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REVIEW ARTICLE

Gynecology

Laparotomic versus robotic surgery in elderly patients with endometrial cancer: A systematic review and meta-analysis

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Abstract

Background: Although robotics has been shown to improve outcomes in some high-difficulty surgical category patients, it is unclear if such an approach may improve outcomes in elderly patients with endometrial carcinoma (EC).

Objective: To compare robotic and laparotomic surgery in the treatment and staging of elderly EC patients.

Materials and methods: A systematic review and meta-analysis was performed assessing the risk of overall, intra-operative, and peri-operative complications associated with the surgical approach (laparotomic vs robotic) for elderly patients with EC by relative risk (RR). Pooled means ± standard deviation of length of stay were compared with the unpaired *t* test. Subgroup analyses for overall complications were performed based on different age cut-offs (>70, >65, and >75 years) and severity of complications (minor and major). A value of P less than 0.05 was considered significant.

Results: Five studies with 7629 EC patients were included. Pooled RR for robotic compared with laparotomic surgery was 0.40 ($P < 0.001$) for overall, 0.46 ($P = 0.18$) for intra-operative, and 0.43 ($P < 0.001$) for peri-operative complications. Pooled difference between means ± standard deviation of length of stay for robotic versus laparotomic surgery was −3.34 ($P < 0.001$). At subgroup analyses, pooled RR of overall complications for robotic surgery versus laparotomic surgery was 0.34 ($P < 0.001$) in the >70 years, 0.51 ($P < 0.01$) in the >65 years, 0.20 ($P = 0.12$) in the >75 years groups. Pooled RR was 0.50 ($P = 0.1$) in the minor complications subgroup, and 0.42 ($P = 0.002$) in the major complications subgroup.

Conclusion: Robotics might be a viable alternative to the laparotomic approach for EC in elderly patients because it significantly decreases the risk of overall and peri-operative complications (mainly major complications), and the length of stay when compared with laparotomy. The decrease in risk of overall complications is greater with increasing patient age.

Antonio Mollo and Renato Seracchioli contributed equally to this study.

KEYWORDS
cancer, endometrium, laparotomy, robotics, surgery, tumor

1 | INTRODUCTION

Endometrial carcinoma (EC) is the most common gynecologic malignancy in the western world, with an increase in both incidence and mortality in the last two decades.[1–7] Patient age affects both EC incidence and mortality.[8–11] In fact, EC occurs mostly after the menopause, with median age at diagnosis being 61 years.[12] On the other hand, survival rate declines with age: patients aged 20–49 years at diagnosis have a disease-specific 5-year survival rate of 89.7%, whereas those older than 70 years at diagnosis have a disease-specific 5-year survival rate of 78.6%.[13] Moreover, age also affects surgery, which has a critical role in EC treatment, staging, and prognosis.[14,15] In particular, in patients undergoing laparotomy for EC, it has been demonstrated that as age increases, the risk of post-operative surgical complications, medical complications, length of stay in hospital, and mortality also increase.[16] It appears crucial to identify the best surgical approach in elderly patients with EC.

The development of minimally invasive surgery techniques such as laparoscopic and robotic surgery has revolutionized the treatment of gynecologic cancers and has become the preferred approach for the treatment of apparent early-stage disease.[17–19] Robotic surgery has been shown to improve outcomes even more than laparoscopy in some high-difficulty surgical categories, such as obese patients.[20–22] However, it is unclear if the robotic approach can improve outcomes in elderly patients with EC.

The aim of this study was to compare robotic and laparotomic surgery in the treatment and staging of elderly EC patients.

2 | MATERIALS AND METHODS

2.1 | Study protocol

The study was performed according to an a priori defined protocol for systematic review and meta-analysis. The whole study was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement and checklist.[23] Each review stage was performed by two blinded authors, and disagreements were solved by a discussion with other authors.

2.2 | Search strategy

Several searches were performed using MEDLINE, Google Scholar, EMBASE, Web of Sciences, Scopus, ClinicalTrial.gov, OVID, and Cochrane Library as electronic databases, from their inception to March 2020. Several combinations of the following words were adopted: "endometr*"; "neoplasia"; "carcinoma"; "cancer"; "tumor"; "tumour"; "malignancy"; "surgery"; "robotic"; "laparotomy"; "open"; "minimally invasive"; "age"; "old"; "years"; "elderly". Review of articles also included the abstracts of all references retrieved from the eligible articles.

