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Nephrectomy Complication Is a Risk Factor of Clinically Meaningful Decrease in Health Utility among Living Kidney Donors

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ABSTRACT

Objectives: To assess the clinically relevant change in health state utility (HSU) in living kidney donors and whether this change value is constant across measures and clinical conditions and is useful for health economics studies. We aimed to 1) measure the change in the HSU score for living kidney donors from before donation to 3 months after donation and 2) estimate the minimal important decrease (MIDe) in the HSU score for living kidney donors and its associated clinical factors. **Methods:** Data from a prospective multicenter observational study measuring quality of life of kidney donors by the three-level EuroQol five-dimensional questionnaire (EQ-5D-3L) and the six-dimensional health state short form (SF-6D) before donation and at 3 months after donation provided HSU scores. Two methods were used to derive the MIDe: the anchor-based method and the distribution-based (standard error of measurement) method. Logistic regression was used to identify clinical factors associated with the MIDe after donation. **Results:** In total, 228 and 216 donors completed the EQ-5D-3L and the SF-6D, respectively. Mean HSU scores were 0.932 and 0.823 before donation and 0.895 and 0.764 at 3 months after donation. HSU scores were significantly decreased at 3 months, and 18.5% of donors rated their global health as "somewhat worse." By the EQ-5D-3L and the SF-6D, the MIDe was estimated at −0.113 and −0.116 with the anchor-based method and −0.075 and −0.077 with the distribution-based method. Risk of decreased HSU score was significantly associated with clinical complications but only marginally with surgical technique. **Conclusions:** A short-term clinically relevant decrease in HSU was significantly associated with clinical complications in kidney donors. Preventing perioperative complications is of prime importance in kidney donation.

Keywords: clinical complications, health state utility, living kidney donors, minimal important decrease.

Introduction

The number of living kidney donations has increased in recent years in European countries [1,2]. The most important reason for this increase is the expanding gap between the availability of deceased-donor organs and the demand for kidney transplants because of the increasing number of patients with permanent kidney replacement therapy. Receiving a kidney from a living donor is better for all health outcomes than receiving one from a deceased donor [3]. Nevertheless, these apparent medical benefits for transplantation recipients have to be balanced against the possible harms to living donors. Although many potential kidney donors are willing to accept the risk of nephrectomy to help their loved ones, the medical community must quantify these risks as well as possible and make this information available to people considering donation.

Several studies have shown that living kidney donation is safe and associated with low risk of complications and even low risk of mortality [4,5]. Living kidney donation is practiced with the expectation that the risk of short- and long-term harm to the donor can be outweighed by the psychosocial benefits of donor altruism and the improvement in recipient health. The practice, however, involves minimally invasive nephrectomy among young and relatively healthy adults, which implies that mortality or perioperative complications are not sufficient to evaluate the health consequences of donation. In this case, evaluating the

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psychological harms to donors, such as their health-related quality of life (HRQOL), is of prime importance [6].

The concept of health state utility (HSU) was developed by economists for cost-utility analyses and reflects patient and society views. It does not refer to the usefulness of the individual or the condition of the individual but rather refers to the desirability or preference the individual exhibits for the condition [7]. The HSU score ranges from 0 (dead) to 1 (representing the best imaginable health). Some instruments allow for a negative value, corresponding to a state perceived worse than death.

Living kidney donation is a societal issue that involves the society view in addition to the donor view. The HSU is an important outcome for measuring the impact of donation combining the society and donor views. The health impact of donation is measured as the change in the HSU score from pre- to postdonation. Although donors and physicians are not directly interested in HSU scores in routine practice, they might be interested if practices were improved by the results of utility research studies. So, one of the challenges with use of the HSU is determining the significance of any differences observed.

The minimal important difference (MID), developed by Jaeschke et al. [8], is defined as "the smallest difference in score in the domain of interest which patients would perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management." The MID is a measure of responsiveness representing the smallest subjective difference in an outcome score that represents a clinically important change for the patient. Then, determining the magnitude of change from pre- to postdonation corresponding to an MID of living kidney donors would be helpful and meaningful for researchers and would help improve practice.

Because donors are considered healthy before donation, we may expect a decrease in the HSU score in the short-term after donation. Thus, one could determine the minimal important decrease (MIDe), which measures the negative impact of kidney donation. The MIDe is useful when such a decrease is clinically relevant. This impairment can be related to postsurgical clinical conditions of the donor. Therefore, we aimed to 1) measure the change in the HSU score for living kidney donors from before donation to 3 months after donation and 2) estimate the MIDe in the HSU score for living kidney donors and its clinical associated factors.

