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Systematic Review / Meta-analysis

Laparoendoscopic single-site adrenalectomy versus multi-port laparoendoscopic adrenalectomy: A systemic review and meta-analysis

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ABSTRACT

Background: To investigate the outcomes of laparoendoscopic single-site adrenalectomy (LESS-A) compared to multi-port laparoendoscopic adrenalectomy (m-LA).

Methods: Studies comparing LESS-A with m-LA were identified from PubMed, Embase, and Cochrane Library before June 2020. Post-operative pain, resumption outcomes, and perioperative outcomes were analyzed. We conducted meta-analyses using the Mantel-Haenszel method with random-effects model. Subset analyses were conducted according to peritoneal and retroperitoneal approaches. A small study effect was illustrated using funnel plots and Egger's test.

Results: One randomized controlled trial (RCT) and nineteen retrospective cohort studies involving 1554 patients were included for analyzed. Pooled analysis showed that LESS-A had significantly lower postoperative pain scores (MD −0.77, 95%CI −1.45 to −0.10) and less pain medication used (RR 0.74, 95%CI 0.60 to 0.91) compared to m-LA. Besides, LESS-A had significantly shorter hospital stays (MD −0.75, 95%CI −1.18 to −0.33), shorter duration of oral intake resumption (MD −0.33, 95%CI −0.60 to −0.06), and better cosmetic satisfaction (SMD 1.15, 95%CI 0.21 to −2.09). As for perioperative outcomes, LESS-A led to significant longer operative time (MD 13.43, 95%CI 4.08 to 22.77). No significant differences were observed in terms of the remaining perioperative outcomes.

Conclusions: LESS-A is associated with less post-operative pain and quicker recovery duration. However, the longer operative time of LESS-A compared with m-LA is a drawback.

1. Introduction

Minimal-invasive surgery has evolved rapidly and has gradually replaced open surgery. Since Gagner et al. [1] reported the first laparoscopic adrenalectomy (LA) in 1992, LA has been the gold standard treatment for adrenal tumors [2,3]. Laparoscopic surgery is a better alternative to open procedure because of its advantages, including reduced surgical trauma, decreased complications and morbidity, shorter recovery period, and increased cost-effectiveness [4–8]. The conventional multiport laparoscopic approach, which requires at least three ports to provide a wide intra-operative view, constitutes an invasive approach. Following the comprehensive progression of laparoscopic experiences, various instruments and techniques have been developed. In 2005, Hirano and colleagues [9] first reported their experience of performing a retroperitoneoscopic adrenalectomy by using a single-port technique, which was demonstrated to be effective and relatively minimally invasive. Since then, laparoendoscopic single-site adrenalectomy (LESS-A) has increasingly gained popularity as a treatment for adrenal lesions [10–13].

In the past few years, numerous comparative studies have investigated whether LESS-A presents considerable advantages over multi-port laparoendoscopic adrenalectomy (m-LA) or can be an alternative

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treatment option [13–35]. Three meta-analyses [36–38] compared the surgical outcomes of LESS-A and m-LA by analyzing approximately 225 cases of LESS-A and 449 cases of m-LA [25–35]. However, the results of the three meta-analyses presented considerable discrepancies in terms of outcomes, including operative time, length of hospital stay, post-operative pain scores, and required analgesic doses. Moreover, these meta-analyses did not include many recent lines of evidence, which remarkably influenced the results [14–24]. To clarify the confusion concerning outcomes, we performed an updated meta-analysis of all available comparative studies to reassess the efficacy, safety, and potential advantages of LESS-A compared with m-LA in the treatment of patients with adrenal tumors.

2. Materials and methods

This was a prospective systematic review that began on February 26, 2020. The study protocol was written beforehand, and the primary design was registered on PROSPERO (CRD42020170633). The research team involved two urologists and a researcher experienced in systematic review and meta-analysis. The two urologists also had experience in conducting systematic reviews and meta-analyses. The authors conducted this study in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [39] and Assessing the methodological quality of systematic reviews (AMSTAR) [40] guidelines for evidence selection, quality assessment, evidence synthesis, and research reporting. PRISMA and AMSTAR checklists (with overall confidence rating) were presented in Supplementary Material Tables S4 and S5, respectively.

2.1. Data source and search

Basic eligibility criteria for evidence selection were defined before a comprehensive search was conducted. The following studies were included: (1) Studies that recruited patients with adrenal tumors and (2) studies that performed a comparative evaluation of the outcomes of patients who underwent LESS-A and m-LA. According to these criteria, the relevant keywords laparoendoscopic, single-site, and adrenalectomy, in free-text, medical subject headings (MeSH in PubMed and Emtree in EMBASE), and abbreviations were used for the literature search. The keywords were combined with appropriate Boolean operators to develop a primary search strategy without limitations on language and published data. The primary search was conducted on PubMed, Cochrane Library (including Cochrane CENTRAL), and Embase. The final search was completed on June 17, 2020 (Table S1).

2.2. Study selection

After potential studies were identified, two authors (TET and PCW) excluded irrelevant studies by screening the title and abstract as per the exclusion criteria. The exclusion criteria were as follows: (1) Studies that recruited patients with diseases other than adrenal tumors, (2) studies that used treatments other than LESS-A and m-LA, (3) studies without details of patients' characteristics or results, and (4) studies that might have employed identical patients for measuring outcomes. In case of any disagreements between the two authors, the corresponding author (YNK) made the final judgment regarding study selection.

2.3. Data extraction and quality assessment

Two authors (JCW and PCW) individually reviewed all selected trials for data extraction and risk of bias assessment. Trial characteristics and outcome data were extracted. The trial characteristics data included trial name, year of publication, article type, case number, the age and body mass index (BMI) of patients, and tumor size. The outcome data included postoperative pain and medication used outcomes, resumption outcomes, and peri-operative outcomes. The risk of bias of the randomized controlled trial and observational studies was assessed using the Cochrane risk of bias (RoB) tool and the Newcastle-Ottawa Scales (NOS) tool, respectively. The third author (TET) made the final judgment in the risk of bias assessment (Tables S2, S3).

