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Pure versus hand-assisted retroperitoneoscopic live donor nephrectomy: a retrospective cohort study of 1508 transplants from two centers

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Abstract

Background Although minimally invasive procedures have been established as the standard for a donor nephrectomy, there are many different surgical techniques described in the literature. The aim of this study is to compare the outcomes of kidney transplant procedures using the pure retroperitoneoscopic donor nephrectomy (PRDN) and hand-assisted retroperitoneoscopic donor nephrectomy (HARDN) techniques.

Methods A retrospective study involving 1508 transplant procedures was conducted; 874 were PRDN procedures; and 634 were HARDN. We reviewed the outcomes of the PRDN and HARDN groups, which were performed at two different centers over an identical time period.

Results Donors in the PRDN group had a longer operation time ($P<0.0001$), reduced estimated blood loss ($P<0.0001$), less open conversion ($P=0.0002$), lower postoperative serum C-reactive protein levels ($P<0.0001$), and a shorter postoperative hospital stay ($P<0.0001$) than the HARDN group. Recipients in the PRDN group had lower serum creatinine levels at postoperative day 1–6 and the decreased incidence of slow graft function ($P=0.0017$) than the HARDN group. The HARDN procedure was an independent risk factor for the incidence of acute rejection ($P=0.0211$) and graft loss ($P=0.0193$).

Conclusions Our study suggests that the PRDN procedure is less invasive for donors as it results in reduced blood loss, lower postoperative serum CRP levels, and a shorter postoperative stay than the HARDN procedure. Additionally, PRDN provides a better outcome for recipients as it lowers the incidence of acute rejection and improves graft survival compared to HARDN.

Keywords Kidney transplantation · Minimally invasive surgery · Hand-assisted · Retroperitoneoscopic donor nephrectomy · Acute rejection

For patients with end-stage renal disease, living donor kidney transplantation decreases the morbidity and mortality of patients on the waiting list who have potential living donors. The procedure has several advantages over deceased-donor kidney transplantation, including better human leukocyte antigen (HLA) matching, shorter ischemic and waiting times, less need for immunosuppression, availability of more intensive desensitization, and lower risk of infection [1]. In 1995, to decrease the morbidity associated with open living donor nephrectomy, Ratner et al. [2] performed the first laparoscopic living donor nephrectomy. Since then, modifications to the laparoscopic technique have been introduced and laparoscopic procurement of living donor kidneys is considered to be a standard procedure for living donor renal transplantation in most renal transplant centers worldwide. However, there are many different surgical techniques for this procedure, including the pure/hand-assisted laparoscopic, retroperitoneoscopic, and robot-assisted donor nephrectomy, and preference differs between centers [3, 4]. Minimally invasive procedures should be established as the standard donor nephrectomy in order to reduce morbidity and improve the donor's quality of life [5–7]. Moreover, less-invasive procedures with early graft function are also expected to increase the donor pool as well as improving

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graft survival [8, 9]. As in our previous reports [10, 11], we have been trying to establish the pure retroperitoneoscopic donor nephrectomy (PRDN) technique since 2001; however, there are few reports regarding the use of pure/hand-assisted retroperitoneoscopic donor nephrectomy (HARDN). In the review by Kirsten et al., these procedures are detailed in only 3% of the report [12]. There have been no reports examining the outcome between PRDN and HARDN groups with a sufficient amount of sampling data. Therefore, in the present study, we reviewed the outcomes of these two procedures over a set period of time.

Materials and methods

The Japan Academic Consortium of Kidney Transplantation (JACK) is an ongoing multicenter, retrospective, observational study comprising eight transplant centers (Tokyo Women's Medical University, Toda Chuo General Hospital, Ohkubo Hospital, Kyushu University, Yachiyo Medical Center, Jyoban Hospital, Tomishiro Central Hospital and The Jikei University School of Medicine) in Japan. The consortium is a collaborative effort designed to develop an epidemiological database and to improve the quality of care for donors and patients undergoing kidney transplantation. Patient information collected includes demographic data, medical history, treatment, procedures, and follow-up information. The relevant ethics committee of each participating medical center approved the protocol for this study, and all patients provided written informed consent. JACK is registered with the University Hospital Medical Information Network (UMIN000018327).

