ORIGINAL ARTICLE

Clinical outcomes in donors and recipients of kidney transplantations involving medically complex living donors – a retrospective study

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SUMMARY

We retrospectively compared the post-transplantation graft survival and the donor's estimated glomerular filtration rates (eGFRs) following living donor kidney transplantations (LDKTs) involving medically complex living donors (MCLDs) (the elderly and patients with obesity, hypertension, diabetes mellitus, or reduced renal function) and standard living donors (SLDs). The clinical data on patients who underwent LDKTs at our institution from 2006–2019, including 192 SLDs and 99 MCLDs, were evaluated. Regarding recipients, the log-rank test and multivariable Cox proportional hazards analyses showed a higher incidence of overall and death-censored graft loss in the recipients who received kidneys from MCLDs (Hazard ratio = 2.16 and 3.25, $P = 0.015$ and 0.004, respectively), after adjusting for recipient-related variables including age, sex, duration of dialysis, ABO compatibility, and donor-specific antibody positivity. Regarding donors, a linear mixed model showed significantly lower post-donation eGFRs (−2.25 ml/min/1.73 m^2, $P = 0.048$) at baseline in MCLDs than SLDs, but comparable change (difference = 0.01 ml/min/1.73 m^2/year, $P = 0.97$). In conclusion, although kidneys from MCLDs are associated with impaired graft survival, the donation did not adversely affect the MCLDs' renal health in at least the short-term. LDKTs involving carefully selected MCLDs would be an acceptable alternative for recipients with no SLDs.

Transplant International 2020; 33: 1417–1423

Key words
estimated glomerular filtration rate, living donor kidney transplantation, medically complex living donor, standard living donor

Received: 17 March 2020; Revision requested: 14 April 2020; Accepted: 6 July 2020; Published online: 29 September 2020

Introduction

The shortage of donors is a major obstacle in kidney transplantation today. Several studies have established the criteria for evaluating the quality of kidneys procured from deceased donors as well as strategies for optimizing the allocation of suboptimal kidneys [1–3]. However, few studies have examined the outcomes of kidneys obtained from medically complex living donors (MCLDs) [4–7].

In Japan, the number of kidneys available from deceased donors is considerably low. Hence, 89% of the

doi:10.1111/tri.13699

1742 kidney transplantations performed in 2017 used kidneys from living donors [8]. To cope with the shortage of deceased donors, the Japanese Transplantation Committee (JTC) established the following criteria for MCLDs in 2014: age of 71–80 years, body mass index (BMI) of 30–32 kg/m^2, blood pressure ≤ 130/80 mmHg with antihypertensive agents (albuminuria with < 30 mg/g creatinine), diabetes mellitus with hemoglobin A1c (HbA1c) levels ≤ 6.5% (National Glycohemoglobin Standardization Program) with oral hypoglycemic agents (albuminuria with < 30 mg/g creatinine), or glomerular filtration rates of 70–80 ml/min/1.73 m^2 (measured using inulin, radioisotopes, or creatinine clearance methods) [9]. Standard living donors (SLDs) were defined as having an age of 20–70 years, blood pressure ≤ 140/90 mmHg without any antihypertensive agents, BMI < 30 kg/m^2, absence of diabetes mellitus or impaired glucose tolerance confirmed by a morning fasting blood glucose ≤ 126 mg/dl and HbA1c levels ≤ 6.2% without hypoglycemic agents, and glomerular filtration rates ≥ 80 ml/min/1.73 m^2. The JTC guidelines are different in several aspects from the other guidelines such as the Amsterdam Forum guideline. Their unique point is allowing well-controlled diabetes mellitus as a donor comorbidity. The threshold for BMI is set lower in the JTC guidelines considering that the Japanese have a smaller body size.

To date, there is only one report on the clinical outcomes of kidney transplants from MCLDs, as defined by the JTC, but it included only 14 MCLDs and 47 SLDs [10]. Using a larger cohort, this single-center, retrospective study evaluated the post-transplantation outcomes of MCLDs and the recipients of kidney transplants from MCLDs.