2.4. Data synthesis and analysis

Mean difference (MD) and risk ratio (RR) were used in the study's quantitative synthesis for analyzing the continuous outcomes and binary outcomes of the trials, respectively. This study conducted a meta-analysis using the Mantel-Haenszel method. Generally, the Mantel-Haenszel method is preferred over the inverse variance method. All analyses were conducted using the random-effects model. The results are expressed as the MD/RR and 95% confidence interval (CI). Additionally, subset analyses were conducted according to different surgical techniques (transperitoneal or retro-peritoneal approach).

To assess the quality of the pooling results, we determined heterogeneity and the small study effect. Heterogeneity was assessed using I [2] and p values of Cochran Q. An I [2] value higher than 50% or a p value of Cochran Q lower than 0.10 (a rigorous threshold for heterogeneity detection) was defined as high heterogeneity. To explore the source of heterogeneity, we conducted a sensitivity analysis using the subset design. The subset was stratified by surgical technique. A small study effect was illustrated using funnel plots and Egger's test. Pooled results were deemed affected by a small bias when the p value of Egger's test was lower than 0.05. All funnel plots and Egger's tests were presented in the supplementary materials (Figs. S1–S10).

3. Results

3.1. Search results

A total of 575 studies were identified from the three important biomedical databases, of which 165 were duplicated. Among the remaining 410 studies, 381 were excluded after title, abstract, and article type screening. Thereafter, we retrieved full-text articles of the 29 remaining studies for further review. Nine studies were excluded because of superimposed population (n = 7) and unavailable results (n = 2). Finally, the data sources of the eligible studies were examined and found to be 20 studies. These 20 studies were included in the current study for qualitative and quantitative synthesis (Fig. 1).

3.2. Characteristics and quality of included studies

The 20 included studies recruited 608 patients treated with LESS-A and 946 patients treated with m-LA from Korea, Taiwan, China, Japan, Brazil, the United States, Spain, Germany, Czech Republic, Portugal, Lithuania, and Turkey between 2000 and 2018 (Table 1). The sample size of the studies ranged from 22 to 210 patients. A commercially available multichannel port device was used for LESS-A in the majority of the studies [13–15,19–21,24–26,28,30,31,33,41]. Three studies used a single glove or a commercially available multichannel port device [22,32,42]. In two studies, a home-made single-port device made using single-layered sterile surgical glove was used [29,35]. A retroperitoneum approach was adopted by 11 studies, whereas an umbilicus or a subcostal incision was performed in the remaining 9 studies. For m-LA, three or four ports were made, and both transperitoneal and retroperitoneal access approaches were reported.

3.3. Outcomes of postoperative pain and medication used

Eight studies reported postoperative pain scores of 562 patients [13,14,16,21,24,28,30,31]. The overall pooled estimates demonstrated significantly lower postoperative pain scores for LESS-A than for m-LA (MD −0.77, 95% CI −1.45 to −0.10, $p = 0.02$), with high heterogeneity (I^2 = 93%) (Fig. 2). Additionally, the study conducted a subgroup

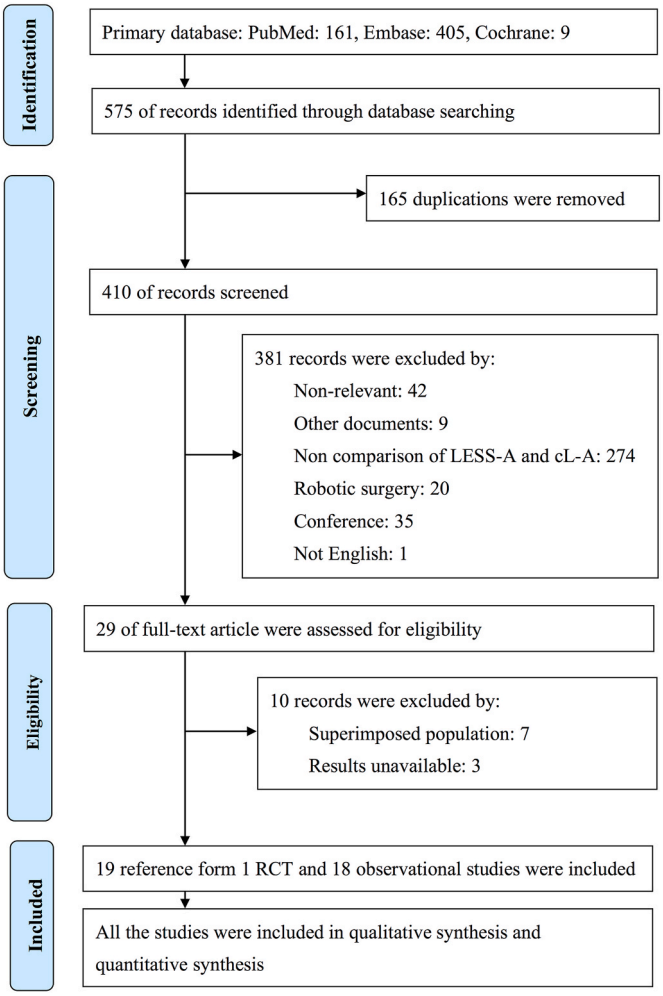

Fig. 1. Flow diagram of study selection.

analysis according to peritoneal or retroperitoneal approach methods. Results revealed no significant difference in postoperative pain scores between LESS-A and m-LA in the subset analysis. Five studies reported the use of postoperative pain medication [13,15,19,30,33]. Postoperative pain medication was administered to 48.03% patients (73/152 patients) treated with LESS-A, and the percentage was 69.27% (133/192 patients) for those treated with m-LA. Pooling results demonstrated that LESS-A had significantly low relative risk associated with the use of postoperative pain medication (RR 0.74, 95% CI 0.60–0.91, $p = 0.0171$, $I^2 = 3\%$) (Fig. 3).

