Review Article
Long-term outcomes of laparoscopic versus open donor nephrectomy for kidney transplantation: a meta-analysis

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Abstract: Laparoscopic surgery is widely used for living donor nephrectomy and has demonstrated superiority over open surgery by improving several outcomes, such as length of hospital stay and morphine requirements. The purpose of the present study was to compare the long-term outcomes of open donor nephrectomy (ODN) versus laparoscopic donor nephrectomy (LDN) using meta-analytical techniques. The Web of Science, PubMed and Cochrane Library databases were searched, for relevant articles published between 1980 and January 20, 2020. Lists of reference articles retrieved in primary searches were manually screened for potentially eligible studies. Outcome parameters were explored using Review Manager version 5.3. The evaluated outcomes included donor serum creatinine levels, incidence of hypertension or proteinuria at 1 year postoperative, donor health-related quality of life, donation attitude, and graft survival. Thirteen of the 111 articles fulfilled the inclusion criteria. The LDN group demonstrated similar 1 year outcomes compared with ODN with respect to serum creatinine levels (weighted mean difference [WMD] -0.02 mg/dL [95% confidence interval (CI) -0.18-0.13]; P=0.77); hypertension (odds ratio [OR] 1.21 [95% CI 0.48-3.08]; P=0.68); proteinuria (OR 0.28 [95% CI 0.02-3.11]; P=0.30); and donation attitude (OR 4.26 [95% CI 0.06-298.27]; P=0.50). Donor health-related quality of life and recipient graft survival were also not significantly different between the groups analyzed. Thus, the long-term outcomes between LDN and ODN for living donor kidney transplantation are similar.

Keywords: Long-term outcomes, living donor nephrectomy, open donor nephrectomy, laparoscopic donor nephrectomy, meta-analysis

Introduction

Laparoscopic donor nephrectomy (LDN) is a commonly used technique since its introduction in 1995. Currently, many transplant centers choose LDN over open donor nephrectomy (ODN) as a primary surgical option for a variety of reasons. For example, although ODN is associated with shorter warm ischemia [1] and operative times [1], patients undergoing LDN benefit from a decreased length of hospitalization [2], an earlier return to employment [2], and less pain [3], without compromising graft function.

As the number of patients diagnosed with end-stage renal disease is increasing, the imbalance between the supply and demand of donor kidneys has become increasingly evident. This situation has been mitigated, to some degree, by live kidney donation. Concurrently, laparoscopic surgery has attracted much attention because of its short-term advantages. However, it remains unclear whether LDN has the same advantages as ODN in the long-term.

The aim of the present study was to compare the long-term outcomes of patients who had undergone LDN or ODN. We conducted a systematic review with meta-analysis of the available literature to investigate the long-term outcomes of laparoscopic versus open surgery techniques. The outcomes assessed included

serum creatinine levels, hypertension rates, and proteinuria at 1 year postoperative, health-related quality of life, donation attitude, and graft survival.

Materials and methods

Literature search strategy

Databases, such as PubMed, Web of Science, and Cochrane Library, were searched for studies comparing LDN and ODN and published between 1980 and January 2020. The medical subject heading search terms included "open", "laparoscopic", "donor nephrectomy", "kidney transplantation", and "long-term outcomes/impacts/functions" in the title or abstract. The related-articles function was used to broaden the search to conference abstracts and other potentially relevant studies. The last search date was January 20, 2020. All searches were independently performed by two of the authors (LW and LZ), and discrepancies were resolved in consultation with the senior author (HD).

Inclusion and exclusion criteria

Studies were included in the current systematic review with meta-analysis, if they fulfilled the following criteria: randomized controlled trial (RCT) or retrospective comparative study (e.g. case-control or cohort study); comparison of ODN versus LDN in any age group; and evaluation of at least one outcome of interest (donor serum creatinine levels and rate of hypertension or proteinuria at 1 year postoperative, donation attitude, donor health-related quality of life, and graft survival). When two studies were reported by the same institution, we included only the most recent publication, unless the study outcomes were mutually exclusive or measured at different times.