2.3 | Study selection

All peer-reviewed studies which allowed extraction of data about complications associated with laparotomic and robotic surgery for staging and treatment of elderly patients with EC were included. Exclusion criteria were: studies with overlapping data with other included studies, case reports, and reviews. No restriction was applied for language.

2.4 | Risk of bias within studies assessment

The assessment of risk of bias within studies was performed following the Methodological Index for Non-Randomized Studies (MINORS).[24] Eight domains related to risk of bias were assessed in each included study: (1) Aim (i.e. if the aim was clearly stated); (2) Inclusion of consecutive patients (i.e. if all eligible patients were included in the study); (3) Prospective data collection (i.e. if data collection was performed following an a priori defined study protocol); (4) End points (i.e. if end points considered were appropriate to the aim); (5) Unbiased assessment of the study end point (i.e. if the study endpoint was evaluated without bias); (6) Follow up (i.e. if the follow up was appropriate to assess the study end points); (7) Loss to follow up (i.e. if no more than 5% of patients were lost to follow up); and (8) Prospective calculation of the study size (i.e. if information about the level of statistical significance and estimates of power when comparing the outcomes were reported). Authors judged each domain as "low risk", "unclear risk", or "high risk" of bias based on whether data were "reported and adequate", "reported but inadequate", or "not reported", respectively.

2.5 | Data extraction

Data from included studies were extracted without modification of the original data according to the PICO (Population, Intervention or risk factor, Comparator, Outcomes) items.[23] The "Population" of our study was patients over the age cut-off who underwent surgery for EC. The age cut-off was 70 years for two studies,[25,26] 65 years for two studies,[27,28] and 75 years for the remaining study.[29] "Intervention" (or risk factor) was robotic surgery for EC. "Comparator" was laparotomic surgery for EC. "Outcomes" were divided into primary outcome and secondary outcomes. Primary outcome was the rates of overall complications associated with the surgical approach, whereas secondary outcomes were the rate of intra-operative complications, the rate of peri-operative complications, and the mean length of stay in hospital. In the case of data reported as percentage, the number of events was calculated from the total number of patients in the group.

2.6 | Data analysis

The risk of overall complications (primary outcome), intra-operative complications, and peri-operative complications (secondary outcomes) associated with the surgical approach (laparotomic vs robotic) for elderly patients with EC was assessed by calculating relative risk (RR). The RR was calculated for each included study and as pooled estimate, and was graphically reported on forest plots, with 95% confidence interval (CI). Statistical significance of RR comparing the laparotomic and robotic groups was assessed using the *Z* test with significant *P* value being <0.05.

As another secondary outcome, the means ± standard deviation (SD) of length of stay in hospital (in days) associated with the surgical approach (laparotomic vs robotic) for elderly patients with EC were calculated for each included study and as pooled estimate, and it were graphically reported on forest plot, with 95% CI. Means ± SD were compared between the laparotomic and robotic groups by using the unpaired *t* test with significant *P* value less than 0.05.

The random effect model of DerSimonian-Laird was adopted for all analyses.

Statistical heterogeneity among studies was evaluated by adopting the inconsistency index I^2: heterogeneity was judged as null for $I^2 = 0$, insignificant for $0 < I^2 \leq 25\%$, low for $25 < I^2 \leq 50\%$, moderate for $50 < I^2 \leq 75\%$ and high for $I^2 > 75\%$, as previously reported.[30-33]

Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) was used for the analysis.

Additional analyses were performed as subgroup analyses. Some subgroups were based on the age cut-off of patients adopted in the included studies: 70, 65, and 75 years.

Other subgroups were based on severity of complications: minor and major. We defined minor complications as grade I–II complications from the Clavien-Dindo classification,[34] and major complications as grade III–V complications.

In each subgroup, the risk of overall complications associated with the surgical approach (laparotomic vs robotic) for patients with EC was assessed as described for the main analyses.

3 | RESULTS

3.1 | Study selection

A total of 378 studies were identified through electronic searches; 140 studies remained after removal of duplicates, 32 after title screening, and 11 after abstract screening. After assessment for eligibility, five studies with 18 802 patients were included in the qualitative and quantitative analyses[25–29] (see Figure S1).

3.2 | Characteristics of the included studies and patients

All the included studies were designed as retrospective cohort studies.