3.4. Resumption outcomes

Of the included studies, 14 reported the length of hospital stay after surgery [15,16,19–22,25,28–33,42]. Patients treated with LESS-A had significantly shorter hospital stays than those treated with m-LA (MD −0.75, 95% CI −1.18 to −0.33, $p = 0.0005$, $I^2 = 90\%$) (Fig. 4). The subgroup analysis revealed that patients treated with LESS-A with a retroperitoneal approach had significantly shorter hospital stay than those treated with m-LA patients. Nine studies reported the time taken for resumption of oral intake [13,15,20,21,25,29,30,32,42]. Pooled synthesis reported significantly shorter time for resumption of oral intake in patients treated with LESS-A than in those treated with m-LA (MD −0.33, 95% CI −0.60 to −0.06, $p = 0.0153$), with high heterogeneity ($I^2 = 95\%$) (Fig. 5).

Four studies reported postoperative cosmetic satisfaction outcomes [14,20,21,30]. One study used the SCAR scale and three used the cosmetic satisfaction scale. Standardization was performed to combine the results of different measurement scales. The overall pooled estimates demonstrated significantly better cosmetic satisfaction in patients treated with LESS-A than in those treated with m-LA (SMD 1.15, 95% CI 0.21–2.09, $p = 0.016$, $I^2 = 92\%$) (Fig. 6).

3.5. Perioperative outcomes

Operative time was reported in 19 studies [13–16,19–22,24–26,28–33,42]. The operative time was significantly longer in LESS-A than in m-LA (MD 13.43, 95% CI 4.08–22.77, $p = 0.0049$, $I^2 = 91\%$) (Fig. 7). No significant differences were observed between LESS-A and m-LA in terms of the remaining perioperative outcomes, namely estimated blood loss (EBL), transfusion rate, conversion rate, and complication rate

Table 1
Characteristics of the included studies.

Studies	Article type	LESS-A versus conventional-LA									
		Case number (n)		Age (mean)		Sex (male/female)		BMI (mean)		Tumor size (mean) (mm)	
		LESS-A	CL-A	LESS-A	CL-A	LESS-A	CL-A	LESS-A	CL-A	LESS-A	CL-A
Agcaoglu 2018	Retrospective cohort study	44	36	49.4	52.2	16/28	20/18	27.9	29.1	36.6	41.3
Beisa 2012	Retrospective cohort study	5	20	58	56	1/4	7/13	30	28	14	21
Carvalho 2019	Retrospective cohort study	36	57	48.7	59.7	13/23	22/35	NA	NA	27.52	47.9
Chen 2016	Retrospective cohort study	63	72	50.3	47.5	30/33	28/44	24.9	25	40	37
Chen 2019	Retrospective cohort study	40	36	55.2	52.6	17/23	16/20	22.2	21.5	23	26
Hirsawa 2014	Retrospective cohort study	70	140	51.2	50.9	38/32	57/83	23	23.1	28	26.4
Hora 2014	Retrospective cohort study	18	17	59.3	60.2	NA	NA	26.9	28.5	43.7	36.1
Jeong 2009	Retrospective cohort study	9	17	46[a]	43.8[a]	4/5	11/16	NA	NA	28	43
Kwak 2011	Retrospective cohort study	10	12	43.7	51.08	5/5	6/6	24.08	26.17	32.5	30.08
Lin 2011	Retrospective cohort study	21	28	50.7	51.7	12/9	14/14	25.6	24.6	18 (g)	15 (g)
Machado 2017	Retrospective cohort study	20	80	45	50	8/12	50/30	24.2	25.4	NA	NA
Shi 2011	Retrospective cohort study	19	38	57[a]	57[a]	8/11	21/27	29.8	29	2.1	3
Sho 2016	Retrospective cohort study	37	24	54.5	53	17/20	14/10	27	26.8	32.2	31.9
Tunca 2011	Retrospective cohort study	22	74	43.3	43.4	4/18	28/46	NA	NA	33.4	47
Vidal 2012	Randomized controlled trial	20	20	63	50	8/12	5/15	NA	NA	30	30
Walz 2010	Retrospective cohort study	47	47	43.3	42.2	17/30	17/30	25.1	25.2	23	26
Wang 2012	Retrospective cohort study	13	26	47.2	43.9	8/5	10/16	24.9	25.1	20	24
Wang 2016	Retrospective cohort study	51	65	48.1	50.3	23/28	26/39	37.3	36.7	27	28
Wu 2016	Retrospective cohort study	45	71	50.8	51.3	28/21	34/35	27.8	25.5	1.8 (g)	1.8 (g)
Yuan 2014	Retrospective cohort study	21	42	47[a]	46[a]	14/7	26/16	24	24.6	53	53

[a] Median.

