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Brief Communication

Minimally invasive versus abdominal radical trachelectomy for early-stage cervical cancer: a systematic review and meta-analysis

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Abstract: The safety of minimally invasive surgery (MIS) for cervical cancer has been questioned. This systematic review and meta-analysis aimed to compare the clinical outcomes of patients with cervical cancer who underwent MIS and abdominal trachelectomy. We searched for and subsequently analyzed studies published in PubMed, Embase, Cochrane Central Register of Controlled Trials, International Clinical Trials Registry Platform, and Clinical Trials.gov from their inception until April 10, 2023. Six studies with 1,079 participants were included, constituting 512 and 567 patients in the MIS and abdominal surgery groups, respectively. No significant difference was observed in the overall survival (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.16-1.65; I^2=0.0%; P=0.881), recurrence rate (RR, 1.26; 95% CI, 0.68-2.33; I^2=0.0%; P=0.815), and death rate (RR, 0.54; 95% CI, 0.23-1.31; I^2=0.0%; P=0.680) between the MIS and abdominal surgery groups. No significant difference was found in urinary tract complication (RR, 0.78; 95% CI, 0.28-2.17; I^2=0.0%; P=0.603), cerclage erosion (RR, 0.90; 95% CI, 0.34-2.43; I^2=0.0%; P=0.650), or cervical stenosis (RR, 0.69; 95% CI, 0.22-2.18; I^2=0.0%; P=0.885) between both groups. However, significant differences in blood loss and length of hospital stay were observed between both groups. Among 49 females who attempted to get pregnant, 31.3% (5/16) and 51.5% (17/33) in the MIS and abdominal surgery groups, respectively, succeeded in conceiving. We established that laparoscopic and abdominal radical trachelectomy had similar efficacies for treating patients with early cervical cancer, with no significant differences in survival, tumor recurrence, and mortality rates. Additionally, they showed no significant differences in pregnancy-related outcomes. However, owing to the limited number of studies, more high-quality cohort studies are required to confirm these findings.

Keywords: Trachelectomy, laparoscopic, minimally invasive surgery, cervical cancer, meta-analysis, fertility

Introduction

Due to the widespread cervical cancer screening and human papillomavirus vaccination, the incidence of cervical cancer has dropped by approximately 2% per year in Hispanic females aged over 50 years in the United States. However, the annual incidence of cervical cancer increased by 2% between 2012 and 2019 in the younger Hispanic population [1]. Due to the rising incidence of cervical cancer in young females and the increasing trend of delayed fertility decisions, the treatment of cervical cancer faces difficulties regarding performing radical resection and preserving fertility.

Dargent et al. first performed a trachelectomy in 1994, and since then, excellent oncological and obstetric outcomes have been reported. A trachelectomy includes vaginal, abdominal, and minimally invasive surgeries (MIS) (laparoscopic and robot-assisted), which were first reported in 1994, 1997, and 2005, respectively; all routes were reported as optimal alternatives to radical hysterectomy for patients who desire to preserve fertility. The minimally invasive approach has advantages, including cosmetic appearance, good visualization, and shorter hospital stays. A previous study reported an increase in the use of MIS in trachelectomy, which has become the dominant surgical route since 2011 [2].

In 2018, the Laparoscopic Approach to Carcinoma of the Cervix (LACC) trial reported a decreased survival rate with MIS for radical hysterectomy compared with abdominal hysterectomy [3], with similar results being reported in other studies [4, 5]. Since then, the safety of MIS in cervical cancer has been questioned. Notably, the National Comprehensive Cancer Network 2023 recommends these three trachelectomy approaches: vaginal, abdominal, or MIS. However, the recommendation category for MIS is 2B due to a lack of data regarding oncological outcomes [6].

Recently, systematic reviews of laparotomy and endoscopy have been published; however, these articles included individual cases and case series rather than controlled studies [7-9]. To the best of our knowledge, no meta-analysis of the oncological, obstetric, and perioperative outcomes of MIS and abdominal trachelectomy for early cervical cancer has been published. To address this, we aimed to conduct a systematic review and meta-analysis to compare the clinical outcomes of patients with cervical cancer who underwent MIS or abdominal trachelectomy.

Methods

Protocol registration

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and registered with the International Prospective Register of Systematic Reviews (CRD4202340728) [10].