Patients

We reviewed data from 1508 consecutive transplant procedures at the Tokyo Women's Medical University and the Kyushu University from October 2003 through to August 2015. At both centers, we adopted a uniform immunosuppressant/graft biopsy protocol and a limited number of surgeons who are experts in living kidney transplantation. The final follow-up assessment was carried out on 31 December 2017. Donor parameters analyzed included operating time, time to procurement, estimated blood loss, warm ischemic time (WIT), total ischemic time (TIT), serum C-reactive protein (CRP) level at postoperative day (POD) 1, and days of postoperative stay. WIT indicates the time from clamping of the renal artery to flushing of the kidney with cold solution. Assessment of recipients' outcomes included analysis of serum creatinine levels, slow graft function (SGF; serum creatinine level is more than 3.0 mg/dl at 4 days after transplantation), delayed graft function (DGF; patients required hemodialysis after transplantation due to acute tubular necrosis), biopsy-proven acute rejection rate within 1 year after transplantation, and cumulative recipient/graft survival rate. These data were collected retrospectively using hospital charts.

Perioperative management

All recipients were treated with triple immunosuppressive drugs, consisting of methylprednisolone, calcineurin inhibitor (tacrolimus or cyclosporine), and antimetabolic agents (mycophenolate mofetil, azathioprine, or mizoribine) in addition to basiliximab induction. Rituximab and plasmapheresis were added in patients who underwent ABO-incompatible transplantation, those who received a second graft, and those who were presensitized with positive flow-cytometric panel-reactive antibody testing. All donors received standard general anesthesia without epidural analgesia. Local anesthesia (up to 40 ml of 0.75% ropivacaine) was injected into all incisions at the end of the donor nephrectomy. Intravenous analgesics, including pentazocine and acetaminophen, were given during the first 24 h; donors were then generally converted to oral acetaminophen between 12 and 24 h after nephrectomy. All donors had the urinary catheter removed on POD 1 and were permitted to be discharged after POD 3–5. The preoperative CRP levels of the donors were examined to exclude donors with active inflammatory diseases. The CRP level on POD 1 was examined to monitor the postoperative course of the donors and compare the degree of inflammation after that. The CRP level on POD1 was not determined with the aim of changing the treatment policy. No intervention was initiated for those with a high CRP level on POD 1.

The surgical procedure for PRDN

We described in detail the technique for the PRDN surgical procedure in our previous reports [10, 11]. The donor was placed in a lateral decubitus position, and the position of the operative table was flat, not bent. Three retroperitoneoscopic ports were inserted in all cases. The first 10-mm port was inserted into the axillary line between the iliac crest and the 12th rib and was used as a camera port. This camera port was created by finger dissection in the abdominal wall muscle layer. The second 12-mm port was inserted at the angle of the 12th rib and the lateral margin of the iliocostal muscle. The third port was inserted 5 cm above the anterior spine of the iliac bone. A retroperitoneal working space was developed with a balloon dilator (OMSPDB1000; Covidien, Minneapolis, MN). We used a 10 mm-flexible fiberscope (Olympus, Tokyo Japan). The retroperitoneal space was insufflated to a pressure of 8 mmHg. We isolated the vessels with a vessel loop and tried not to touch the renal artery as much as possible to prevent vascular spasm.

Before transection of the renal arteries and veins, a 5-cm Pfannenstiel incision was made and an anterior vesical space (Retzius cavity) was created by finger dissection. This space was connected to the retroperitoneal space that had already been created by the dissection of the kidney and ureter. A wound retractor (Alexis Wound Retractor; Applied Medical Resources, Rancho Santa Margarita, CA, USA) was placed in the Pfannenstiel incision to maintain the pneumoretroperitoneum. An Endo Catch II (Medtronic, Minneapolis, USA), which is a specimen pouch, was inserted through this incision and a laparoscopic retrieval bag was placed under the kidney. Next, the renal artery and vein were divided with an endovascular stapler without heparin administration before clamping the artery. The kidney was placed into the bag and extracted through the Pfannenstiel incision.

The surgical procedure for HARDN

The patient was placed in a 70-degree oblique position, donor-side up. The table was flexed to maximize the retroperitoneal space and stretch the peritoneum. A 6-cm incision was made below the umbilical. The peritoneum was left intact, and a preperitoneal space was created through blunt manual dissection. A hand-assist device, GelPort (Applied Medical, Rancho Santa Margarita, CA, USA), was placed in the wound. The surgeon's left hand was placed between the abdominal wall and the peritoneum in order to peel the peritoneum off. A blunt 12-mm working port was then placed to the donor-side of the hand port, and the peritoneum was moved medially by blunt manual dissection. Gas (CO_2) was insufflated into the retroperitoneal space at a pressure of 8 mmHg. A second 12-mm blunt port was introduced high on the subcostal margin. We used a 10-mm-flexible fiberscope (Olympus, Tokyo Japan). A third 5-mm blunt port was placed in the flank below the costal margin. The ureter was dissected down to the iliac vessels, and the Gerota's fascia was opened. The upper pole of the kidney was then dissected free. The vascular pedicle was dissected, and the artery was freed down to the aorta. The artery and the vein were divided with an endovascular stapler without heparin administration before clamping the artery, and the kidney was removed by hand.

