

## Laparoendoscopic Single-site Adrenalectomy versus Conventional Laparoscopic Adrenalectomy: An Updated Meta Analysis

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**Purpose:** Previous meta-analyses that compared the outcome of laparoendoscopic single-site adrenalectomy (LESSA) and conventional laparoscopic adrenalectomy (CLA) have not shown consistent results. The aim of this meta-analysis was to reassess current evidence regarding the efficacy and safety of LESSA versus CLA.

**Materials and Methods:** A literature search of PubMed, Embase, Medline, and the Cochrane Library was performed to identify eligible articles up until September 2015. Quantitative variables were calculated using the weighted mean differences (WMDs), and qualitative variables were pooled using odds ratios (ORs).

**Results:** Ten retrospective studies, including a total of 704 cases, were identified. Patients in the LESSA group benefitted from shorter length of hospital stay (95% confidence interval [CI]: -1.27 to -0.36, WMD: -0.81,  $P < .001$ ) and better postoperative pain scores (95% CI: -1.51 to -0.99, WMD: 1.25,  $P < .001$ ). There was no significant difference between the two techniques in operative time, estimated blood loss, resumption of oral intake, dose of analgesic required, perioperative complications, conversion, transfusion, or pain medications required.

**Conclusion:** Based on current evidence, LESSA appear to be a safe and feasible alternative to CLA with a shorter length of hospital stay and lower postoperative pain scores in certain patients. We await high-quality, double-blind randomized clinical trials with long-term follow-up to confirm and update the findings of this analysis; future studies should focus on failure of technique, cosmesis, and cost.

**Keywords:** adrenal glands; surgery; adrenalectomy; methods; laparoscopy; treatment outcome; minimally invasive surgical procedures.

### INTRODUCTION

With the advent of laparoscopic surgery in the early 1980s, minimally invasive surgery has continued to evolve. Since Gagner first reported laparoscopic adrenalectomy (LA) in 1992,<sup>(1)</sup> laparoscopic surgery for benign adrenal tumors has become the gold standard for treatment.<sup>(2,3)</sup> Several studies have shown its advantages compared with open adrenalectomy, such as decreased complications, a shorter postoperative length of hospital stay, and reduced costs.<sup>(4-7)</sup> However, the ‘conventional’ laparoscopic approach requires three or four widely spaced access ports, and remains highly invasive. Recently, with the development of laparoscopic techniques and instrumentation, as well as

surgical experience, a minimally invasive surgery – so-called single-incision laparoscopic surgery (SILS) – has gained popularity as a method of achieving a “scarless” abdomen through a single incision. In 2005, Hirano and colleagues reported the first experience of a single-incision, retroperitoneoscopic, single-port adrenalectomy.<sup>(8)</sup> Subsequently, laparoendoscopic single-site adrenalectomy (LESSA) has been shown to be feasible for the treatment of benign adrenal tumors.<sup>(9-11)</sup> To date, many studies have been conducted to determine the advantages of surgical outcomes of LESSA versus LA.<sup>(12-20)</sup> Two meta-analyses comparing conventional laparoscopic adrenalectomy (CLA) and LESSA were reported by Hu and colleagues and Wang and colleagues. in 2012,<sup>(21,22)</sup>

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which summarized and reviewed 171 cases of LESSA compared with 272 cases of CLA<sup>(12-20)</sup> and showed a longer operative time and lower postoperative visual analog pain score in LESSA, and comparable results for complications, time to oral intake resumption, and estimated blood loss between the two groups. More recent publications were not investigated in these previous meta-analyses, which remain controversial.<sup>(23-25)</sup> Thus, there is a need for an updated meta-analysis to reassess the safety and efficacy of the two procedures and to determine whether LESSA is an acceptable alternative to CLA for the treatment of benign adrenal tumors.

## MATERIALS AND METHODS

### Literature Search

A systematic literature search of the Embase, Cochrane, and PubMed databases was performed to identify studies comparing LESSA with CLA (to September 2015). The following medical subject heading (MeSH) terms and words were used in the search, in all possible combinations: ‘laparoscopic,’ ‘single-site,’ ‘single port,’ ‘single incision,’ ‘single access,’ and ‘adrenalectomy.’ A second-level search included a manual search of the reference lists of all the relevant studies, systematic reviews, and previous meta-analyses to identify potentially eligible studies.