Studies were excluded if they failed to meet the inclusion criteria or had replicated the results of previously described cohorts. We also excluded studies that investigated minimal incision ODN or robotic LDN and those published in a language other than English.

Data extraction

All studies were independently analyzed by two reviewers (LW and LZ), who extracted the following data from each article: year of publication; first author; study design; study population characteristics; inclusion and exclusion criteria; matching criteria; and number of subjects undergoing each technique.

The extracted outcomes were donor serum creatinine levels, rates of hypertension or proteinuria at 1 year postoperative, donor health-related quality of life, donation attitude, and graft survival. Quality of life was assessed using Short-Form-36 (SF-36), which is multi-item scale measuring several health domains: physical functioning (PF), role limitations caused by physical health problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations caused by emotional problems (RE), and mental health (MH).

Quality assessment

The study quality was evaluated by LW and LZ. The Cochrane risk of bias tool was used to evaluate the quality of RCTs. This tool assesses random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. The quality of observational studies was evaluated using the Newcastle-Ottawa Scale [4], which examines three factors: patient selection, comparability of study groups, and assessment of outcomes. A score from 0 to 9 stars was determined for each study. RCTs and observational studies achieving ≥5 stars, 3-4 stars, and ≤2 stars were considered high-quality, moderate quality, and low quality, respectively.

Statistical analysis

Review Manager version 5.3 (R Foundation for Statistical Computing, Vienna, Austria) was used to examine the outcome parameters, including serum creatinine levels, hypertension, proteinuria, health-related quality of life, donation attitude, and graft survival. Weighted mean differences (WMDs) with corresponding 95% confidence intervals (CIs) were used for continuous data (creatinine and health-related quality of life). This represented differences in means between the LDN and ODN groups and accounted for sample size. Odds ratios (ORs) with a corresponding 95% CIs were used for dichotomous data (hypertension, proteinuria, donation attitude, and graft survival). This represented the odds of an event occurring in the
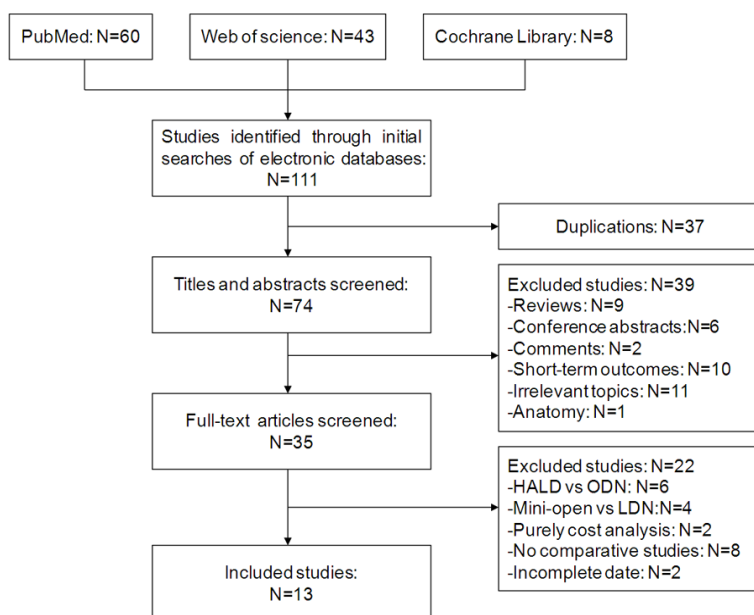
Figure 1. HALD = hand-assisted laparoscopic living donor nephrectomy. Flow diagram of studies identified, included, and excluded. According to the inclusion and exclusion criteria, 13 publications were ultimately selected for inclusion in the meta-analysis.

LDN and ODN group divided by the odds of event occurring in the ODN group. For continuous data, presented as means and ranges, standard deviations (SDs) were calculated using statistical algorithms. Heterogeneity between the studies was measured using the I^2 statistic and Cochran's Q test (Mantel-Haenszel chi-square test). When significant heterogeneity (chi-square P-value <0.1) was observed, a random-effects model was selected for the meta-analysis; otherwise, a fixed-effect model was used. An OR <1 favored the LDN group, and the point estimate of the OR was considered statistically significant at the P<0.05 level if the 95% CI did not include 1.