Allograft biopsy policy and pathological interpretation

We performed a protocol biopsy (PB) at 3 and 12 months post-transplantation. All rejection episodes were biopsy-proven including antibody-mediated and T-cell mediated rejection. Specimens were scored according to the Banff 2013 classification [13]. If the patients showed an unexplained increase in the serum creatinine concentration, including DGF lasting for more than 7 days, we performed an "indication biopsy" using the same procedure.

Statistical analysis

Results are presented as mean ± standard deviation for normally distributed variables, as median (range) for abnormally distributed variables, and as count and percentage for categorical variables. Continuous variables were nonparametrically analyzed using the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test where appropriate. Univariate and multivariate logistic regression analyses were performed to determine the factors associated with acute rejection. The incidence of patient and graft survivals were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios and perform tests. A multivariable Cox model was used to assess the risk factors. Variables with a P value < 0.10 in the univariate analysis were included in the multivariate analysis. Patients were censored at the last follow-up visit if graft failure had not occurred. A P value of < 0.05 was considered significant. All statistical data were generated using JMP 13 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the study population

Characteristics stratified by operative procedures are shown in Table 1. No significant differences were observed with respect to donor/recipient age, sex, number of HLA mismatches, ABO incompatibility, and history of splenectomy. Patients in the HARDN group had a higher donor preoperative body mass index (BMI) ($P < 0.0001$), lower rate of kidney transplant history ($P = 0.0008$) and preoperative donor-specific antibody (DSA; $P < 0.0001$), and a shorter duration of dialysis than those in the PRDN group ($P = 0.0007$). As for the induction of immunosuppressants, there was a significantly lower use of mycophenolate mofetil (*MMF;* $P < 0.0001$), basiliximab ($P < 0.0001$), and splenectomy ($P = 0.0212$), and increased use of rituximab ($P < 0.0001$) in the PRDN group compared to the HARDN group. The follow-up period of the HARDN group was significantly shorter than the PRDN group ($P < 0.0001$).

Peri- and postoperative outcome of the donor and recipient

Table 2 presents the perioperative and postoperative outcomes of the donor and recipient. Donors in the PRDN

Table 1 Characteristics of the study population

Variables	PRDN ($n=874$)	HARDN ($n=634$)	*P* value
Donors			
Age (years)	56.1 ± 10.4	55.0 ± 11.5	0.0577
Men	307 (35.1%)	237 (37.4%)	0.3682
Pretransplant body mass index (kg/m^2)	22.3 ± 2.5	23.0 ± 3.2	< 0.0001
Left nephrectomy	840 (96.1%)	616 (97.2%)	0.2648
Preoperative serum CRP level (mg/dl)	0.10 ± 0.22	0.09 ± 0.19	0.5345
Recipients			
Age (years)	41.5 ± 17.4	43.0 ± 16.4	0.1027
Men	550 (62.9%)	382 (60.3%)	0.2913
Duration of dialysis (months)[a]	25 (10–60)	19 (0–66)	0.0007
Mean HLA mismatches number	2.9 ± 1.5	2.9 ± 1.5	0.7656
Kidney transplant history	57 (6.5%)	18 (2.8%)	0.0008
ABO-incompatibility	248 (28.4)	181 (28.6%)	0.9522
Preoperative DSA	232 (26.6%)	78 (13.1%)	< 0.0001
Induction of immunosuppression			
Tacrolimus/cyclosporine A	828/45	598/36	0.6571
MZ AZA/MMF	38/836	0/634	< 0.0001
Basiliximab	785 (89.8%)	617 (97.3%)	< 0.0001
Rituximab	532 (60.9%)	207 (32.7%)	< 0.0001
Splenectomy	38 (4.4%)	14 (2.2%)	0.0212
Follow-up period (months)	91.1 ± 42.2	78.6 ± 36.0	< 0.0001

Data are presented as mean ± standard deviation, median (range), *n*, or *n* (%)