Materials and methods

Ethical compliance

The Institutional Review Board and the Ethics Committee of the Jichi Medical University Hospital approved the present study (#A19-097). As the study design was retrospective and observational, informed consent from the study subjects was not required.

Case selection and endpoints

Clinical data for patients who underwent living donor kidney transplantation (LDKT) at the Jichi Medical University Hospital from April 2006 to March 2019 were obtained from medical records. Donor conditions were re-evaluated based on the JTC guidelines, and the donors were classified as either standard or medically complex. Inclusion criteria for the analysis were (i) a recipient who underwent LDKT and a donor who underwent laparoscopic nephrectomy, (ii) both the recipient and donor were ≥ 20 years of age, and (iii) the donor met the criteria for an SLD or MCLD as mentioned above.

The endpoints for the recipients were overall graft survival and death-censored graft survival. The overall graft survival was calculated from the date of transplantation to the date of irreversible graft failure (indicated by a return to long-term dialysis) or death. Follow-up was censored at the date of the last visit with a functional graft by the end of November 2019 [11]. Death-censored graft survival was calculated similarly, except that the follow-up was censored at the date of death if the graft was still functional at that time. The endpoint for the donors was the postoperative estimated glomerular filtration rate (eGFR), which was calculated using the Modification of Diet in Renal Disease formula, modified for the Japanese population [12].

Immunosuppression

Our standard regimen for immunosuppression included basiliximab as induction therapy; tacrolimus or cyclosporine, mycophenolate mofetil, and methylprednisolone as initial maintenance medications; and tacrolimus or cyclosporine, mycophenolate mofetil, and methylprednisolone or everolimus as long-term maintenance medications. ABO-incompatible and donor-specific antibody (DSA)-positive recipients received desensitization therapy with rituximab and plasmapheresis.

Statistical analysis

Regarding recipient endpoints, Kaplan–Meier curves for overall graft survival and death-censored graft survival were generated, and comparisons between the SLD and MCLD groups were performed using the log-rank test. Multivariable Cox proportional hazards regression analyses were conducted to examine the relationship between donor status (medically complex or standard) and graft survival. The following recipient-related factors were used to adjust for bias: age, sex, duration of dialysis, ABO compatibility, and the presence of DSAs, which required desensitization therapies. Regarding donor endpoints, linear mixed model analysis was performed to evaluate whether donor status (medically complex or standard) affected the trajectory of their

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eGFR [13]. Independent variables included in the linear mixed model were donor status, the time points (in years) at which the respective eGFR measurement was obtained, the interaction terms between donor status and time, and donors' sex. Additionally, we included a random intercept and random slope for the time to account for individual random effects in the trajectory of eGFR. We modeled the random intercept and random slope as a bivariate normal distribution with unstructured covariance matrix to allow a potential correlation between them.

All analyses were performed using R version 3.6.2 software (R Foundation for Statistical Computing, Vienna, Austria). P values < 0.05 were considered statistically significant.

Results

Between April 2006 and March 2019, 309 LDKTs were performed at our hospital. There were 192 SLDs and 99 MCLDs; 18 donors were excluded from the present study as they had recipients aged < 20 years ($n = 11$), had missing HbA1c data ($n = 3$), had BMI above 32 kg/m^2 ($n = 2$), had an HbA1c level> 6.5% ($n = 1$), or were undergoing insulin therapy ($n = 1$). The patient characteristics are summarized in Table 1. All patients were Japanese. The renal function of all donors was evaluated using the creatinine clearance method. There were no significant differences in the background characteristics of the recipients of kidneys from SLDs vs. MCLDs.

The linear mixed model analysis of donor endpoints included 5414 eGFR measurements in 291 donors over a median follow-up period of 1643 days. The median, minimal, and maximal numbers of eGFR measurements per patient were 17, 4, and 80, respectively. The average time interval between measurements was 100 days.

Recipient endpoints

As determined via Kaplan–Meier analysis (Fig. 1), the overall graft survival and death-censored graft survival rates in the SLD group at 5 and 10-years after transplantation were 93.9/96.9% and 75.5/86.6%, respectively. The corresponding rates in the MCLD group were 82.2/90.6 and 48.8/53.8%, respectively. The overall graft survival and death-censored graft survival rates were significantly higher in the SLD group than in the MCLD group ($P = 0.008$ and 0.001, respectively).