Methods

Kidney Donors

We used data for donors included in the DOVIREIN (DOnneurs VIvants de REIN) study from June 2010 to November 2012. This was an observational multicenter prospective study monitoring the HRQOL of living kidney donors by surgical techniques used for kidney sampling. The study started in June 2010 and was approved by the institutional review board (CCTIRS notification OMG/JD/10.033; CNIL authorization 910068, ClinicalTrials.gov no. 10.039). From 22 public hospitals covering the whole French territory, all donor-recipient couples were invited to participate and were included after they gave their written informed consent before donation surgery.

Demographic and Clinical Data

Demographic and clinical data were collected before and after donation and included surgical techniques used (lombotomy, laparoscopic surgery hand-assisted, laparoscopic surgery, and robotic surgery), the nephrectomy side, clinical complications, and number of complications. Clinical complications referred to surgical or medical health events (hematoma, infections, disembowelling, thromboembolic, and other) that occurred during the first 3 months after donation.

HSU Measurement

The HSU can be empirically generated by generic preference-based measures such as the HRQOL. The HRQOL of donors was measured by generic instruments, the three-level EuroQol five-dimensional questionnaire (EQ-5D-3L) [9] and the Medical Outcomes Study 36-item short form (SF-36) [10], and was collected the day before donation and at 3-month follow-up.

The six-dimensional health state short form (SF-6D) [11] was developed from 11 questions of the SF-36. It is a multidimensional health classification system assessing the six domains of physical functioning, role limitation, social functioning, pain, mental health, and vitality, with one to six levels for each domain. An SF-6D health state is defined by one level from each domain, for 18,000 possible health states. The SF-6D scoring algorithm was developed by the standard gamble method [12] from a sample of 249 among a representative sample of the UK population. HSU scores generated by the SF-6D range from 0.29 to 1.00, with 1.00 representing full health and 0.29 representing the worst possible health state defined by the SF-6D (i.e., all domains being at the worst level) [12].

The EQ-5D-3L consists of five items or dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) with three answer categories—no problem (1), some problems (2), or severe problems (3)—for 243 possible health states. The EQ-5D-3L can be reported as a preference-based single number, with mean values obtained for the general population in France [13] by using the time trade-off method. This resulting HSU score ranges from −0.543 to 1.00, with 1.00 representing "full health," 0 "death," and negative values a health state "worse than death" [14].

MIDe Estimation

We derived the MIDe for the EQ-5D-3L and the SF-36 by using the most common methods for estimating the MIDe for HRQOL instruments: the anchor-based and distribution-based methods [15,16]. For the anchor-based method, we used a Global Rating of Change (GRoC) scale with seven levels, asking donors at the end of follow-up how they rated their general health as compared with 3 months ago: "much better" (1), "better" (2), "somewhat better" (3), "about the same" (4), "somewhat worse" (5), "worse" (6), or "much worse" (7). Given that donors are considered "relatively healthy before donation," it made sense to determine the MIDe, which measures the negative impact of kidney donation, and we assumed that a subgroup with a response of "somewhat worse" would represent a group with a small but meaningful decrease in the HSU score after donation. The MIDe of the HSU was the mean change score from baseline to follow-up for donors who rated their health "somewhat worse" [8,17]. For the distribution-based method, the MIDe was defined as 1 standard error of measurement (SEM) [18], estimated in the entire sample as follows:

$$\mathrm{SEM} = \sigma_x \times \sqrt{1 - \mathrm{ICC}_{(t1,t2)}},$$

where σ_x is the SD of the instrument at baseline and $\mathrm{ICC}_{t1,t2}$ is the intraclass correlation coefficient (ICC) between the HSU scores measured before donation (t1) and 3 months after donation (t2). To interpret the MIDe in the context of living kidney donors, data are presented as negative values. Only donors with a negative change equal or greater than the MIDe were considered to have a clinically relevant decrease in the HSU score.