### Inclusion and Exclusion Criteria

Titles and abstracts of all identified articles were screened and we included studies that satisfied the following criteria: (1) compared LESSA and CLA, (2) LESSA performed using laparoscopic or retroperitoneoscopic techniques through a mono port or a single large port (the operative technique can be described as “laparoscopic,” “single-port,” “single-incision,” “mono port,” “single large port,” “retroperitoneoscopic,” “conventional laparoscopic,” “3-port laparoscopic” or “4-port laparoscopic”), (3) applied the same approach in the CLA and LESSA group, (4) available in full-text, (5) written in English, and (6) reported at least one of the following outcomes: operative time, length of hospital stay, estimated blood loss (EBL), resumption of oral intake, postoperative pain scores, perioperative complications, conversion, cosmetic satisfaction score, recovery time, convalescence transfusion and pain medication requirement, dose of analgesic required, and interval to return to work/routine activity. If two studies from the same institution were identified, the most recent or most informative was selected (unless they were reports from clearly different periods or data from overlapping patients could be subtracted).

### Outcome Measures

Outcome variables were considered suitable for analysis if they met the following criteria: (1) continuous outcomes reported as means and standard deviations, and (2) identical variables reported by a minimum of two studies. Outcome variables considered most suitable for analysis were as follows: operative time, length of hospital stay, EBL, resumption of oral intake, postoperative pain scores, doses of analgesic required, perioperative complications, conversion, transfusion, and pain medication required. If sufficient data were available, perioperative complications were subdivided into postoperative and intraoperative complications. If units used for the end points were not uniform, we attempted to convert them for ease of analysis.

### Data Extraction and Quality Assessment

Data were extracted from each study by two independent reviewers (Shike Wu and Hao Lai); agreement was achieved through discussion when necessary. We did not use any particular method for estimating standard deviations. The following data were extracted: first author, study period, study design, characteristics of study population, indications for surgery, number of subjects operated on with each technique, and perioperative outcomes. All studies were retrospective comparative studies and none was a randomized clinical trial (RCT). According to The Oxford 2011 Levels of Evidence,<sup>(26)</sup> the Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of studies.<sup>(27)</sup> This scale contains eight items, categorized into three dimensions, selection, comparability, and outcome. A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories and two stars for comparability. A score of 0–9 (as stars) was allocated to each study: studies with a Newcastle-Ottawa score  $\geq 6$  were considered to be of high quality.

### Statistical Analysis

Statistical analyses were performed using Stata software (version 12.0; Stata Corp., College Station, TX, USA). For continuous variables, we calculated weighted mean differences (WMDs) with 95% confidence intervals (CIs). For dichotomous variables, we used odds ratios (ORs) and a fixed-effects model. We used the  $\chi^2$  test and the  $I^2$  statistic to assess heterogeneity between studies, with a  $P$  value of  $< .05$  indicating statistical significance and the  $I^2$  statistic  $> 50\%$  was considered to represent significant heterogeneity. A random-effects model was used if there was significant heterogeneity. Sensitivity and subgroup analyses were used to explore potential causes of heterogeneity. Subgroup analyses were performed to examine whether results that com-