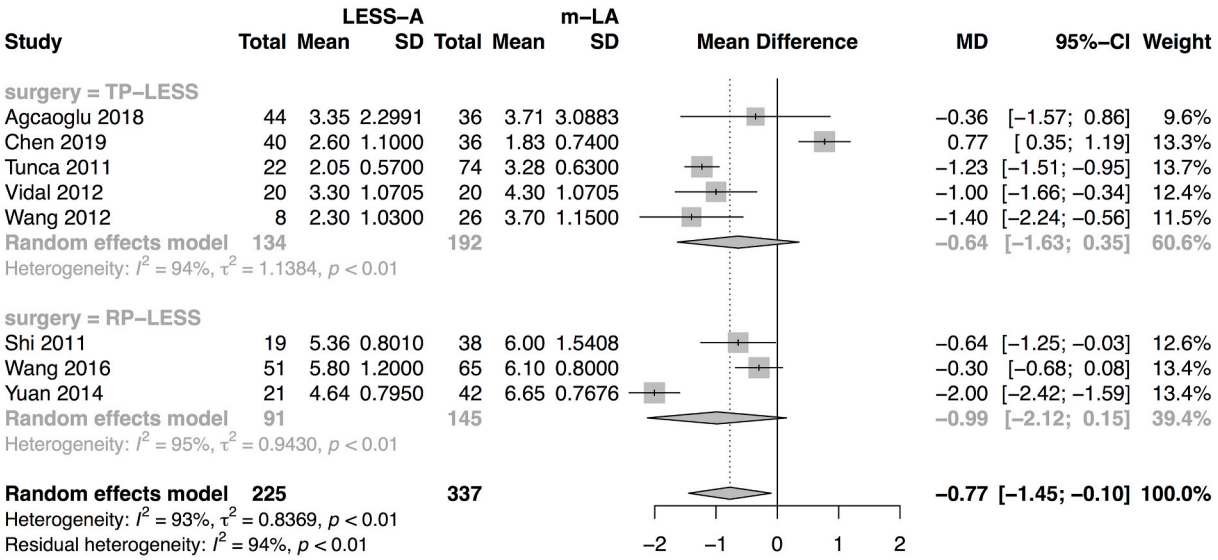

Fig. 2. Forest plot of LESS-A versus m-LA in terms of post-operative pain scores.

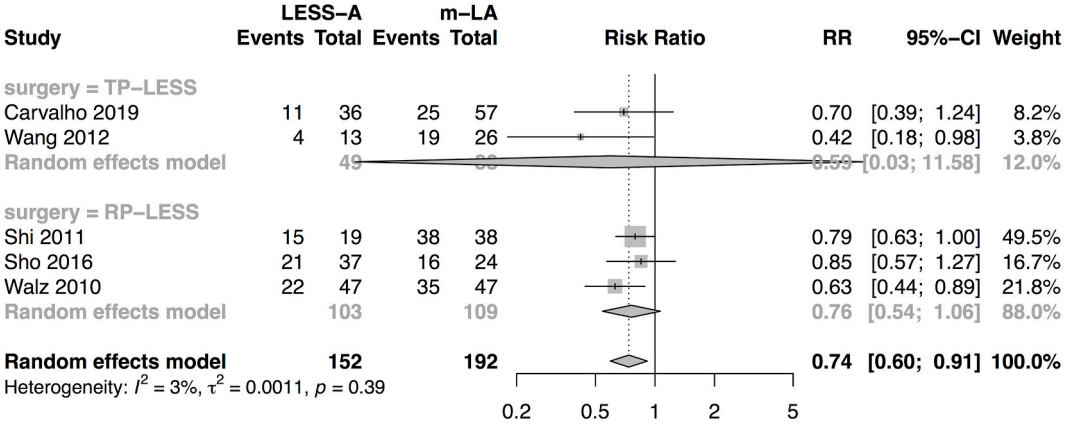

Fig. 3. Forest plot of LESS-A versus m-LA in terms of post-operative pain medication used.

(Figs. 8–11).

4. Discussion

A comprehensive review and analysis were employed to synthesize 20 studies comprising 608 patients treated with LESS-A compared with 946 patients treated with m-LA. Our study indicated that those treated with LESS-A had significantly better subjective and resumption outcomes compared with those treated with m-LA. Moreover, patients treated with LESS-A had comparable perioperative outcomes with those treated with m-LA, except for longer operative time. LESS-A is a safe and feasible operation, except for elder or high-risk populations due to the longer operative time. Barring the drawback that increment in operative time increases mortality of and morbidity in elderly patients [43], LESS-A offers benefits in terms of postoperative pain and resumption.

The present findings suggested that patients treated with LESS-A experienced significantly less postoperative pain than those treated with m-LA patients, with limited effect and high heterogeneity. LESS-A surgery is less invasive than conventional laparoscopic surgery and involves less tissue damage, which could explain the reduced postoperative pain. This finding is similar to that of a previous meta-analysis by Wu et al., including 10 studies with a total number of 704 cases [38], the outcomes of which we updated with a larger sample size. The previous synthesis analyzed pain score outcome from only two studies with 130 cases; by contrast, we expanded the number of studies to eight studies with 562 cases. However, our findings concerning postoperative pain are highly heterogeneous. The high heterogeneity can be attributed to certain factors. Most included studies employed the visual analog scale (VAS) to measure pain scores, which is a self-rating scale. The different time points of measurement contributed to the heterogeneity and bias. Six studies mentioned inconsistent time points of measurement. Different time points of measurement influenced the postoperative pain scores. Nevertheless, the LESS-A group was given significantly less postoperative analgesic medication than the m-LA group. The two findings consistently indicate that LESS-A offers lower postoperative pain.