BMI, body mass index; CRP, C-reactive protein; DSA, donor-specific antibodies; HARDN, hand-assisted donor nephrectomy; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; MZ, mizoribine; PRDN, pure retroperitoneoscopic live donor nephrectomy

[a]Median (interquartile range)

Table 2 Perioperative and postoperative outcomes of the donors and recipients

Variables	PRDN ($n=874$)	HARDN ($n=634$)	*P* value
Donors			
Operative time (min)	251 ± 92	185 ± 63	< 0.0001
Time to procurement of the graft (min)	199 ± 80	110 ± 51	< 0.0001
Time after procurement (min)	52 ± 19	75 ± 24	< 0.0001
Estimated blood loss (ml)	39 ± 47	196 ± 235	< 0.0001
WIT (min)	4.4 ± 1.4	4.1 ± 2.4	0.0178
TIT (min)	91 ± 32	134 ± 42	< 0.0001
Serum CRP level at POD1 (mg/dl)	3.5 ± 1.8	11.0 ± 3.5	< 0.0001
Postoperative hospital stay (days)	3.4 ± 1.1	6.9 ± 2.9	< 0.0001
Recipients			
SGF	9 (1.0%)	21 (3.3%)	0.0017
DGF	0 (0%)	0 (0%)	
Biopsy-proven acute rejection	142 (16.3%)	149 (23.5%)	0.0005

Data are presented as mean ± standard deviation, median (range), *n*, or *n* (%)

CRP, C-reactive protein; DGF, delayed graft function HARDN, hand-assisted donor nephrectomy; PRDN, pure retroperitoneoscopic live donor nephrectomy; SGF, slow graft function; TIT, total ischemia time; WIT, warm ischemia time

group had a longer operative time ($P < 0.0001$) and time to procurement of the graft ($P < 0.0001$), less estimated blood loss ($P < 0.0001$), longer WIT ($P = 0.0178$), shorter TIT ($P < 0.0001$), lower serum CRP levels ($P < 0.0001$), and a shorter postoperative hospital stay ($P < 0.0001$) than those in the PRDN group. Recipients in the PRDN group had a reduced incidence of SGF ($P = 0.0017$) and acute rejection ($P = 0.0005$). DGF caused by the donor nephrectomy procedure was not seen in either group. Table 3 shows the complications experienced by the donors and recipients. A modification of the Clavien classification system [14], which describes procedure-related complications, was used to grade the severity of all complications. Grades 3 and 4 complications did not occur in our study group. In total, there were 81 Clavien classifiable complications recorded among the study group (33 events in 32 persons in the PRDN group and 49 events in 43 persons in the HARDN group). There was a significantly higher incidence of grade 1 and 2c complications in the HARDN group than the PRDN group ($P = 0.0207$ and $P = 0.0002$, respectively). In the PRDN group, there were four iatrogenic injuries requiring operative procedures including two abdominal incisional hernia, one pneumothorax requiring drainage, one bladder injury. In the HARDN group, the one iatrogenic injury requiring operative procedure was small bowel obstruction with strangulation caused by a port site hernia.

Recipient and graft survival

Figure 1 shows the cumulative recipient survival rates after transplantation. The recipient survival rate was not significantly different between the two groups (Fig. 1A, $P = 0.3667$). Graft loss occurred in a total of 99 cases, the death-censored cumulative graft survival rate was not significantly different between the two groups (Fig. 1B, $P = 0.0718$).

Serum creatinine levels of recipients after transplantation

Figure 2 shows the serum creatinine levels of recipients after transplantation. At POD 1–6, serum creatinine levels in the HARDN group were significantly higher than those in the PRDN group. After POD 7, there was no significant difference in the serum creatinine levels between the two groups.

Risk factors for biopsy-proven acute rejection within 1 year after transplantation

Multivariate Cox regression analyses identified the HARDN procedure (odds ratio [OR], 1.41; 95% confidence interval [CI] = 1.05–1.89; $P = 0.0211$), number of HLA mismatches (OR, 1.24; 95% CI = 1.13–1.36; $P < 0.0001$), previous kidney transplantation history (OR, 2.30; 95% CI = 1.34–3.96; $P = 0.0037$), preoperative DSA (OR, 1.45; 95% CI = 1.04–2.02; $P < 0.0316$), and rituximab (OR, 0.73; 95% CI = 0.55–0.99; $P = 0.0436$) as independent predictive factors for acute rejection (Table 4).