**Table 1.** Characteristics of included studies.

| First Author   | Study Design | Study Period | Country | LESSA      | LESS   | CL           | Number   | Age (years)                 | BMI (kg/m <sup>2</sup> )    | LESSA       | CLA         |
|----------------|--------------|--------------|---------|------------|--|--------------|----------|-----------------------------|-----------------------------|-------------|-------------|
|                |              |              |         | Procedures | Device   | Device       |          |                             |                             | LESSA / CLA | LESSA / CLA |
| Jeong, 2009    | RA           | 2001-2009    | Korea   | LESSA      | Umbilicus through a 2-cm incision  | 3 or 4 ports | 9 / 17   | 46.0 / 43.8                 | NA                          | 4 / 5       | 11 / 6      |
| Walz, 2010     | RA           | 2000-2008    | Germany | SARA       | Single-access approach   | 3 ports      | 47 / 47  | 43.3 / 42.2                 | 25.1 ± 3.9 / 25.2 ± 3.9     | 17 / 30     | 17 / 30     |
| Tunca, 2012    | RA           | 2006-2010    | Turkey  | SILA       | Through a 2-cm umbilical incision  | 3 ports      | 22 / 74  | 43.3 ± 10 / 43.4 ± 12.3     | NA                          | 4 / 18      | 29 / 45     |
| Lin, 2012      | RA           | 2006-2011    | Taiwan  | LESSA      | With a 2- to 3-cm skin incision just beneath the tip of the 12th rib                             | 3 or 4 ports | 21 / 28  | 50.7 (34-74) / 51.7 (25-71) | 25.6 / 24.6                 | 12 / 9      | 14 / 14     |
| Wang, 2012     | RA           | 2009-2011    | China   | LESSA      | A 2-3-cm through the umbilicus of 8 patients and a 2-3 cm subcostal incision of 5 patients       | NA           | 13 / 26  | 47.2 ± 9.31 / 43.9 ± 10.27  | 24.9 ± 3.10 / 25.1 ± 4.16   | 8 / 5       | 10 / 16     |
| Shi, 2011      | RA           | 2009         | China   | LESS-ARA   | A 2.5- to 3-cm transverse skin incision made below the lower margin of the 12th rib              | 3 ports      | 19 / 38  | 57.0 / 57.0                 | 29.8 / 29.0                 | 8 / 11      | 21 / 17     |
| Kwak, 2011     | RA           | 2008-2009    | Korea   | LAMP       | At 2 fingerbreadths below the costal margin at the midclavicular line through a 2.5-cm incision. | 3 ports      | 12 / 10  | 51.08 / 43.70               | 24.08 ± 4.01 / 26.17 ± 3.11 | 6 / 6       | 5 / 5       |
| Hirasawa, 2014 | RA           | 2001-2013    | Japan   | LESSA      | Through the umbilicus or the side of the navel to approach the intraperitoneal space             | 3 or 4 ports | 70 / 140 | 51.2 ± 11.5 / 50.9 ± 11.5   | 23.0 ± 3.6 / 23.1 ± 3.6     | NA          | NA          |
| Hora, 2014     | RA           | 2008-2014    | Czech   | LESS AE    | Quadport + in short pararectal incision OR in the subcostal region, an additional 3 mm grasper   | NA           | 15 / 15  | 59.3 ± 13.3 / 60.2 ± 11.9   | 26.9 ± 4.3 / 28.5 ± 2.0     | NA          | NA          |
| Wen, 2013      | RA           | NA           | Taiwan  | LESSRA     | A 3-cm skin incision below the tip of the 12th rib   | 3 ports      | 27 / 54  | 48.79 ± 1.69 / 49.62 ± 2.39 | 24.55 ± 6.37 / 25.20 ± 4.43 | 14 / 13     | 32 / 22     |

**Abbreviations:** RA, retrospective analysis; LESS, laparoendoscopic single-site; CL, conventional laparoscopic; LESSA, laparoendoscopic single-site adrenalectomy; LESSAE or LESS-ARA or LESS RA, laparoendoscopic single-site retroperitoneoscopic adrenalectomy; LAMP, laparoscopic adrenalectomy through mono port; SILA, single-incision laparoscopic adrenalectomy; SARA, single-access retroperitoneoscopic adrenalectomies; CLA, conventional laparoscopic adrenalectomy; BMI, body mass index; M, male; F, female; NA, not available; R, right; L, left. All values are number or mean ± SD or mean.

pared LESSA with CLA varied by different approaches (transperitoneal and retroperitoneal). Publication bias was evaluated by a funnel plot.

## RESULTS

In total, 122 studies were identified by the electronic searches; no further study was identified through other sources. **Figure 1** depicts a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for study inclusion and exclusion. After removing duplicate results, 116 records remained. Of these, on reviewing the titles and abstract, 97 obviously

irrelevant articles were rejected. Thus, 19 relevant articles comparing LESSA and CLA were considered suitable for the pooled analysis. Nine articles (seven with unavailable data and two repeated studies) were excluded by reading the full-text articles.<sup>(19,20,28-34)</sup> Finally, 10 studies were included in the analysis.<sup>(12-18,23-25)</sup> The methodological quality of the included studies was relatively high, with a score of six or seven stars: the assessment of the included studies is shown in **Figure 2**.

### Study and Patient Characteristics

The articles included in the quantitative synthesis were published between 2009 and 2014, with a total of 255

