Should kidney volume be used as an indicator of surgical occasion for patients with autosomal dominant polycystic kidney disease?

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Abstract
To investigate the best surgical occasion of laparoscopic cyst decortications (LCDs) in patients with autosomal dominant polycystic kidney disease (ADPKD), in accordance with the renal volume (RV). We retrospectively analyzed 135 (65 male and 70 female) patients with ADPKD who underwent LCD between June 2011 and October 2015. Patients were divided into 4 groups according to the volume of the operated kidney measured from computed tomography scans: group A (28 patients, RV < 500 mL), group B (63 patients, RV = 500–1000 mL), group C (30 patients, RV = 1000–1500 mL), and group D (14 patients, RV > 1500 mL). We studied postoperative indicators at least 1-year follow-up. For each RV group, therapeutic responses of LCD in these patients with ADPKD were assessed by improvement of clinical parameters and manifestations. A significant glomerular filtration rate (GFR) improvement was found in RV group B (31.8 ± 11.1 mL/min; final GFR 36.9 ± 12.7 mL/min; \( P < 0.01 \)), and RV group C (21.1 ± 8.7 mL/min; final GFR 27.4 ± 9.2 mL/min; \( P < 0.01 \)). RV group C had much higher GFR improvements than did RV group B (\( P < 0.01 \)). In addition, refractory pain in patients of RV groups B, C, and D was much relieved by LCD treatment. Compared with other RV groups, blood pressures in patients with ADPKD of RV group D were also improved (\( P < 0.01 \)). Our study indicates that RV could be used to evaluate LCD clinical outcomes in patients with ADPKD. The results of LCD for patients with ADPKD with RV between 500 and 1500 mL were encouraging, especially with regards to renal function improvement and pain relief. Therefore, RV may become a useful marker to predict the timing of LCD surgery in patients with ADPKD.

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease, BP = blood pressure, GFR = glomerular filtration rate, HTKV = height-adjusted TKV, LCD = laparoscopic cyst decortication, RPR = relative pain relief, RV = renal volume, TKV = total kidney volume.

Keywords: autosomal dominant polycystic kidney disease, decortication, laparoscopy, renal volume

1. Introduction
Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease affecting all ethnic groups worldwide with an incidence of 1:500 to 1000. Renal cysts grow exponentially in ADPKD.[1,2] Laparoscopic cyst decortication (LCD) has been widely applied in patients with ADPKD, which reduces renal mass, decreases hydrostatic pressure in cysts, diminishes pain, is beneficial for blood pressure (BP) management, and postpones disease progression into end-stage renal disease (ESRD).[3] However, controversy remains over the timing of LCD surgery in these patients with ADPKD. Some studies indicated that the LCD could be carried out when the single cyst is larger than 4 cm in diameter. LCD could also be considered when hematuria flank pain occurred.[4] Furthermore, a study suggested that ADPKD should be treated with LCD as early as possible[5] because patients with giant kidney volume would not benefit from LCD treatment.[6] Although there is still no widely accepted indication for LCD in ADPKD treatment, several studies have shown that renal volume (RV) is significantly associated with the clinical outcomes of patients with ADPKD.[2,6,10] However, to our knowledge, no reports have demonstrated whether RV could be used to evaluate LCD clinical outcome in these patients. In this study, we retrospectively enrolled patients with ADPKD who have received LCD treatment in our hospital since 2007. By analyzing preoperative and postoperative RV, hypertension, flank pain, and renal functions (glomerular filtration rate, GFR), we determined whether RV is a potential marker for LCD treatment in patients with ADPKD and which RV stage of ADPKD is appropriate to use LCD treatment.

2. Research design and study conduct
Between June 2013 and January 2016, 163 patients with ADPKD were admitted to our hospital and 28 patients were excluded (23 patients chose conservative therapy and 5 patients lacked 12 months follow-up data after surgery). In total, 135 cases of
enrolled patients (65 male and 70 female) underwent unilateral LCD. Intraoperative observed indicators, including operative duration (OD), bleeding volume (BV), blood transfusion rate (BTR), days of postoperative hospitalization (DPH), and postoperative complications were recorded and compared. All these patients were followed-up postoperatively for at least 1 year and clinical data were recollected at 1 year after surgery, including GFR, BP, and pain levels. Patients were divided into 4 groups according to the volume of the operated kidney measured from computed tomography (CT) scans: group A (28 patients, RV < 300 mL), group B (63 patients, RV = 300–1000 mL), group C (30 patients, RV = 1000–1500 mL), and group D (14 patients, RV > 1500 mL). Table 1 summarizes patients’ characteristics.

