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ORIGINAL ARTICLE

Early renal function recovery and long-term graft survival in kidney transplantation

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SUMMARY

Following kidney transplantation (KTx), renal function improves gradually until a baseline eGFR is achieved. Whether or not a recipient achieves the best-predicted eGFR after KTx may have important implications for immediate patient management, as well as for long-term graft survival. The aim of this cohort study was to calculate the renal function recovery (RFR) based on recipient and donor eGFR and to evaluate the association between RFR and long-term death-censored graft failure (DCGF). We studied 790 KTx recipients between January 1990 and August 2014. The last donor SCr prior to organ procurement was used to estimate donor GFR. Recipient eGFR was calculated using the average of the best three SCr values observed during the first 3 months post-KTx. RFR was defined as the ratio of recipient eGFR to half the donor eGFR. 53% of recipients had an RFR ≥1. There were 127 death-censored graft failures (16%). Recipients with an RFR ≥1 had less DCGF compared with those with an RFR <1 (HR 0.56; 95% CI 0.37–0.85; $P = 0.006$). Transplant era, acute rejection, ECD and DGF were also significant determinants of graft failure. Early recovery of predicted eGFR based on donor eGFR is associated with less DCGF after KTx.

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Key words
estimated glomerular filtration rate, graft survival, renal function, renal function recovery, serum creatinine

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Introduction

Kidney transplantation (KTx) remains the treatment of choice for the majority of patients with end-stage kidney disease (ESKD) due to the significant survival and quality-of-life benefits compared with dialysis [1]. As the prevalence of ESKD increases however, the number of patients waiting for KTx continues to rise while the rate of transplantation remains static [2–4].

The relative shortage of organs for KTx drives the need to both increase the donor pool and prolong the lifespan of kidney allografts. Various predictors of long-term graft survival have been identified, including renal function at 1 year post-transplant, as well as a clinical course of acute rejection, infection and inadequate immunosuppressive therapy [5–7]. In addition, post-transplant anaemia, blood pressure control and the presence of diabetes have been reported as significant determinants of graft survival [8–12]. However, these factors reflect a longitudinal assessment of the post-transplant course, and few early predictors of long-term outcomes have been studied [13]. Risk factors that are recognized early in the clinical course may be important for the identification of recipients vulnerable to

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long-term complications, and to understand processes crucial to the longevity of the graft.

The use of more marginal quality kidneys has become widespread in an attempt to increase the donor pool and decrease the waiting time to transplantation. However, expanded criteria donor (ECD) kidneys are also associated with a higher risk of ischaemic injury and delayed graft function [14,15]. This in turn may increase the risk of rejection and affect long-term outcomes [16,17]. Despite growing variability in donor kidney quality, the potential recovery of a kidney from ischaemic injury sustained during transplantation has not been quantified or evaluated. The achievement of a best-estimated glomerular filtration rate (eGFR) relative to the function of the donor is a concept that has not previously been evaluated as a predictor of long-term graft survival [18]. Failure to reach a predicted eGFR, based on donor eGFR, may raise the suspicion of rejection and may prompt appropriate diagnostic steps. Therefore, the aim of this study was to quantify renal function recovery (RFR) as the ratio of recipient eGFR to half the donor eGFR prior to organ procurement and to evaluate the association of RFR with long-term graft survival.

Materials and methods

This retrospective single-centre cohort study was approved by the McGill University Health Centre Research Ethics Board (Approval and Protocol number 13-278-SDR). Adult KTx recipients transplanted between 1 January 1990 and 2 August 2014 were identified from the McGill University Health Centre Multi-Organ Transplant Program database for inclusion in the study. Recipients of multi-organ transplants (n = 121), living donor KTx (n = 302), paediatric donors (n = 42), those with graft failure or death within 90 days (n = 74), donor serum creatinine (SCr) >150 (n = 29) and those lost to follow-up (n = 30) were excluded. Patients who received more than one KTx within the study period were censored at the time of the second transplant (n = 24).