**Table 2.** Histopathological data of the adrenal adenomas.

| First Author  | No. LESSA / CLA | FA      | NFA     | CS     | PH      | HY     | APA     | CSD     | Metastasis | AC    | Myelolipoma | MH    | PCS | Others  |
|---------------|-----------------|---------|---------|--------|---------|--------|---------|---------|------------|-------|-------------|-------|-----|---------|
| Jcong, 2009   | 9 / 17          | NA      | 3 / 6   | 1 / 2  | 5 / 9   | NA     | NA      | NA      | NA         | NA    | NA          | NA    | NA  | 1 / 0   |
| Walz, 2010    | 47 / 47         | NA      | NA      | 6 / 6  | 15 / 15 | NA     | NA      | 20 / 20 | NA         | NA    | NA          | NA    | NA  | 6 / 6   |
| Tunca, 2012   | 22 / 74         | NA      | 3 / 17  | 7 / 18 | 8 / 26  | NA     | NA      | NA      | 0 / 3      | 0 / 3 | NA          | NA    | NA  | 4 / 7   |
| Lin, 2012     | 21 / 28         | 11 / 19 | 7 / 4   | NA     | 3 / 5   | NA     | NA      | NA      | NA         | NA    | NA          | NA    | NA  | NA      |
| Wang, 2012    | 13 / 26         | NA      | 6 / 7   | 2 / 6  | 0 / 3   | 5 / 10 | NA      | NA      | NA         | NA    | NA          | NA    | NA  | NA      |
| Shi, 2011     | 19 / 38         | NA      | 5 / 7   | 4 / 11 | 3 / 5   | 7 / 15 | NA      | NA      | NA         | NA    | NA          | NA    | NA  | NA      |
| Kwak, 2011    | 12 / 10         | 3 / 5   | NA      | 3 / 1  | 2 / 0   | 1 / 4  | NA      | NA      | 0 / 1      | NA    | 1 / 0       | 0 / 1 | NA  | NA      |
| Hirasawa 2014 | 70 / 140        | NA      | NA      | 6 / 36 | 15 / 24 | NA     | 35 / 67 | NA      | NA         | NA    | NA          | NA    | NA  | 14 / 13 |
| Hora, 2014    | 15 / 15         | 10 / 12 | NA      | NA     | 3 / 2   | NA     | NA      | NA      | 2 / 1      | NA    | NA          | NA    | NA  | NA      |
| Wen, 2013     | 27 / 54         | NA      | 11 / 12 | 4 / 7  | 0 / 1   | NA     | NA      | 10 / 30 | 0 / 1      | NA    | NA          | NA    | NA  | 2 / 3   |

**Abbreviations:** No., numbers; FA, functional adenoma; NFA, nonfunctioning adenoma; CS, Cushing's syndrome; APA, aldosterone-producing adenoma; PH, pheochromocytoma; CSD, Conn's syndrome; AC, adrenal cyst; HY, hyperaldosteronism; MH, medullary hyperplasia; PCS, Pre-Cushing's syndrome; NA, not available.

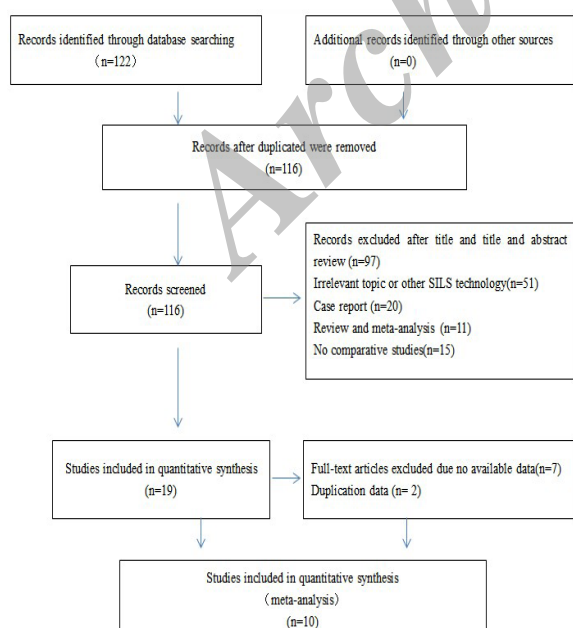
patients treated with LESSA and 449 patients treated with CLA. The sample size of the trials ranged from 9 to 140. Characteristics of the patients are summarized in **Table 1**. For LESSA, a commercially available multi-channel port device was used.<sup>(15-18,24,25)</sup> In one study, a home-made single-port device was inserted at the umbilicus through a 2-cm incision: a single-layered sterile surgical glove was then used.<sup>(13,23)</sup> One study used a single glove or commercially available multi-channel port.<sup>(14)</sup> The umbilicus or subcostal incision represented the most used access site. For CLA, three or four ports were made. Both transperitoneal and retroperitoneal access approaches were reported. Histopathological data of the

adrenal adenomas are summarized in **Table 2**.

