

Compensation Capacity of The Living-Related Donor's Remnant Kidney and Recipient's Transplanted Kidney

Xin Huang

Ruijin Hospital

Binbin Ma

Ruijin Hospital Luwan Branch

Wenhao Lin

Ruijin Hospital

Kun Shao

Ruijin Hospital

Huimin An

Ruijin Hospital

Jun Dai

Ruijin Hospital

Danfeng Xu

Ruijin Hospital

Peijun Zhou

Ruijin Hospital

Juping Zhao (✉ zjp11317@rjh.com.cn)

Ruijin Hospital

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Abstract

Background: Compensatory renal growth following nephrectomy is common. We try to explore the compensatory capacity of the living-related donor's remnant kidney and recipient's transplanted kidney in terms of the glomerular filtration rate (GFR) one month after transplantation.

Methods: Clinical data of 94 patients who received living-related kidney transplantation in our hospital between June 2007 and December 2017 were reviewed retrospectively. GFR was calculated by ^{99m}Tc -DTPA detection. The GFR compensatory capacity of donor's remnant and donated kidneys in their new milieus after transplantation was compared. The differential value (D-value) of split renal function was defined as postoperative GFR - preoperative ipsilateral GFR. The compensatory percentage (C-percentage) of split renal function was defined as $(\text{postoperative GFR} - \text{preoperative ipsilateral GFR}) / \text{preoperative ipsilateral GFR}$.

Results: The median D-value of the donor's remnant kidney increased by $20.8 \text{ ml}/(\text{min} \cdot 1.73\text{m}^2)$ [IQR=8.9-29.6 $\text{ml}/(\text{min} \cdot 1.73\text{m}^2)$] with a C-percentage of 46.6% (IQR=17.0%-73.0%). The median D-value of the donated kidney increased by $30.6 \text{ ml}/(\text{min} \cdot 1.73\text{m}^2)$ [IQR=19.8-42.3 $\text{ml}/(\text{min} \cdot 1.73\text{m}^2)$] with a C-percentage of 67.8% (IQR=39.6%-94.7%). Multivariable analysis showed that only split preoperative GFR in the donor was the independent predictor for C-percentage of the split kidney.

Conclusions: Renal function could be well preserved and compensated after kidney donation in most donors and recipients in Chinese population. Healthy donors with a good GFR before operation possessed a mighty functional compensation capacity.

Background

Compensatory growth of the contralateral kidney to promote significant restoration of the lost renal function is a common phenomenon after unilateral radical nephrectomy [1,2]. The glomerular filtration rate (GFR) is a generally accepted parameter to evaluate the renal function. Living-donor kidney transplantation (LKT) has been recommended as a safe treatment for patients with end-stage renal failure worldwide by virtue of a short duration of organ ischemia, rapid recovery of the graft, and fewer complications [3]. However, the application of LKT in China is still restricted due to the traditional idea and the insufficiency of the evidence in the renal compensation capacity.

LKT is an optimal model to explore the compensatory capacity of split renal function from the donor kidney in real world, because GFR alteration in a recipient who has progressed to uremia before transplantation can clearly show the compensatory capacity of the donated kidney. So we sought to make a retrospective analysis on GFR changes of the recipient's transplant kidney from his/her live-related donor and the donor's remnant kidney, and explore the GFR compensation capacity of donor's both kidneys in their new milieus.

Methods

Study population

We reviewed all cases (136 pairs) of LKT performed in our center between June 2007 and December 2018. A total of 94 pairs of LKT with integrated information (especially preoperative and post-operative GFR) were enrolled in this study. Written informed consent was obtained from all participants and/or their legal guardian/s. Operations were approved by the Ethics Committee of Ruijin Hospital of Shanghai Jiaotong University School of Medicine, China. This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments (as revised in 2013) or comparable ethical standards. We attested that no organs were procured from prisoners. All living kidneys donated were procured under the supervision of the Regulations of Organ Transplantation of the People's Republic of China, without violating the privacy of donors.