Of the 18 802 patients, 7629 were over the age cut-off. The age cut-off was 70 years for two studies,[25,26] 65 years for two studies,[27,28] and 75 years for one study.[29] Of patients over the age cut-off, 6130 underwent laparotomic surgery for EC, and 1472 underwent robotic surgery (Table 1). The body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) of patients ranged from 17 to 50, with no significant difference between laparotomic and robotic groups in two studies,[25,28] and a significantly lower BMI in the robotics group in one study[26] (Table 2). From the included studies with available data, no significant difference was reported between laparotomic and robotic groups for FIGO (the International Federation of Gynecology & Obstetrics) stage of EC,[25,26] American Society of Anesthesiologists score,[28] and the Charlson comorbidity index score[26]; the latter was significantly lower in the robotic group in one study[27] (Table 2). No data about genetic or other clinical conditions underlying EC pathogenesis was reported in the included studies.

Characteristics of surgery and data about primary and secondary outcomes are shown for each included study in Tables 3 and 4, respectively.

3.3 | Risk of bias within study assessment

All the included studies were judged at low risk of bias in the “Aim”, “Prospective data collection”, “End points”, “Unbiased assessment of the study end point”, “Follow up”, and “Loss to follow up” domains.

For the “Inclusion of consecutive patients” domain, all included studies were judged at unclear risk of bias because they did not report whether all eligible patients were included in the study, with the exception of one study, which was judged at low risk of bias.[25]

For the “Prospective calculation of the study size”, all included studies were judged at unclear risk of bias because they did not report information about the level for statistical significance and estimates of power when comparing the outcomes.

Authors’ judgements are reported graphically in the Supplementary material (Figure S2).

3.4 | Main analyses

All included studies were eligible for analysis of all outcomes, with the exception of the study by Backes et al.,[26] which was excluded

TABLE 1 Characteristics of the included studies

Study	Setting	Design	Study period	Study population	Patients over age cut-off, N			
					Age cut-off, y	Total	Laparotomy	Robotics
2016 Backes[26]	The Ohio State University Wexner Medical Center, Columbus and Florida Hospital Cancer Institute, Orlando	Retrospective cohort study	2003–2009	778	70	182	93	89
2014 Lavoue[25]	McGill University, Montreal	Retrospective cohort study	2003–2007 2008–2013	472	70	163	50	113
2014 Doo[28]	University of Colorado, Aurora	Retrospective cohort study	2010–2012	228	65	73	47	26
2016 Guy[27]	University of Colorado School of Medicine, Aurora and Columbia University, New York	Retrospective cohort study	2008–2010	16 980	65	7142	5914	1228
2016 Bourgin[29]	Centre Hospitalier Universitaire de Rennes, Rennes	Retrospective cohort study	2006–2014	344	75	69	26	16
Total				18 802	65–75	7629	6130	1472

TABLE 2 Characteristics of patients in the included studies[a]

Study	Age, years		BMI			FIGO Stage, n					Charlson comorbidity index score			ASA score				
						Lap.		Rob.						Lap.		Rob.		
	Lap.	Rob.	Lap.	Rob.	*P*	I–II	III–IV	I–II	III–IV	*P*	Lap.	Rob.	*P*	1–2	≥3	1–2	≥3	*P*
2016 Backes[26]	75 (70–86)	75 (70–92)	30 (17–49)	28 (19–50)	<0.001	71	22	77	12	0.078	–	–	–	–	–	–	–	–
2014 Lavoue[25]	76.8 ± 4.6	77.9 ± 5.4	29.3 ± 6.6	29.5 ± 6.7	0.87	38	12	87	26	0.30	–	–	–	66	47	28	22	0.86
2014 Doo[28]	73.1 ± 7.0		30.2 ± 7.8		0.42	–	–	–	–	–	8.7 ± 3.3	7.6 ± 2.8	0.15	–	–	–	–	–
2016 Guy[27]	73.6 ± 6.7	73.4 ± 6.7	–		–	–	–	–	–	–	2.6 ± 1.1	2.5 ± 0.8	<0.001	–	–	–	–	–
2016 Bourgin[29]	80 (75–89)		27 ± 6.5		–	–	–	–	–	–	–	–	–	–	–	–	–	–

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); Lap., laparotomic surgery group; Rob., robotic surgery group; SD, standard deviation.

[a]Values are given as mean ± standard deviation or as mean (range).