Eligibility criteria

All potentially eligible studies, including randomized controlled trials and prospective or retrospective cohort studies, compared the perioperative, oncological, and reproductive outcomes of patients with early cervical cancer treated with minimally invasive (laparoscopic or robotic) or abdominal radical trachelectomy. Additionally, all studies were published in peer-reviewed journals in English. Articles published as conference abstracts, commentaries, or narrative reviews were excluded. Only the largest sample size was included when the data subsets were published in more than one article.

Specifically, the inclusion criteria were studies with the following features: 1) patients with early-stage cervical cancer, 2) patients who underwent MIS, 3) compared the MIS and abdominal surgical routes, and 4) outcome measures including overall survival (OS), recurrence, fertility outcomes, obstetric outcomes, perioperative outcomes, and surgical complication between the MIS and laparotomy groups. Studies with the following features were excluded: 1) treatment with radiation or chemotherapy, 2) histological subtype of neuroendocrine, clear cell, or serous cell type or metastatic carcinoma, 3) clinically advanced disease (FIGO 2018 stages IB3 to IV), and 4) previous history of subtotal hysterectomy.

Search strategy and study selection

We searched PubMed, Embase, the Cochrane Central Register of Controlled Trials, the International Clinical Trials Registry Platform, and ClinicalTrials.gov, from their inception until March 20, 2023. Additionally, the reference lists of published reviews and retrieved articles were checked for additional trials. The search strategy was tailored to each database (Embase, for example, see **Appendix**), and the search terms included “trachelectomy”, “cervical cancer”, and “cervical carcinoma”.

Two researchers (HC and LH) independently screened titles and abstracts to assess the eligibility of the studies. After the initial selection, the full texts of all potential articles were independently read by two researchers (HC and LH) for further evaluation. Disagreements between the authors were resolved through discussion with XT.

Data extraction

Data were extracted by two independent reviewers (LH and YC) and recorded in a standardized database. They used a predefined data extraction form that included the methods, study quality, participants, and outcomes, and they were blinded to the trial authors, institutions, sources of funding, and acknowledgments. For missing data, the authors were emailed; however, no replies were received.

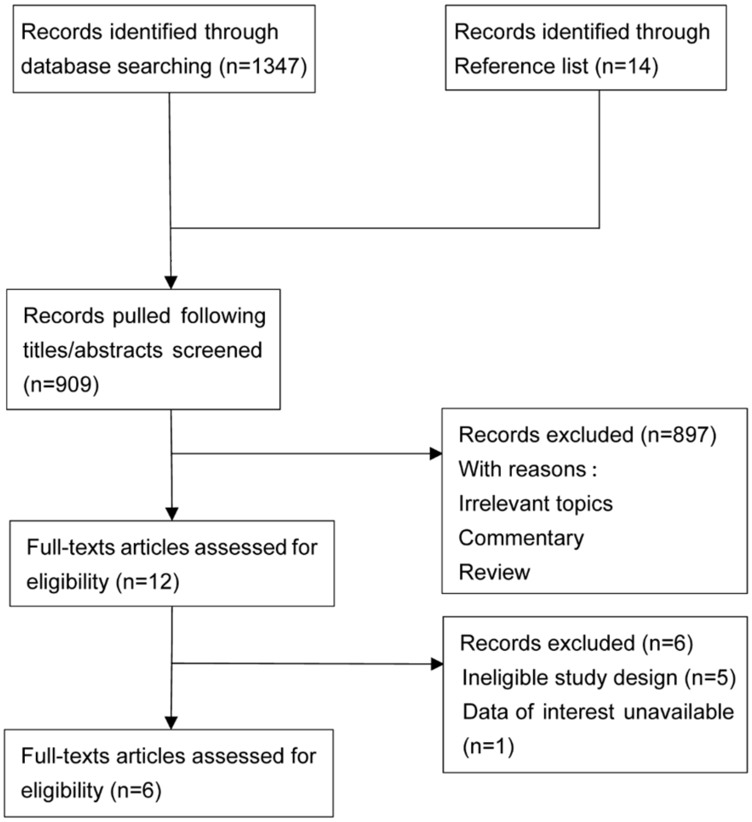

Figure 1. Flowchart of the study selection.