The multivariable Cox proportional hazards regression analyses showed that the MCLD group had a significantly higher incidence of overall graft loss and death-censored graft loss compared to the SLD group [hazard ratio (HR) = 2.16 and 3.25, 95% confidence interval (CI) = 1.16–4.03 and 1.47–7.23, $P = 0.015$ and 0.004, respectively] (Table 2).

Donor endpoints

A linear mixed model showed that the MCLD group had a significantly lower mean eGFR at the postdonation baseline (difference = −2.25 ml/min/1.73 m^2, 95% CI = −4.71 to −0.40, $P = 0.048$) than the SLD group; however, there was no statistically significant difference in the mean eGFR slope per year between these two groups (difference = 0.01 ml/min/1.73 m^2/year, 95% CI = −0.52 to 0.54, $P = 0.97$) (Table 3).

Discussion

The present study demonstrates that the renal outcomes in recipients of kidneys from MCLDs are unfavorable compared to the outcomes in recipients of kidneys from SLDs. It also showed comparable renal outcomes of MCLDs vs. SLDs, thereby validating the JTC guidelines for MCLD selection. To date, only a single study has examined the clinical outcomes of living donor kidney transplants from MCLDs, defined as per the JTC criteria [10]. In that study, the 5-year graft survival rate did not differ significantly between the MCLD and SLD groups, although the eGFR of recipients was significantly lower in the MCLD group ($n = 14$) than in the SLD group ($n = 47$). The eGFRs of donors were reported to be consistently and statistically significantly lower in the MCLD group than those in the SLD group during the two-year follow-up period; however, they declined comparably in both groups [10]. Regarding recipient outcomes, there was a difference within the studies presumably owing to our larger cohort size and longer follow-up periods; our study suggested worse graft survival of recipients, and the previous study did not. Regarding donor outcomes, almost similar results were obtained in both studies, except for a longer follow-up period in the present study; renal functions of donors were different within the groups at the postdonation baseline but the differences did not increase over time.

During the selection of MCLDs for LDKT, two important factors need particular attention: the quality of the donated kidney and the potential long-term harm to the donor [14].

Regarding kidney quality, in the present study, the incidence of overall and death-censored graft loss was

Table 1. Demographics and baseline characteristics of recipients and donors.

Variable	Medically complex living donors (n = 99)	Standard living donors (n = 192)
Recipients		
Age, years; mean (SD)	48.3 (12.9)	47.6 (13.3)
Male, *n* (%)	58 (58.6)	116 (60.4)
Primary disease leading to transplantation, *n* (%)		
Glomerulonephritis	37 (37.4)	75 (39.1)
Diabetes mellitus	28 (28.3)	36 (18.8)
Polycystic kidney disease	4 (4.0)	14 (7.3)
Hypertension/nephrosclerosis	3 (3.0)	10 (5.2)
Unknown	11 (11.1)	24 (12.5)
Others	16 (16.2)	33 (17.2)
Duration of dialysis, years; median (IQR)	1.42 (0.28–3.31)	1.54 (0.61–3.86)
ABO-incompatible, *n* (%)	25 (25.3)	65 (33.9)
Donor-specific antibody-positive, *n* (%)	10 (10.1)	15 (7.8)
Donors		
Age, years; mean (SD)	64.1 (9.3)	54.9 (9.9)
Male, *n* (%)	51 (51.5)	71 (37.0)
HLA-A, B, DR matching		
Numbers of mismatches, mean (SD)	3.1 (1.6)	3.3 (1.6)
No mismatch kidney, *n* (%)	6 (6.1)	12 (6.2)
Relationship between donors and recipients, *n* (%)		
Donation to spouse	36 (36.4)	95 (49.5)
Donation to child	56 (56.6)	60 (31.2)
Donation to sibling	5 (5.1)	22 (11.5)
Donation to parent	0 (0.0)	10 (5.2)
Donation to other relative	2 (2.0)	5(2.6)
Pre-donation eGFR, ml/min/1.73 m^2; mean (SD)	86.1 (17.7)	89.6 (19.4)
Medically complex factor, *n* (%)		
Hypertension	65 (65.7)	
Elderly (age of 71–80 years)	30 (30.3)	
Diabetes mellitus	22 (22.2)	
Reduced renal function*	5 (5.1)	
Obesity (BMI of 30–32 kg/m^2)	5 (5.1)	
Number of medically complex factors, *n* (%)		
1	75 (75.8)	
2	20 (20.2)	
3	4 (4.0)	