TABLE 3 Characteristics of surgery in the included studies[a]

Study	Hyster-ectomy	Oophor-ectomy	Lymph node dissection: Pelvic Lap.	Pelvic Rob.	Pelvic *P*	Para-aortic Lap.	Para-aortic Rob.	Para-aortic *P*
2016 Backes[26]	100	100	87	98	0.007	77	67	0.18
2014 Lavoue[25]	100	100	8.4 ± 5.4	8.8 ± 4.1	0.81	–		–
2014 Doo[28]	98.6	98.6	67.1		0.42	52.1		0.09
2016 Guy[27]	100	97.5	71.1[b]	79.2[b]	<0.001[b]	–		–
2016 Bourgin[29]	100	100	–		–	–		–

Abbreviations: Lap., laparotomic surgery group; Rob., robotic surgery group.

[a]Values are given as mean ± standard deviation or as percentage.

[b]Data refer to unspecified lymph node dissection.

TABLE 4 Primary and secondary outcomes in laparotomic and robotic surgery groups of patients with endometrial cancer over the age cut-off[a]

Study	Sample size Lap.	Sample size Rob.	Overall complications Lap.	Overall complications Rob.	Intra-operative complications Lap.	Intra-operative complications Rob.	Peri-operative complications Lap.	Peri-operative complications Rob.	Length of stay, d Lap.	Length of stay, d Rob.	Length of stay, d *P*
2016 Backes[26]	93	89	90	29	16	2	74	27	4	1	0.001
2014 Lavoue[25]	50	113	38	30	5	6	33	24	8.0 ± 5.8	3.1 ± 6.3	0.000
2014 Doo[28]	47	26	35	7	7	1	28	6	4.4 ± 2.0	2.2 ± 1.9	<0.01
2016 Guy[27]	5914	1228	2832	325	242	72	2590	253	5.1 ± 4.90	2.00 ± 2.09	<0.001
2016 Bourgin[29]	26	16	8	1	2	0	6	1	10.7 ± 7.9	4.5 ± 3.3	–

Abbreviations: Lap., laparotomic surgery group; Rob., robotic surgery group.

[a]Values are given as number or as mean ± standard deviation.

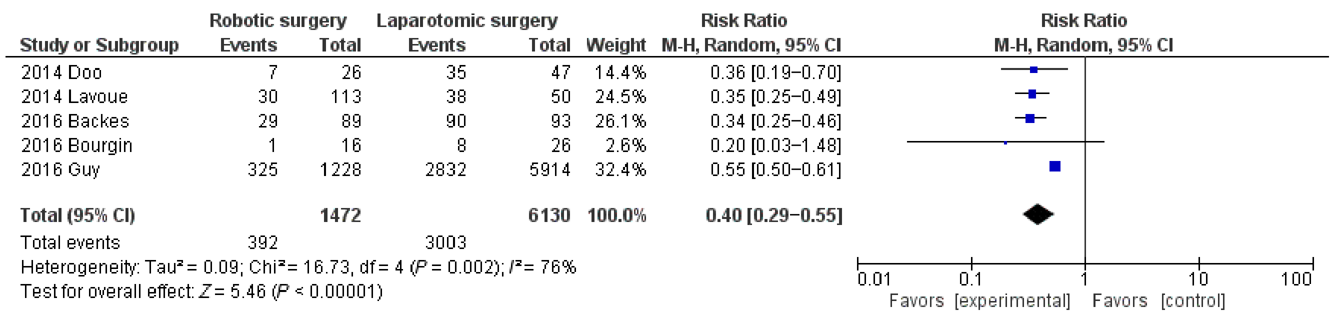

FIGURE 1 Forest plot of individual studies and pooled relative risk for overall complications in robotic surgery and laparotomic surgery groups of patients treated for endometrial cancer [Colour figure can be viewed at wileyonlinelibrary.com]

from analysis about length of stay in hospital because it did not report the outcome as mean ± SD.

Pooled RR of overall complications for robotic surgery compared with laparotomic surgery for EC was 0.40 (95% CI 0.29–0.55, $P < 0.001$, with moderate heterogeneity ($I^2 = 76\%$) (Figure 1).

Pooled RR of intra-operative complications for robotic surgery compared with laparotomic surgery for EC was 0.46 (95% CI 0.15–1.42, $P = 0.18$), with high heterogeneity ($I^2 = 76\%$) (Figure 2). Pooled RR of peri-operative complications for robotic surgery compared with laparotomic surgery for EC was 0.43 (95% CI 0.37–0.50, $P < 0.001$), with insignificant heterogeneity ($I^2 = 14\%$) (Figure 3). Pooled difference between means ± SD of length of stay in hospital for robotic and laparotomic surgery was −3.34 (95% CI −4.36 to −2.31, $P < 0.001$) with moderate heterogeneity ($I^2 = 70\%$) (Figure 4).