Our study demonstrated that LESS-A had better resumption outcomes, including faster resumption of oral intake, shorter length of hospital stays, and higher cosmesis scores. Previous meta-analyses by Hu et al., Wang et al., and Wu et al., with an inclusion of 9 to 10 studies, have not reported significant difference in resumption of oral intake; however, this benefit was observed in our study after inclusion of an additional 10 more studies. [36–38] Reducing postoperative pain and opioid use can prevent postoperative ileus, and early postoperative oral feeding can shorten hospital stay and facilitate faster recovery [44–48]. Cosmesis is one of the advantages of single-site incision laparoscopic surgery, and it is associated with body image and self-esteem [49,50]. Four included studies reported aesthetic outcomes, but no standardized

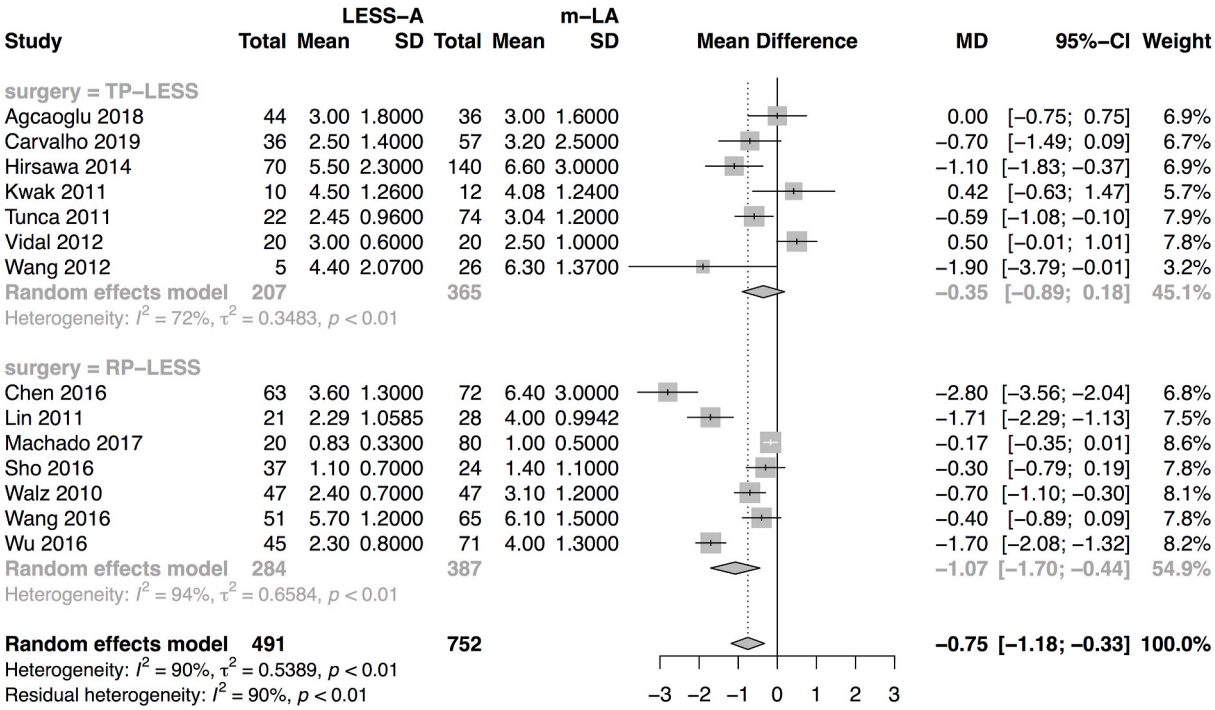

Fig. 4. Forest plot of LESS-A versus m-LA in terms of length of hospital stay.

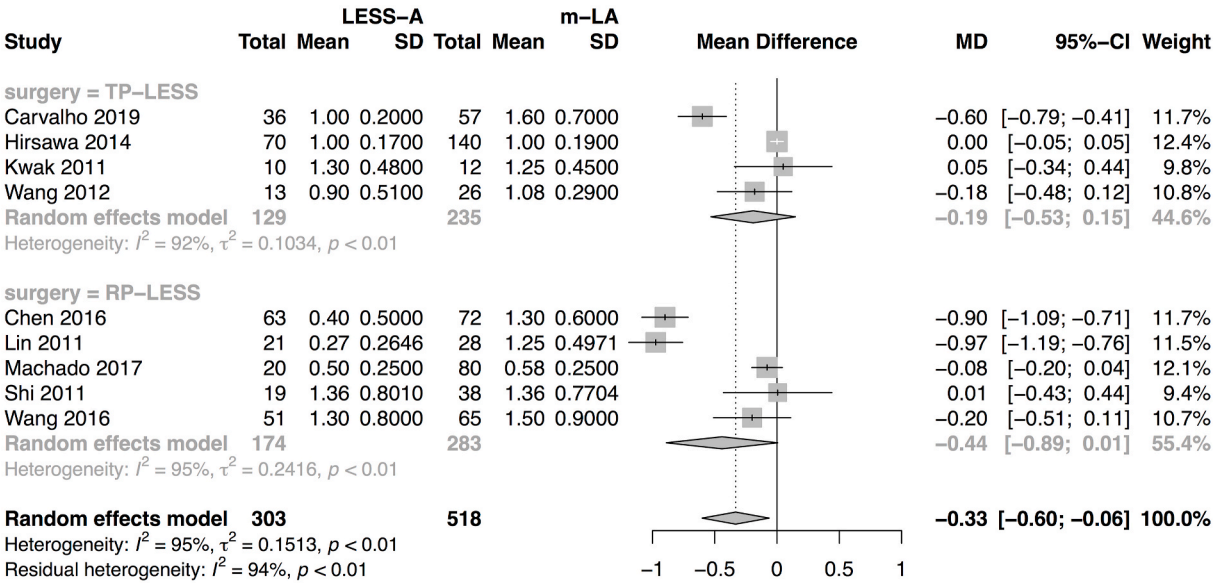

Fig. 5. Forest plot of LESS-A versus m-LA in terms of resumption of oral intake.

measurement tools were employed to evaluate them. Future studies are warranted for establishing standardized measurement tools and assessing the benefits of cosmesis and better body image in subgroups of age or sexes.

