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WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone marrow transplantation, bone transplantation, bone-patellar tendon-bone grafting, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, transplantation immunology, and vascularized composite allotransplantation.

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ORIGINAL ARTICLE

Prospective Study

Living kidney donor assessment: Kidney length *vs* differential function

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Abstract

BACKGROUND

The key question in living kidney donor assessment is how best to determine the contribution of each kidney to overall renal function and guide selection of which kidney to donate, ensuring safety of procedure and good outcome for both recipient and donor. It is thought that a length difference > 2 cm may indicate significant difference in function and therefore need for measurement of differential function.

AIM

To determine the effect of using kidney length to decide which kidney to donate in a retrospective cohort of potential donors.

METHODS

All 333 potential living kidney donors between January 2009 and August 2018 who completed assessment were retrospectively evaluated. Donor assessment was performed as per United Kingdom guidelines. Data included age, sex, kidney length (cranio-caudal) obtained by computed tomography/ultrasonography,51-chromium ethylenediamine tetraacetatic acid measured glomerular filtration rate, mercapto acetyl tri glycine split function and vascular anatomy. There were 48 exclusions due to inadequate data or incomplete investigations. Statistical analysis was performed using Excel pivot tables and GraphPad Prism. Correlation between kidney length and differential function was determined with Pearson's correlation coefficient.

RESULTS

Of 285 potential donors included in the study, there were 144 males (mean age 49.9 ± 14.75) and 141 females (mean age 51.2 ± 11.23). Overall, the Pearson's correlation between differences in length and divided function of kidney pairs

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was 0.1630, $P = 0.0058$. Of 73 with significant difference (> 10%) in divided function, 18 (24.7%) had no difference in kidney length; 54 (74%) had a difference of < 2 cm and only one of > 2 cm. Using a length difference of > 1 cm would only predict significant difference in divided function in 8/34 (23.5%) of cases. Using a difference of > 2 cm as cut off for performing split function would lead to false reassurance in 72 patients (6 had > 20% difference in divided function whereas 66 had 10%-20% difference).

CONCLUSION

Length difference between kidney pairs alone is not sufficient to replace measurement of divided function. This issue requires a randomised controlled trial to resolve it.

Key words: Kidney transplantation; Living kidney donor assessment; Kidney length; Kidney volume; Differential function; Glomerular filtration rate

Core tip: Selection of which kidney to donate is of critical importance in living kidney donation. The decision-making process based on divided function and vascular anatomy was used to validate a retrospective "what if" analysis of prospectively reported kidney length measurements in a cohort of 285 potential donors. This study shows a significant risk for making wrong/harmful decision (removing the significantly better functioning kidney) if kidney length alone is used for decision making -25% if using 2 cm difference as cut off. Difference in length between kidney pairs alone is not sufficient to replace measurement of divided function.

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INTRODUCTION

The continuing scarcity of deceased organs coupled with the evidently better results associated with living donor transplantation has focused attention on living donor wellbeing and long-term outcome. The risk of developing end-stage renal disease, cardiovascular disease and increased all-cause mortality in donors[1] demands that every effort must be made to eliminate risks in living donors. This is in line with the well-known principle of "*primum non nocere*" ("first do no harm"). The goals of assessment of living kidney donors are to ensure the donor is well enough to go through the donation process with minimal or no morbidity and avoidance of mortality; that the recipient achieves an uncomplicated transplant with a beneficial long-term outcome. Donor welfare and safety is paramount; therefore, potential candidates must have sufficient renal function post donation in order to minimize future risks when living with a single kidney. The aim is to retrieve the kidney that will allow the donor to preserve the better kidney[2]. Sometimes this means that a multi-artery left kidney is preferable to a right kidney[3].