3.5 | Additional analyses

Two studies were included in the 70 years cut-off subgroup,[25,26] two studies in the 65 years subgroup,[27,28] and one study in the 75 years subgroup.[29]

Pooled RR of overall complications for robotic surgery compared with laparotomic surgery for EC was 0.34 (95% CI 0.27–0.43, $P < 0.001$, $I^2 = 0\%$) in the 70 years subgroup (Figure 5a), 0.51 (95% CI

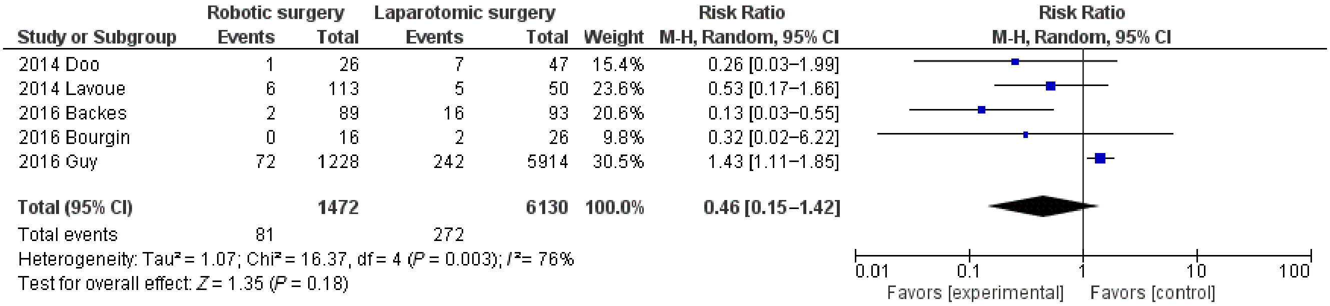

FIGURE 2 Forest plot of individual studies and pooled relative risk for intra-operative complications in robotic surgery and laparotomic surgery groups of patients treated for endometrial cancer [Colour figure can be viewed at wileyonlinelibrary.com]

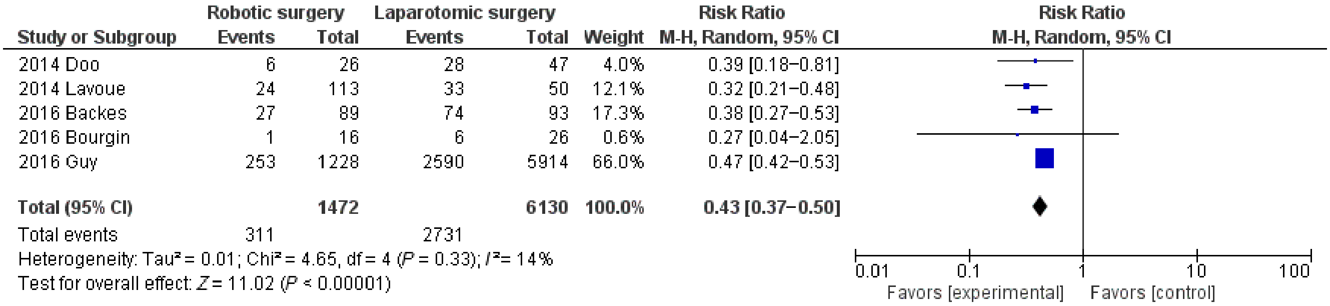

FIGURE 3 Forest plot of individual studies and pooled relative risk for peri-operative complications in robotic surgery and laparotomic surgery groups of patients treated for endometrial cancer [Colour figure can be viewed at wileyonlinelibrary.com]