Generally, patients treated with LESS-A were benefitted in terms of postoperative pain and resumption compared with those treated with m-LA. Additionally, in our subset analysis, the benefits are more evident for LESS-A surgery when the retroperitoneal approach was adopted. The adrenal gland is a retroperitoneal organ that is mediosuperior to the kidney. A wide operative view was achieved by adopting a transperitoneal approach; however, surgeons are required to enter the white line of Toldt and retract the liver or the spleen. The adrenal gland can be approached directly through the retroperitoneal approach without obscuring other visceral organs; however, the operation field may be limited for large adrenal tumors. Although our study did not compare both approaches, our findings are consistent with the meta-analysis including 5 trials with a total of 244 participants by Arrezo et al., which compared transperitoneal and retroperitoneal laparoscopic adrenalectomy in adults and concluded that retroperitoneal adrenalectomy had an earlier start of oral intake and ambulation [51].

Our synthesis revealed significantly longer operative time for LESS-A than for m-LA, with high heterogeneities in overall and subset analyses. Different numbers of trocar design in m-LA and additional assistant trocar in LESS-A in some included trials contributed to the inconsistent operation time. Nevertheless, learning curve is one of the most important factors associated with operative time. Hirsawa et al. reported the

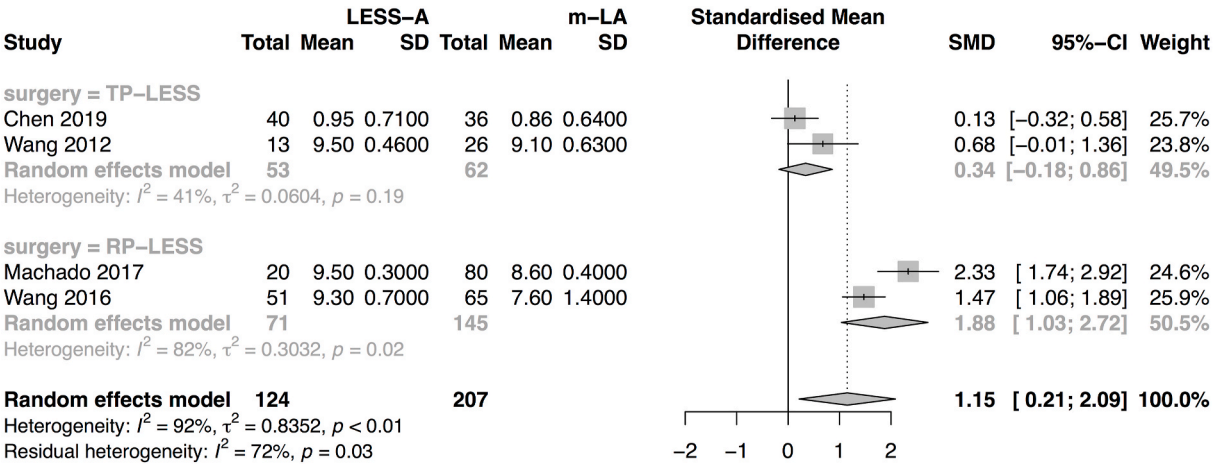

Fig. 6. Forest plot of LESS-A versus m-LA in terms of post-operative cosmetic satisfaction.

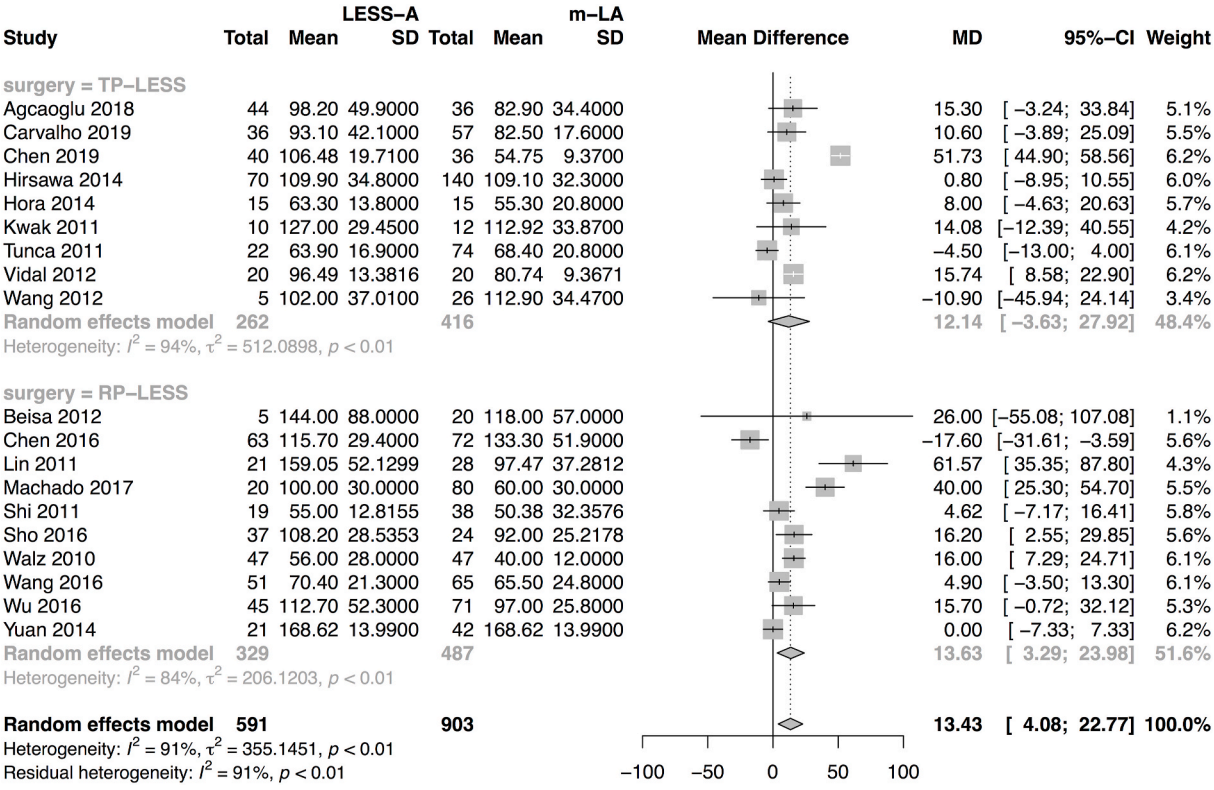

Fig. 7. Forest plot of LESS-A versus m-LA in terms of operative time.

differences in operative time between the first 12 operations and the operations that followed performed by the same surgeon, and mean operative time was reduced from 128 to 106 min after 12 cases. Fukumoto et al. [52] demonstrated that surgeons acquired master-level expertise after 30 operations and performed the operation at a significantly shorter operative time. The disparities in the sample size of the included LESS-A studies were tremendous, ranging from 9 to 70 patients.