Results

The initial literature searches retrieved 111 potentially eligible articles (**Figure 1**). Based on the title, author, and publisher, 37 publications were excluded because of duplication. After reviewing the titles and abstracts, an additional 39 articles (including reviews, comments, early outcomes, and irrelevant research studies) were excluded. After reading the full text, 22 studies (including those investigating mini-open surgery, hand-assisted laparoscopic surgery and LDN alone [with no comparison to ODN]) were further excluded. Thus, 13 studies were included in the final meta-analysis. Agreement between the two reviewers was 98% for study selection and 99% for quality assessment.

Characteristics of eligible studies

The characteristics of the 13 studies fulfilling the inclusion criteria are summarized in **Table 1**. Three studies were RCTs and 10 were retrospective studies. The 13 studies included a total of 5,641 patients, of whom 1,288 (22.83%) underwent LDN and 4,353 (77.17%) underwent ODN.

Methodological quality of included studies

Thirteen studies were included in this research. Only three of the studies were RCTs [1, 5, 6]. The other 10 studies were retrospective in design [3, 7-15]; none of these studies adhered to a suitable allocation scheme, as the surgical technique was selected by the operating surgeon. The Cochrane risk of bias assessment of the three RCTs indicated that only one RCT used a balanced randomization method [1].

Serum creatinine level at 1 year postoperative

Serum creatinine levels at 1 year after donation were reported in two studies [7, 9] that involved a total of 235 donors. There was significant heterogeneity between the studies (P=0.02). Using a random-effects model, meta-analysis revealed that the serum creatinine levels at 1 year postoperative were similar between the LDN and ODN groups (WMD -0.02 mg/dL [95% CI -0.18-0.13]); P=0.77 (**Figure 2A**).

Hypertension rate at 1 year postoperative

Hypertension at 1 year postoperative was described in two studies [7, 11] and included a total of 225 donors. Hypertension rates were not significantly different between the two groups (OR 1.21 [95% CI 0.48-3.08]); P=0.68 (**Figure 2B**).

Table 1. Characteristics of the included studies

Study	Year	Design type	Patient, no. LDN	Patient, no. ODN	Matching	Follow-up, mo.	Quality score
Nasser et al.	2005	RCT	100	100	1, 2, 3, 5, 6, 7	12	★★★★★★
Frank	2016	R	131	30	1 ,2, 3, 5, 6	49-94	★★★★★
Marit Helen	2007	RCT	50	46	1, 2, 5, 6	12	★★★
Oscar Kenneth	2016	R	200	2642	1, 2, 4, 5, 6	12	★★★★
Moukarzel	2015	R	38	43	1, 2, 3, 5, 6	12	★★★★
Genc	2011	R	40	34	1, 2, 3, 5, 6	12	★★★★
Giessing	2005	R	44	62	1, 3, 5, 6	12	★★★
Buell	2005	R	46	21	1, 2, 3, 5, 6	12	★★★★★
Ithaar	2005	R	101	35	1, 2, 5, 6	36	★★★
Taweemonkongsap	2011	R	129	114	1, 2, 3, 5, 6	60	★★★★
Nicholas	2010	R	315	1159	1, 2, 5, 6	120	★★★
Skacar	2004	R	40	40	1, 2, 5, 6	36	★★★
Nicholson	2010	RCT	54	27	1, 2, 3, 5, 6, 7	60	★★★★★★