The primary outcomes included survival data and recurrence rate. The secondary outcomes included fertility outcomes (cervical incompetence, pregnancy rate, infertility rate, natural conception rate, and *in vitro* fertilization rate); obstetric outcomes (time interval between the radiation therapy surgery and pregnancy, overall mean length of time during which conception was attempted, number of pregnancies, mode of delivery, spontaneous abortion, induced abortion, drug abortion, preterm birth, premature rupture of membranes, fetal growth restriction, and full-term birth); and perioperative outcomes (operation time, blood loss, hospital stay, and complication).

Risk of bias assessment

Two reviewers (LH and YC) independently assessed the quality of the included studies. Differences were resolved by discussion, and if no consensus was reached, a third review author (HC) was involved. Cohort studies were assessed using the Newcastle-Ottawa Scale (NOS) based on three categories: the selected cases, comparability of groups, and assessment of outcomes. Studies that were awarded six or more stars were classified as high-quality.

Statistical analysis

STATA 16.0 (StataCorp, College Station, TX, USA) was used for the meta-analysis. Whenever appropriate, we calculated odds ratios (ORs) or hazard ratios (HRs) together with 95% confidence intervals (CIs). HRs with 95% CIs were used to combine data regarding survival outcomes. For studies reporting survival data only in the form of Kaplan-Meier curves, Engauge Digitizer 4.1 was used to extract survival data, and HRs and CIs were calculated according to methods reported in the literature [11, 12]. Moreover, $P<0.05$ was considered statistically significant for the meta-analysis. Heterogeneity between studies was assessed using the I^2 test: $I^2<30\%$, 30-50%, and ≥50% were considered low, moderate, and high heterogeneity, respectively. Owing to the low heterogeneity in most studies, we used a fixed-effects model to combine the data.

Results

Study selection and characteristics

The study selection process is illustrated in **Figure 1**. In total, 909 articles were retrieved after duplicates were removed. After screening the titles and abstracts, 12 full texts were retrieved for subsequent assessment. Six articles were excluded after reading the full texts. Finally, six studies with 1,079 participants were included in this review [2, 13-17], constituting 512 and 567 patients in the MIS and abdominal surgery groups, respectively. Finally, all the included studies were retrospective cohort studies and were awarded six or more stars according to the NOS criteria. The general characteristics of the included studies are summarized in **Table 1**.

Table 1. The included basic characteristics of the studies

Study	Study duration	Age (median age)		Histological type	Stage	Lymph node counts		Number of patients		Conversion to hysterectomy		Follow up time (months)		Tumor size (mm)		Study type
		MIS	ART			MIS	ART	MIS	ART	MIS	ART	MIS	ART	MIS	ART	
Nick 2012 [13]	2005 to 2011	28.9		squamous adenosquamous adenocarcinoma	IA1 with LVSI 1A2, 1B1	18	22	12	25	4	1	10.8	26.4	21.5	23	Single center retrospective study
Kucukmetin 2014 [14]	2004 to 2014	28	26	squamous adenosquamous	IB1	19	12	11	16	1	0	9	43	13	20	Single center retrospective study
Vieira 2015 [15]	2002 to 2013	30.1	29.3	squamous adenosquamous adenocarcinoma mixed	IA1 with LVSI 1A2, 1B1	17	22	42	58	5	3	25	66	-	-	Single center retrospective study
Matsuo 2018 [2]	2010 to 2015	31	29	squamous, adenocarcinoma, or others	IA2-IB	-	-	144	102	-	-	37	40	-	-	Multicenter retrospective study
Salvo 2021 [16]	2010 to 2015	31	32	squamous adenosquamous adenocarcinoma	IA2-IB1	-	-	288	358	-	-	37.2	66	12	15	Multicenter retrospective study
He 2022 [17]	2005 to 2017	30		squamous adenosquamous adenocarcinoma	IA1, IA2 1B1	-	-	15	18	-	-	-	-	-	-	Single center retrospective study