In accordance with the Kidney Disease: Improving Global Outcomes guideline [3] living organ recipients are limited to people who are spouses, lineal blood relatives or collateral blood relatives within three generations of living organ donors. Donor evaluation included the performance status, anatomical parameters by spiral computed tomography angiography, serum creatinine (SCr), GFR, and the psychosocial condition. Each pair of the donor and the recipient underwent blood grouping, HLA typing and lymphocytotoxicity cross-matching test.

Renal function assessment

The glomerular filtration rate (GFR), as a main parameter to evaluate the renal function, was calculated by ^{99m}Tc-DTPA detection in the donors and recipients perioperatively. The differential value (D-value) of split renal function was defined as postoperative GFR - preoperative ipsilateral GFR. The compensatory percentage (C-percentage) of split renal function was defined as (postoperative GFR - preoperative ipsilateral GFR)/preoperative ipsilateral GFR. Knowing that the SCr remains stable one month after surgery in most scenarios [4], we chosen the GFR at one month after LKT as the primary endpoint.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) and compared using Mann-Whitney test. Categorical variables were compared using the chi-square and Fisher's exact tests. Association between C-percentage of split renal function and the clinical parameters was evaluated using linear regression analysis. All p values were two-tail and p < 0.05 was considered statistically significant. Data were analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographics and general Data

This study included 94 donors (35 men and 59 women), who ranged in age from 21 to 64 years with a median of 49 (IQR=39-54) years at the time of kidney donation, and the demographics are listed in **Table 1**. Laparoscopic donor nephrectomy (LDN) was performed in 12 donors who donated left kidneys, and open donor nephrectomy (ODN) was applied in the rest 82 donors. The 94 donors included 4 pairs of spouses and 90 pairs of blood relatives within three generations.

Change of donors' remnant kidneys in terms of GFR

The median GFR of the donor's remnant kidney was 46.1 ml/(min·1.73 m²) [IQR=41.2-51.0 ml/(min·1.73 m²)] before surgery and 66.8 ml/(min·1.73 m²) [IQR=58.5-76.5ml/(min·1.73 m²)] at 1 month after nephrectomy (**Table 1**). The median D-value of GFR increased by 20.8 ml/(min·1.73 m²) [IQR=8.9-29.6ml/(min·1.73 m²)] with a C-percentage of 46.6% (IQR=17.0-73.0%) . The renal function was well preserved in 84(89.4%) donors, and slightly decreased in the other 10(10.6%) donors within a month, with a median negative C-percentage of 16.9% (IQR=8.4-25.6%).

Using 20% as the criterion for qualified compensation of the remnant kidney, we found that 67 cases met with the criterion and the remaining 27 cases failed, with an overall qualified compensation rate of 71.3% (67/94). Using receiver operator characteristic curve for analysis of the subjects, the cutoff point of GFR of the donors' remnant kidney was 44.7 ml/(min·1.73 m²) before surgery, sensitivity 0.82 and specificity 0.63.

The clinical data at one-year follow-up showed that the median D-value of GFR increase of the donor's remnant kidneys was 23.5 ml/(min·1.73 m²) (IQR=15.7-29.4 ml/(min·1.73 m²)), and the median C-percentage was 49.5% (IQR=32.2-64.9%), showing no significant difference as compared with that at one month after surgery. These results showed that the donor's renal function remained at a safe and stable level one month after donation.

Change of recipients' transplanted kidneys in terms of GFR

The median GFR of the donated kidneys was 47.0 ml/(min·1.73 m²)[IQR=41.8-52.5 ml/(min·1.73 m²)] before surgery; the median GFR of the donated kidneys was 81.0 ml/(min·1.73 m²)[IQR=68.4-89.0 ml/(min·1.73 m²)] at 1 month after donation, showing that the D-value increased by 30.6 ml/(min·1.73m²) [IQR=19.8-42.3ml/(min·1.73m²)] and C-percentage was 67.8% (IQR=39.6%-94.7%).

Correlation between the side of donation and the GFR C-percentage

Eighteen donors donated their right kidneys, in whom postoperative GFR of the remnant kidneys was 64.0 ml/(min·1.73 m²) [IQR=61.1-75.4 ml/(min·1.73 m²)], with the D-value increasing by 20.6 ml/(min·1.73 m²) [IQR=6.9-28.2 ml/(min·1.73 m²)] and an overall GFR C-percentage of 45.4%(14.5%-74.0%). The other 76 donors donated their left kidneys, in whom the overall postoperative GFR C-percentage was 46.6% (18.5%-72.2%) (p=0.870). The GFR C-percentage of the right-kidney donated was 79.4% (28.2%-112.8%), and that of the left-kidney donated was 64.8% (39.9%-93.6%) (p=0.834) (**Table 1**).