LDN, laparoscopic donor nephrectomy; ODN, open donor nephrectomy; R, retrospective; RCT, randomized controlled trial. Matching: 1, age; 2, gender; 3, body mass index; 4, previous abdominal surgery; 5, anatomic complexity (more than one artery, vein, and/or ureter); 6, matched for follow-up; 7, operating surgeon/team.
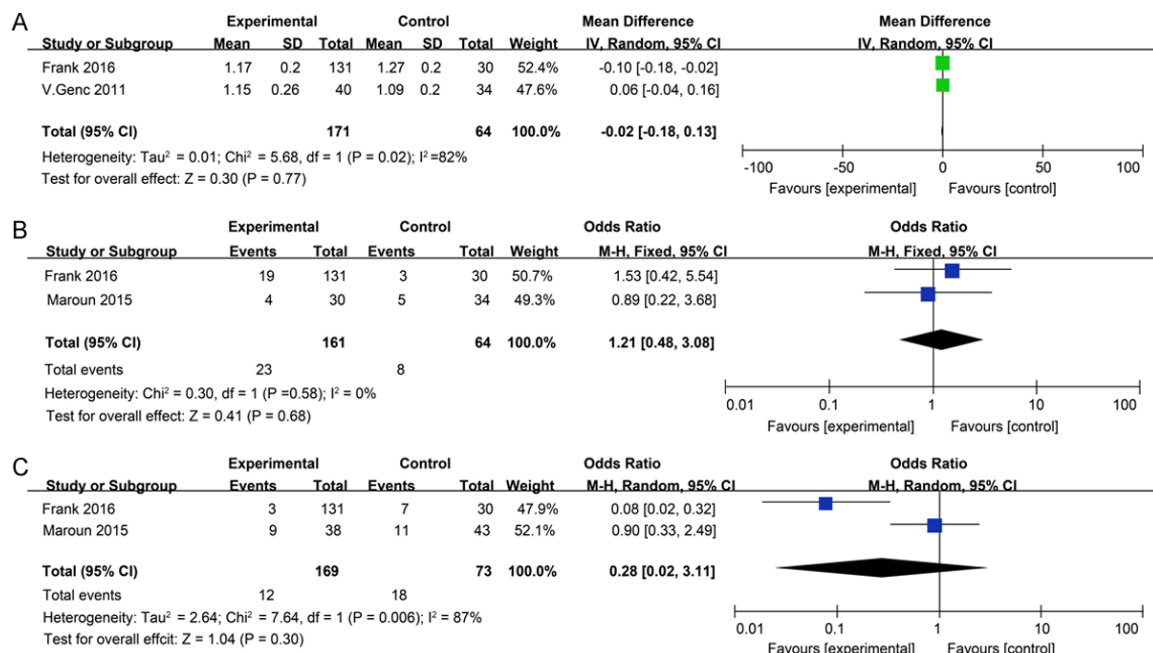

Figure 2. Forest plots comparing serum creatinine level, hypertension rates, and proteinuria rates at 1 year post-operative between LDN and ODN groups. A. Using a random-effects model, meta-analysis revealed that serum creatinine levels were similar between LDN and ODN groups. B. Hypertension rates were not significantly different between groups. C. Proteinuria rates were also not significantly different between groups.

Proteinuria rate at 1 year postoperative

The proteinuria rates at 1 year after surgery were reported in two studies, which demonstrated marked heterogeneity (*P*=0.006) [7, 11]. The available data were too limited to perform an adequate meta-analytic comparison, but no difference in proteinuria rates was observed between groups (OR 0.28 [95% CI 0.02-3.11]) (**Figure 2C**).

Health-related quality of life

Health-related quality of life was assessed in two studies [5, 9]. The meta-analysis results for each SF-36 dimension were as follows: PF: WMD 0.77 (95% CI -1.52-3.06; *P*=0.51); RP: WMD 0.75 (95% CI -2.55-4.06; *P*=0.66); BP: WMD -1.64 (95% CI -4.00-0.71; *P*=0.17); GH: WMD -0.06 (95% CI -2.46-2.35; *P*=0.96); VT: WMD 0.34 (95% CI -2.00-2.67]; *P*=0.78), SF: WMD 1.09 (95% CI -1.39-3.57; *P*=0.39), RE: WMD 0.00 (95% CI -3.81-3.82; *P*=1.00), and MH: WMD 0.59 (95% CI -1.24-2.42]; *P*=0.53) (**Figure 3A-H**). There were no significant differences in any dimension between groups.

Donation attitude

Assessment of whether donors would select the same surgical technique in the future was reported in two studies [7, 10], which exhibited marked heterogeneity (*P*=0.0008). Therefore, a random-effects model was used for the meta-analysis. Overall, the available data suggested that both groups of donors would choose the same surgical technique again, with no significant difference between groups (OR 4.26 [95% CI 0.06-298.27]; *P*=0.50) (**Figure 4**).