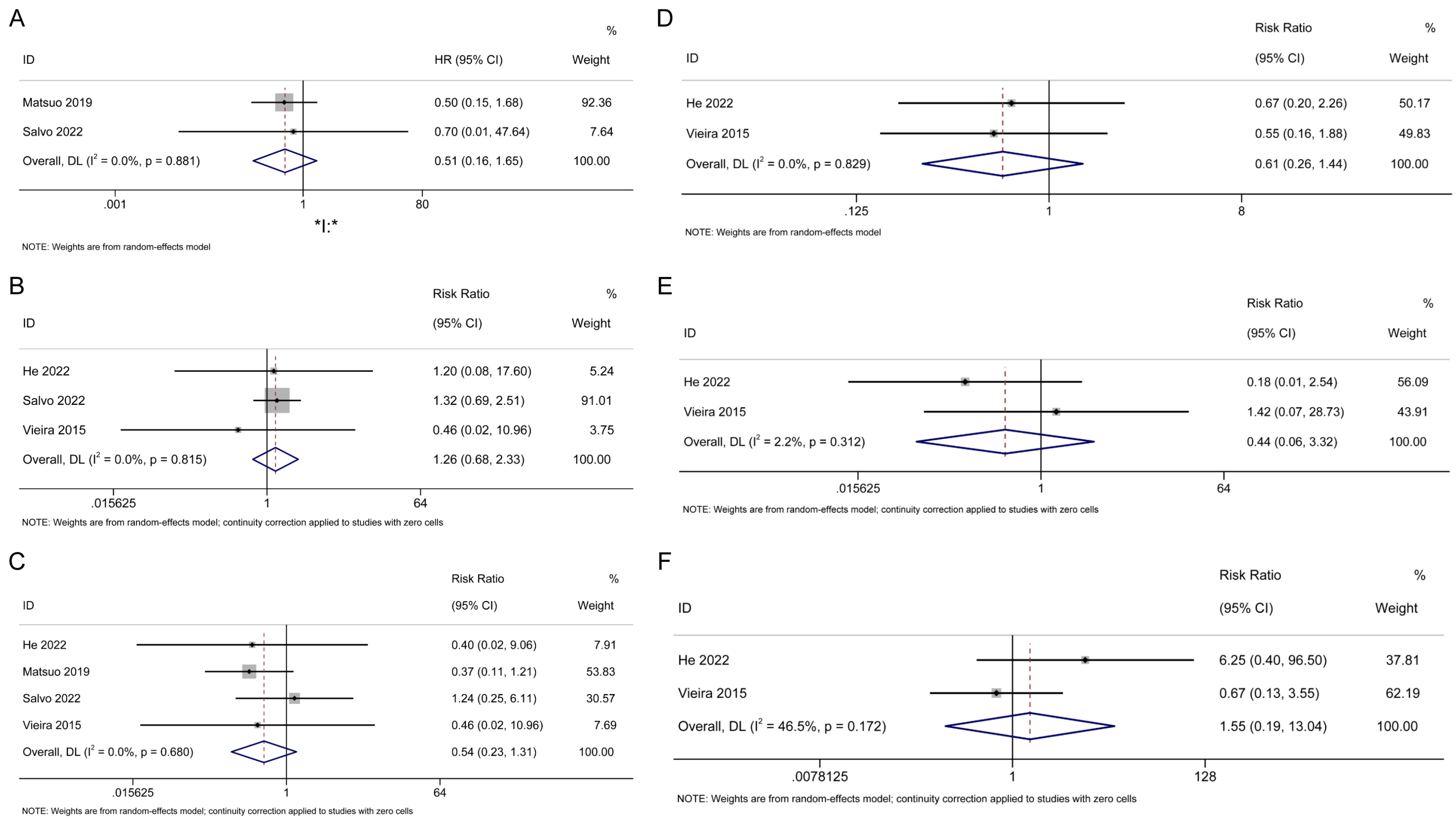

Figure 2. Forest plot of ontological and fertility outcomes in the MIS and abdominal groups. A. Overall survival. B. Recurrence rates. C. Death rates. D. Fertility rates. E. Term delivery rates. F. Preterm delivery rates.

Table 2. Fertility and obstetric outcomes

Outcomes	Study	MIS	Abdominal
Fertility, % (n/N)	He 2022	33.3% (3/9)	50.0% (3/6)
	Vieira 2015	28.6% (2/7)	51.9% (14/27)
Term delivery, % (n/N)	He 2022	0 (0/3)	75.0% (3/4)
	Vieira 2015	0 (0/3)	6.3% (1/16)
Preterm delivery, % (n/N)	He 2022	66.7% (2/3)	0 (0/4)
	Vieira 2015	33.3% (1/3)	50% (8/16)
Miscarriage, % (n/N)	Vieira 2015	33.3% (1/3)	25% (4/16)
Ongoing pregnancy, % (n/N)	He 2022	33.3% (1/3)	25% (1/4)
	Vieira 2015	33.3% (1/3)	18.8% (3/16)
Conceive through IVF, % (n/N)	He 2022	0 (0/3)	50.0% (2/4)
Natural conception, % (n/N)	He 2022	100% (3/3)	50.0% (2/4)