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

*Reduced renal function meant glomerular filtration rates of 70–80 ml/min/1.73 m^2 measured using creatinine clearance method.

significantly higher in the MCLD group than in the SLD group. There are several possible reasons for this large difference compared to the relatively small difference in donor outcomes. These include the fact that kidneys with low functional reserve could be vulnerable to ischemia-reperfusion injuries [15] and that older donor age could be a risk factor for acute rejection [16].

Some reports suggest that kidneys from MCLDs negatively impact the short- and long-term outcomes in the recipients [4–6]. However, the quality of kidneys from MCLDs may be better than those from deceased donors. According to a previous report, patients with transplants from older living donors survive longer than those with transplants from deceased donors [4]. Therefore, for patients who have no SLDs, accepting a kidney from an MCLD may have a greater survival benefit than waiting for one from a deceased donor while on dialysis. However, as higher mortality rates were reported in patients with failed grafts than in those on dialysis

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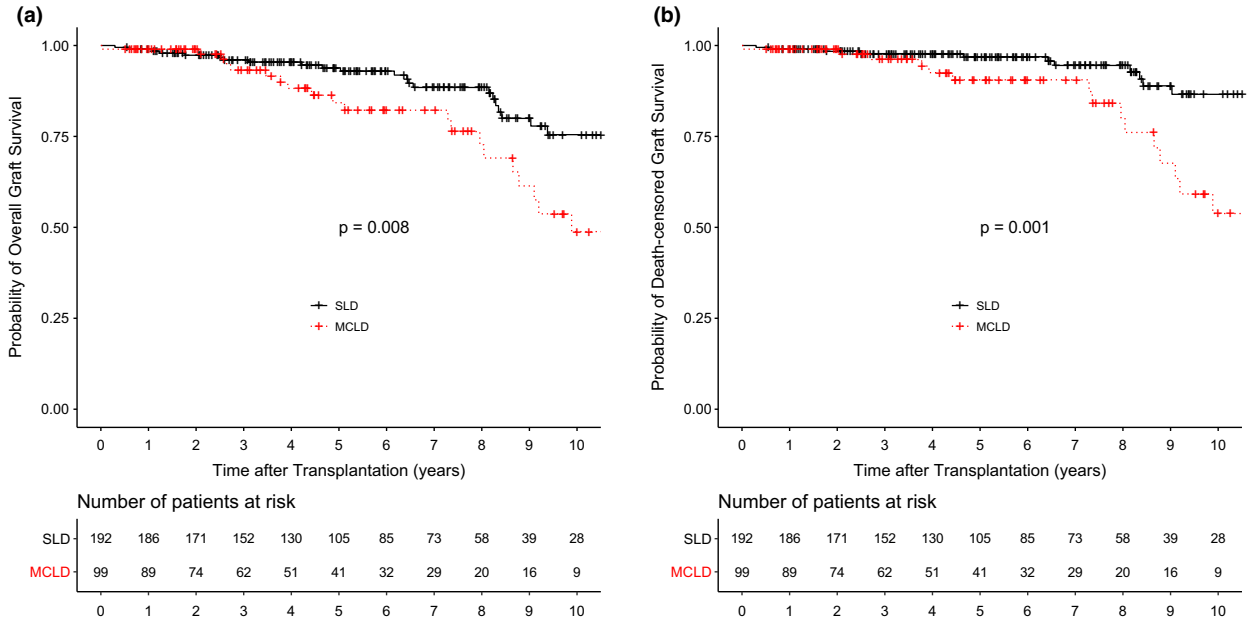

Figure 1 Kaplan–Meier plots for (a) overall and (b) death-censored graft survival. P values were determined by the log-rank test. MCLD, medically complex living donor; SLD, standard living donor.