Correlation between donor age and the GFR C-percentage

They were categorized in two groups: group A ≤ 50 years (n=55), and group B >50 years (n=39). The median GFR C-percentage of the remnant kidneys was 58.2% (IQR=31.8%-86.3%) in group A and 26.6% (IQR=6.7%-51.9%) in group B (p=0.005) at 1 month after donation. The median GFR C-percentage of the donated kidneys was 67.9% (IQR=47.6%-93.9%) and 67.8% (IQR=36.1%-95.0%) in group A and B respectively (p=0.675) (**Table 2**).

Correlation between donor gender and the GFR C-percentage

The median D-value of GFR increase of the male and female remnant kidneys was 17.9 ml/(min \cdot 1.73 m²) [IQR=4.8-29.5ml/(min \cdot 1.73 m²)] and 23.1 ml/(min \cdot 1.73 m²) [IQR=11.2-29.7ml/(min \cdot 1.73m²)] respectively (p=0.489) at 1 month after donation. The GFR C-percentage of the male and female donors was 82.7% (IQR=43.8%-108.1%) and 61.3% (38.5%-86.2%) in donated kidneys respectively (P=0.050)(**Table 3**).

Correlation between the renal transplantation procedures and the GFR C-percentage

The median C-percentage of the remnant kidneys in ODN and LDN groups was 42.8% (IQR=13.3%-70.6%) and 56.6% (IQR=31.4%-82.5%) respectively (p=0.179). The median C-percentage of the donated kidneys in ODN and LDN was 67.8% (IQR=38.9%-94.4%) and 75.9% (IQR=56.3%-99.6%) respectively (p=0.427). No significant difference was observed in the GFR compensation rate in either the remnant and transplanted kidneys.

Multivariate analysis of factors affecting the GFR C-percentage

Univariate analysis showed that donors aged ≤ 50 years and the preoperative GFR of the remnant kidney were significantly associated with C-percentage of the remnant kidneys after operation (p= 0.006 and p<0.001), while donors' gender and the side of donation were not significantly associated with it (p=0.562 and p=0.870 respectively). Multivariable analysis showed that preoperative GFR of the donors' remnant kidneys was an independent predictor of its remnant GFR compensation capacity after operation. C-percentage of the donated kidneys was independently associated with preoperative GFR of the donated kidneys (p< 0.001), but not donor's age (p=0.675), gender (p=0.051) or the side of donation (p=0.834).

Discussion

The kidney presents a functional reserve capacity after unilateral nephrectomy [1,2]. Many studies reported that the donor's global renal function decreased immediately after kidney donation [5]. Although most of these studies compared the global GFR of the bilateral kidneys before donation with that of the single kidney preserved after nephrectomy [5], they did not compare the functional change of the same donor's remnant and donated kidney in their new milieus after operation. The renal function of split kidneys from living donors can be monitored perioperatively in real world. In this study, we sought to

measure the initial GFR of the split kidney and compare it with the kidney preserved and donated respectively, aiming to explore the potential compensation capacity of the split kidney from living donors.

Time and mechanism of the renal compensation phenomenon

Compensatory renal growth of the remnant kidney starts within hours following nephrectomy and reaches a stable compensatory state in varying periods post-operation. For human living kidney donation, GFR of donors and recipients was compensated and remained stable about one month after operation [6,7]. Gong et al.[6] reported that donor's mean GFR remained stable at (85.2 ± 17.6) ml/(min \cdot 1.73 m²), (87.2 ± 15.9) ml/(min \cdot 1.73m²), (82.1 ± 14.6) ml/(min \cdot 1.73m²) and (83.0 ± 13.7) ml/(min \cdot 1.73 m²) 5 days, 3 months, 1 year and more than one year after LKT respectively. Knowing that the GFR reached stability about one month after operation in most related studies [4-7], we used GFR at one month after operation as the main parameter for analysis.