### Outcome Measurements

#### Operative time

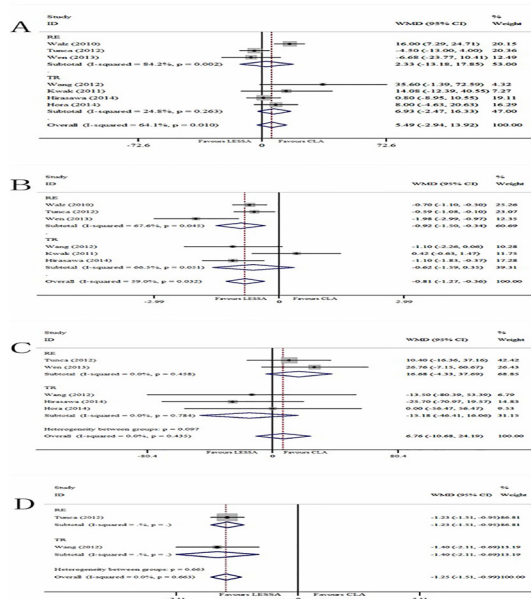
All included studies reported operative time,<sup>(12-18,23-25)</sup> three were not reported as means and standard deviations and were excluded.<sup>(12,14,15)</sup> Subgroup analyses showed no significant difference in the retroperitoneal (RE) group (95% CI: -13.18 to 17.85, WMD: 2.33,  $P = .768$ ) or the transperitoneal (TR) group ( $P = .148$ ). The overall pooled estimates also support this finding between the two groups (95% CI: -2.94 to 13.92, WMD: 5.49,  $P = .202$ ;  $I^2 = 64.1\%$ ,  $P = .010$  for heterogeneity; **Figure 3A**).

**Figure 1.** Flow diagram of the literature search.

|               | Selection                                |   |                           |  | Comparability   | Outcome               |  |                                  |
|---------------|--|---|---------------------------|--|---|-----------------------|--|----------------------------------|
|               | Representativeness of the exposed cohort | Selection of the non exposed cohort cases | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcome to occur | Adequacy of follow up of cohorts |
| Jeong2009     | —  | ★   | ★                         | ★  | ★   | ★                     | —  | ★                                |
| Walz2010      | —  | ★   | ★                         | ★  | ★★  | ★                     | ★  | ★                                |
| Tunca2012     | —  | ★   | ★                         | ★  | ★   | ★                     | ★  | ★                                |
| Lin2012       | —  | ★   | ★                         | ★  | ★   | ★                     | ★  | ★                                |
| Wang2012      | —  | ★   | ★                         | ★  | ★★  | ★                     | —  | ★                                |
| Shi2011       | —  | ★   | ★                         | —  | ★★  | ★                     | ★  | ★                                |
| Kwak2011      | —  | ★   | ★                         | —  | ★★  | ★                     | —  | ★                                |
| Hirasawa 2014 | —  | ★   | ★                         | —  | ★★  | ★                     | ★  | ★                                |
| Hora2014      | —  | ★   | ★                         | ★  | ★★  | ★                     | ★  | ★                                |
| Wen2013       | —  | ★   | ★                         | ★  | ★★  | ★                     | ★  | ★                                |

A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability, the total score ranges from 0 to 9.

**Figure 2.** Quality assessment of included studies with the Newcastle-Ottawa scale.



**Figure 3.** **A)** Forest plot of the comparison of LESSA versus CLA in terms of operative time; **B)** Forest plot of the comparison of LESSA vs. CLA in terms of length of hospital stay; **C)** Forest plot of the comparison of LESSA vs. CLA in terms of estimated blood loss (EBL); **D)** Forest plot of the comparison of LESSA vs. CLA in terms of postoperative pain scores. **Abbreviations:** LESSA, laparoendoscopic single-site adrenalectomy; CLA, conventional laparoscopic adrenalectomy; EBL, estimated blood loss.

### Length of Hospital Stay

Six studies reported the length of hospital stay.<sup>(13,16-18,23,24)</sup> Subgroup analyses showed significant differences in the RE group (95% CI: -1.50 to -0.34, WMD: -0.92,  $P = .002$ ); however, there was no significant difference in the TR group (95% CI: -1.59 to 0.35, WMD: 0.62,  $P = .221$ ). The overall pooled estimates showed significant difference between the two groups (95% CI: -1.27 to -0.36, WMD: -0.81,  $P < .001$ ;  $I^2 = 59.0\%$ ,  $P = .032$  for heterogeneity; **Figure 3B**).

### EBL

Five studies reported EBL.<sup>(16,18,23-25)</sup> Subgroup analyses showed no significant difference in the RE group (95% CI: -4.33 to -37.69, WMD: 16.68,  $P = .120$ ) or the TR group ( $P = .341$ ). The overall pooled estimates also supported this finding between the two groups (95% CI: -10.68 to 24.19, WMD: 6.76,  $P = .448$ ;  $I^2 = 0.0\%$ ,  $P = .435$  for heterogeneity; **Figure 3C**).

### Resumption of Oral Intake

Seven studies reported resumption of oral intake<sup>(12-15,18,23,24)</sup> of which four included standard mean difference values.<sup>(13,18,23,24)</sup> Subgroup analyses showed no significant difference in the RE group (95% CI: -0.05 to 0.05, WMD: -0.00,  $P = .867$ ); however, there was a significant difference in the TR group (95% CI: -0.78 to -0.32, WMD: -0.55,  $P < .001$ ). The overall pooled

estimates showed no significant difference between the two groups (95% CI: -0.47 to 0.12, WMD: -0.17,  $P = .240$ ;  $I^2 = 86.3\%$ ,  $P < .001$  for heterogeneity).