Survival and recurrence

The OS rates of the MIS and abdominal surgery groups were not significantly different (HR, 0.51; 95% CI, 0.16-1.65; I^2=0.0%; P=0.881; **Figure 2A**) [2, 16]. Matsuo et al. [2] reported that the 4-year OS rates were 95.7% (95% CI, 88.7-98.4%) for the MIS group and 92.3% (95% CI 83.5-96.5%) for the laparotomy group.

The pooled recurrence rates were 5.5% and 4.4% [15-17], and the pooled death rates were 1.4% and 2.3% in the MIS and abdominal surgery groups, respectively [2, 15-17]. Lastly, no significant difference was observed in the recurrence (RR 1.26; 95% CI, 0.68-2.33; I^2=0.0%; P=0.815; **Figure 2B**) and death rates (RR 0.54; 95% CI, 0.23-1.31; I^2=0.0%; P=0.680; **Figure 2C**) between the MIS and abdominal surgery groups [2, 15-17].

Fertility and obstetric outcomes

Four studies reported fertility and obstetric outcomes (**Table 2**) [13-15, 17]. Among the 49 females who had attempted to get pregnant, 31.3% (5/16) in the MIS group and 51.5% (17/33) in the abdominal surgery group conceived successfully. Specifically, in a study by Kucukmetin et al. [14], none of the patients in the MIS group and one in the abdominal group conceived successfully. Moreover, Nick et al. [13] reported that none of the patients in the MIS group and four in the abdominal surgery group succeeded in conceiving. However, these two studies did not mention the number of patients who attempted to conceive in each group. Furthermore, no significant difference existed in the fertility rates in females attempting to conceive in the MIS and abdominal surgery groups (RR, 0.61; 95% CI, 0.26-1.44; I^2=0.0%; P=0.829; **Figure 2D**) [15, 17].

In the MIS group, no term delivery was observed; however, 50% (3/6) of deliveries were preterm. In the abdominal surgery group, 20.0% (4/20) and 40.0% (8/20) preterm deliveries were observed. Additionally, we observed no significant difference in term (RR, 0.44; 95% CI, 0.06-3.33; I^2=0.0%; P=0.312; **Figure 2E**) and preterm delivery rates (RR, 1.55; 95% CI, 0.19-13.04; I^2=0.0%; P=0.172; **Figure 2F**) between the two groups [15, 17]. Miscarriage rates were 33.3% (1/3) and 25% (4/16) in the MIS and abdominal surgery groups, respectively. Lastly, through limited data, we found that all patients (3/3) in the MIS group became pregnant through natural conception, and 50.0% (2/4) and 50.0% (2/4) of the patients in the abdominal surgery group became pregnant through natural conception and IVF, respectively.

Perioperative outcomes and surgical complications

Four studies reported the perioperative outcomes (**Table 3**) [13-15, 17]. The mean operative time was 272-320 min in the MIS group and 192.5-328 min in the abdominal surgery group. The mean blood loss was 50-232 mL and 192.5-328 mL in the MIS and abdominal surgery groups, respectively. Additionally, the mean length of hospital stay was 1-6.2 days in the MIS group and 4-8.5 days in the abdominal surgery group. Moreover, we observed significant differences in blood loss and the length of hospital stay between the MIS and abdominal surgery groups in all four studies. Excluding the studies conducted by Kucukmetin et al. [14], all other studies reported no difference in operation times between the two surgical routes.