Response Shift

Changes in internal standards may hamper the interpretation of within-individual changes over time. The most commonly used

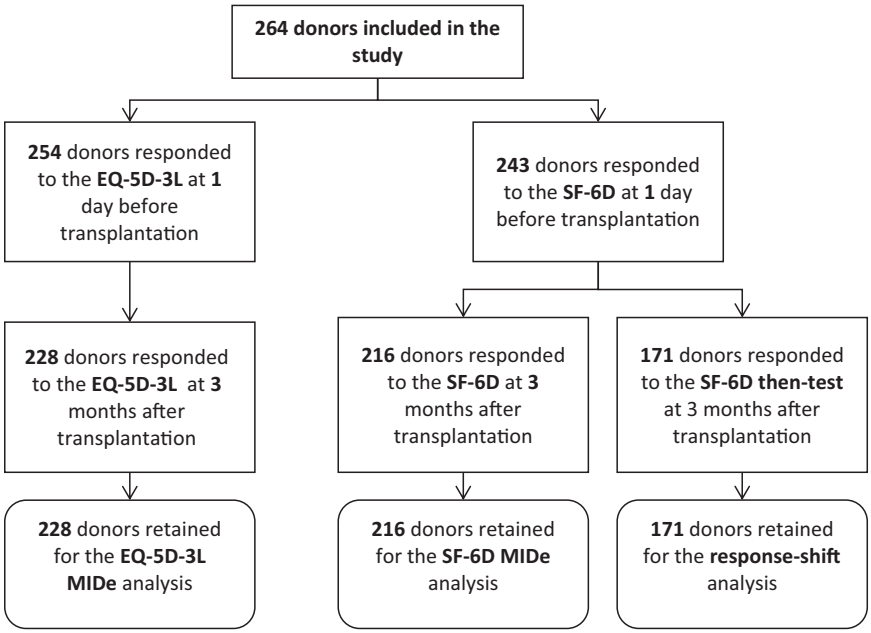

Fig. 1 – Donors with completed questionnaires at baseline and follow-up. EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; MIDe, minimal important decrease; SF-6D, six-dimensional health state short form.

method for detecting such a change or "recalibration response shift" [19] is the retrospective pretest and post-test design [20], also known as the "then-test." At the end of follow-up, the SF-36 then-test was administered after donors completed the SF-36 post-test questionnaire. Donors were asked to think back to how they felt at the start of the study (before donation) and answer retrospectively. A significant difference between the then-test and the pretest (SF-6D) mean HSU score was considered a response shift effect.

Statistical Analysis

The baseline sociodemographic and clinical characteristics of donors are described as mean ± SD for continuous variables and percentages (%) for categorical variables. Because global measures of change are expected to be correlated more with the 3-month follow-up than with the initial state [21,22], we calculated Spearman rank-order (ρ) correlations for the GRoC scale with baseline and 3-month HSU scores to ensure the validity of the scale. Baseline and 3-month HSU scores by the SF-6D and the EQ-5D-3L are described as mean ± SD. The mean HSU scores at baseline and 3 months were compared by paired-samples *t* test. The response shift effect was tested by comparing the baseline score with the then-test HSU score by paired-samples *t* test.

The MIDe was estimated for each instrument used. With the anchor-based method, the mean change in the HSU score for donors who rated their global health as "somewhat worse" at 3 months was considered the MIDe threshold. With the distribution-based method, we used analysis of variance to calculate the MIDe by using the SD of the mean HSU score at baseline and the ICC between the baseline and 3-month HSU scores.

Donors with a decrease in the HSU score greater or equal to the calculated MIDe (for each instrument and each method) were considered to have a clinically relevant decrease in health HSU. Then we assessed the association between clinical factors and a clinically relevant decrease in HSU (outcome) by multivariate logistic regression models, estimating odds ratios (ORs) and 95% confidence intervals (CIs). A *P* value of less than 0.05 was considered statistically significant. Analyses involved the use of SAS version 9.3 (SAS Institute, Cary, NC).

Results

Among the 264 donors included in the DOVIREIN study, 228 and 216 had complete data for the EQ-5D-3L and the SF-6D (at baseline and 3-month follow-up), respectively, and 171 completed the SF-6D then-test questionnaire (Fig. 1). A total of 237 donors had completed at least one of the two questionnaires (Table 1). The mean age of the study sample was 50.2 ± 10.7 years, mostly comprising women (58.6%), married or living with a partner (89.0%) and with children (84.0%). Nephrectomy was mostly from the left side (84.8%) and a complication occurred in 48.5% of cases, with a mean of 1.4 ± 0.7 complications.