Determining whether both kidneys contribute equally or significantly differently to overall function is fundamental to the decision as to which kidney to donate. In the context of living kidney donation, this involves accurate determination of the donor glomerular filtration rate (GFR) and ensuring that it is within the recommended range as advised by the British Transplantation Society/Renal Association (BTS/RA) Guidelines[2]; and evaluation of renal parenchyma, urinary system and vascular anatomy by means of ultrasonography (US), Computed tomography (CT) or magnetic resonance angiography; and only removing the kidney with the lower contribution when the divided function is significantly different. The key question is how best to determine the contribution of each kidney to the overall function. Isotope differential renal function is not uniformly performed in all transplant centres, with many relying on kidney size measurements. Such an approach is supported by the BTS/RA Living Donor Kidney Transplantation Guidelines (2018)[2] which states that differential kidney function, determined by ^{99m}Technitium dimercaptosuccinic acid (^{99m}TcDMSA) is recommended where there is > 10% variation in kidney size or significant renal anatomical abnormality. It further states that, "A difference in size of 2 cm or more indicates the possibility of a significant difference in GFR between the two kidneys". Until the recent BTS/RA Guidelines[2], our centre performed mercapto acetyl tri glycine (MAG3) split function and CT and/or US imaging for all patients. This study aimed to determine the effect of using kidney length to decide which kidney to donate in a retrospective cohort of potential donors. It also studied the correlation between differences in kidney length and split renal function; whether a difference in length of > 2 cm is associated with significant differences in divided function; and whether a < 1 cm difference is sufficient evidence that the split renal function is not significantly different between both kidneys.

MATERIALS AND METHODS

This retrospective evaluation of prospectively collected data on potential living kidney donors was approved by the institutional review board and individual informed consent was waived. During the period between January 2009 and August 2018, all potential living kidney donors who completed the assessment process up to CT angiography were studied whether they proceeded to donation or not. Donor assessment was performed as per United Kingdom guidelines.

Kidney length

Pole to pole (cranio-caudal) length as determined by CT and/or ultrasound scan (US) was documented for each kidney in all prospective donors. Where data from both modalities of imaging were available, CT length measurement was used preferentially over US imaging to assess length of kidney. Length measured on US scan was only used where CT was not reported, not completed, or unavailable as completed at different centres, or where CT reports were not specific to true length of kidneys. Other dimensions of the kidney were not reported in this centre.

Determination of GFR and divided function

Each potential donor underwent 51-chromium ethylenediamine tetraacetatic acid (^{51}Cr-EDTA) scans for GFR measurement (Brochner-Mortensen GFR for 1.73 m^2 BSA). To determine the split or divided function, a radioisotope renogram with diuretic followed by an indirect micturating cystourethrogram combined with a MAG3 scan was performed with the diuretic administered at the same time as the radiopharmaceutical to ensure good diuresis. Divided function was calculated using geometric mean data. Uptake of tracer in both kidneys as well as normal drainage and excretion bilaterally; evidence of obstruction in either kidney; evidence of reflux on the indirect micturition cystogram component of the study were determined/ reported.

Pre-donation assessment culminated in CT imaging in order to assess length measurement, renal pathology and vascular anatomy. For potential donors with qualifying GFR, the divided function (if ≤ 20%) in conjunction with the vascular anatomy was used to guide suitability decision for donation and appropriate selection of which kidney to donate. The renal length was not utilised in the decision making process during the study period.

The list of potential donors and their key data was maintained prospectively on an Excel spreadsheet. Further information was retrieved from the renal computer system – VitalData Clinical Information System (Vitalpulse Limited 1997-2019). Imaging results were obtained from Insignia Medical Systems [Insight PACS (Picture Archiving and Communication Systems)].

Data collected included donor age, sex, GFR, differential function, US kidney length, CT kidney length and donated GFR. The differences in length and the differential function between left and right kidney pairs were categorised as shown in Table 1 for the purpose of analysis. The donated GFR was calculated as a percentage of the total donor GFR according to the split function of the donated or potentially donated kidney[4].