Graft survival at 1, 3, and 5 years

Graft survival at 1, 3, and 5 years were reported in six [9, 12-16], two [12, 14], and three [13, 15, 16] studies, respectively. Meta-analysis using the fixed effects model revealed, no significant differences in graft survival at 1,3, and 5 years between the LDN and ODN (1 year: OR 0.90 [95% CI 0.54-23.67], *P*=0.67; 3 years: OR 0.67 [95% CI 0.22-2.04], *P*=0.48; and 5 years: OR 1.27 [95% CI 0.91-1.77], *P*=0.16) (**Table 2**).

Discussion

With advances in laparoscopic technology, many investigators have compared perioperative variables, such as warm ischemia and operating times between LDN and ODN [1, 2]. However, some previous studies have focused on the outcomes of kidney transplant recipients, with less attention devoted to long-term outcomes of donors after LDN or ODN. Accordingly, the objective of this paper was to compare a donors' long-term outcomes after LDN versus ODN using meta-analytic techniques. The meta-analysis included three RCTs

and 10 retrospective studies, with a total of 5,641 patients. In the long-term, there were no differences between surgical techniques, with donors exhibiting similar outcomes after LDN and ODN.

Serum creatinine level

Serum creatinine levels are the most direct and effective indicators of kidney function. The present study demonstrated that the nephrectomy technique did not affect the short-term serum creatinine levels in kidney donors [12]. Two studies [7, 9] reported no differences in donor serum creatinine levels, 1 year after undergoing nephrectomy, between those who underwent LDN or ODN. When data from these studies were combined in the current meta-analysis, we also observed no difference in creatinine levels between the LDN and ODN groups. Prior to undergoing nephrectomy, the health of the potential donors was fully assessed. This included an evaluation of bilateral kidney function, which is used to select the kidney to be harvested. When there is a difference in function between donor kidneys, the better functioning organ is left in place to ensure the health and safety of the donor. Therefore, it is important to accurately evaluate the donor when choosing the kidney to be harvested.

Hypertension

No differences in hypertension rates were found between LDN and ODN in our meta-analysis. However, a separate study emphasized the importance of long-term blood pressure follow-up after kidney donation [17]. For example, Dorry et al. [18] reported that 7% of donors developed hypertension during a 6-year follow-up after donation. These findings were further supported in other studies, in which the proportion of live kidney donors requiring antihypertensive treatment after donation was reported as 21%-24% [19, 20].

