates of delayed graft function may reflect center practice, not center performance. *Am J Transplant.* (2009) 9(6):1460–6. doi: 10.1111/j.1600-6143.2009.02651.x

30. Hoogland ER, Snoeijs MG, Winkens B, Christaans MH, van Heurn LW. Kidney transplantation from donors after cardiac death: uncontrolled versus controlled donation. *Am J Transplant.* (2011) 11(7):1427–34. doi: 10.1111/j.1600-6143.2011.03562.x

31. Wong G, Teixeira-Pinto A, Chapman JR, Craig JC, Pleass H, McDonald S, et al. The impact of total ischemic time, donor age and the pathway of donor death on graft outcomes after deceased donor kidney transplantation. *Transplantation.* (2017) 101(6):1152–8. doi: 10.1097/TP.0000000000001351

32. Heylen L, Pirenne J, Samuel U, Tieken I, Naesens M, Sprangers B, et al. The impact of anastomosis time during kidney transplantation on graft loss: a eurotransplant cohort study. *Am J Transplant.* (2017) 17(3):724–32. doi: 10.1111/ajt.14031

33. Mori G, Cerami C, Facchini F, Fontana F, Alfano G, Giovanni R, et al. Kidney transplantation from circulatory death donors: monocentric experience. *Transplant Proc.* (2019) 51(9):2865–7. doi: 10.1016/j.transproceed.2019.07.012

34. Lauronen J, Peräsaari JP, Saarinen T, Jaatinen T, Lempinen M, Helanterä I. Shorter cold ischemia time in deceased donor kidney transplantation reduces the incidence of delayed graft function especially among highly sensitized patients and kidneys from older donors. *Transplant Proc.* (2020) 52(1):42–9. doi: 10.1016/j.transproceed.2019.11.025

35. van der Vliet JA, Warlé MC. The need to reduce cold ischemia time in kidney transplantation. *Curr Opin Organ Transplant.* (2013) 18(2):174–8. doi: 10.1097/MOT.0b013e32835e2a08

36. Guignard R, Mourad G, Mariano-Goulart D. Utility of postsurgical renal scintigraphy to predict one-year outcome of renal transplants in patients with delayed graft function. *Nucl Med Commun.* (2011) 32(4):314–9. doi: 10.1097/MNM.0b013e3283446297

37. Benjamens S, Pol RA, de Geus-Oei LF, de Vries APJ, Glaudemans AWJM, Berger SP, et al. Can transplant renal scintigraphy predict the duration of delayed graft function? A dual center retrospective study. *PLoS One.* (2018) 13(3): e0193791. doi: 10.1371/journal.pone.0193791

38. Sachpekidis C, Schepers R, Marti M, Kopp-Schneider A, Alberts I, Keramida G, et al. Tc-MAG3 diuretic renography: intra- and inter-observer repeatability in the assessment of renal function. *Diagnostics (Basel).* (2020) 10(9):709. doi: 10.3390/diagnostics10090709