### 3. Measurement and definitions

#### 3.1. Criterion for LCD surgery

Patients diagnosed with ADPKD with a single cyst larger than 4 cm in diameter and with hypertension, hematuria, cyst infection, or refractory pain will be recommended to receive a single LCD surgery. Patients with severe kidney pain or unilateral enlarged RV were eligible for surgery.

#### 3.2. Surgical procedure

All 135 cases underwent laparoscopic unilateral decortication of polycystic kidney by intraperitoneal route. Patients lay on their healthy side at a 20° incline and general anesthesia was achieved via tracheal intubation. After pneumoperitoneum was established below the connection of the costal margin and the midclavicular line, we used a 10-mm puncture needle to successfully puncture parallel to the umbilical parasternal line and then below the costal margin anterior axillary line to establish pneumoperitoneum with a 5-mm puncture. A longitudinal incision was made on retroperitoneum along with lateral sulci with ultrasonic scalpel to fully open renal fascia and free the kidney. Cysts with a large volume and high tension that were visible on the kidney surface were prioritized for excision via cyst wall resection and other visible cysts were subsequently excised. Laparoscopic ultrasound imaging was used to guide drainage of the grossly undetectable cysts.

#### 3.3. Intraoperative observed indicators

Indicators included OD, BV, BTR, DPH (Table 2), and postoperative complications (such as urine leakage, intestinal adhesion and obstruction, retroperitoneal hematoma; Table 3).

#### 3.4. Renal function analyses

Renal function was evaluated by GFR (renal dynamic Tc99 scintigraphy). All data were collected preoperatively, postoperatively at the 12th month and each follow-up visit (Table 4).

#### 3.5. Blood pressure control

The effect of LCD on BP control was evaluated by use of the antihypertensive therapeutic index (ATI), measured with the

### Table 1

Characteristics of ADPKD patients of different groups.

| Characteristic                        | Group A | Group B | Group C | Group D |
|--------------------------------------|---------|---------|---------|---------|
| Age                                  | 45.4±7.3 | 47.3±9.8 | 46.1±5.8 | 47.5±7.5 |
| Sex                                  |         |         |         |         |
| Male                                 | 13      | 26      | 17      | 9       |
| Female                               | 15      | 37      | 13      | 5       |
| Chronic kidney disease               |         |         |         |         |
| No., %                               |         |         |         |         |
| 1                                    | 14 (60.0) | 22 (34.9) | 3 (10) | 1 (7.1) |
| 2                                    | 7 (25.0) | 21 (33.3) | 4 (13.3) | 2 (14.3) |
| 3                                    | 4 (14.3) | 19 (30.2) | 17 (56.7) | 6 (42.9) |
| 4                                    | 3 (10.7) | 1 (23.6) | 4 (13.3) | 3 (21.4) |
| 5                                    | 0 (0) | 0 (1.6) | 2 (6.7) | 2 (14.3) |
| Serum creatinine, μmol/L             | 98.2±27.1 | 103.5±56.0 | 225.9±117.8 | 176.7±46.7 |
| GFR, mL/min/1.73 m²                   | 35.5±13.7 | 31.8±11.1 | 21.1±8.7 | 18.2±9.5 |
| Blood pressure (MAP mmHg)            | 104.0±9.7 | 110.1±13.3 | 118.7±13.2 | 116.2±16.6 |
| Hypertension no. (%) antihypertensive treatment | 16 (57.1) | 48 (76.2) | 26 (86.7) | 10 (71.4) |
| Operated kidney volume, mL           | 420.2±87.8 | 761.6±131.6 | 1221.4±117.9 | 2194.4±572 |

GFR = glomerular filtration rate, MAP = mean arterial pressure.

### Table 2

The comparison of operative data between patients in 4 groups.

| Group | Operative duration, min | Bleeding volume, mL | Blood transfusion rate, % | Days of postoperative hospitalization, d |
|-------|-------------------------|---------------------|----------------------------|-----------------------------------------|
| A     | 72.3±5.2                | 35.0±7.2            | 0.3±0.7                    | 3.5±0.7                                 |
| B     | 77.3±6.2                | 39.0±8.2            | 0.3±0.8                    | 3.8±0.8                                 |
| C     | 102.3±9.2               | 255.0±35.8          | 13.3                       | 6.5±1.1                                 |
| D     | 136.3±9.8               | 340.0±27.2          | 64.3                       | 8.5±1.3                                 |

No significant differences were observed in operative duration, bleeding volume, blood transfusion rate, days of postoperative hospitalization between groups A and B (P > 0.05), while significant differences were observed in these parameters between groups A and C (P < 0.05), groups A and D (P < 0.05), groups B and C (P < 0.05), groups B and D (P < 0.05), and groups C and D (P < 0.05), respectively.
formula \(\text{[dose of BP medication 1/maximum permissible dose 1]} + \text{[dose of BP medication 2/maximum permissible dose 2]} + \text{etc)} \times 10.1^{10}\) The ATI was calculated preoperatively and at each follow-up (Table 5).