Some researchers have also compared the blood pressure of kidney donors with that of the general population. The results indicated no differences in the incidence of hypertension among kidney donors compared with the general population. However, only a few prospective studies have been published to evaluate changes in blood pressure after donation. In
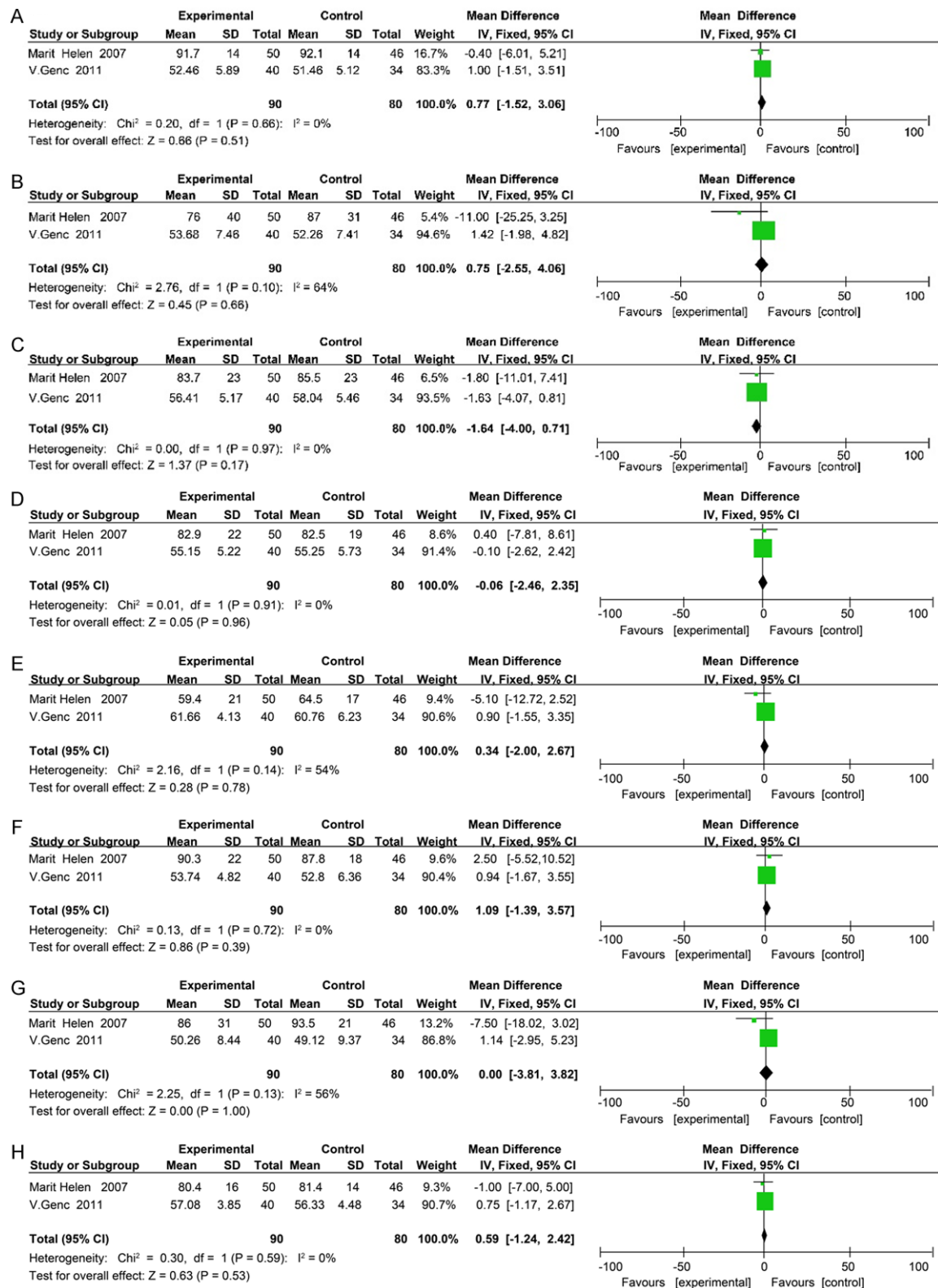
Figure 3. Forest plots comparing the eight SF-36 dimensions between LDN and ODN groups. A. PF dimension. B. RP dimension. C. BP dimension. D. GH dimension. E. VT dimension. F. SF dimension. G. RE dimension. H. MH dimension.
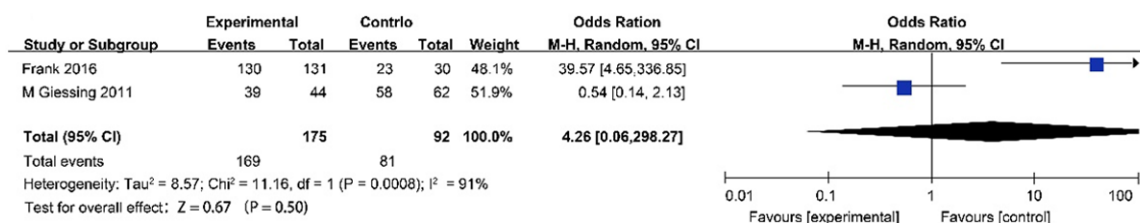
Figure 4. Forest plot comparing donation attitude between the LDN and ODN groups. There was no significant difference in the proportion of donors who would choose the same surgical technique again between groups.