Exclusions

Forty eight potential donors were excluded from the study: 31 due to inadequate reporting of imaging (no length measurement was available, either from CT or US); 14 due to incomplete investigations (late withdrawal from the process, no CT or no MAG3); and three due to inadequate data from an external unit that performed the assessment.

Table 1 Categorisation according to different parameters

Length difference	Difference in divided function	Category
> 2 cm	> 20%	4
1.01-2.0 cm	10%-20%	3
0.01-1.0 cm	< 10%	2
0	0%	1

Statistical analysis

Detailed information on the potential donors were entered in to an Excel database and analysed using Excel pivot tables. Further statistical analysis was conducted using GraphPad Prism (GraphPad Software, San Diego, CA, United States). The difference between means was tested using the *unpaired t-test*. Correlation between kidney length and divided function; and difference in length of kidney pairs versus differential function were determined using Pearson's correlation coefficient. A $P < 0.05$ was regarded as statistically significant.

RESULTS

Of the 285 included in the study, there were 144 males (mean age 49.9 ± 14.75) and 141 females (mean age 51.2 ± 11.23). The difference between the means of 1.3 [95% confidence interval (CI): −1.7615 to 4.3615; t = 0.8358; u = 283] was not statistically significant (P = 0.4040). The average GFR of female potential donors of 86.85 ± 13.51 mL/min was comparable to the 89.63 ± 14.66 mL/min for male potential donors. The difference between the means of -2.78 (95%CI from -6.0707 to 0.5073; t = 1.6648; u = 283; SED = 1.671) was not statistically significant (P = 0.0971).

The length of kidneys was determined by CT scan in 237 (83.2%) potential donors and by US alone in 48 (16.8%). Correlation between the cranio-caudal length of kidneys and their contribution to overall function is shown in Figure 1. Whereas there was no significant association with the left kidneys (Pearson r = −0.0029 (95%CI: −0.1191 to 0.1133); R^2 = 8.687e^{-006}; P = 0.9605), there was a statistically significant correlation with the right kidneys [Pearson r = 0.1303 (95%CI: 0.01438 to 0.2429); R^2 = 0.01699; P = 0.0278].

Correlation between difference in length according to imaging modality and divided function of kidney pairs is shown in Figure 2. Though weak, CT-measured kidney length provided a stronger correlation with divided function than US-measured length in this series (R^2 = 0.0378 *vs* 0.0019 respectively). Overall, the correlation between differences in length and differential function of kidney pairs was 0.1630 (Pearson's) (95%CI from 0.0477 to 0.2740; R^2 = 0.0266; P = 0.0058; Figure 3).

The frequency distribution of the differences in length and divided function between 285 kidney pairs is shown in Figure 4. Fifty seven (20%) donors had no difference in the length of their kidneys compared to 40 who had no difference in the divided function of their kidney pairs – x^2 = 3.5904, P = 0.058. However, when the proportion of donors with a difference in length above 1 cm (34/285) was compared with those with a differential function of 10% or higher (73/285), this was found to be highly statistically significant – x^2 = 17.5001, P = 0.00003. Of 34 potential donors with a difference in length of at least 1 cm, seven had differential function of 10%-20% with one over 20% (Table 2). Conversely, of seven patients with > 20% difference in function, only one had > 2 cm difference in length (2.3 cm; Table 3). In the remaining six the difference in length ranged from −1 to 0.3. Three of these have donated, three were declined, one donor has moved from the area.

Of 73 with a significant difference in divided function (categories 3 and 4, Table 2), 18 (24.7%) had no difference in kidney length; 54 (74%) had a difference of < 2 cm and only one of > 2 cm. Only these 73 (25.6%) potential donors would present any dilemma regarding which kidney to select for donation, if at all. Of these, using difference in length alone would lead to a false reassurance in 65 as the difference in length would be < 1.0 cm - only eight would raise the need for measurement of differential function. Similarly, using a difference in length of 2 cm as cut off for performing split function would lead to false reassurance in 72 patients (6 had > 20% difference in divided function whereas 66 had 10%-20% difference).