Table 3 Complications of the donors and recipients [14]

Grade complication	PRDN ($n = 874$)	HARDN ($n = 634$)	P value
1. Non-life threatening complications (total)	25 (2.9%)	33 (5.2%)	0.0207
Surgical site infection	4 (0.5%)	3 (0.5%)	
Atelectasis	1 (0.1)	4 (0.6%)	
Postoperative hematoma	10 (1.1%)	1 (0.2%)	
Iatrogenic injuries not requiring operative procedure	1 (0.1%)	0 (0%)	
Ileus resolving spontaneously	0 (0%)	3 (0.5%)	
Slow graft function (recipients)	9 (1.0%)	21 (3.3%)	
2. No residual disability			
2a. Requires only use of medication (total)	2 (0.2%)	3 (0.5%)	0.4198
Transfusion	2 (0.2%)	3 (0.5%)	
2b. Requires additional therapeutic intervention (total)	6 (0.7%)	5 (0.8%)	0.8201
Ureteral complication (recipient)	2 (0.2%)	1 (0.2%)	
Ileus	0 (0%)	3 (0.5%)	
Iatrogenic injury requiring operative procedures	4 (4.6%)	1 (0.2%)	
2c. Open conversion	0 (0%)	8 (1.3%)	0.0002
3. Residual disability	0 (0%)	0 (0%)	
4. Renal failure or death	0 (0%)	0 (0%)	

33 Events of 32 persons in the PRDN group and 49 events of 43 persons in the HARDN group

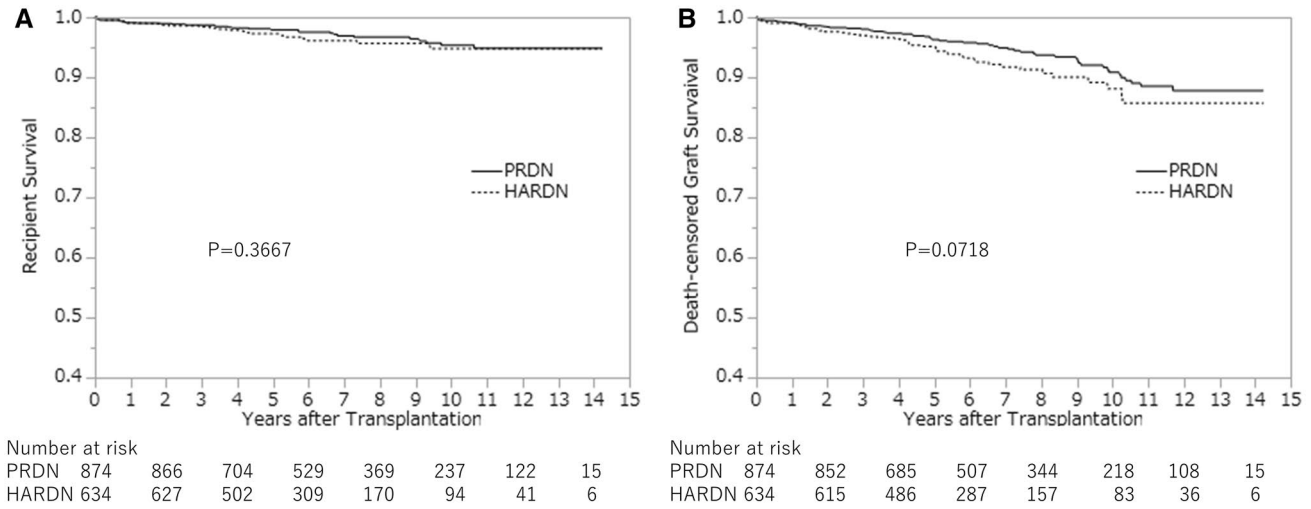

Fig. 1 **A** Cumulative recipient survival rates after transplantation. The recipient survival rate was not significantly different between the two groups ($P=0.3667$). **B** Death-censored cumulative graft survival rates. The graft survival rate was not significantly different between the two groups ($P=0.0718$)