### Postoperative Pain Scores

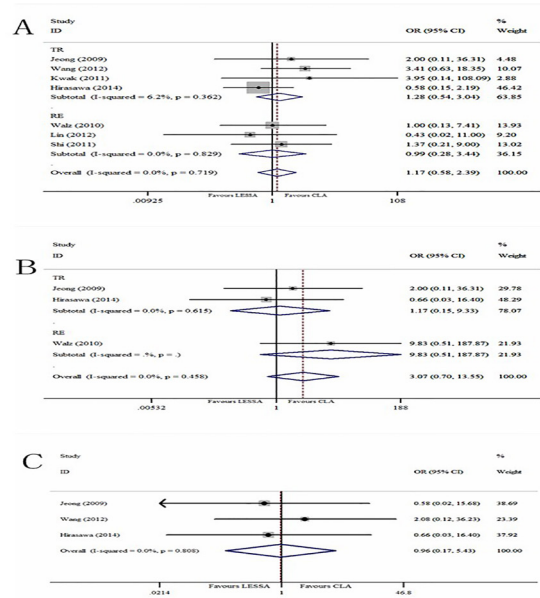
Two studies were available for analysis.<sup>(16,18)</sup> Subgroup analyses showed significant differences in the RE group (95% CI: -1.51 to -0.95, WMD: -1.23,  $P < .001$ ) and the TR group ( $P < .001$ ). The overall pooled estimates also supported this finding between the two groups (95% CI: -1.51 to -0.99, WMD: -1.25,  $P < .001$ ;  $I^2 = 0.0\%$ ,  $P = .663$  for heterogeneity; **Figure 3D**).

### Doses of Analgesic Required

Two studies reported the doses of analgesic required.<sup>(23,24)</sup> Subgroup analyses showed no significant difference in the RE group (95% CI: -0.41 to 0.41, WMD: 0.00,  $P = 1.000$ ) or the TR group ( $P = .098$ ). The overall pooled estimates also supported this finding between the two groups (95% CI: -0.44 to 0.10, WMD: -0.17,  $P = .210$ ;  $I^2 = 14.5\%$ ,  $P = .279$  for heterogeneity).

### Pain Medication Requirement

Three studies including 183 patients reported pain medication requirements.<sup>(15,17,18)</sup> There were 41 patients who needed pain medication (51.90%) in the LESSA group and 57 (54.81%) in the CLA group. Subgroup analyses showed no significant difference in the RE group (95% CI: 0.65 to 2.83, WMD: 1.36,  $P = .414$ ) or the TR group



**Figure 4.** **A)** Forest plot of the comparison of LESSA vs. CLA in terms of perioperative complications; **B)** Forest plot of the comparison of LESSA vs. CLA in terms of conversion; **C)** Forest plot of the comparison of LESSA vs. CLA in terms of transfusion.

**Abbreviations:** LESSA, laparoendoscopic single-site adrenalectomy; CLA, conventional laparoscopic adrenalectomy.

( $P = .801$ ). The overall pooled estimates also supported this finding between the two groups (95% CI: 0.16 to 4.88, OR: 0.87,  $P = .875$ ;  $I^2 = 72.2\%$ ,  $P = .027$  for heterogeneity).

### Perioperative Complications

The incidence of perioperative complication was reported in seven studies.<sup>(12-15,17,18,24)</sup> There were 13 complications (7.34%) in the LESSA group and 22 (6.54%) in the CLA group. Subgroup analyses showed no significant difference in the RE group (95% CI: 0.28 to 3.44, WMD: 0.99,  $P = .985$ ) or the TR ( $P = .578$ ). The overall pooled estimates also supported this finding (95% CI: 0.58 to 2.39, OR: 1.17,  $P = .659$ ;  $I^2 = 0.0\%$ ,  $P = .719$  for heterogeneity; **Figure 4A**).

### Conversion

Three studies including 330 patients reported conversion events.<sup>(12,17,24)</sup> The conversion rate was 3.97% (5/126 patients) for LESSA compared with 0.98% (2/202 patients) for CLA. Subgroup analyses showed no significant difference in the RE group (95% CI: 0.51 to 187.87, WMD: 9.83  $P = .129$ ) or the TR group ( $P = .882$ ). The overall pooled estimates also supported this finding between the two groups (95% CI: 0.70 to 13.55, OR: 3.07,  $P = .139$ ;  $I^2 = 0.0\%$ ,  $P = .458$  for heterogeneity; **Figure 4B**).