Compensatory renal growth following nephrectomy is predominantly due to renal cell hypertrophy [1,8]. The mechanisms that sense and respond to renal volumetric reduction which generate renal growth remain elusive. Two main mechanisms have been proposed. One ascribes it to the increased activity of the remnant kidney that leads to hypertrophy, and the other attributes it to the release of kidney specific factors such as insulin-like growth factor 1, epidermal growth factor and hepatocyte growth factor and pathways such as mammalian target of rapamycin in response to unilateral nephrectomy [1,8].

GFR compensation capacity of the remnant kidney

Several studies have reported on the compensatory capacity of remnant kidneys after nephrectomy [2,4,9]. Chien et al. reported that GFR of donor's remnant kidney compensated from 58.2 ml/(min \cdot 1.73m²) to 79.6 ml/(min \cdot 1.73m²), with a 36.9% increase in C-percentage [4]. Our finding is consistent with the results from other centers in term of the tendency, indicating an acceptable and reasonable compensation in the remnant kidney. In our study, GFR in the remnant kidney averaged a 46.6% increase, which is better than 36.9% reported by Chien.

We also observed a case with the highest C-percentage in a 43-year-old father who donated the left kidney to his 22-year-old son. GFR of the father's right kidney was 51.3 ml/(min \cdot 1.73 m²) before operation and increased to 107.0 ml/(min \cdot 1.73 m²) after operation, with a C-percentage of 108.6%, indicating that the remnant kidney of a healthy donor possesses a powerful compensation capacity after donation to meet the physiological needs of the donor.

Impact of donor's age on renal function compensation

Serrano et al. [10] reported that donors in the optimal group were significantly younger, the optimal/suboptimal ratio being 56.0 ± 10.4 vs. 60.7 ± 8.7 years ($p=0.018$). Univariate analysis in our study showed a significantly higher GFR C-percentage of the remnant kidneys in younger donors ≤ 50 years than that in older donors (58.2% vs. 26.6% , $p=0.005$). The above results showed that the remnant kidneys

of younger donors have higher compensation capabilities, which is in line with the natural psychological tendency that the renal function decreases with age in ordinary healthy people. However, it is interesting to find that there was no significant difference in the GFR compensation rate of the donated kidneys in the recipients' bodies between the young and old donor age groups [67.9% (IQR=47.6-93.9%) vs. 67.8% (IQR=36.1-95.0%), $p=0.675$]. The reason may be that transplanted kidneys are affected by multiple factors in the new milieu of the recipients, such as immunological and hemodynamic factors, all of which may attenuate the impact of age on the grafts.

Preoperative assessment of nadir GFR for the kidney to be donated

The donated kidney has to adapt to the new milieu before it can gradually recover its function and compensatorily develop its infiltrating capacity in the recipient's body. Further sub-group analysis of our study showed that among 12 donors with donated GFR $< 40 \text{ ml}/(\text{min}\cdot 1.73\text{m}^2)$ before donation, the median GFR D-value was $30.4 \text{ ml}/(\text{min}\cdot 1.73\text{m}^2)$ (IQR= $25.7\text{-}37.1 \text{ ml}/(\text{min}\cdot 1.73 \text{ m}^2)$) and C percentage was 90.2% (IQR= $67.8\text{-}127.4\%$). In the group with GFR of the donated kidneys $\geq 40 \text{ ml}/(\text{min}\cdot 1.73\text{m}^2)$ before donation, the median GFR D-value was $18.2 \text{ ml}/(\text{min}\cdot 1.73 \text{ m}^2)$ (IQR= $6.8\text{-}28.1 \text{ ml}/(\text{min}\cdot 1.73 \text{ m}^2)$) and C-percentage was 62.0% ($38.4\%\text{-}92.7\%$). This indicates that donated kidneys with a relatively low GFR before operation have an even more powerful compensatory capability because the donated kidney is fully compensated in the body of the recipient.