Change in HSU

Table 2 presents the mean HSU scores for donors over time. At all times, HSU scores were higher with the EQ-5D-3L than with the SF-6D. The mean HSU score before donation was 0.93 ± 0.09 (range 0.49–1.00) by the EQ-5D-3L and 0.82 ± 0.09 (range 0.58–1.00) by the SF-6D. Among the 216 donors responding to the GRoC scale, 130 (60.2%) considered their global health "about the same" and 40 (18.5%) "somewhat worse" at 3 months after donation (data not shown). Twelve (5.5%) donors rated it "much better" and only one (0.4%) rated it "much worse." A worse GRoC score was significantly correlated with lower HSU score by the SF-6D ($\rho = -0.25$; $P = 0.0002$) and the EQ-5D-3L ($\rho = -0.19$; $P = 0.005$) at follow-up, with no significant correlation with baseline scores.

The mean HSU score decreased 3 months after donation for each instrument (EQ-5D-3L: −0.04; 95% CI −0.05 to −0.02; $P < 0.0001$; SF-6D: −0.05; −0.07 to −0.04; $P < 0.0001$). No response shift effect was found with the SF-6D (mean HSU score not significantly different between pretest and then-test; $P = 0.19$).

Table 1 – Sociodemographic and clinical characteristics of kidney donors (n = 237).

Characteristic	N	% or mean ± SD
Age (y)	237	50.2 ± 10.7
Sex, female	139	58.6
Weight status, overweight/obese	112	47.3
Marital status, married or living with partner	210	89.0
With children	199	84.0
No. of children	199	2.4 ± 0.9
Family degree relation with recipient		
Parents	66	27.8
Siblings	76	32.1
Partner	69	29.1
Son or daughter	7	3.0
Other	19	8.0
With professional activity	176	74.3
Social and professional category		
Executives	42	17.8
Middle-level profession	20	8.5
Farmers, craftsmen, business leaders	24	10.2
Employees, manual workers	106	44.9
Unemployed, students	44	18.6
Family income level		
<€1200/mo	13	5.7
€1200–2400/mo	84	36.8
≥€2400/mo	131	57.5
Surgical techniques used		
Lombotomy	49	20.7
Laparoscopic surgery hand-assisted	62	26.2
Laparoscopic surgery	60	25.3
Robotic surgery	66	27.8
Nephrectomy side, left	201	84.8
With clinical complications*	115	48.5
No. of complications	115	1.4 ± 0.7

Note. Data are number (%) unless indicated.

* Surgical or medical health events (hematoma, infections, disembowelling, thromboembolic, and other) that occurred during the first 3 mo after donation.

MIDe of HSU and Its Associated Factors

With the anchor-based method, the MIDe for a worsening change in HSU was −0.113 and −0.116 by the EQ-5D-3L and the SF-6D, respectively (Table 3). Overall, 14% (32 of 228) and 25% (54 of 216) of donors reached the MIDe threshold by the EQ-5D-3L and the SF-6D, respectively. The minimal changes were lower with the distribution-based method: MIDe was −0.075 and −0.077 by the EQ-5D-3L and the SF-6D, respectively. Overall, 33.7% (77 of 228) and 37.5% (81 of 216) of donors reached the MIDe threshold by the EQ-5D-3L and the SF-6D, respectively.

Risk of clinically relevant decrease in the HSU score (decrease ≥ MIDe) was associated with clinical complications (Table 4). Compared with donors without complications, those with at least one complication were more likely to show a clinically relevant decrease in the HSU score with the anchor-based method (EQ-5D-3L: OR 2.2; 95% CI 1.0–4.9; SF-6D: 2.4; 95% CI 1.3–4.6) or with the distribution-based method (EQ-5D-3L: OR 1.7; 95% CI 1.0–3.1; SF-6D: 1.8; 95% CI 1.0–3.1). The risk of clinically relevant decrease in the HSU score was low with laparoscopic surgery by the EQ-5D-3L and the distribution-based method (OR 0.4; 95% CI 0.2–1.0) and for right-side nephrectomy by the SF-6D and the anchor-based method (OR 0.3; 95% CI 0.1–1.0). Risk of clinically relevant decrease in the HSU score did not differ by surgical technique or by nephrectomy side by the EQ-5D-3L.

Discussion

This study showed a statistically significant decrease in HSU scores for kidney donors at 3 months after donation whatever the HSU measurement used, especially when donors reported worse general health at baseline. The estimated MIDe in HSU scores was higher with the anchor-based method than with the distribution-based method (i.e., it was sensitive to method of estimation) but was similar for the two instruments within each method. Whatever the method or instrument used, the risk of clinically relevant decrease in the HSU score was associated with clinical complications but only marginally or not at all with surgical technique of nephrectomy.