Recipient eGFR was calculated using the average of the best three SCr values observed during the first 3 months post-transplant. SCr was measured at the commencement of dialysis sessions for patients with delayed graft function (DGF). The last donor SCr prior to organ procurement was used to estimate donor GFR. All GFR estimates were calculated using the CKD-Epi equation [19]. RFR was the exposure variable and was defined as the ratio of recipient eGFR to half the donor eGFR. Recipients who achieved an RFR ≥1 by 3 months post-transplant were compared to those who achieved an RFR <1. The outcome measures were death-censored graft failure (DCGF) and total graft failure, with a minimum follow-up of 1 year.

Statistical analysis

Categorical data were described using frequencies and percentages. Continuous data were described using the mean and standard deviation for normally distributed data. The distribution of baseline characteristics across categories of the exposure variable was evaluated using parametric and nonparametric statistics as appropriate. The nonlinear association between RFR and the log hazard of outcome was graphically assessed with multivariable regression splines using the *mvrs* STATA command.

Cumulative probabilities of study endpoints were graphically assessed using the Kaplan–Meier product limit method, and differences across survival functions were examined using the log-rank test.

To assess the independent association between the exposure and outcome, we built multivariable Cox proportional hazards models. Covariables that were associated with post-transplant outcomes in univariate analysis, as well as those that were thought to be theoretically relevant, were considered for inclusion in the models. The final models were adjusted for ECD, aetiology of ESKD, HLA mismatch, recipient age, recipient gender, delayed graft function (DGF), acute rejection and transplant era. The proportional hazards assumption was tested using scaled Schoenfeld residuals. No important departures from proportionality were detected. Because recipient eGFR at 3 months and RFR could not both be entered into the same multivariable model due to collinearity, we compared two multivariable models: one where RFR was the main exposure variable and another model where recipient eGFR at 3 months replaced RFR as the exposure variable. Receiver operator characteristic curves and C-statistics were generated to compare these models.

Predictors of low RFR (recipients with an RFR <1 compared with those with an RFR ≥1) were assessed in a multivariable logistic regression model. The covariables entered in this model were selected based on theoretical considerations and were the following: recipient age, recipient gender, diabetes, ECD, acute rejection <90 days post-transplant, DGF, donor gender and a low donor-to-recipient weight ratio, defined as a ratio below the median. All statistical analyses were performed using STATA, version 13.0 (StataCorp, College Station, TX, USA). A two-sided P value <0.05 was considered statistically significant.

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Results

There were 1412 KTx performed during the study period, of which 820 were eligible for inclusion into the study. Thirty patients were excluded due to missing graft or patient survival data, and 790 were included in the analysis. Immunosuppression was administered according to a protocol consisting of induction therapy and maintenance immunosuppression. From January 1990 to June 2012 inclusive, induction immunosuppression consisted of antithymocyte globulin (Thymoglobulin®; Genzyme, Mississauga, ON, Canada). From July 2012 onwards, protocol induction therapy consisted of alemtuzumab (Campath®; Genzyme). Between January 1990 and December 1996 inclusive, the maintenance immunosuppression protocol consisted of prednisone, cyclosporine (Neoral®; Novartis Pharmaceuticals Canada Inc., Dorval, QC, Canada) and azathioprine. From January 1997 onwards, maintenance immunosuppression consisted of prednisone, tacrolimus (Prograf®; Astellas Pharma Canada Inc., Mississauga, ON, Canada) and mycophenolate mofetil (Cell-Cept®; Hoffmann-La Roche Ltd, Mississauga, ON, Canada). The ratio of RFR was ≥1 in 421 recipients (53.3%) and <1 in 369 recipients (46.7%). There were 255 graft losses in total, including 98 deaths with a functioning graft and 127 death-censored graft losses. Table 1 shows the baseline characteristics of the cohort.

Renal function recovery showed a U-shaped relationship to graft failure, with the lowest level of graft failure observed at an RFR between 1 and 2 (Figs 1 and 2). As very few patients had an RFR >2 and the confidence interval for the association between RFR and the log hazard DCGF was very wide above this level, we selected a single cut point of RFR 1 for further analysis. An RFR ratio ≥1 was associated with less DCGF compared with an RFR <1 (Fig. 3, $P < 0.001$) with an adjusted hazard ratio (HR) of 0.56 (95% CI 0.37–0.85; $P = 0.006$). Multivariable Cox regression analysis identified ECD, acute rejection, DGF and transplant era as further significant determinants of DCGF (Table 2). Further multivariable modelling identified a low donor-to-recipient weight ratio, DGF, early acute rejection and ECD as factors associated with an RFR <1 (Table 3).