The strengths of our study included the 2-fold expanded numbers of evidence and participants compared to the previous meta-analyses, and the comprehensive analyses conducted to investigate peri-operative and post-operative outcomes of LESS-A. However, this meta-analysis also had certain limitations. First, most trials were retrospective, except for one randomized controlled trial. Second, high heterogeneities were observed in outcomes. Matching criteria, surgeon's expertise, operative procedures, use of single-port devices, and different measurement time points all possibly contributed to the heterogeneity. Future studies are suggested to control these factors to reduce the heterogeneity. Third, most trials did not investigate the outcomes of different tumor size or pathology. We could not analysis if LESS-A is suitable to large adrenal tumor. Fourth, the cost of LESS-A was not mentioned in most of the included studies. To investigate the cost-effectiveness of this new technique, more studies should report the expense. Lastly, we only analyzed short-term outcomes post-operatively due to the lack of data in each studies. Studies presenting outcomes of longer-term follow up periods are warranted in the future.

5. Conclusion

Our results revealed that LESS-A is a safe and feasible operation

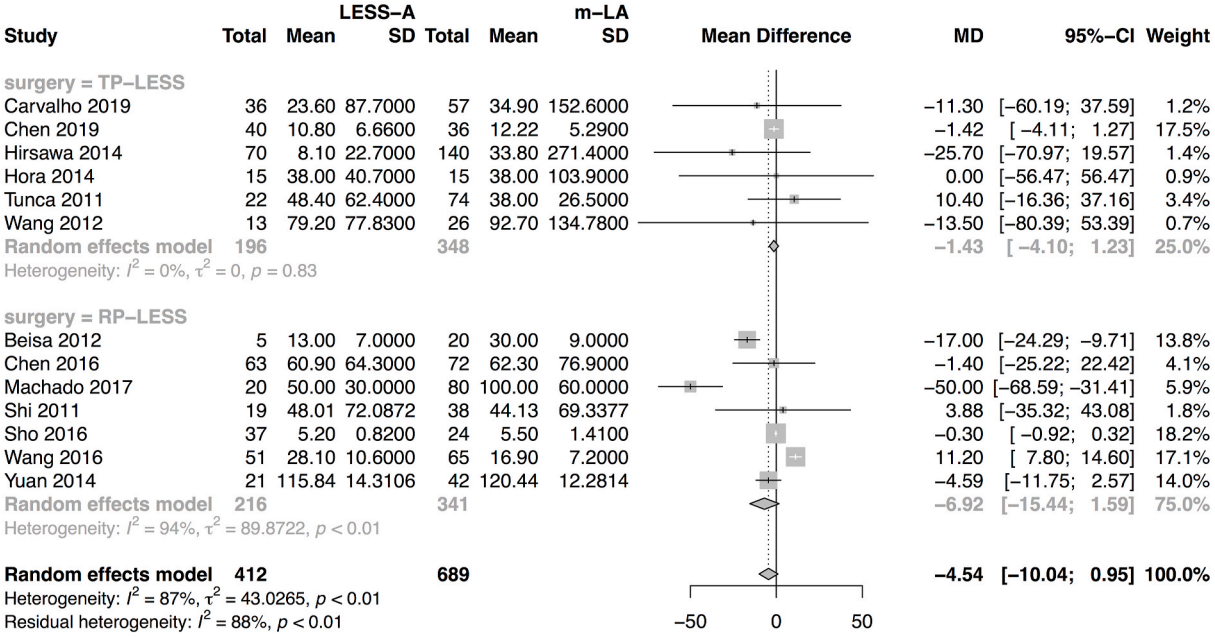

Fig. 8. Forest plot of LESS-A versus m-LA in terms of estimated blood loss.

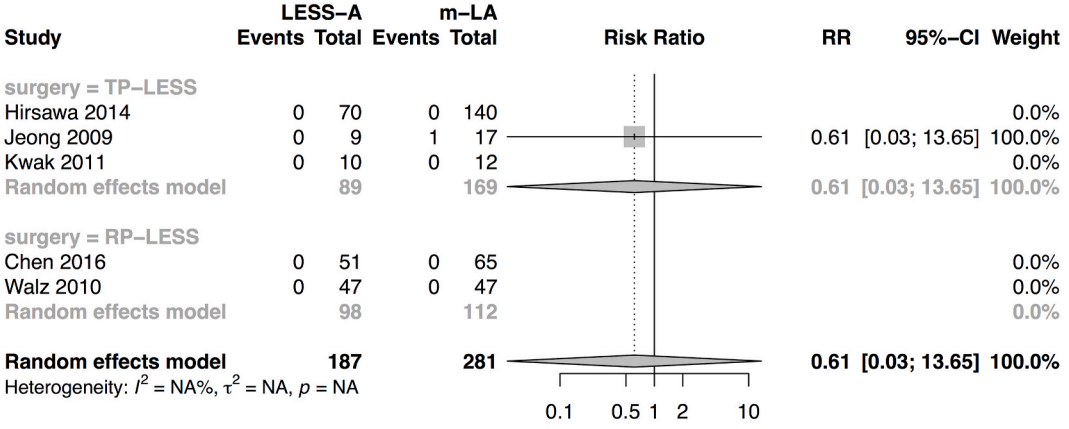

Fig. 9. Forest plot of LESS-A versus m-LA in terms of transfusion rate.