Table 2. Multivariable Cox proportional hazards regression analyses for overall and death-censored graft survival.

	Overall graft survival		Death-censored graft survival	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Medically complex living donor (vs. standard living donor)	2.16 (1.16–4.03)	0.015	3.25 (1.47–7.23)	0.004
Recipient's age (years, continuous)	1.02 (1.00–1.05)	0.063	0.98 (0.95–1.02)	0.308
Recipient's sex (male vs. female)	2.59 (1.25–5.36)	0.011	2.16 (0.90–5.20)	0.086
Duration of dialysis (years, continuous)	1.00 (0.98–1.02)	0.779	1.00 (0.98–1.03)	0.794
ABO-incompatible (vs. ABO-compatible)	0.69 (0.33–1.44)	0.320	0.40 (0.12–1.38)	0.147
Donor-specific antibody-positive (vs. antibody-negative)	4.07 (1.15–14.45)	0.030	1.67 (0.21–13.39)	0.631

CI, confidence interval.

without a history of transplantation [17], the pros and cons of kidney transplants from MCLDs need to be weighed carefully to identify candidates who can benefit from such transplants. To establish the criteria for candidate selection, more information is needed on the characteristics of the recipients who benefitted from MCLD transplantations and the extent of their benefits.

Regarding donor safety, the present study demonstrates that the eGFR at the postdonation baseline is lower in MCLDs than in SLDs, but the eGFR changing slopes were comparable in both groups. The difference in the eGFRs at the postdonation baseline (−2.25 ml/min/1.73 m^2 in MCLDs vs. SLDs) seemed to represent the difference of those at the pre-donation point (86.1 ml/min/1.73 m^2 in MCLDs and 89.6 ml/min/1.73 m^2 in SLDs) and did not increase over time. This small difference could affect the donor selection especially when considering young donor candidates with long life expectancies. However, there seemed to be no differences in the safety of donors after donation, if they had enough eGFR levels compared to their individual life expectancies. We should estimate the lifetime risk of each donor before permitting them to donate their kidneys.

Glomerular basement membrane thickness seen on 1-h biopsy of the donated kidney was reported to be the important factor for predicting worse postdonation donors' renal function but was not associated with donor status (MCLDs vs. SLDs) [18]. This suggests that the presence of mild comorbidities is not a major factor leading to renal function impairment after donation, and factors other than comorbidities affect the postdonation renal function more. This hypothesis might

Table 3. Linear mixed model analyses for postdonation eGFR.

	Estimated value (95% CI)	*P* value
Mean eGFR differences at the postdonation baseline*		
In MCLDs vs. SLDs	−2.25 (−4.47 to −0.40)	0.048
Mean eGFR changing slope per year		
In SLDs	0.26 (−0.03 to 0.56)	0.078
In MCLDs	0.27 (−0.54 to 1.09)	
In MCLDs vs. SLDs	0.01 (−0.52 to 0.54)	0.971

Adjusted for sex.

CI, confidence interval; MCLD, medically complex living donor; SLD, standard living donor.

*The postdonation baseline means when the variable "time points (in years) at which the respective eGFR measurement was obtained" is zero.

explain why there was no difference in the eGFR changing slopes between MCLDs and SLDs in the present study. However, this could be the result of compensatory hypertrophy of the remaining kidney or hyperfiltration in the remnant nephrons, which could eventually lead to renal insufficiency [19,20]. Thus, long-term studies are needed to evaluate parameters in addition to eGFRs (e.g., cardiovascular events, the incidence of initiation of dialysis, and overall survival) to evaluate donor safety more thoroughly.

The present study has several limitations. First, it was a retrospective cohort study, and unobserved confounders may have introduced bias. Second, our results may not be generally applicable, as an all-Asian cohort was used. Finally, the size of the cohort and the length of follow-up were insufficient. Larger and longer-term studies are needed to draw definitive conclusions regarding donor safety.