Three studies reported conversion rates to hysterectomy [13-15]. The pooled conversion rates were 15.4% (10/65) and 4.0% (4/99) for the MIS and abdominal surgery groups, respec-

Table 3. Perioperative outcomes and surgical complications

Outcomes	Study	MIS	Abdominal	*p*-Value
Operation time	He 2022	316.00±39.06	299.4±88.05	0.48
(mean ± SD or mean range)	Vieira 2015	272 (130-441)	270 (150-373)	0.78
	Kucukmetin 2014	320 (210-410)	192.5 (105-270)	<0.001*
	Nick 2012	294 (207-379)	328 (203-392)	0.26
Blood loss	He 2022	232.00±149.77	716.67±308.07	<0.05*
(mean ± SD or mean range)	Vieira 2015	50 (10-225)	300 (50-1100)	<0.0001*
	Kucukmetin 2014	85 (50-3000)	800 (250-1600)	<0.001*
	Nick 2012	62.5 (25-450)	300 (50-1100)	0.0001*
Hospital stays	He 2022	6.20±2.34	8.50±2.36	<0.05*
(mean ± SD or mean range)	Vieira 2015	2 (0-24)	6 (1-23)	<0.0001*
	Kucukmetin 2014	4 (2-6)	7 (5-18)	0.003*
	Nick 2012	1 (1-2)	4 (3-9)	<0.01*
Conversion to hysterectomy, % (n/N)	Vieira 2015	11.9% (5/42)	5.2% (3/58)	0.27
	Kucukmetin 2014	9.1% (1/11)	0 (0/16)	0.219
	Nick 2012	33.3% (4/12)	4.0% (1/25)	0.03
Urinary tract complication, % (n/N)	Vieira 2015	9.5% (4/42)	10.3% (6/58)	0.99
	Nick 2012	13% (1/8)	25% (6/24)	0.81
Cerclage erosion, % (n/N)	Vieira 2015	11.9% (5/42)	10.3% (6/58)	0.74
	Kucukmetin 2014	0 (0/10)	6.3% (1/16)	0.42
	Nick 2012	0 (0/8)	17% (4/24)	0.54
Cervical stenosis, % (n/N)	Vieira 2015	7.1% (3/42)	8.6% (5/58)	0.99
	Kucukmetin 2014	0 (0/10)	6.3% (1/16)	0.42
	Nick 2012	0 (0/8)	13% (3/24)	0.73

*P<0.05.

tively. Additionally, the conversion rates to hysterectomy differed significantly between the groups (RR 3.50; 95% CI, 1.19-10.26; I^2=0.0%; P=0.595; **Figure 3A**). The reasons for conversion to hysterectomy included close or involved surgical margins on frozen sections.

Three studies reported surgical complications (**Table 2**) [13-15]. The pooled urinary tract complication rates were 10.0% (5/50) in the MIS group and 14.6% (12/82) in the abdominal surgery group. The pooled cerclage erosion rates were 8.3% (5/60) and 11.2% (11/98) in the MIS and abdominal surgery groups, respectively. Additionally, the pooled cervical stenosis rates in the MIS and abdominal surgery groups were 5.0% (3/60) and 9.2% (9/98), respectively. Lastly, no significant difference was observed in urinary tract complication (RR, 0.78; 95% CI, 0.28-2.17; I^2=0.0%; P=0.603; **Figure 3B**), cerclage erosion (RR, 0.90; 95% CI, 0.34-2.43; I^2=0.0%; P=0.650; **Figure 3C**), or cervical stenosis (RR, 0.69; 95% CI, 0.22-2.18; I^2=0.0%; P=0.885; **Figure 3D**) rates between the two groups.

Discussion

The meta-analysis revealed no significant differences in OS, recurrence, and death rates between abdominal and minimally invasive radical trachelectomy. Smith et al. [7] included 955 abdominal trachelectomies and 120 minimally invasive trachelectomies with median follow-up times of 48 and 26 months, respectively. They reported recurrence rates of 3.3% for abdominal trachelectomy and 0% for laparoscopic trachelectomy and median death rates of 1.5% for abdominal trachelectomy and 0% for laparoscopic trachelectomy. Additionally, they reported a median 5-year OS of 98.6% for abdominal trachelectomy, with no reports for laparoscopic trachelectomy [7]. Therefore, this review reports excellent oncological outcomes for both surgical routes and does not recommend a specific route. Only a small number of cases with stage IB2 cervical cancer were included in our meta-analysis; therefore, we could not perform a subgroup analysis based on the tumor size on the different surgical methods. A recent systematic review reported