### Transfusion

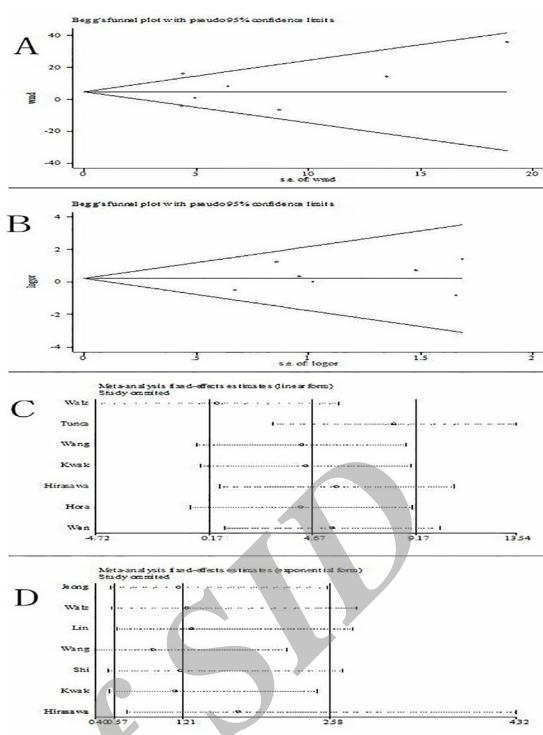
Three studies including 275 patients reported transfusion in the TR group only.<sup>(12,18,24)</sup> There was one (1.09%) transfusion in the LESSA group and three (1.64%) in the CLA group; a pooled analysis showed no significant difference (95% CI: 0.17 to 5.43, OR: 0.96,  $P = .964$ ;  $I^2 = 0.0\%$ ,  $P = .808$  for heterogeneity) between the two groups (**Figure 4C**).

### Risk of Publication Bias

A funnel plot of the studies included in our primary outcome of perioperative complications was prepared to explore publication bias. The scatter-distributed shapes of the funnel plots for operative time and perioperative complications were symmetrical, indicating no evidence of publication bias among the included studies (**Figures 5A and 5B**; other data not shown).

### Sensitivity Analysis

Sensitivity analysis was conducted to assess the effect of study quality. A single study involved in the meta-analysis was deleted each time to reflect the influence of each individual data set on the pooled ORs. The corresponding pooled ORs were essentially unaltered, indicating that our results were statistically sound (**Figures 5C and 5D**; other data not shown).



**Figure 5.** **A)** Funnel plot for operative time; **B)** Funnel plot for perioperative complications; **C)** Sensitivity analysis for operative time; **D)** Sensitivity analysis for perioperative complications.

## DISCUSSION

This meta-analysis of 10 retrospective comparative studies including 704 patients showed that LESSA had similar outcomes to those of CLA, without significant differences in terms of operative time, EBL, doses of analgesic required, perioperative complications, conversion, transfusion, resumption of oral intake, or pain medication requirement. LESSA was also associated with reduced postoperative pain and a shorter length of hospital stay, despite controversies with respect to operative time and length of hospital stay in previous meta-analyses.

Indeed, previous meta-analyses demonstrated a significantly increased operating time for SILS.<sup>(21,22)</sup> Those results were inconsistent with the results of this analysis, which concluded that there was no difference between the two groups. In our meta-analysis, five studies reported a prolonged operating time in the LESSA group,<sup>(13,17,18,24,25)</sup> but two showed the opposite.<sup>(16,23)</sup> A sensitivity analysis of the pooled studies showed a consistent result. However, different sides of surgery and the various designs of ports (transperitoneal and retroperitoneal) may have great impacts on operative time. Only one study reported operative time on different sides,<sup>(25)</sup> so no subgroup analysis on different sides could be conducted. Also, an additional trocar was required

for liver retraction in three studies,<sup>(16,18,25)</sup> which may have increased operative time. In addition, this difference in operative time may be due to the learning curve; unfortunately, only one study explicitly described the previous experience of the operating surgeons,<sup>(24)</sup> so a subgroup analysis could not be performed on this issue. Furthermore, the sample size in each study was different. All these factors may have contributed to heterogeneity and influenced the results. Thus, future RCTs are needed to confirm the finding of this study. Considering the similar operative times, which is a surprising result, confirming a clear learning-curve effect in the LESSA treatment group, and the ability of surgeons in using the new devices for LESSA, will likely reduce the technical difficulties.<sup>(35)</sup>