The data on number of vessels was missing in two patients. Of the remaining 283, there were single vessels in 207 left kidneys and 200 right kidneys; and there were two or more vessels in 76 left kidneys and 83 right kidneys. The distribution of multiple

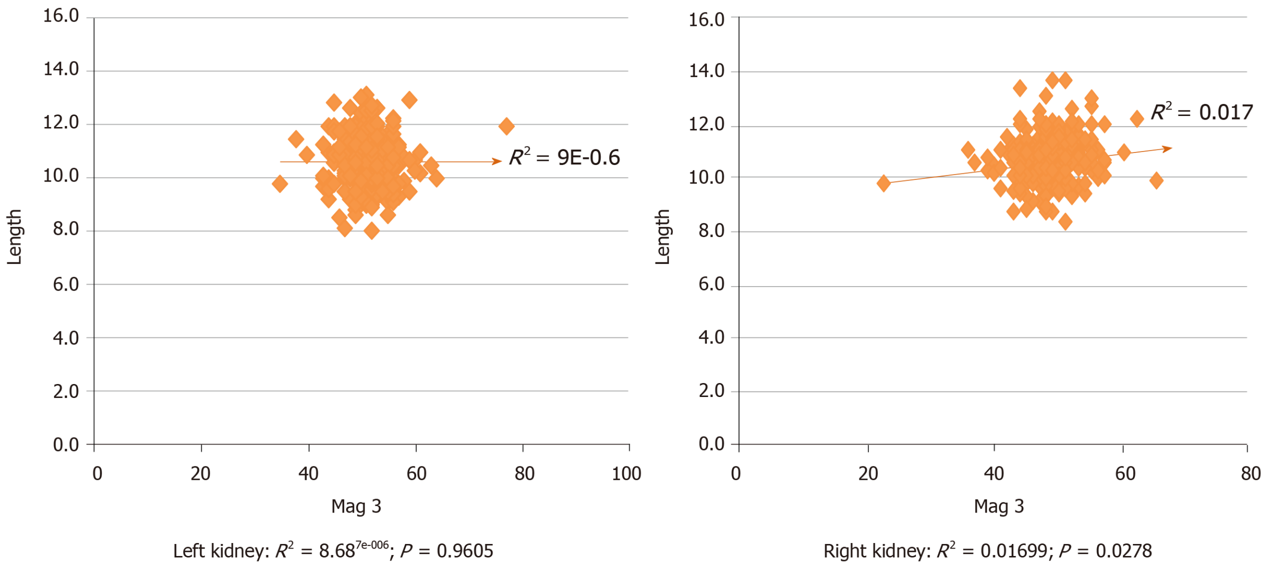

Figure 1 Correlation of kidney length with divided function (differential function x donor glomerular filtration rate) for 285 kidney pairs.

vessels between left and right kidneys was not statistically different x^2 = 0.4286; P = 0.5126.

DISCUSSION

The key findings in this study include the following: Equal sex distribution among potential donors whose mean ages and GFRs were comparable; weak correlation between difference in length and divided function of kidney pairs (CT-measured kidney length provided a stronger correlation than US-measured length); the proportion of donors with a difference in length above 1 cm (34/285) was statistically significantly different from those with a differential function of 10% or higher (73/285); and of 73 with a split function greater than 10, 18 (24.7%) had no difference in kidney length; 54 (74%) had a difference of < 2 cm and only one of > 2 cm. Furthermore, using a difference in length of 2 cm as cut off for performing split function would lead to false reassurance in 72 patients (25%).