Currently, it is difficult to define the acceptable nadir GFR value of the kidney to be donated before operation. Most transplantation centers recommend $\geq 40 \text{ ml}/(\text{min}\cdot 1.73 \text{ m}^2)$ as the cutoff value [3,11]. But as the compensation capability of the donated kidney is higher than that of the remnant kidney as shown in our study, donated kidneys with an estimated GFR value $< 40 \text{ ml}/(\text{min}\cdot 1.73 \text{ m}^2)$ before operation can still be considered as potential candidates for donation. We suggest that the GFR criterion for kidney donation could be selectively reduced to $30 \text{ ml}/(\text{min}\cdot 1.73 \text{ m}^2)$ in potential donors. Of course, the baseline GFR of the remnant kidney should be maintained at a $\geq 40 \text{ ml}/(\text{min}\cdot 1.73 \text{ m}^2)$ level so as to guarantee that the donor's remnant kidney has a good filtering function after nephrectomy [12].

Our study has some limitations. First, it is of retrospective nature with all data retrieved from a single center, which may bring about tertiary selection bias. In addition, sample is relative small due to the gradual application of LKD in our country. Therefore, further studies are required to focus on the compensatory growth after kidney donation.

Conclusion

The human kidney has a powerful compensation capability. Renal function could be well preserved and compensated after kidney donation in most donors and recipients. Healthy donors with a good GFR before operation possess a mighty functional compensation capacity.

Abbreviations

BMI: Body mass index; C-percentage: Compensatory percentage; D-value: Differential value; GFR: Glomerular filtration rate; IQR: Interquartile range; LDN: Laparoscopic donor nephrectomy; LKT: Living-donor kidney transplantation; ODN: open donor nephrectomy; SCr: Serum creatinine

Declarations

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Authors' contributions

All authors listed above have contributed sufficiently to be included as authors. All of the authors had full access to the data for this study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Juping Zhao, Danfeng Xu and Peijun Zhou conceived and designed the study. Xin Huang, Binbin Ma, Kun Shao and Huimin An performed the surgeries. Binbin Ma, Wenhao Lin and Jun Dai analyzed the data and drafted the manuscript. All of the authors revised the article critically, gave final approval of submission and agreed to be accountable for all aspects of the work.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was granted by the Ethics Committee of Ruijin Hospital of Shanghai Jiaotong University School of Medicine, China.

Written informed consent for participation was obtained from all participants and/or their legal guardian/s.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interests. The results presented in this paper have not been published previously in whole or part.

Author details

¹Department of Urology, Ruijin Hospital of Shanghai Jiaotong University School of Medicine, Shanghai 200025, China.

²Department of Urology, Ruijin Hospital Luwan Branch of Shanghai Jiaotong University School of Medicine, Shanghai 200020, China.

†These authors contributed fully and equally to this work.

* co-corresponding author

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Tables

Table 1 Change in split renal function of the remnant and donated kidneys in terms of donation side

	Overall	Right donated	Left donated	<i>P</i>
Donors (<i>n</i> =)	94	18	76	
Male (%)	35(37.2)	7(38.9)	28(36.8)	0.872
Age [yr] median(IQR)]	49 (39-54)	48 (34-54)	49 (40-54)	0.713
BMI [(kg/m ²),median(IQR)]	23.3 (21.0-25.2)	22.0 (20.5-25.1)	23.4 (21.3-25.2)	0.856
Overall GFR before donation [ml/(min·1.73 m ²),median(IQR)]	93.6(85.7-102.8)	90.7(83.8-100.3)	93.6 (87.2-103.2)	0.696
GFR of remnant kidney before donation [ml/(min·1.73 m ²),median(IQR)]	46.1(41.2-51.0)	45.4(40.8-50.3)	46.4(41.3-51.1)	0.967
GFR of remnant kidney at 1 month after donation[ml/(min·1.73 m ²),median(IQR)]	66.8(58.5-76.5)	64.0(61.1-75.4)	67.0(57.6-76.9)	0.798
GFR D-value of remnant kidney [ml/(min·1.73 m ²),median(IQR)]	20.8(8.9-29.6)	20.6(6.9-28.2)	20.8(9.3-30.0)	0.837
GFR C-percentage of remnant kidney at 1 month after donation [% ,median(IQR)]	46.6(17.0-73.0)	45.4(14.5-74.0)	46.6(18.5-72.2)	0.870
GFR of donated kidney before donation[ml/(min·1.73 m ²),median(IQR)]	47.0(41.8-52.5)	44.64(40.5-50.4)	47.2(42.6-53.9)	0.524
GFR of donated kidney at 1 month after donation [ml/(min·1.73 m ²),median(IQR)]	81.0(68.4-89.0)	80.6(71.4-97.9)	81.0(68.3-89.0)	0.796
GFR D-value of donated kidney [ml/(min·1.73 m ²),median(IQR)]	30.6(19.8-42.3)	31.5(18.4-54.4)	29.4(20.0-42.0)	0.902
GFR C-percentage of donated kidney at 1 month after donation [% ,median(IQR)]	67.8(39.6-94.7)	79.4(28.2-112.8)	64.8(39.9-93.6)	0.834