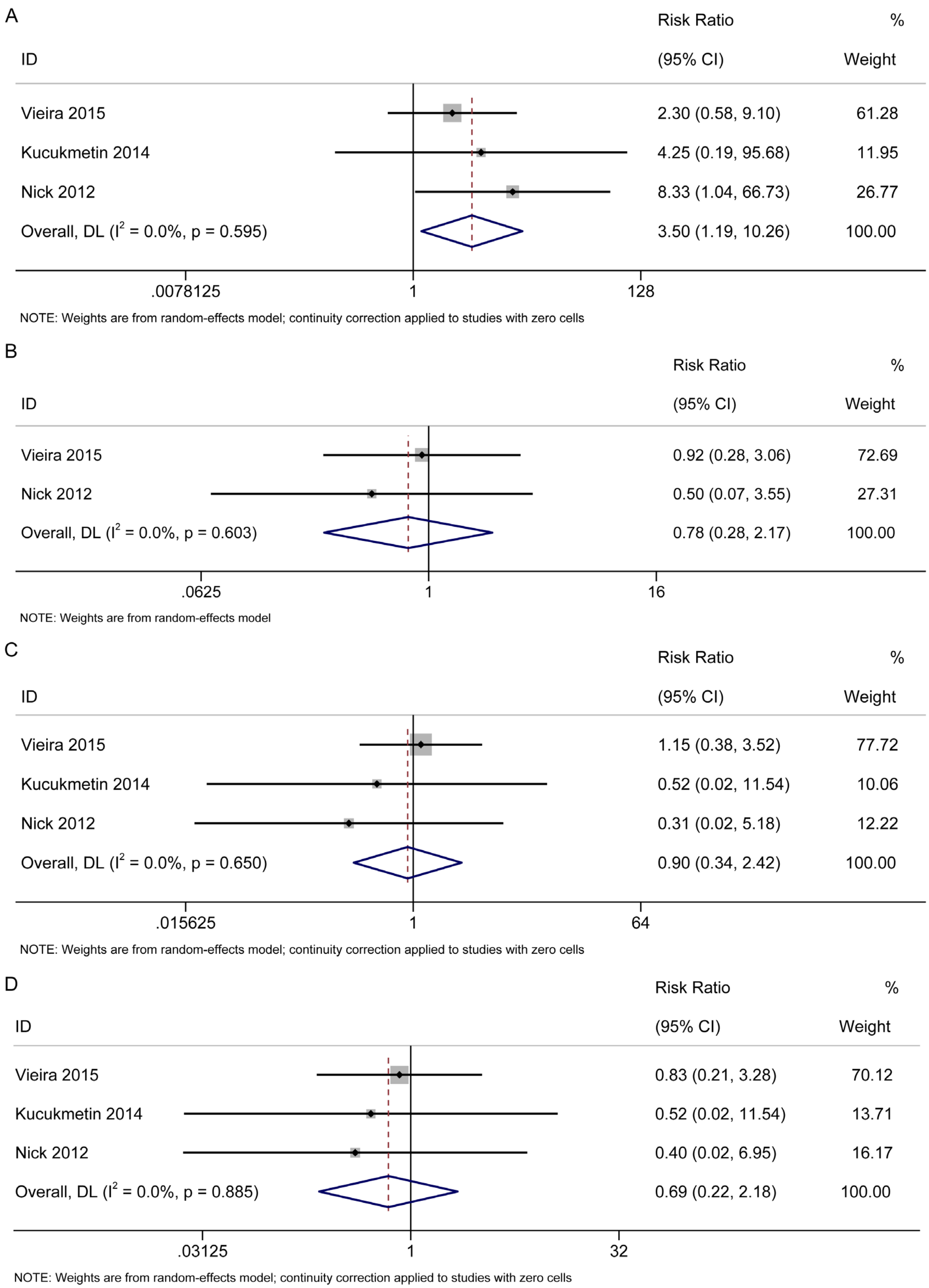

Figure 3. Forest plot of conversion to hysterectomy and surgical complication in the MIS and abdominal groups. A. Rates of conversion to hysterectomy. B. Rates of urinary tract complication. C. Rates of cerclage erosion. D. Rates of cervical stenosis.

a lower recurrence rate for stage IB2 cervical cancer with abdominal trachelectomy than with the laparoscopic route and the same recurrence rate for stage IB1 cervical cancer with both methods [8]. However, this study included individual cases and case series in the two groups, reducing the strength of the evidence. Furthermore, the oncological outcomes of the two surgical routes were similar; therefore, even though the use of minimally invasive routes is being questioned by the LACC trials and related studies, surgeons should not abandon minimally invasive trachelectomy in cases of stage IB1 cervical cancer. Nevertheless, the indications for fertility surgery in patients with stage IB2 cervical cancer should be carefully considered, and the risks should be discussed with patients who wish to preserve their fertility. Lastly, a meta-analysis of the safety of MIS in trachelectomy is needed for patients with stage IB2 cervical cancer.