Table 2. Meta-analytic comparisons of health-related quality of life between LDN and ODN

Outcomes of interest	Studies, No.	LDN patient, No.	ODN patient, No.	WMD/OR (95% CI)	P value	Study heterogeneity			
						X^2	df	I^2, %	P value
serum creatinine levels	2	171	64	-0.02; [-0.18, 0.13]	0.77	5.68	1	82	0.02
hypertension	2	161	64	1.21; [0.48, 3.08]	0.68	0.30	1	0	0.58
proteinuria	2	169	73	0.28; [0.02, 3.11]	0.30	7.64	1	87	0.006
PF	2	90	80	0.77; [-1.52, 3.06]	0.51	0.20	1	0	0.66
RP	2	90	80	0.75; [-2.55, 4.06]	0.66	2.76	1	64	0.10
BP	2	90	80	-1.64; [-4.00, 0.71]	0.17	0.00	1	0	0.97
GH	2	90	80	-0.06; [-2.46, 2.35]	0.96	0.01	1	0	0.91
VT	2	90	80	0.34; [-2.00, 2.67]	0.78	2.16	1	54	0.14
SF	2	90	80	1.09; [-1.39, 3.57]	0.39	0.13	1	0	0.72
RE	2	90	80	0.00; [-3.81, 3.82]	1.00	2.25	1	56	0.13
MH	2	90	80	0.59; [-1.24, 2.42]	0.53	0.30	1	0	0.59
donation attitude	2	175	92	4.26; [0.06, 298.27]	0.50	11.16	1	91	0.0008
graft survival at 1 year	6	737	1409	0.90; [0.54, 23.67]	0.67	1.67	5	0	0.89
graft survival at 3 year	2	141	75	0.67; [0.22, 2.04]	0.48	0.10	1	0	0.75
graft survival at 5 year	3	443	1118	1.27; [0.91, 1.77]	0.16	0.61	2	0	0.74

LDN, laparoscopic donor nephrectomy; ODN, open donor nephrectomy; WMD, weighted mean difference; OR, odds ratio; PF, physical functioning (whether health conditions interfere with normal physical activity); RP, role-physical (functional limitations due to physical health problems); BP, bodily pain (pain levels and how pain affects daily activities); GH, general health (individuals' self-assessment of health status and trend); VT, vitality (individuals' subjective perceptions of energy and fatigue); SF, social functioning (impact of physical and psychological problems on quantity and quality of social activities); RE, role-emotional (functional limitations because of emotional problems); and MH, mental health (motivation, depression, behavioral or emotional loss, and subjective psychological feelings).

one of these studies, Kasiske et al. compared 182 donors with 173 healthy non-donors, all of whom were followed for 36 months after donation. In this study, blood pressure did not differ significantly between the donors and non-donors during the follow-up period [21]. By contrast, Berber et al. reported a higher incidence of hypertension in donors aged >55 years, when followed for more than 10 years, compared with the general population [22]. Moreover, Holscher et al. also found a 19% increased risk of hypertension in donors at a median of 6 years after donation, compared with a weighted cohort of healthy controls [23]. The development of hypertension is often multifactorial, and the risk for hypertension is correlated with age and body mass index. Donors require appropriate post-donation medical care and a healthy lifestyle to minimize the development of long-term morbidity. However,

the method of donor nephrectomy does not appear to influence the incidence of subsequent hypertension among kidney donors.

Proteinuria

Proteinuria indicates the presence of nephron hyperfiltration and may be an early indicator of renal parenchymal damage [7]. In our meta-analysis, we found no statistical difference in proteinuria rates between LDN and ODN. Previous investigators emphasized the importance of long-term monitoring of urine protein levels in kidney donors [24]. Kidney donation may result in a small increase in urinary albumin levels, which do increase over time after donation, because of hyperfiltration of a single nephron from the reduced renal mass. Nevertheless, the choice of nephrectomy technique (LDN versus ODN) does not appear to affect the presence or absence of proteinuria.

Health-related quality of life

In this study, we used SF-36 to compare the donors' health-related quality of life between LDN and ODN. Few studies have investigated the effects of different nephrectomy techniques on donor quality of life; most studies have examined changes in the quality of life after donation. Our meta-analysis detected no significant differences between LDN and ODN with respect to a donors' long-term health-related quality of life.