An RFR ≥1 was also associated with less total graft failure compared with an RFR <1 in both univariable (Fig. 4) and multivariable analyses (adjusted HR 0.72, 95% CI 0.54–0.96, $P = 0.026$, Table 4). There was no significant association between RFR and mortality (Fig. 5).

Recipient eGFR at 3 months was also associated with DCGF (HR 0.98; 95% CI 0.97–0.99; $P < 0.001$, Table S1), and comparison of the two models showed overlapping ROC curves with no difference in C-statistic between the two models (Fig. S1).

Discussion

The most important finding of this study is that early RFR quantified as a function of donor eGFR is significantly associated with long-term graft outcomes. Death-censored graft failure at 10 years post-transplant was approximately 15% in the RFR ≥1 group, compared with 27% in the RFR <1 group, a finding that has not previously been reported. Furthermore, the risk of DCGF was approximately 45% lower for recipients with an RFR ≥1 compared with recipients with an RFR <1 in an adjusted analysis.

The relationship between RFR and graft failure is nonlinear and is represented by a U-shaped curve. Optimal graft survival occurred at an RFR between 1 and 2, with increased graft failure noted at the extremes of RFR. The wide confidence intervals at these extremes reflect the smaller number of patients with an RFR <0.5 or >2. At the lower extreme of the curve, it seems intuitive that recipients who do not achieve the potential of the transplanted kidney, as defined by the donor function, will have poorer long-term outcomes. In this case, the degree of RFR may reflect the ability of the allograft to recover from injuries imposed in the acute peri-transplant period, and in particular to ischaemia–reperfusion injury (IRI).

At the upper extreme of the U-shaped curve, an RFR >2 was also associated with increased graft failure. A high RFR ratio may represent underestimation of the donor GFR, allograft hyperfiltration or discrepancies in allograft nephron mass compared with recipient size, which has been associated with poorer long-term graft survival [20]. However, given the small number of recipients with RFR >2 in this cohort, it is not possible to draw any firm conclusions in this range.

The baseline characteristics of the two groups differed with regard to donor and recipient age and weight, donor gender, ECD, CIT, DGF and acute rejection. However, when these factors were entered into a multivariable model, only acute rejection, ECD, DGF and transplant era remained as significant determinants of DCGF, which is consistent with previous reports [16,17]. Predictors of a low RFR also included DGF, ECD, early acute rejection, recipient age and gender. This is consistent as ECD kidneys are known to be associated with IRI and DGF [14,15], and supports the hypothesis that the degree of RFR may reflect the transplant kidney's ability to recover from these early injuries.

Table 1. Baseline characteristics of the cohort.