3.6. Pain control
Pain assessment was based on a telephone or interview questionnaire. Pain relief was assessed using a pain analog scale; Pain assessment was based on a telephone or interview questionnaire.

3.7. Renal volume calculation
Length, width, and thickness of both kidneys of the patients with CT before surgery were measured by 2 surgeons independently and the mean value was calculated. The improved elliptic volume formula was used to calculate RV. RV (\(\mu \text{L}\)) = \((4/3)\pi \times \text{(width}/4 + \text{thickness}/4)^2 \times \text{(length}/2).\)\(^{71}\)

3.8. Statistical analyses
SPSS 17.0 software, IBM, Armonk, NY was used to perform the Student \(t\) test, Fisher exact test, and \(\chi^2\) test when comparing differences in means and proportions, respectively. The \(\chi^2\) test or Fisher exact test was used for categorical variables and the Student \(t\) test was used for continuous variables. All tests were 2-tailed and were defined as significant for \(P<0.05\).

4. Results
4.1. Operative data
A total of 135 procedures in 65 men and 70 women were performed. There were no perioperative deaths. Detailed intraoperative data were showed in Table 2. The ODs in groups A to D were 58 to 93 minutes (72.3 \(\pm\) 5.2 minutes), 63 to 102 minutes (77.3 \(\pm\) 6.2 minutes), 93 to 135 minutes (102.3 \(\pm\) 9.2 minutes), and 102 to 175 minutes (136.3 \(\pm\) 9.8 minutes), respectively. BV in groups A to D were 15 to 65 mL (35.0 \(\pm\) 7.2 mL), 25 to 75 mL (39.0 \(\pm\) 8.2 mL), 150 to 620 mL (255.0 \(\pm\) 35.8 mL), and 230 to 850 mL (340 \(\pm\) 27.2 mL), respectively. No patient received a blood transfusion in groups A and B, meanwhile the average postoperative GRF of patients in group D even seems worse than in other groups (\(P<0.05\)).

4.2. Postoperative complications
Postoperative complications mainly included urine leakage (B: 2/63, C: 2/30, D: 2/14), abdominal infection (A: 1/28, B: 1/63, C: 2/30, D: 1/14), ileus (B: 1/63, D: 1/14), and intestinal injury (D: 1/14). No significant differences of ATI (antihypertensive therapeutic index) were observed in group A, B, and C (\(P>0.05\)), when significant decline existed in group D (\(P<0.01\)).

4.3. Renal function outcomes
At the 12th month of follow-up, compared with preoperative data, the GFR of patients in groups B and C increased significantly (\(P<0.05\); Table 4). Moreover, the GFR increase in group C was statistically greater than that of group B (\(P<0.01\)). Meanwhile, there was no statistical significance in GFR at 12 months after operation, patients in groups B, C, and D obtained substantial pain relief, but there were no significant differences among these 3 groups (\(P>0.05\)). RPR = relative pain relief.

### Table 3
The comparison of postoperative complications in 4 groups.

| Group | Cases | Urine leakage | Abdominal infection | Ileus | Intestinal injury | No./total, % |
|-------|-------|---------------|---------------------|-------|------------------|--------------|
| A     | 28    | 0             | 1                   | 0     | 0                | 1/28 (3.6)   |
| B     | 63    | 2             | 2                   | 0     | 0                | 4/63 (6.3)   |
| C     | 30    | 2             | 1                   | 0     | 0                | 2/30 (6.7)   |
| D     | 14    | 2             | 2                   | 0     | 1                | 1/14 (7.1)   |

\(P<0.05\) vs group D. The total postoperative complications rate in group D was significantly higher than in other groups (\(P<0.05\)).