Among SF-36 dimensions, BP is the most studied because surgical pain has a number of effects on postoperative recovery. The presence of BP is strongly associated with a reduced quality of life. Many studies have demonstrated differences in BP scores between LDN and ODN at 1-year post-donation, with LDN yielding better scores. Andersen et al. found that SF-36 BP scores were significantly higher in the laparoscopic group at 1 month after donation [6]. In addition, Perry et al. [25] reported similar results using version 2 of the SF-36, with their LDN group demonstrating a significantly higher quality of life and BP scores at approximately 6 12 months after surgery. However, this difference was not observed at 1 year after surgery. Another study [6] found that both ODN and LDN groups reached baseline scores for most SF-36 dimensions at 12 months. Differences in other SF-36 items have been found in a small number of studies. One study reported that only the RP dimension was significantly better in the LDN group than in the ODN group [9]. Scores for VT and RE have been reported to baseline levels by 6 weeks after LDN [6].

Some studies have compared the quality of life between kidney donors and the general population. Isotani et al. [26] found no adverse effects of ODN on the quality of life, compared with the general population in the United States, as exhibited by similar SF-36 scores [27]. However, donors scored higher than the general population in some dimensions, including BP and MH, indicating that kidney donation positively affected their quality of life. This may reflect the beneficial effects of organ donation for the recipient. Recipients are typically relatives or friends of the donor, and the opportunity to help these individuals can improve the donor's attitude toward life.

Quality of life is the result of interactions between many factors, including the experience of postoperative pain, as confirmed by Michael et al. [6]. Reductions in postoperative pain and associated improvements in convalescence after minimal access surgery may have important effects on a donor's quality of life. LDN has been reported to improve a donor's quality of life in terms of reduced pain, shorter in hospital length of stay, and shorter period away from work after surgery, compared with ODN [25]. However, this effect was statistically significant at only 1 year after donation. Nevertheless, many other factors can influence the quality of life. Malfunction or failure of the transplanted kidney, most often associated with a decrease in the recipient's quality of life, may negatively impact the donor's quality of life as well [10].

Donation attitude

Donor safety is the primary consideration in any live donor transplant program, and the effects of donor complications require careful appraisal. Some investigators have focused on the willingness of living organ donors to donate again. One study reported that 90% of donors were willing to donate again if they were in the same situation, which was consistent with the findings of other studies [26]. Another group reported that, if donors were given the opportunity to choose the surgical technique (ODN versus LDN), they would prefer LDN during the repeat surgery [10]. Specifically, 99% of donors who underwent LDN reported that they would choose the same surgical approach, whereas only 67% of donors in the ODN group, who were aware of the alternative minimally invasive option, would choose the open surgical technique in the future [7]. Most donors choose a minimally invasive method when presented with the hypothetical scenario of repeat donation [10]. Overall, most donors would choose to donate again; however, it is debatable whether they would choose the same surgical method. There was no difference in the number of donations between LDN and ODN in our meta-analysis, suggesting that the willingness to donate was not affected by the surgical method. Donation may have a positive effect on donors, and most respondents report a closer emotional relationship with the recipient after donation [28]. Health concerns may subside with time, and feelings of donation are less frequent in

patients who donated a kidney in previous years.

Graft survival

Long-term, high-quality graft survival is considered the ultimate goal of kidney transplantation. Prolonged survival of a transplanted kidney is affected by many factors, but the donor's nephrectomy technique does not appear to influence graft survival [12-16]. This finding was reported previously and is further supported by the results of our current meta-analysis.

Limitations

This systematic review with meta-analysis has several limitations. Firstly, the date donation date differed between groups, with most ODNs performed before implementation of LDN programs. Secondly, most of the included studies were observational in design, were not conducted at multiple centers, and were performed by surgeons with varying levels of expertise. Thirdly, almost all studies were retrospective; as such, patients were required to recall detailed information after the donation, which may have introduced recall bias.

In conclusion, LDN is currently the primary method of living donor nephrectomy. Based on the results of this systematic review with meta-analysis, LDN and ODN appear to result in similar long-term outcomes, including donor serum creatinine levels, incidence of hypertension, and incidence of proteinuria at 1-year post-donation, donor health-related quality of life, donation attitude, and graft survival.

Disclosure of conflict of interest

None.

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