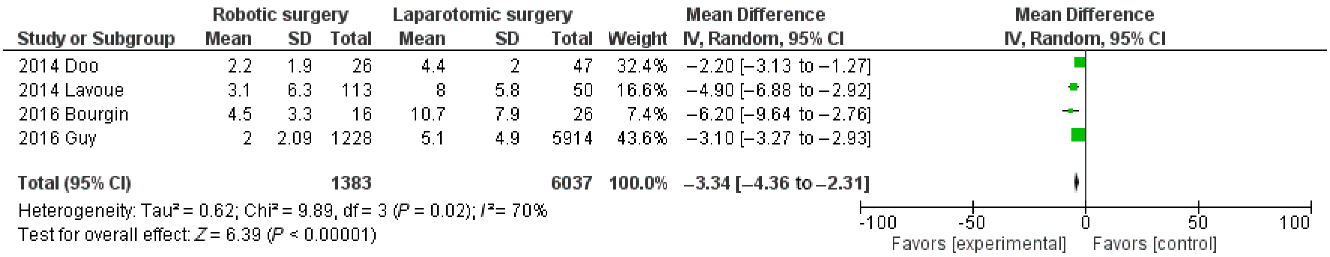

FIGURE 4 Forest plot of individual studies and pooled mean ± standard deviation (SD) for length of stay in hospital in robotic surgery and laparotomic surgery groups of patients treated for endometrial cancer [Colour figure can be viewed at wileyonlinelibrary.com]

0.37–0.71, $P < 0.001$, $I^2 = 37\%$) in the 65 years subgroup (Figure 5b), and 0.20 (95% CI 0.03–1.48, $P = 0.12$; I^2 not applicable) in the 75 years subgroup (Figure 5c).

All included studies were suitable for the subgroup analysis of severity of complications. Pooled RR of overall minor complications for robotic surgery compared with laparotomic surgery for EC was 0.50 (95% CI 0.21–1.16, $P = 0.1$), with moderate heterogeneity ($I^2 = 84\%$) (Figure 6a).

Pooled RR of overall major complications for robotic surgery compared with laparotomic surgery for EC was 0.42 (95% CI 0.25–0.72, $P = 0.002$), with moderate heterogeneity ($I^2 = 75\%$) (Figure 6b).

4 | DISCUSSION

This study shows that robotic surgery decreases the risk of overall and peri-operative complications, and the length of stay in hospital when compared with laparotomy in the treatment and staging of elderly patients with EC. In particular, the risk decreased about 2.5 times for overall and peri-operative complications, and the length of stay decreased by about 3.5 days. The decrease in risk of overall complications was greater when the age-cut off went up, with a five-fold reduced risk in patients over 75 years of age. Moreover, the increase in the risk of overall complications mainly regarded major complications. On the other hand, no significant difference was found in intra-operative complications and overall minor complications.

Such findings may be due to the advantages of robotic surgery that involve both the surgeon and the patient. Robotic surgery makes use of a sophisticated surgical platform capable of reproducing, by miniaturizing them, the movements of the human hand within the body cavity or within the operating field.[35,36] It offers the possibility of seeing the operating field in three dimensions, and by filtering and making any operator tremors almost impossible, it eliminates the typical laparoscopic fulcrum controlled by the surgeon and allows