In conclusion, kidneys from MCLDs might be associated with impaired graft survival in the recipients. However, donating a kidney is unlikely to have adverse effects on the renal health of the MCLDs in at least the short-term after the donation. LDKTs involving carefully selected MCLDs would, therefore, be acceptable alternatives for recipients who have no SLDs.

Authorship

YK: participated in research design, research performance, manuscript preparation, and data analysis. TY: participated in research design and manuscript preparation. TS and KH: participated in research design, manuscript preparation, and data analysis. ST, TK, TS, TS, MS, and AM: participated in research performance. JK, AF, SA, MS, HK, and TF: participated in research design.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.

REFERENCES

1. Port FK, Bragg-Gresham JL, Metzger RA, *et al.* Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. *Transplantation* 2002; **74**: 1281.
2. Rao PS, Schaubel DE, Guidinger MK, *et al.* A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation* 2009; **88**: 231.
3. The New Kidney Allocation System (KAS). Frequently asked questions. Available at: http://optn.transplant.hrsa.gov/media/1235/kas_faqs.pdf
4. Englum BR, Schechter MA, Irish WD, *et al.* Outcomes in kidney transplant recipients from older living donors. *Transplantation* 2015; **99**: 309.
5. Massie AB, Leanza J, Fahmy LM, *et al.* A risk index for living donor kidney transplantation. *Am J Transplant* 2016; **16**: 2077.
6. Rehse G, Halleck F, Khadzhynov D, *et al.* Validation of the Living Kidney Donor Profile Index in a European cohort and comparison of long-term outcomes with US results. *Nephrol Dial Transplant* 2019; **34**: 1063.
7. Serrano OK, Yadav K, Bangdiwala A, *et al.* Age alone is not a contraindication to kidney donation: Outcomes of donor nephrectomy in the elderly. *Clin Transplant* 2018; **32**: e13287.
8. Japanese Society for Clinical Renal Transplantation and the Japan Society for Transplantation. Annual progress report from the Japanese Renal Transplant Registry: number of renal transplantations in 2017 and a follow-up survey. *Jpn J Transplant* 2018; **53**: 89.
9. Morozumi K. Clinical practice guidelines for renal transplant donors and recipients in Japan. *Jpn J Transplant* 2014; **49**: 410.
10. Oikawa M, Hatakeyama S, Narita T, *et al.* Safety and effectiveness of marginal donor in living kidney transplantation. *Transplant Proc* 2016; **48**: 701.

11. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.13 Analysis of patient and graft survival. *Nephrol Dial Transplant* 2002; **17**: 60.
12. Matsuo S, Imai E, Horio M, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982.
13. Leffondre K, Boucquemont J, Tripepi G, Stel VS, Heinze G, Dunkler D. Analysis of risk factors associated with renal function trajectory over time: a comparison of different statistical approaches. *Nephrol Dial Transplant* 2015; **30**: 1237.
14. Bozkurt B, Kilic M. Marginal donors in renal transplantation. *Transplant Proc* 2015; **47**: 1273.
15. Polichnowski AJ, Lan R, Geng H, Griffin KA, Venkatachalam MA, Bidani AK. Severe renal mass reduction impairs recovery and promotes fibrosis after AKI. *J Am Soc Nephrol* 2014; **25**: 1496.
16. Kidney Disease: Improving Global Outcomes Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9**: S1.
17. Rao PS, Schaubel DE, Jia X, Li S, Port FK, Saran R. Survival on dialysis post-kidney transplant failure: results from the Scientific Registry of Transplant Recipients. *Am J Kidney Dis* 2007; **49**: 294.
18. Kubota Y, Hatakeyama S, Narita I, Shimada M, Hashimoto Y, Ohyama C. Clinical impact of glomerular basement membrane thickness on post-donation renal function in living donors. *Int J Urol* 2019; **26**: 309.
19. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int* 1996; **49**: 1774.
20. Taner T, Iqbal CW, Textor SC, Stegall MD, Ishitani MB. Compensatory hypertrophy of the remaining kidney in medically complex living kidney donors over the long term. *Transplantation* 2015; **99**: 555.