	Total cohort	RFR ≥1 (*n* = 421)	RFR <1 (*n* = 369)	*P* value
Recipient characteristics				
Recipient age (years, mean ± SD)	54 ± 13	53 ± 14	55 ± 12	0.017
Age groups (years)				
<50	272 (34)	159 (38)	113 (31)	0.091
50–<60	209 (27)	109 (26)	100 (27)	
≥60	309 (39)	153 (36)	156 (42)	
Male recipient gender	509 (64)	274 (65)	235 (64)	0.682
Recipient weight (kg, mean ± SD)	75.2 ± 15.8	73.1 ± 16.4	77.4 ± 14.9	<0.001
Transplant era before 1997	110 (14)	56 (13)	54 (15)	0.589
Cause of ESKD				
Glomerulonephritis	250 (32)	131 (31)	119 (32)	0.968
Diabetes	160 (20)	84 (20)	76 (21)	
Renovascular	61 (8)	32 (8)	29 (8)	
Polycystic kidney disease	109 (14)	56 (13)	53 (14)	
PN/IN	32 (4)	17 (4)	15 (4)	
Other	174 (22)	98 (23)	76 (21)	
Recipient SCr at 3 months (μmol/l)				
Mean ± SD	153 ± 82	113 ± 36	193 ± 94	<0.001
Range	(53–788)	(53–514)	(80–788)	
Median (IQR)	136 (99–173)	99 (94–129)	165 (141–215)	
Recipient eGFR at 3 months (ml/min/1.73 m^2)				
Mean ± SD	49 ± 20	63 ± 17	35 ± 13	<0.001
Range	(5–117)	(7–117)	(5–71)	
Median (IQR)	48 (33–63)	63 (51–73)	35 (27–44)	
Donor characteristics				
Donor age (years, mean ± SD)	50 ± 16	47 ± 16	53 ± 15	0.001
Male donor gender	429 (55)	247 (59)	182 (49)	0.005
Donor weight (kg, mean ± SD)	75.2 ± 16.5	77.3 ± 17.2	72.8 ± 15.2	<0.001
Terminal donor SCr (μmol/l)				
Mean ± SD	71 ± 24	79 ± 25	61 ± 19	<0.001
Range	(20–147)	(21–147)	(20–126)	
Median (IQR)	65 (53–85)	75 (58–96)	58 (48–71)	
Terminal donor eGFR (ml/min/1.73 m^2)				
Mean ± SD	97 ± 23	92 ± 24	103 ± 20	<0.001
Range	(33–172)	(33–153)	(52–172)	
Median (IQR)	99 (83–111)	94 (75–109)	102 (93–113)	
ECD	414 (52)	197 (47)	217 (59)	0.001
Transplant characteristics				
Low donor-to-recipient weight ratio	394 (50)	172 (41)	222 (60)	<0.001
HLA mismatch				
0–1	35 (4)	18 (4)	17 (5)	0.399
2–3	315 (40)	177 (42)	138 (38)	
4–6	437 (56)	224 (53)	213 (58)	
CIT (hours, mean ± SD)	17.3 ± 6.5	16.8 ± 6.5	17.9 ± 6.4	0.032
DGF	169 (21)	76 (18)	93 (25)	0.014
Acute rejection				
No rejection	646 (82)	356 (85)	290 (79)	0.026
<90 days post-transplant	57 (7)	21 (5)	36 (10)	
>90 days post-transplant	87 (11.0)	44 (10.5)	43 (11.7)	

Values represent number (%) unless otherwise specified. RFR, renal function recovery; SD, standard deviation; ESKD, end-stage kidney disease; PN, pyelonephritis; IN, interstitial nephritis; SCr, serum creatinine; IQR, interquartile range; eGFR, estimated glomerular filtration rate; ECD, expanded criteria donor; HLA, human leucocyte antigen; CIT, cold ischaemic time; DGF, delayed graft function. Low donor-to-recipient weight ratio defined as a ratio below the median.

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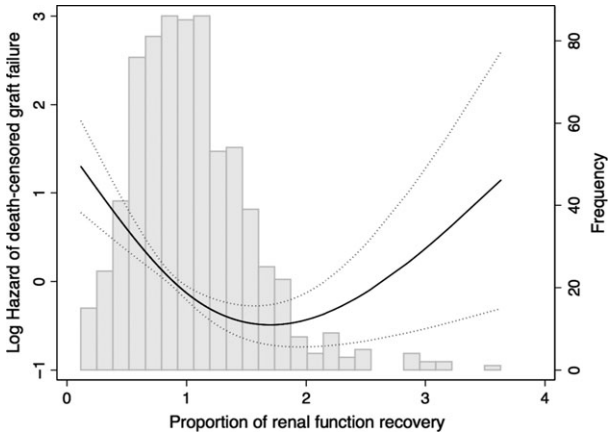

Figure 1 Relationship between renal function recovery (RFR) and death-censored graft failure (DCGF). Dashed lines represent 95% confidence intervals. There is a U-shaped relationship between RFR and DCGF, with optimal graft survival occurring at RFR 1-2.

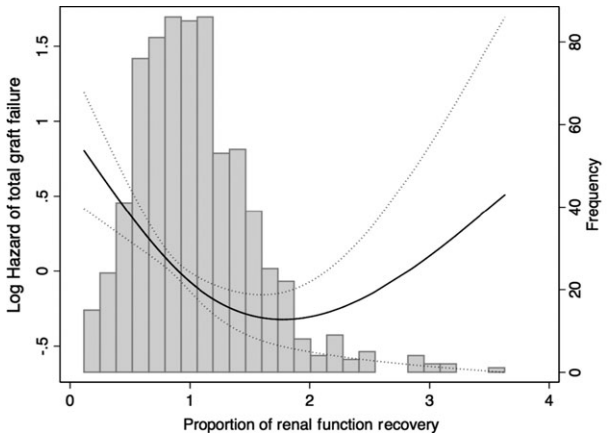

Figure 2 Relationship between renal function recovery (RFR) and total graft failure. Dashed lines represent 95% confidence intervals. There is a U-shaped relationship between RFR and total graft failure, with optimal graft survival occurring at RFR 1-2.