IQR = interquartile range; BMI = body mass index; GFR = glomerular filtration rate; D-value = differential value; C-percentage = compensatory percentage.

Table 2 Change in split renal function of the remnant and donated kidneys sorted by donors' age

	≤50 year [group A]	>50 year(group B)	<i>P</i>
Donors (<i>n</i> =)	55	39	
Male (%)	34.5	41.0	0.522
Age [yr] median(IQR)]	43(31-47)	55(54-57)	<0.001
Global GFR of donated kidney before donation [ml/(min·1.73 m ²),median(IQR)]	93.6(85.9- 101.4)	93.7(85.4- 104.7)	0.474
GFR of remnant kidney before donation [ml/(min·1.73 m ²),median(IQR)]	46.0(41.4- 50.3)	46.6(41.2- 54.6)	0.288
GFR of remnant kidney at 1 month after donation [ml/(min·1.73 m ²),median(IQR)]	68.1(62.1- 78.3)	63.0(54.8- 71.3)	0.675
GFR D-value of remnant kidney at 1 month after donation [ml/(min·1.73 m ²),median(IQR)]	25.1(16.4- 36.6)	11.8(3.9- 23.6)	0.005
GFR C-percentage of remnant kidney at 1 month after donation [%],median(IQR)]	58.2(31.8- 86.3)	26.6(6.7- 51.9)	0.005
GFR D-value of donated kidney at 1 month after donation [ml/(min·1.73 m ²),median(IQR)]	31.6(23.3- 42.6)	27.1(19.1- 40.2)	0.829
GFR C-percentage of donated kidney at 1 month after donation [%],median(IQR)]	67.9(47.6- 93.9)	67.8(36.1- 95.0)	0.675

IQR = interquartile range; GFR = glomerular filtration rate; D-value = differential value; C-percentage = compensatory percentage.

Table 3 Change in split renal function of the remnant and donated kidneys by donor's gender

	Male	Female	<i>P</i>
Donor (<i>n</i> =)	35	59	
Age [yr] median(IQR)]	49(26-54)	48(43-54)	0.01
Global GFR of donated kidney before donation[ml/(min·1.73 m ²),median(IQR)]	93.7(90.4-102.4)	93.6(85.3-102.7)	0.582
GFR of remnant kidney before donation[ml/(min·1.73 m ²),median(IQR)]	47.8(43.6-51.3)	45.6(41.1-50.3)	0.559
GFR of remnant kidney at 1 month after donation [ml/(min·1.73 m ²),median(IQR)]	62.2(55.6-74.1)	67.5(61.9-76.8)	0.673
GFR D-value of remnant kidney at 1 month after donation [ml/(min·1.73 m ²),median(IQR)]	17.9(4.8-29.5)	23.1(11.2-29.7)	0.489
GFR C-percentage of remnant kidney at 1 month after donation [% ,median(IQR)]	36.7(9.1-83.3)	52.1(21.6-70.6)	0.562
GFR D-value of donated kidney at 1 month after donation [ml/(min·1.73 m ²),median(IQR)]	34.6(24.4-47.7)	28.7(18.9-39.2)	0.045
GFR C-percentage of donated kidney at 1 month after donation [% ,median(IQR)]	82.7(43.8-108.1)	61.3(38.5-86.2)	0.050

IQR = interquartile range; GFR = glomerular filtration rate; D-value = differential value; C-percentage = compensatory percentage

Supplementary Files

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