### Table 4
The comparison of GFR preoperatively and postoperatively in 4 groups.

| Group | Cases | The average GFR preoperatively, \(\text{mL/min}\) | The average GFR 12 months postoperatively, \(\text{mL/min}\) | \(P\) |
|-------|-------|-----------------------------------------------|--------------------------------------------------|------|
| A     | 28    | 35.5 \(\pm\) 13.7 | 36.7 \(\pm\) 12.9 | >0.05 |
| B     | 63    | 31.8 \(\pm\) 11.1 | 36.9 \(\pm\) 12.7 | <0.05 |
| C     | 30    | 21.1 \(\pm\) 8.7 | 24.4 \(\pm\) 9.2  | <0.01 |
| D     | 14    | 18.2 \(\pm\) 8.8 | 15.8 \(\pm\) 9.6  | >0.05 |

At the 12th month of following up, compared to the preoperative data, the average GFR of patients in group B (\(P<0.05\)) and group C (\(P<0.01\)) increased significantly. No statistical significance changes was found in group A, meanwhile the average postoperative GFR of patients in group D even seems like worse than before.

### Table 5
The comparison of hypertension preoperatively and postoperatively in 4 groups.

| Group | Cases | ATI Preoperatively | ATI 12 months postoperatively | \(P\) |
|-------|-------|--------------------|-------------------------------|------|
| A     | 28    | 0.36 (0.2–1.10)    | 0.27 (0.18–1)                | >0.05|
| B     | 63    | 2.64 (0.76–0.4)    | 2.44 (0.74–0.4)              | >0.05|
| C     | 30    | 9.54 (0.21–3)      | 9.14 (0.20–6)                | >0.05|
| D     | 14    | 11.21 (3.0–25.43)  | 9.23 (3.0–20.0)              | <0.01|

No significant differences of ATI (antihypertensive therapeutic index) were observed in group A, B, and C (\(P>0.05\)), when significant decline existed in group D (\(P<0.01\)).

### Table 6
The pain control effect in 4 groups.

| Group | Cases | Number of patients obtained RPR >50% at 6 months postoperatively/number of patients with pain before operation | Number of patients obtained RPR <50% at 12 months postoperatively/number of patients with pain before operation |
|-------|-------|---------------------------------------------------------------|---------------------------------------------------------------|
| A     | 28    | 1/5                                                            | 25                                                             |
| B     | 63    | 26/22                                                         | 27/22                                                         |
| C     | 30    | 20/25                                                         | 22/25                                                         |
| D     | 14    | 13/13                                                         | 12/13                                                         |

At 12 months after operation, patients in groups B, C, and D obtained substantial pain relief, but there were no significant differences among these 3 groups (\(P>0.05\)). RPR = relative pain relief.
changes was found in groups A and D (P > 0.05). Figure 1 illustrates post-LCD trends in GFR of each patient in groups A to D who underwent this procedure.

4.4. Hypertension outcomes

No significant differences of hypertension were observed in groups A to C preoperatively and postoperatively (P > 0.05). Group D was significantly different from groups A to C (P < 0.01; Table 5).

4.5. Pain control outcomes

Following the alleviation of flank pain, significantly increased bloating was seen in groups B, C, and D compared with presurgery (P < 0.01), but there were no significant differences among these 3 groups (P > 0.05; Table 6).

5. Discussion

ADPKD is the most common hereditary renal disease that could progress into ESRD, and there is no radical treatment. Of all patients with ADPKD, at least half will progress to ESRD by age 60 years. In 1911, Rosingh initially reported 3 patients in which cysts were treated with pain relief and renal functional improvement was observed. However, in New England Journal of Medicine in 1957, Bricker and Patton reported 2 patients with mild renal insufficiency preoperatively and both patients had worsening renal function after cyst decortication. Therefore, research into cyst decortication for ADPKD was abandoned for nearly 20 years. Until, in the 1980s, Ye et al reported open surgical cyst decortication for ADPKD again. They analyzed 96 patients with ADPKD; 91% and 77% patients acquired pain relief in 6 months and 5 years after cyst decortication, respectively. Most importantly, no deterioration in renal function was observed postoperatively. Subsequently, research interest in surgical cyst decortication for ADPKD increased. In 1996, Elashry et al initially reported 5 LCD procedures in ADPKD. In 2012, Haseebuddin et al examined the long-term impact of LCD on renal function, hypertension, and pain control in patients with ADPKD, at a mean follow-up of 10.9 years, and noted that a cautious approach with LCD should be taken in patients with poor preoperative renal function. At this time, there were still some controversies in LCD for ADPKD, for example, regarding the most appropriate indicator for the surgery of ADPKD, severe back pain, uncontrollable hypertension, hematuria, recurrent infections, or CKD stage based on the National Kidney Foundation staging system?