Our observation that a low donor-to-recipient weight ratio is associated with a higher risk of RFR <1 is consistent with recent reports in the literature. Al-Sehli *et al.* used an adaptation of the Cockroft–Gault formula to calculate expected SCr post-transplant based on donor and recipient characteristics and found that extremes of donor-to-recipient weight ratio correlated with discrepancies between expected and observed serum creatinine [21].

The calculation of RFR assumes that both kidneys contribute equally to donor eGFR. This is supported by scintigraphic studies of differential renal function in potential living kidney donors, which demonstrate an average difference in creatinine clearance of 6 ml/min, or 5% of renal function, between right and left

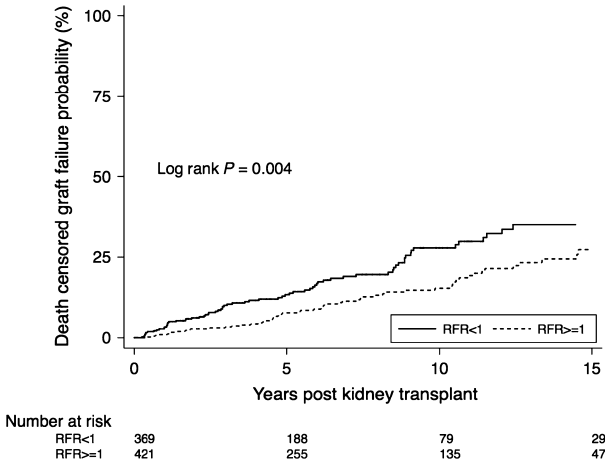

Figure 3 Kaplan–Meier curve of renal function recovery (RFR) and death-censored graft failure (DCGF) from 3 months post-transplant. Solid line represents RFR <1, and dashed line represents RFR ≥1. Recipients with RFR ≥1 had significantly less DCGF compared with those with RFR <1.

kidneys [22]. Furthermore, calculation of RFR is dependent on GFR estimating equations and therefore assumes that the SCr on which donor eGFR and recipient eGFR are based was in steady state. It is possible that AKI was present in donor kidneys, although we addressed this by the exclusion of those with donor SCr >150 μmol/l. Nevertheless, this remains an arbitrary and perhaps conservative cut-off for the detection of donor AKI, and the inclusion of cases of donor AKI could lead to an overestimation of the degree of RFR.

A time point of 3 months post-transplant was chosen for the evaluation of recipient renal function as it represents a reasonable point by which a steady state might be expected to develop. Although it has been demonstrated that SCr and eGFR at 6 months and 1 year predict long-term graft survival [23–25], few studies have examined 3 months as a single time point predictor of long-term outcomes. In this study, the recipient renal function at 3 months could not be entered into the multivariable analysis, as it is a component of RFR and would have introduced collinearity to the model. To evaluate the relationship between eGFR at 3 months and graft failure, we constructed a separate multivariable model using 3-month eGFR as the explanatory variable instead of RFR. This demonstrated an association between eGFR at 3 months and DCGF, and simple comparison of the predictive value of 3-month eGFR and RFR for DCGF using ROC curves were found to be equivalent. Nevertheless, RFR may provide additional information beyond the function at 3 months as it suggests a target eGFR for

Table 2. Multivariable Cox proportional hazards model of determinants of death-censored graft failure.