This study is unique in presenting the results of a retrospective "what if" analysis of prospectively reported kidney length measurements that were not used in the decision-making process as to which organ to donate. The decisions were made on the basis of divided function and vascular anatomy. Analysis of a large number of potential donors this way provides a useful tool in validating the use of kidney size alone in making decisions about which kidney to donate. Our study measured kidney length by CT and US in line with many authors. In a study of 100 living kidney donors, Ninan and co-workers[5] demonstrated that ultrasonographically measured bipolar kidney length was more accurate than measurements using plain X-ray, intravenous urography, and renal angiogram. However, they also found that US tends to underestimate while radiological methods overestimated the size of the kidney. Widjaja *et al*[6] showed there was significant correlation between ultrasound measured length and CT volume (r = 0.74, P < 0.01). Our decision to prefer CT-measured kidney length is supported by Kang and co-workers[7] who showed that abdominal coronal CT section assessed kidney length more accurately than other radiological methods.

Our study shows low but significant correlation between differences in length between kidney pairs and divided function (Figure 3). The distribution of the differences in length and divided function was not similar (Figure 4). Kidney size can be estimated by measuring renal length, renal volume, cortical volume, or renal weight. Kidney length provides a good indication of kidney size[8] and close correlation with GFR[9,10]. However, Sanusi *et al*[11] showed a positive correlation between US-determined kidney volume and GFR and suggested that kidney volume was a better indicator of kidney size in health or renal disease. Though the donor kidney size (length, weight or volume) is now largely accepted as a predictive factor for recipient allograft function[9,10,12] and as an important predictor of long term donor kidney function[13], volumetric measurement of the donor kidneys provide better

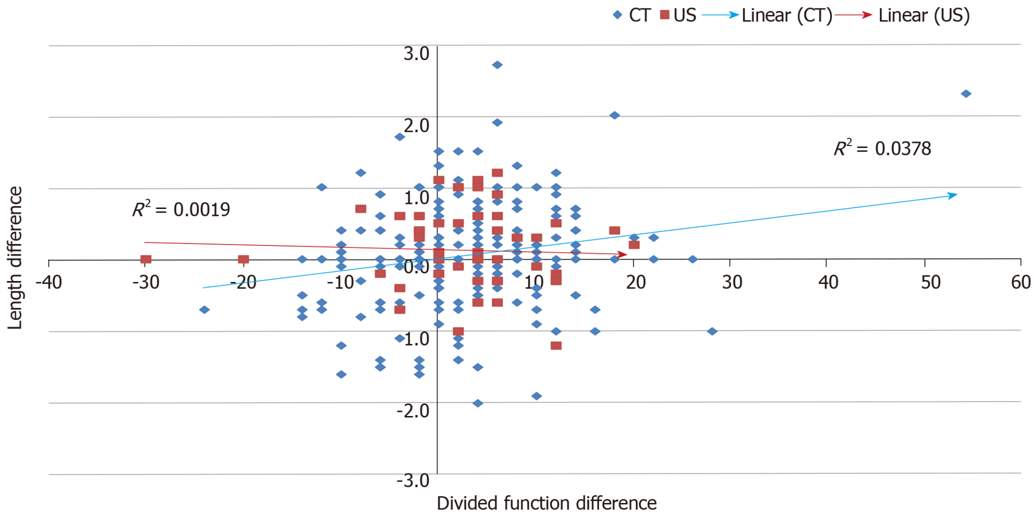

Figure 2 Correlation between difference in length and divided function of kidney pairs according to imaging modality. CT: Computed tomography; US: Ultrasonography.

correlation with donor kidney function and possibly with outcomes[6,9,12,14]. It is not clear why right kidneys had better (significant) correlation between length and divided function (Figure 1). We speculate that this may have to do with the shapes of the kidneys and that such differences would be eliminated on volume-based analysis.

This study highlights the significant potential for making wrong/harmful decision (removing the significantly better functioning kidney) if kidney length alone is used for decision making. A wrong decision would be made possible in 65/285 (23%) if the trigger for measuring split function were a difference in length of 1 cm; and in 72/285 (25%) if 2 cm were used in the presence of significantly different divided function. If length difference alone was used all could have been allowed to donate except one with a difference of 2.3 cm and a differential function of 54. A length difference greater than 1 cm would only predict a significant difference in divided function in 8/34 (23.5%) of cases. By measuring the split function, it would be possible to consider donation even in potential donors with a greater than 20% differential function. As shown in Table 3, if the concept of donated GFR was considered when using kidneys with the smaller contribution to overall function in potential donors with significant difference in divided function, three or possibly four of these donors would qualify.