The MIS group had less blood loss and shorter hospital stays than the abdominal surgery group. Although MIS was introduced later than abdominal trachelectomy, their operative times were not significantly different. We believe that because of the rare nature of this type of surgery, several included retrospective analyses were conducted in well-known institutions, and the doctors were proficient in laparoscopy; therefore, the difference caused by the learning curve may have had relatively little impact. Furthermore, our review of the available evidence suggests that the proportion of intraoperative conversion to radical hysterectomy was higher in the MIS group, mainly because the lesion remained close to another lesion or involved the incisal margin. The incidence of residual lesions in the specimens did not differ between the two surgical methods [13-15], verifying that the difference in conversion rates may not be associated with the type of technique [15].

The surgical route did not affect postoperative morbidity, including urinary tract complications, cerclage erosion, and cervical stenosis, consistent with previous studies. A previous review of 485 cases of laparoscopic trachelectomy reported that cervical stenosis was the most common postoperative complication, with an incidence rate of 9.5% [18]. Another review reported that 485 patients underwent abdominal trachelectomy, and the incidence rate of cervical stenosis was 9.5% [18]. Li et al. [19] reviewed 1,547 patients who underwent radical trachelectomy and reported no significant difference between the surgical approaches in the incidence of stenosis. Notably, cervical stenosis affects obstetrical outcomes and the quality of life of patients after trachelectomy; however, surgical dilatation can resolve most cases, and more attention should be paid to this issue after trachelectomy.

The main objective of a radical trachelectomy is to preserve fertility and ensure favorable oncological outcomes. Our meta-analysis, consistent with several previous studies, revealed no significant differences in fertility, term delivery, and preterm delivery rates between patients who attempted to conceive in the MIS and abdominal groups. This indicates that the two surgical routes did not affect the reproductive rate [7, 9]. This contrasts previous studies that reported that the MIS group had a higher pregnancy rate than the abdominal surgery group [8, 20]. Notably, the different follow-up times in the MIS and abdominal trachelectomy groups in these studies may have affected the statistical findings on the reproductive outcome. Therefore, MIS for radical trachelectomy preserved fertility with satisfactory outcomes, making it an attractive approach.

This study has some limitations. First, due to the rarity of the surgical methods and differences in the patients' fertility requirements, conducting randomized controlled studies is difficult. Therefore, the literature included in this meta-analysis were all retrospective studies, leading to a defect in the research design. Second, the number of cases included was relatively limited because of the rarity of the surgical procedures. More high-quality controlled studies are expected to confirm the safety of laparoscopic applications in the future. Third, some data were presented in a form that could not be meta-analyzed with other literature data. Although we sent a letter to the authors seeking assistance, we did not receive any of the required data. Fourth, studies were insufficient to perform subgroup analysis based on tumor size and the use of laparoscopic versus robotic surgery. Finally, the follow-up time for the MIS and abdominal surgery groups in some studies varied, which may have affected pregnancy and tumor outcomes. Longer follow-up periods are required in future studies.

In conclusion, the current evidence shows that laparoscopic and abdominal radical trachelectomies have similar efficacy in treating patients with early cervical cancer, with no significant differences in survival, tumor recurrence rate, and mortality rate. Furthermore, both methods showed no significant differences in pregnancy-related outcomes. However, owing to the limited number of studies, more high-quality cohort studies are required.

Disclosure of conflict of interest

None.

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Appendix. Embase OVID search strategy

#1 trachelectomy. ab, fx, hw, kf, kw, ot, rx, ti

#2 cervical cancer. ab, fx, hw, kf, kw, ot, rx, ti

#3 cervical carcinoma. ab, fx, hw, kf, kw, ot, rx, ti

#4 2 or 3

#5 1 and 4

#6 remove duplicates form 5

Key: ab=abstract, fx=floating subheading word, hw=heading word, kf=keyword heading word, kf=keyword heading word, kw=keyword heading, ot=original title, rx=rare disease supplementary concept, ti=title, tx