	Adjusted HR	95% CI	*P* value
RFR (≥1 vs. <1)	0.56	0.37–0.85	0.006
Recipient age			
<50 years*	1.00		
50–<60 years	1.11	0.71–1.76	0.644
≥60 years	0.89	0.55–1.44	0.646
Recipient gender (M vs. F)	1.05	0.72–1.54	0.807
ECD (Yes vs. No)	1.82	1.25–2.67	0.002
Transplant era (≥1997 vs. <1997)	0.58	0.37–0.91	0.017
DGF (Yes vs. No)	1.81	1.21–2.69	0.004
Acute rejection			
No rejection*	1.00		
<90 days post-transplant	1.94	1.10–3.42	0.021
>90 days post-transplant	4.35	2.91–6.50	<0.001
Cause of ESKD			
Glomerulonephritis*	1.00		
Diabetes	1.51	0.89–2.57	0.130
Renovascular	2.14	1.20–3.84	0.010
Polycystic kidney disease	0.58	0.28–1.22	0.151
PN/IN	1.55	0.72–3.34	0.262
Other	0.85	0.51–1.44	0.554
HLA mismatch			
0–1*	1.00		
2–3	1.24	0.43–3.60	0.689
4–6	1.73	0.62–4.83	0.297

HR, hazard ratio; CI, confidence interval; RFR, renal function recovery; M, male; F, female; ECD, expanded criteria donor; DGF, delayed graft function; ESKD, end-stage kidney disease; PN, pyelonephritis; IN, interstitial nephritis; HLA, human leucocyte antigen.

*Reference category.

Table 3. Multivariable logistic regression model of predictors of low renal function recovery (RFR <1).

	Adjusted OR	95% CI	*P* value
Recipient age			
<50 years*	1.00		
50–<60 years	1.25	0.85–1.84	0.251
≥60 years	1.39	0.97–1.99	0.075
Recipient gender (F vs. M)	1.25	0.91–1.71	0.171
Diabetes (Yes vs. No)	0.90	0.62–1.30	0.579
ECD (Yes vs. No)	1.44	1.06–1.95	0.018
Early acute rejection (Yes vs. No)	2.04	1.14–3.64	0.016
DGF (Yes vs. No)	1.57	1.09–2.25	0.015
Donor gender (F vs. M)	1.25	0.92–1.68	0.155
Low donor-to-recipient weight ratio	2.12	1.56–2.88	<0.001

OR, odds ratio; CI, confidence interval; F, female; M, male; ECD, expanded criteria donor; DGF, delayed graft function. Early acute rejection defined as acute rejection occurring within 90 days post-transplant. Low donor-to-recipient weight ratio defined as a ratio below the median.

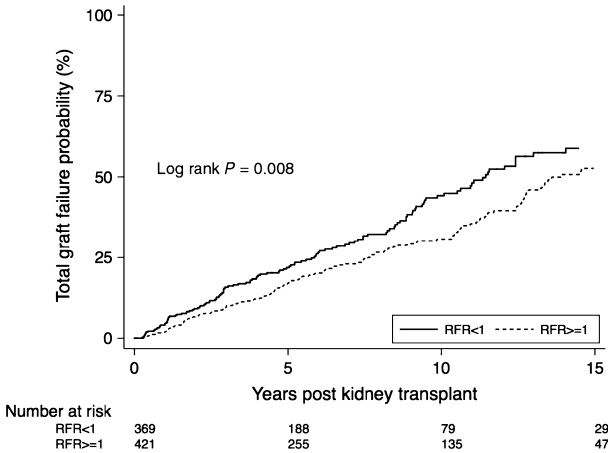

Figure 4 Kaplan–Meier curve of renal function recovery (RFR) and total graft failure from 3 months post-transplant. Solid line represents RFR <1, and dashed line represents RFR ≥1. Recipients with RFR ≥1 had significantly less total graft failure compared with those with RFR <1.

recipients that is dependent on the donor kidney function. This could be used to guide clinical decision-making; for example, a lower RFR may be a trigger for earlier investigation via kidney biopsy, or earlier intervention directed at modifiable risk factors for graft loss.

There were some limitations to this study; in particular, the sample of 790 patients with 127 events was underpowered to determine a precise threshold of RFR at which graft survival was reduced, and necessitated the analysis of RFR as a binary variable with an arbitrary cut point of 1. We were also unable to adequately explore key subgroups of interest, such as recipients of ECD kidneys due to the small number of events per subgroup. In addition, the decision to assess whether RFR at 3 months post-transplant to ensure kidney function had reached a steady state remains somewhat arbitrary and necessitates the exclusion of recipients who died or experienced graft failure prior to this time point. Further analysis should examine the robustness of this time point in the assessment of RFR. Limitation in data collection meant that we were not able to ascertain the return to baseline of Scr after treatment of acute rejection during the first 90 days post-transplant, nor were we able to adjust for comorbidities such as

Table 4. Multivariable Cox proportional hazards model of determinants of total graft failure.