The RV could be a marker of increasing cyst size. In recent years, compared with clinical symptoms or imaging results of B-scan ultrasonography and other techniques, some studies reported that RV is the most sensitive indicator of polycystic kidney disease progression, especially in the early progression prediction. In addition, in 2002, Fick-Brosnahan et al conducted the first sequential quantitative study of total kidney volumes (TKVs) in adults with ADPKD. They followed 229 patients over a mean interval of 7.8 years and their results indicated that there is a significant correlation between increased total RV and declined GFR. In 2006, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease Group found that kidney enlargement resulting from the expansion of cysts in patients with ADPKD is continuous and quantifiable and is associated with the decline of renal function. Higher rates of kidney enlargement are associated with a more rapid decrease in renal function. A subsequent study demonstrated a significant relationship between the change in renal function and the change in RV in a Japanese patient with ADPKD without renal insufficiency. This study concluded that volume measurements can be used as useful markers for disease progression in Japanese patients with ADPKD, and other scholars found that baseline height-adjusted TKV (htTKV) > 600 cm³/m predicted the risk of developing renal insufficiency in patients with ADPKD at high risk for renal disease progression within 8 years of follow-up, thus qualifying htTKV as a prognostic biomarker in ADPKD.

Therefore, we speculated that RV could be an operative indication of decortication for ADPKD. To our knowledge, this is the first study investigating RV as an indicator for LCD surgery of ADPKD. When the RV was <500 mL, the pressure on the renal parenchyma was maintained in a low level, so renal function was not significantly impaired with a normal GFR. Therefore, LCD procedure could not improve GFR level. In this study, patients in group A did not benefit from LCD. No significant differences of AT1 and RPR were observed in group A preoperatively and postoperatively. When the RV increased to 500 to 1300 mL, the kidney started to decompensate with a rapid decline GFR. At the same time, the morbidity of complications, such as hypertension, abdominal compression, pain, and macroscopic hematuria, significantly increased along with increasing RV. For patients in this period of time, a procedure could be performed to remove the cysts, which would relieve pressure on renal parenchyma, improve renal blood supply, maximize the recovery of renal function, postpone disease progression, and control the clinical
symptoms. In this study, the average GFR level of groups B and C increased at 1 year after LCD, similar results were reported by Fryczkowski et al.[23] but no improvement in mean ATI was noted. Due to serve kidney injury in bilateral procedure of renal cyst decortication, the procedures of each side could be performed separately, but this would delay the treatment and lead to deterioration. If the RV was >1500 mL, the kidney would progress into a state of decompensation ability with about a 10% GFR decrease of normal levels, and more serious complications would occur. For patients in this period, the LCD could not improve the renal function significantly, although it might alleviate some symptoms, including abdominal compression, pain, and other complications. In our experience, the renal function of patients with ADPKD would not be improved by LCD when the RV is >1500 mL; moreover, the transfusion rate and postoperative complications rate significantly increased in those patients.

All the patients in our study only received unilateral surgery, so the benefit of BP control was limited. Although we assumed that a bilateral procedure would improve BP control more significantly, which warrants further study.

In conclusion, we believe that it essential that a sensitive marker is found to evaluate the progression of polycystic kidney disease in order to guide clinical treatment and surgical indication. Previous studies have shown that both the conventionally adopted serum creatinine concentration and GFR were not as sensitive as expected at predicting polycystic kidney disease progression, especially in the early stages. Furthermore, GFR measurement is difficult to popularize due to instruments and medication. Our results indicate that RV is a more sensitive indicator to reflect polycystic kidney disease progression. Advantages of RV test include ease, low cost, and noninvasive. Therefore, RV could play a role in the determination of surgical indication and provide some useful information about the procedure outcome.

6. Conclusion
As an LCD operative indicator of polycystic kidney, RV was efficient and feasible. Besides, other factors should be considered as the operative indication, which could involve the outcome of surgery. The results of LCD for patients with ADPKD with a RV between 500 and 1500 mL were encouraging, especially in renal function improvement and pain relief. As a retrospective cohort study, there were still some limitations to our study, so further study with randomized prospective studies is warranted, with more samples and long-term follow-up to confirm the conclusion.

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Author contributions
Xiang Yu-zhu (XY), Qing Tai-guo (QT) and Jin Xun-bo (JX) participated in the patient selection and surgical preparation. Li Bin participated in the data collection and following up management. Yu Jiang carried out the data interpretation, analyses and manuscript writing. Xiong Hui participated in the design of the study and surgery of all patients. All authors read and approved the final manuscript.

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