We observed cross-sectional differences in the HSU score by instrument used, with higher score by the EQ-5D-3L than by the SF-6D, which raises the question of comparability when different instruments are used for the same condition. This difference would be a function of the method used to calculate the HSU and the content of each instrument [22,23]. The HSU estimated with the EQ-5D-3L is derived by the time trade-off method but with the SF-6D by the standard gamble method. The standard gamble method is known to overestimate the HSU, whereas the time trade-off method can under- or overestimate the HSU [23]. Other findings suggest that differences in HSU scores estimated by instruments are attributable to differences in instrument content and their scales [22].

Table 2 – Changes in the HSU score with the EQ-5D-3L and the SF-6D.

The HSU score	Before donation (M0), mean ± SD	3 mo after donation (M3), mean ± SD	Change in the HSU score (M3 − M0)	
			Δ (95% CI)	*P* value
EQ-5D-3L	0.93 ± 0.09	0.89 ± 0.13	−0.04 (−0.05 to −0.02)*	<0.0001
SF-6D	0.82 ± 0.09	0.76 ± 0.12	−0.05 (−0.07 to −0.04)*	<0.0001
SF-6D then-test	–	0.83 ± 0.09	0.01 (−0.005 to 0.03)†	0.19

Note. HSU score: 0 = worst possible health; 1 = full health.

CI, confidence interval; EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; HSU, health state utility; SF-6D, six-dimensional health state short form.

* Paired-samples *t* test comparing the HSU score before donation and 3 mo after donation.

† Paired-samples *t* test comparing direct and then-test HSU score at 3 mo after donation.

Table 3 – Estimated MIDe assessed for each instrument by the anchor-based and distribution-based methods.

MIDe instrument	Anchor-based method*			Distribution-based method†			
	No.	Mean change (95% CI)	SD	No.	SD at baseline	ICC (95% CI)	SEM
EQ-5D-3L	37	−0.113 (−0.156 to −0.070)	0.129	228	0.090	0.308 (0.186 to 0.421)	−0.075
SF-6D	36	−0.116 (−0.154 to −0.077)	0.115	216	0.089	0.251 (0.122 to 0.372)	−0.077

CI, confidence interval; EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; ICC, intraclass correlation coefficient; MIDe, minimal important decrease; SEM, standard error of measurement; SF-6D, six-dimensional health state short form.
* With the Global Rating of Change scale (mean score change).
† With the SEM.

Despite a baseline absolute difference in HSU scores depending on the instrument used, we found similar changes in HSU scores after 3 months by the EQ-5D-3L and the SF-6D, and the MIDe thresholds were similar for the two instruments. So, although comparing absolute HSU scores derived by different instruments seems less appropriate [24,25], one may be able to estimate changes in HSU scores derived by different instruments.

The MIDe threshold was higher when using the anchor-based than the distribution-based method and could be related to the differences in sample sizes used for the estimations. With the anchor-based method, the MIDe was estimated only for donors who rated their health "somewhat worse," whereas with the distribution-based method, all donors were included. According to classical test theory, Wyrwich et al. [26] considered the SEM as sample-independent and better for determining a meaningful change as compared with other distribution-based methods, such as the effect size, for MIDe estimation. Furthermore, the MIDe detected by the two methods does not exactly reflect the same thing. The absolute value of the MIDe by the distribution-based method corresponds to the minimal difference reflecting a clinically relevant change (HSU enhancing or deterioration) for donors, whereas the MIDe by the anchor-based method reflects only a clinically relevant deterioration.

With the anchor-based method, the MIDe by both HSU instruments was larger than results found by Walters and Brazier [27], who used data from eight longitudinal studies of 11 patient groups. This result was relatively predictable, because living kidney donors are a specifically selected healthy population compared with a patient population.

The decrease in HSU was clinically relevant for donors with clinical complications whatever the instrument or method used to calculate the MIDe independent of the surgical technique or nephrectomy side. This result indicates that attention must be paid to preventing clinical complications related to nephrectomy

Table 4 – Factors associated with a clinically relevant decrease* in the HSU score for kidney donors by the instrument and method used (n = 237).