	Adjusted HR	95% CI	*P* value
RFR (≥1 vs. <1)	0.72	0.54–0.96	0.026
Recipient age			
<50 years*	1.00		
50–<60 years	1.30	0.91–1.85	0.147
≥60 years	2.03	1.47–2.80	<0.001
Recipient gender (M vs. F)	0.80	0.61–1.06	0.124
ECD (Yes vs. No)	1.55	1.18–2.04	0.002
Transplant era (≥1997 vs. <1997)	0.50	0.36–0.68	<0.001
DGF (Yes vs. No)	1.39	1.04–1.85	0.027
Acute rejection			
No rejection*	1.00		
<90 days post-transplant	1.36	0.89–2.09	0.158
>90 days post-transplant	2.11	1.52–2.94	<0.001
Cause of ESKD			
Glomerulonephritis*	1.00		
Diabetes	1.70	1.18–2.46	0.004
Renovascular	1.81	1.18–2.77	0.006
Polycystic kidney disease	0.89	0.57–1.40	0.612
PN/IN	1.08	0.58–1.99	0.814
Other	1.13	0.79–1.62	0.507
HLA mismatch			
0–1*	1.00		
2–3	0.98	0.49–1.99	0.964
4–6	1.29	0.65–2.56	0.466

HR, hazard ratio; CI, confidence interval; RFR, renal function recovery; M, male; F, female; ECD, expanded criteria donor; DGF, delayed graft function; ESKD, end-stage kidney disease; PN, pyelonephritis; IN, interstitial nephritis; HLA, human leucocyte antigen.

*Reference category.

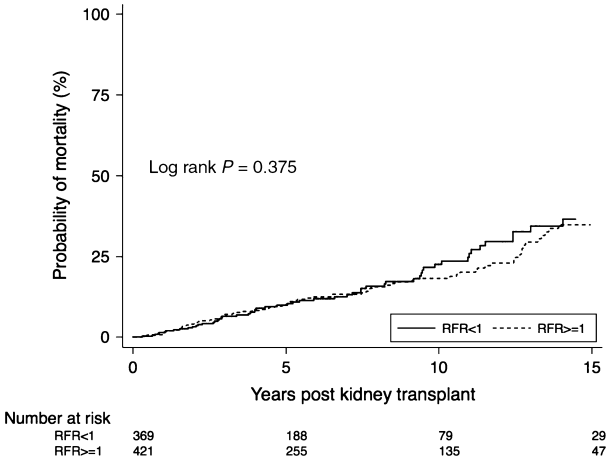

Figure 5 Kaplan–Meier curve of renal function recovery (RFR) and mortality from 3 months post-transplant. Solid line represents RFR <1, and dashed line represents RFR ≥1. There was no significant difference in mortality between recipients with RFR ≥1 and recipients with RFR <1.

cardiovascular disease, time on dialysis and panel reactive antibodies. Our single-centre analysis also reflects a relatively homogeneous Caucasian population, which may limit external validity. Finally, we used a ratio to describe recipient kidney function adjusted for donor function in a manner that is clinically useful and accessible. However, we acknowledge that use of ratios has limitations and, in particular, may not be easily interpreted when the relationship between numerator and denominator is nonlinear. Nevertheless, this is the first analysis to establish the utility of RFR and demonstrate its association with graft outcomes.

In conclusion, RFR can be quantified in terms of donor eGFR, and the early recovery of predicted function is associated with better long-term graft survival. Further analysis of large multicentre data is required to validate this approach and to explore reversible factors associated with RFR that may lead to better long-term outcomes for KTx recipients.

Authorship

All authors: participated in research design and drafting the manuscript. SW, MC and IM: participated in performance of the research and data analysis.

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Conflicts of interest

Dr. Marcelo Cantarovich is the recipient of Education Grants for the McGill University Health Centre Multi-Organ Transplant Program from Astellas and Novartis. The remaining authors declare no conflict of interests.

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None.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Receiver Operator Characteristics Curve for Multivariable Cox Proportional Hazards Models of death-censored graft failure.

Table S1. Multivariable Cox Proportional Hazards Model of Determinants of Death-Censored Graft Failure with recipient eGFR at 3 months as exposure variable.

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