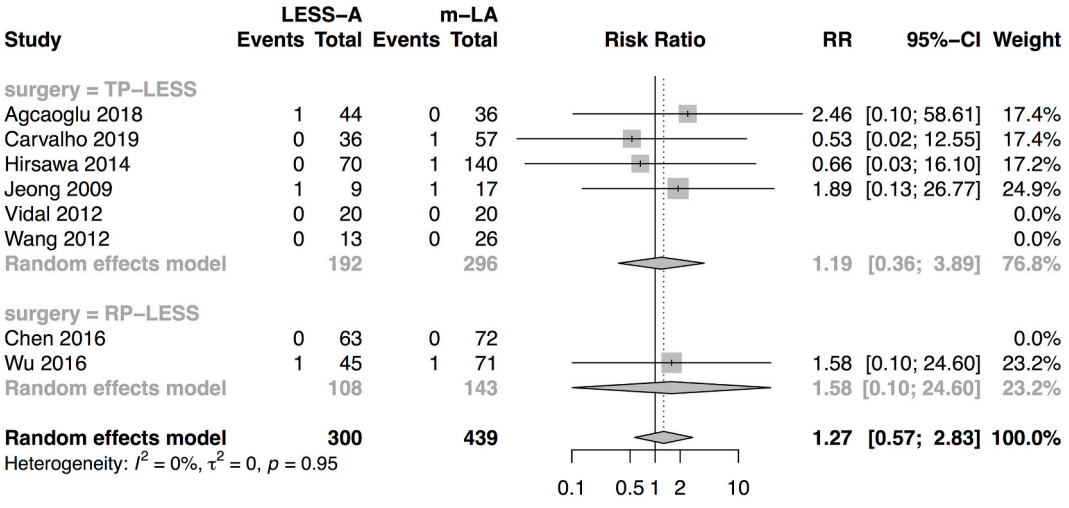

Fig. 10. Forest plot of LESS-A versus m-LA in terms of conversion rate.

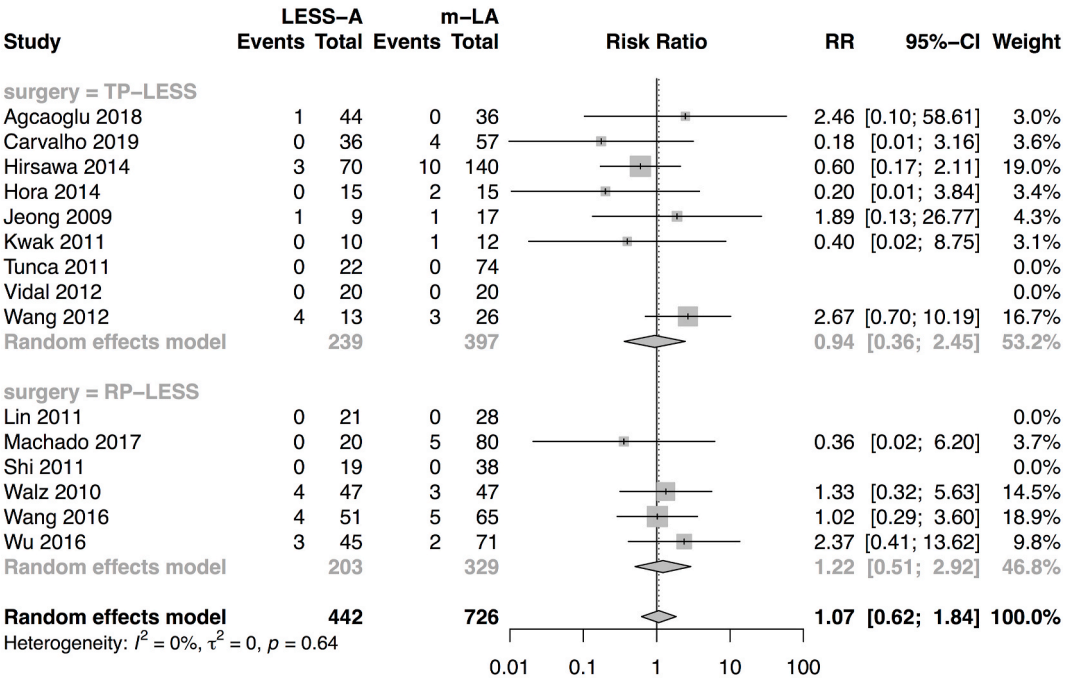

Fig. 11. Forest plot of LESS-A versus m-LA in terms of complication rate.

alternative to m-LA with advantages of less postoperative pain, less postoperative pain medication consumption, and better resumption outcomes. However, the longer operative time of LESS-A compared with m-LA is a drawback, which can be attributed to lesion laterality, additional equipment used, and surgeon's experience. Further randomized controlled trials are warranted to confirm the findings of this analysis.

Ethical Approval

None.

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Author contribution

Jeng-Cheng Wu: Database search, data extraction, and co-first author.

Po-Chien Wu: Database search, data extraction, and data analysis and co-first author.

Yi-No Kang: Data analysis, data extraction, and co-corresponding author.

Ting-En Tai: Study conception, data analysis and producing final manuscript.

Research registration number

Name of the registry: PROSPERO
Unique Identifying number or registration ID: CRD42020170633
Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=170633

Guarantor

Jeng-Cheng Wu, Po-Chien Wu, Yi-No Kang, Ting-En Tai

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Declaration of competing interest

Jeng-Cheng Wu, Po-Chien Wu, Yi-No Kang, and Ting-En Tai declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102388.

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