Postoperative pain is another important endpoint. Less pain was expected in the LESSA group for reduced trocars. However, the size of the fascial incision needed to accommodate the single-incision port may potentially increase pain, although there was no difference in the numbers of patients demanding pain medication and analgesics between the groups. Only two studies provided adequate data on postoperative pain,<sup>(16,18)</sup> providing comparative evidence of limited importance. This observation should be regarded with caution because different or unclear postoperative analgesic protocols between groups may have led to bias in postoperative pain score assessment. Additionally, a lack of evaluator and patient blinding may have influenced the results. The shorter length of hospital stay is an apparent advantage of LESSA over CLA, in contrast to a previous meta-analysis.<sup>(22)</sup> The result is encouraging, because it may reflect faster convalescence and less postoperative pain. In turn, this could decrease hospital costs and may be an important factor for recovery and an earlier return to work. Only one study reported that patients could return to full activities earlier in the LESSA group; more randomized trials are needed to confirm this.<sup>(18)</sup>

The pooled studies showed no difference in EBL between the two groups.<sup>(16,18,23-25)</sup> Four studies reported the resumption of oral intake, which showed no significant difference between the groups, although heterogeneity was observed. A study by Wen and colleagues reported a shorter period before resumption of oral intake in the LESSA group;<sup>(23)</sup> excluding this study from the analysis did not yield different results.

Surgical safety was evaluated in terms of perioperative complications, conversion, and transfusion. The complication rate is broadly considered as a surrogate for surgical competence. LESSA is technically more difficult to perform and may be associated with increased

complication rates. Of the included eight studies, five showed a higher perioperative complication rate in the LESSA group,<sup>(12,13,15,18,25)</sup> although different approaches may have different impacts on perioperative complications. When we divided the surgeries into two approaches, transperitoneal and retroperitoneal, subgroup analyses showed no significant difference between the groups ( $P = .659$ ), similar to the previous meta-analyses.<sup>(21,22)</sup> However, given the different sample sizes in each included study, this result should be viewed with caution; reduced triangulation, fog evacuation, clashing of instruments, and more complex procedures in the LESSA group<sup>(36)</sup> – and the longer operative time – may also increase perioperative complications. The follow-up was insufficient in most of these studies for estimating late complications. Future randomized trials with larger samples and longer-term follow-up are needed to evaluate the rate of complications accurately. Conversion is considered to be a significant factor when counseling patients on the potential risks/benefits of any specific procedure.<sup>(37)</sup> Technological difficulties may also be associated with conversion. The increasing conversion rate has considerably limited the use of LESSA, although in the present study, the conversion rate was found to be similar for both techniques. Bleeding requiring transfusion was reported in three studies; the pooled studies showed no difference in transfusion between the two techniques.<sup>(12,18,24)</sup> Considering the perioperative complications, high-quality and double-blind RCTs with long-term follow-up are required to assess the safety of the new technique.

A previous meta-analysis demonstrated comparable cosmetic satisfaction between the two groups.<sup>(22)</sup> However, a recent study reported higher cosmetic satisfaction among young patients and female patients in the LESSA group.<sup>(31)</sup> Of the included studies, only one reported the outcomes as means and standard deviation,<sup>(18)</sup> so a meta-analysis of cosmetic satisfaction scores was not conducted.

In the included studies, there was no significant difference between the LESSA and CLA groups in terms of basic data such as body mass index (BMI), age, gender, or tumor size, suggesting that our analysis may be more reliable than those of the former studies by reducing the influence of these confounding factors on the results. Nevertheless, our present meta-analysis had several potential limitations. First, all included studies were retrospective analyses and most had a small sample size. Second, a cost analysis to determine whether this new technique is more expensive could not be conducted due to insufficient data from the published re-

ports. Third, heterogeneity was found in operative time, length of hospital stay, resumption of oral intake, and pain medication requirement, which may be attributable to matching criteria, operative techniques, single-port access devices, and different approaches; further studies are required to explore sources of heterogeneity. Finally, the follow-up periods in most reports were insufficient; the studies analyzed here provided relatively short-term findings, so long-term outcomes of LESSA compared with CLA are required to confirm the safety and feasibility of this new technique.

## CONCLUSIONS

In conclusion, based on current evidence, LESSA appear to be a safe and feasible alternative to CLA with a shorter length of hospital stay and reduced postoperative pain scores in certain patients. We await high-quality, double-blind RCTs with longer-term follow-up to confirm and update the findings of this analysis. Future studies should focus particularly on rates of technical failure, cosmesis, and cost.

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Shike Wu, Hao Lai, and Jiangyang Zhao contributed equally to this work and should be considered as co-first authors.

## CONFLICT OF INTEREST

None declared.

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