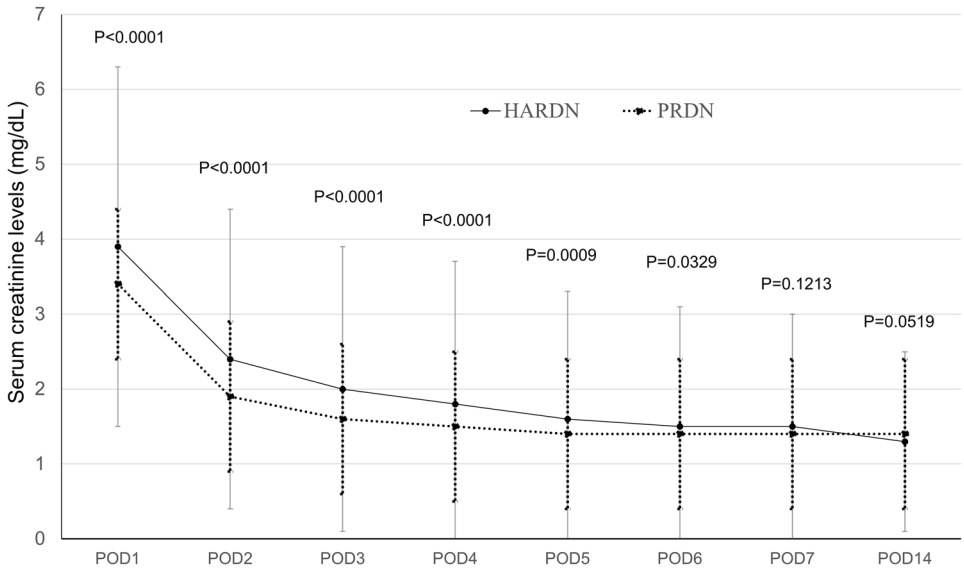

Fig. 2 Serum creatinine levels of the recipients after transplantation. Lines and error bars represent the mean and standard deviation. At postoperative days 1–6, serum creatinine levels in the patients in the HARDN group were significantly higher than those in the PRDN group. After postoperative day 7, there was no significant difference in serum creatinine levels between the two groups

Risk factors against cumulative death-censored graft survival

Multivariate Cox regression analyses identified the HARDN procedure [hazard ratio (HR), 1.69; 95% CI = 1.09–2.63; $P=0.0193$] and kidney transplantation history (HR, 2.89; 95% CI = 1.53–5.08; $P=0.0017$) as independent predictive factors for cumulative death-censored graft survival (Table 5).

Discussion

This retrospective study examines the outcomes between the PRDN and HARDN procedures. The current study showed the following: (1) donors in the PRDN group had less estimated blood loss, lower serum CRP levels after surgery, and a shorter postoperative stay, (2) the recipients in the PRDN group had a lower incidence of SGF and acute rejection than the HARDN group, and (3) the PRDN procedure was an

Table 4 Risk factors for acute rejection

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Donors				
Age (years)	0.98 (0.99–1.00)	0.2775		
Men	1.03 (0.80–1.35)	0.7835		
Pretransplant body mass index (kg/m^2)	1.02 (0.98–1.07)	0.2910		
Left nephrectomy	1.15 (0.55–2.38)	0.7078		
HARDN versus PRDN	1.59 (1.22–2.04)	0.0005	1.41 (1.05–1.89)	0.0211
WIT (min)	1.02 (0.96–1.09)	0.4831		
TIT (min)	1.00 (0.99–1.01)	0.1564		
Recipients				
Age (years)	1.01 (0.99–101)	0.1830		
Men	1.02 (0.78–1.32)	0.8771		
Duration of dialysis (> 23 months)	0.96 (0.74–1.24)	0.7407		
HLA-AB DR mismatches	1.22 (1.11–1.33)	< 0.0001	1.24 (1.13–1.36)	< 0.0001
Kidney transplant history	2.06 (1.24–3.40)	0.0072	2.30 (1.34–3.96)	0.0037
ABO-incompatibility	1.03 (0.77–1.36)	0.8606		
Preoperative DSA	1.57 (1.16–2.12)	0.0045	1.45 (1.04–2.02)	0.0316
Induction of immunosuppression				
Tacrolimus/cyclosporine A	0.51 (0.31–0.84)	0.0106	0.66 (0.36–1.23)	0.2037
MZ/MMF	1.31 (0.61–2.79)	0.4987		
Basiliximab	1.49 (0.85–2.61)	0.1492		
Rituximab	0.69 (0.53–0.89)	0.0047	0.73 (0.55–0.99)	0.0436
Splenectomy	2.30 (1.28–4.12)	0.0081	1.49 (173–3.01)	0.2770

CI, confidence interval; DSA, donor-specific antibodies; HARDN, hand-assisted donor nephrectomy; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; MZ, mizoribine; PRDN, pure retroperitoneoscopic live donor nephrectomy; TIT, total ischemia time; WIT, warm ischemia time

independent prognostic factor for acute rejection and graft survival. These findings suggest that the PRDN procedure appears to be less invasive for the donor and provides a better outcome for the recipient in comparison to the HARDN procedure.