Renal volume is thought to be the most precise predictor of kidney size[15,16]. There is sufficient evidence for correlation from CT based volume measurements to split renal function, that CT volumetric measurement of kidney size could replace the need for split function assessment[17,18]. Halleck *et al*[17] compared CT-measured renal cortex volume with DTPA-clearance combined with MAG3-scintigraphy in 167 consecutive living kidney donors and showed a strong correlation between CT-measured split cortex volume and MAG3-measured split renal function (r = 0.93; P < 0.001). Gardan and co-workers[19] determined pre-donation kidney volume for 105 donors using three methods: Total parenchymal three-dimensional renal volume, total parenchymal renal volume contouring, and renal cortical volume and tested for correlation of each volume with measured GFR. They found that for all methods, total kidney volume was significantly associated with pre-donation GFR (P < 0.001) and concluded that cortical volumetry was the best volumetric technique to use as a surrogate to scintigraphy for estimating pre-donation split renal function. Other workers showed that renal volume calculation using the ellipsoid method (*length x antero-posterior diameter x lateral diameter x* $\pi/6$) compared favourably with volume determined using volumetric software[20]. CT volume can replace nuclear renography for evaluation of relative function, as volume has been shown as a surrogate marker for nephron mass[12,21-24].

This study has important limitations. The retrospective analytical nature of this study resulted in a large number of exclusions due to insufficient, unavailable or non-specific data; and acceptance of kidney length measurements determined by CT or US. It is not clear whether the CT length measurements were all performed in the coronal plane. During the study period, measurement of kidney length was not regarded as a critical component of CT renal angiography and the quality and detail of the reporting varied between radiologists. There is also the possibility of inter-

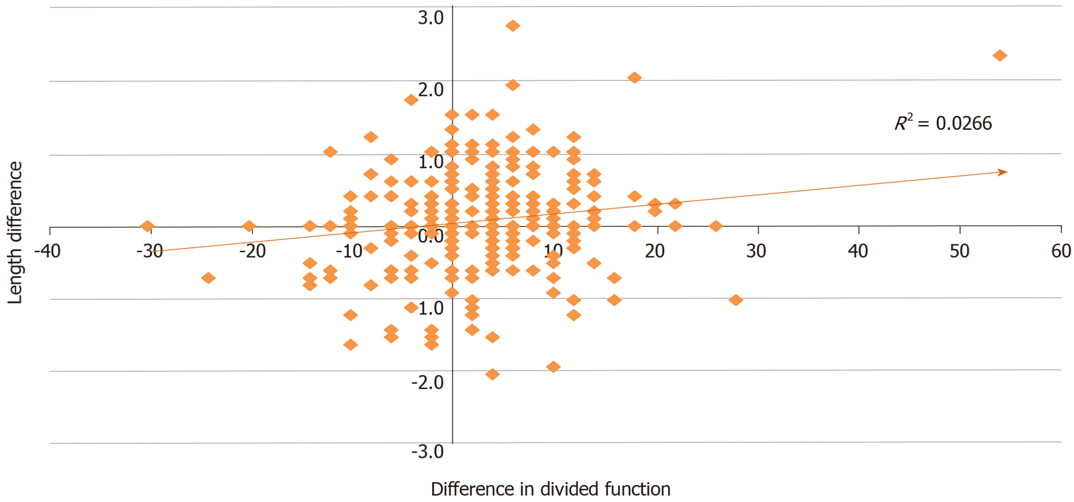

Figure 3 Correlation between differences in length and function of 285 potential donors.

observer variability in reporting kidney lengths. Only measurement for kidney length was available at our centre – other dimensions of the kidney were not reported and it was therefore not possible to calculate kidney volumes using the ellipsoid formula. Furthermore, data on the body habitus of potential donors was scanty and therefore not included in the analysis. Despite the foregoing, the findings of this study provide justification for avoiding the use of kidney length alone in making decisions about which kidney to donate or who needs split function.