Clinical factors	Anchor-based method†				Distribution-based method‡			
	EQ-5D-3L (N = 228)		SF-6D (N = 216)		EQ-5D-3L (N = 228)		SF-6D (N = 216)	
	n = 32 (14.0%)§	OR (95% CI)	n = 54 (25.0%)§	OR (95% CI)	n = 77 (33.7%)§	OR (95% CI)	n = 81 (37.5%)§	OR (95% CI)
Surgical technique								
Lombotomy	11.1		20.5		40.0	1	45.5	
Laparoscopic surgery hand-assisted	15.0		33.9		41.7	1.0 (0.4–2.2)	39.0	
Laparoscopic surgery	13.6		20.4		22.0	**0.4 (0.2–1.0)**	27.8	
Robotic surgery	15.6		23.7		32.8	0.7 (0.3–1.6)	39.0	
Nephrectomy side								
Left	13.8		27.6	1	34.4		39.2	
Right	15.2		11.4	**0.3 (0.1–1.0)**	30.3		28.6	
Complications								
No	9.4	1	17.3	1	27.4	1	30.9	1
Yes	18.9	**2.2 (1.0–4.9)**	33.0	**2.4 (1.3–4.6)**	40.5	**1.7 (1.0–3.1)**	44.3	**1.8 (1.0–3.1)**
Mean number of complications	1.33		1.46		1.42		1.45	

Note. Boldfaced entries indicate statistical significance (multivariate $P < 0.05$).
CI, confidence interval; EQ-5D-3L, three-level EuroQol five-dimensional questionnaire; HSU, health state utility; MIDe, minimal important decrease; OR, odds ratio; SEM, standard error of measurement; SF-6D, six-dimensional health state short form.
* HSU decrease greater than the MIDe.
† With the Global Rating of Change scale (mean score change).
‡ With the SEM.
§ Percentage of donors with clinically relevant decrease.

in living kidney donation. In our study sample, living kidney donors showed a high rate of clinical complications. Nevertheless, the definition of complications was rather broad, including more than classical perioperative complications. The proportion of classical perioperative complications such as infection and bleeding was 7.8% (9 of 115). A recent systematic review reported that these perioperative complications occur in about 7.3% of cases [4].

In this study, we used the EQ-5D-3L rather than the new five-level version. Previous studies reported that the three-level version has a ceiling effect and may not be able to fully discriminate different levels of health status [28]. A prototype five-level version of the EQ-5D was developed for this purpose [29] but was published and available later than the onset of the DOVIREIN (DOnneurs VIvants de REIN) study. Nonetheless, the EQ-5D-3L is a valid instrument and has been used in many studies with consistent results [30].

This study has some limitations. First, checking the HSU 1 day before donation could result in a biased HSU because of the stress or anxiety related to the coming surgery. Stress and anxiety are known risk factors for quality of life [31] and hence risk factors of the HSU. Nevertheless, kidney donation is an altruistic way for living donors, for whom early preparedness for the nephrectomy helps to avoid excess stress and anxiety. Second, repeated measurement of HRQOL over time and subsequent HSU change could be affected by a response shift phenomenon, which was assessed for only the SF-6D questionnaire and found not significant. Assessing the response shift for the EQ-5D-3L as well would have strengthened the conclusions. Third, the HSU score and the MIDe were estimated for the short-term (3 months after donation), whereas other studies often focused on long-term estimation (>1 year). The short-term, however, better reflects the impact of surgical and medical complications in donors rather than the long-term, because the returning of living kidney donors to their baseline HRQOL has been documented within 6 months [32]. We used a non-French value set for the SF-6D because of lack of a French value set.

Despite these limitations, to our knowledge, this study is the first to estimate a threshold of MIDe for living kidney donors by using two generic and popular instruments. The DOVIREIN study included consecutive donor-recipient couples from 22 public hospitals covering the whole French territory for 2 years, thereby suggesting the representativeness of kidney donors. The longitudinal design with a short-term follow-up and the use of different methods to estimate the MIDe are other strengths.

Conclusions

We report a threshold for a significant decrease in the HSU score in the short- term for kidney donors that can be used for managing the donor condition after donation. Further investigation is needed to examine whether the HSU score and the MIDe vary beyond 3 months. This study showed that more than the surgical technique used for kidney removal, clinical complications were associated with a significant and clinically meaningful decrease in the HSU score. Our findings give clues for interpreting changes in donor HSU and for future medico-economics analyses. They can also be used to determine other factors that could be associated with a meaningful change in donor HSU and contribute to improving practice.

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