There have been several reports that have implied the following; bleeding is the most common reason for conversion to open surgery [15], which can be difficult to manage using laparoscopic instruments alone; when hand-assisted techniques are used, the surgeon's finger can compress a bleeding vessel immediately, thus, hand-assistance preserving the tactile sense during the procedure increases the safety [16]. Our experience was different; blunt manual dissection in the HARDN procedure caused much more serous discharge and bleeding. Putting a hand into retroperitoneal space with a narrow working space makes it difficult to dissect freely and worsens the operative view, which sometimes forces the operator to do a blind manipulation with only tactile sense. As a result, increased estimated blood loss and time after procurement for hemostasis are required for the HARDN procedure compared to the PRDN procedure. Although more open conversions were performed in the HARDN group than the PRDN group, this cannot be determined unconditionally because it highly depends on the operator's discretion. Furthermore, donor complications appeared to be comparable between both groups.

Recipient serum creatinine levels at POD 1–6 and the incidence of SGF in the HARDN group were significantly higher than in the PRDN group. SGF represents part of the spectrum of graft injury [17], and it is associated with ischemia time [18] and the deleterious effect of CO_2 pneumoperitoneum on the renal blood flow and function [19]. Experimental studies indicate that the elevated intraabdominal pressure associated with the CO_2 pneumoperitoneum can decrease the renal blood flow [20]. Therefore, manipulation with a hand-assisted procedure during the operation may incur mechanical stress on the graft and cause depletion of blood flow. Although the impairment of the early renal allograft function is not a life-threatening complication because dialysis is available, the initial quality of the allograft function can have an adverse impact on the long-term graft survival particularly when combined with acute rejection [21]. Renal allograft rejection is initiated by the response to injury sustained during the transplant process [22]. Graft injury due to a longer ischemia time induces not only cellular rejection but also humoral responsiveness to HLA antigens on the

Table 5 Risk factors against cumulative death-censored graft survival

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Donors				
Age (years)	1.02 (0.99–1.04)	0.0978	1.02 (0.99–1.04)	0.0905
Men	0.49 (0.51–1.19)	0.2648		
Pretransplant body mass index (kg/m^2)	1.00 (0.93–1.07)	0.9658		
Left nephrectomy	0.70 (0.33–1.79)	0.4180		
HARDN versus PRDN	1.41 (0.94–2.08)	0.0938	1.69 (1.09–2.63)	0.0193
Recipients				
Age (years)	1.00 (0.99–1.01)	0.8137		
Men	1.17 (0.78–1.78)	0.4585		
Duration of dialysis (> 23 months)	0.96 (0.65–1.41)	0.8211		
HLA mismatches	1.12 (0.98–1.28)	0.4086		
Kidney transplant history	3.18 (1.73–5.40)	0.0005	2.89 (1.53–5.08)	0.0017
ABO-incompatibility	1.65 (1.09–2.46)	0.0153	1.48 (0.97–2.25)	0.0712
Preoperative DSA	1.57 (1.01–2.39)	0.0451	1.43 (0.88–2.26)	0.1418
Induction of immunosuppression				
Tacrolimus/cyclosporine A	1.41 (0.67–3.63)	0.3928		
MZ/MMF	1.38 (0.44–8.38)	0.6331		
Basiliximab	1.86 (0.92–4.45)	0.0896	1.47 (0.71–3.57)	0.3180
Rituximab	1.18 (0.79–1.75)	0.4091		
Splenectomy	1.78 (0.83–3.37)	0.1280		

CI, confidence interval; DSA, donor-specific antibodies; HARDN, hand-assisted donor nephrectomy; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; MZ, mizoribine; PRDN, pure retroperitoneoscopic live donor nephrectomy

kidney [23]. Relative hazards for both T-cell- and antibody-mediated acute rejection were reported to be similarly elevated after DGF [24]. Lee et al. suggested that SGF in the early post-transplant period is immunologically active and should be considered as one of the risk factors when determining long-term graft survival in living donor kidney transplantation [9]. The incidence of acute rejection induced by graft injury rapidly increased within 3 months and reached a steady state by 1 year after transplantation [17]. It has been reported that TIT is closely associated with SGF/acute rejection [18]; however, our data showed the HARDN procedure is a more potent independent risk factor for acute rejection. In this study, the donor serum CRP level at POD1 was closely associated with the incidence of acute rejection of recipient (OR, 1.04; 95% CI = 1.01–1.07; $P = 0.0064$). This fact may suggest that a less invasive technique for the donor results in reduced graft injury during the operative period.