In conclusion, length difference between kidney pairs alone is not sufficient to replace measurement of divided function. It may well be that after excluding cases with anatomical abnormalities, volume differences may restrict but not totally eliminate isotopic measurement of divided function in prospective donors. This issue is of vital importance and requires a randomised controlled trial to resolve it.

Table 2 Length difference *vs* differential function (see Table 1 for definition of categories)

Differential functioncategory	Category of length difference				Total
	1	2	3	4	
1	8	29	3		40
2	32	117	22	1	172
3	15	44	7		66
4	3	3		1	7
Total	58	193	32	2	285

Table 3 Seven patients with differential function > 20%

Patient	1	2	3	4	5	6	7
Donor GFR	63	69	69	69	87	93	109
Length difference	0.0	0.0	0.0	2.3	0.3	−0.7	−1.0
MAG3 left (%)	35	61	63	77	61	38	64
MAG3 right (%)	65	39	37	23	39	62	36
ND	−30	22	26	54	22	−24	28
"Donated" GFR of kidney with less function (mL/min)	22.1	26.9	25.5	15.9	33.9	35.3	39.2
Donated	No	Yes	No	No	Yes	No[1]	Yes

[1]Moved out of the area. GFR: Glomerular filtration rate; MAG3: Mercapto acetyl tri glycine; ND: No difference.

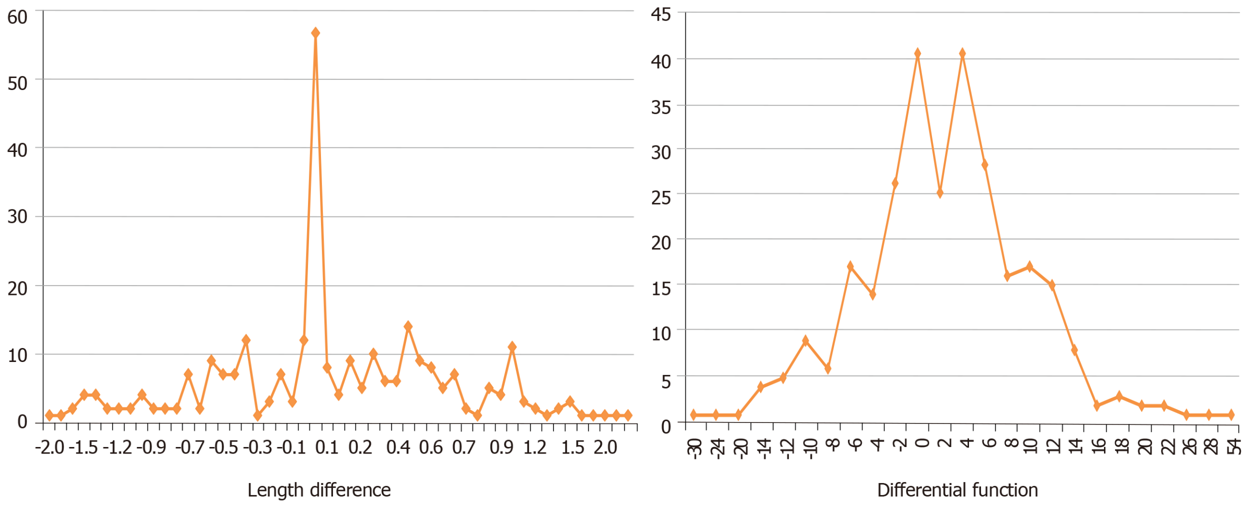

Figure 4 The frequency distribution of the differences in length and divided function between 285 kidney pairs.