Donors who underwent PRDN showed a less marked systemic stress response compared to donors after the HARDN procedure as far as CRP is concerned. Animal studies also suggested that the intensity of the acute phase reaction is directly related to the method of the surgical approach [25, 26]. Moreover, graft extraction by Pfannenstiel incision as we do, which involves muscle-splitting incisions, is less painful [27, 28] compared with muscle-cutting incisions. Pfannenstiel incision is also reported to result in a shorter postoperative stay than midline incision in gynecological surgery [29, 30]. In addition, the reduced estimated blood loss resulted in a shorter postoperative stay for donors in the PRDN group than those in the HARDN group. The postoperative stay in our study is longer than that reported in a previous study in the USA [31]. However, as medical treatment is basically free in Japan, many patients prefer to stay in hospital until they feel that they have completely recovered. The average hospital stay after open donor nephrectomy at our institution is about 9 days (data not shown). This duration of postoperative hospitalization is similar to that reported in Sweden, where the mean postoperative hospital stay was 6.8 (4–9) days for the HARDN group [16]. Recently, it has been suggested that there are higher rates of ileus, readmission, and hernia after laparoscopic donor nephrectomy, which can be mitigated by using a retroperitoneal approach via Pfannenstiel incision due to the noninvasive approach to the intraperitoneal organ [32]. Our purely retroperitoneoscopic technique appears to be one of the most established minimally invasive surgical procedures in living donor kidney transplant donors and is also acceptable for living donor kidney recipients.

The present study has several limitations. First, the fact all PRDN procedures were performed at Tokyo Women's

Medical University and that all HARDN procedures were performed at Kyushu University introduces a potentially large bias. Although the two groups are distinguished by different geographical demographics and different surgical teams, there is a uniform immunosuppressant/graft biopsy protocol and a limited number of surgeons. Levene's test for equality of variances showed that the operation date significantly differed between the HARDN and PRDN groups ($P < 0.0001$). Although the cases in which both procedures were performed occurred over an identical time period, the median operation date in the HARDN group (median: 2012/12/1; interquartile range 2009/9/9–2013/8/30) was significantly later than that in the PRDN group (median 2010/9/15; interquartile range 2007/7/12–2013/4/24). The case volumes in the PRDN and HARDN groups were median: 72.5 (range 54–91) and 53 (14–101) cases/year, respectively. Additionally, not all the surgeons went through the same training. In the HARDN group, the procedures were performed by two surgeons (who each performed 96 and 538 cases, respectively) and no trainees. In the PRDN group, the procedures were performed by three surgeons (who each performed 324, 151, and 113 cases, respectively) and six trainees (who each performed 103, 64, 40, 53, 23, and three cases, respectively). One surgeon in the HARDN group switched from the hand-assisted transperitoneal approach to the retroperitoneoscopic technique after 2 years. Four trainees were in their learning curve during the study period, which affected the operation time, but not estimated blood loss. Although in the PRDN group, the procedure was performed not only by more surgeons, but also by six trainees, and the procedures were performed earlier than in the HARDN group, our study suggests that the PRDN procedure may be less invasive for donors, as it results in reduced blood loss, lower postoperative serum CRP levels, and a shorter postoperative stay than the HARDN procedure. This might suggest that the PRDN procedure is associated with superior safety and training compared with the HARDN procedure, as the tactile sense required during the HARDN procedure cannot be easily taught. Second, it was a retrospective, observational cohort study. The retrospective nature of the study has also limited the nature of the data available and may have affected its quality and rigor. Nevertheless, despite these limitations, our study is the first large-volume, multicenter study to compare the PRDN and HARDN procedures over an identical time period. Thus, the risk of influence from changes or differences in the institutions would be minimal.

In conclusion, our study suggests that the PRDN procedure appears to be less invasive for donors as it results in reduced blood loss, lower postoperative serum CRP levels, and a shorter postoperative stay than the HARDN procedure. Additionally, the PRDN procedure provides a better outcome for recipients with a lower incidence of acute rejection and better graft survival compared to the HARDN procedure.

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Compliance with ethical standards

Disclosures Hiroshi Noguchi, Yoichi Kakuta, Masayoshi Okumi, Kazuya Omoto, Yasuhiro Okabe, Hideki Ishida, Masafumi Nakamura, and Kazunari Tanabe have no conflicts of interest or financial ties to disclose.

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