ARTICLE HIGHLIGHTS

Research background

Potential candidates for kidney donation must have sufficient renal function post donation in order to minimize future risks when living with a single kidney. Currently most transplant units use split function between the kidney pairs in addition to other factors to make a decision on which kidney to donate. However, isotope differential renal function is not uniformly performed in all transplant centres, with many relying on kidney size measurements. Such an approach is supported by the BTS/RA Living Donor Kidney Transplantation Guidelines (2018) which state that differential kidney function, determined by ^{99m}Technitium dimercaptosuccinic acid (^{99m}TcDMSA) is recommended where there is > 10% variation in kidney size or significant renal anatomical abnormality. It further states that, "A difference in size of 2 cm or more indicates the possibility of a significant difference in GFR between the two kidneys". Hence this study.

Research motivation

The key question in living kidney donor assessment is how best to determine the contribution of each kidney to overall renal function and guide selection of which kidney to donate, ensuring safety of procedure and good outcome for both recipient and donor. With many units, particularly in the United Kingdom adopting the use of kidney length in the decision making process, there is risk of making wrong or harmful decisions with respect to living kidney donors unless it can be demonstrated that there is strong correlation between kidney length and split function.

Research objectives

This study aimed to determine the effect of using kidney length to decide which kidney to donate in a retrospective cohort of potential donors. Realisation of this objective would confirm the new approach as safe and reliable otherwise alternative approaches would need to be adopted such as use of kidney volume measurements and where indicated isotope differential renal function.

Research methods

All potential living kidney donors who completed assessment over a ten years period were retrospectively evaluated. Donor assessment was performed as per UK guidelines. This study is unique in presenting the results of a retrospective "what if" analysis of prospectively reported kidney length measurements that were not used in the decision-making process as to which organ to donate. During the study period, decisions were made on the basis of divided function and vascular anatomy. Analysis of a large number of potential donors in this way provides a useful tool in validating the use of kidney size alone in making decisions about which kidney to donate.

Research results

The key findings in this study include the following: Equal sex distribution among potential donors whose mean ages and GFRs were comparable; weak correlation between difference in length and divided function of kidney pairs (CT-measured kidney length provided a stronger correlation than US-measured length); the proportion of donors with a difference in length above 1 cm (34/285) was statistically significantly different from those with a differential function of 10% or higher (73/285); and of 73 with a split function greater than 10, 18 (24.7%) had no difference in kidney length; 54 (74%) had a difference of < 2 cm and only one of > 2 cm. Furthermore, using a difference in length of 2 cm as cut off for performing split function would lead to false reassurance in 72 patients (25%).

Research conclusions

This study highlights the significant potential for making wrong/harmful decision (removing the significantly better functioning kidney) if kidney length alone is used for decision making. A wrong decision would be made possible in 65/285 (23%) if the trigger for measuring split function were a difference in length of 1 cm; and in 72/285 (25%) if 2 cm were used in the presence of significantly different divided function. Length difference between kidney pairs alone is not sufficient to replace measurement of divided function. The findings of this study have important practical implications for clinical practice in avoiding potential harm to living kidney donors. This issue requires a randomised controlled trial to resolve it.

Research perspectives

This study has shown unequivocally that kidney length alone is not sufficient to determine which kidney to donate. It raises the question about the role of kidney volume measurement. The literature suggests that renal volume is the most precise predictor of kidney size. It has been shown by other workers that renal volume calculation using the ellipsoid method (*length x antero-posterior diameter x lateral diameter x π/6*) compares favourably with volume determined using volumetric software. CT based volume measurements of kidneys, (particularly cortical volumetry) correlates well with split renal function, raising the possibility that CT volumetric measurement of kidney size could replace the need for split function assessment. This issue is of vital importance and requires a randomised controlled trial to resolve whether CT-measured split cortex volume, for example is equivalent to MAG3-measured split renal function.

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