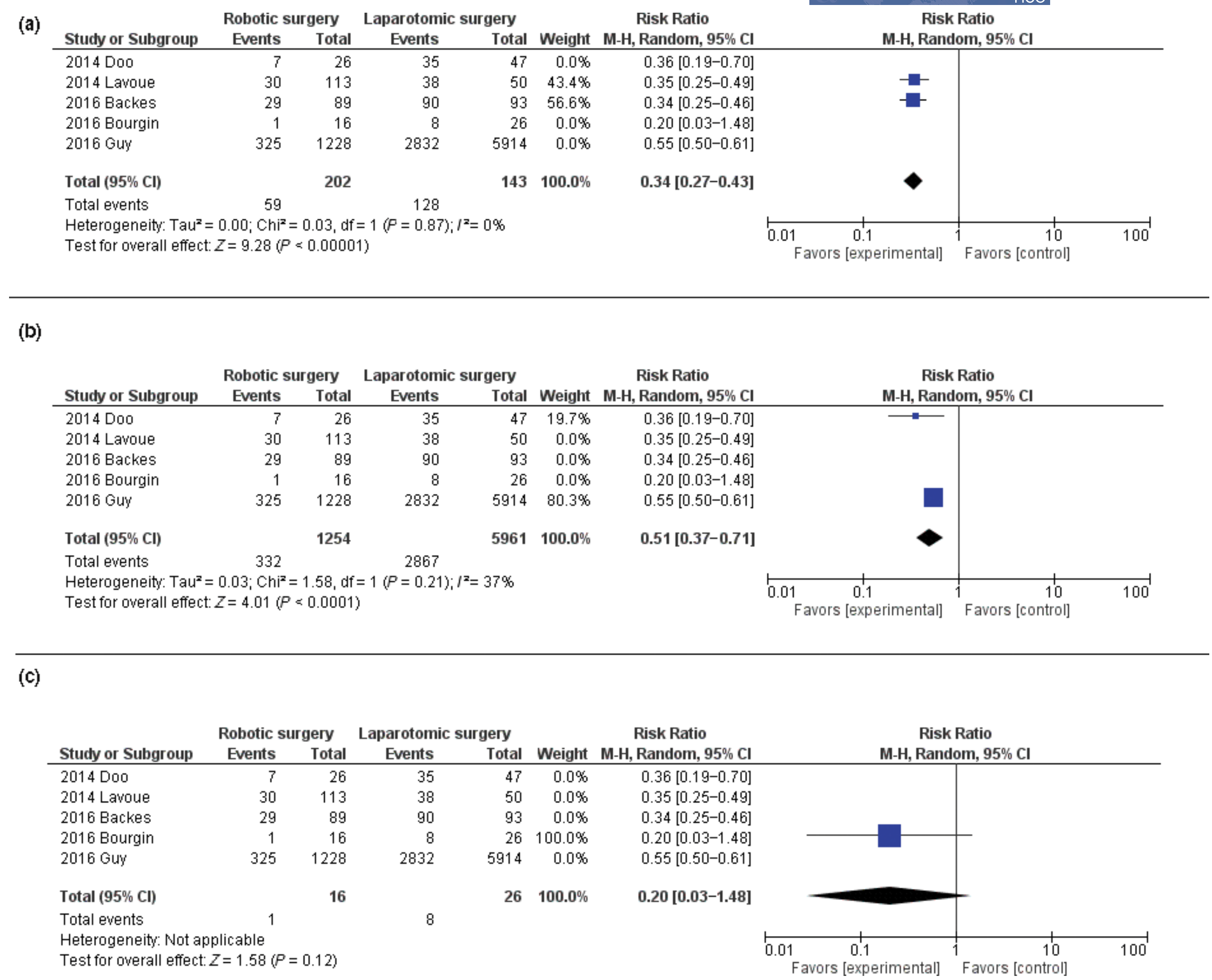

FIGURE 5 Forest plot of individual studies and pooled relative risk for overall complications in robotic surgery and laparotomic surgery groups of patients treated for endometrial cancer stratified for age cut-off as follows: (a) 70 years; (b) 65 years; (c) 75 years [Colour figure can be viewed at wileyonlinelibrary.com]

more natural movements typical of open surgery. In this way, it increases the ease of access and the precision of surgery, especially in narrow spaces, reducing the maneuverability and visibility challenges that surgeons face in confined spaces such as the pelvis.[35–37] Such surgical advantages become even greater in high-difficulty surgical categories, such as obese patients.[38] Concerning patient advantages, robotics requires minimal incisions with a significant decrease in post-operative pain, blood loss, and therefore the need for transfusions, and peri-operative and post-operative infections. This would explain the decrease in length of stay in hospital.

To date, the main limiting factor in the use of robotics is the cost. In fact, in cost-effectiveness analyses, robotic surgery is more expensive compared with traditional laparoscopy and laparotomy.[39] The median actual costs of the robotic surgery are 35% higher per patient than the costs related to traditional laparoscopy.[40,41] Amortization of the robot console and costs involved with robot instrumentation are the major determinants of the incremental costs related to robotic surgery.[42,43] However, amortization may be minimized by increasing the number of operations and by using some reusable devices for multiple operations.[44–46] In addition, the significant decrease in complications and length of stay that we found in elderly patients with EC may also help to reduce the long-term costs of robotic surgery.

However, regardless of the cost issue, decreasing overall and peri-operative complications of surgery is critical in elderly women with EC, who are a high-risk category of patients. Indeed, because of age, elderly patients had significantly higher rates of perioperative surgical complications including ileus, thromboembolic events, cardiac events, wound infections, and postoperative hemorrhage compared with younger patients.[47] Age also affects survival in EC patients[13]; robotics might help to improve oncological and surgical outcomes and quality of life in this high-risk category of EC patients.

This study may be the first meta-analysis comparing robotic and laparotomic surgery in the treatment and staging of elderly patients with EC. We found significant differences in complications and length of stay, which might recommend robotics as a viable alternative to laparotomy for treatment and staging of EC in elderly patients.

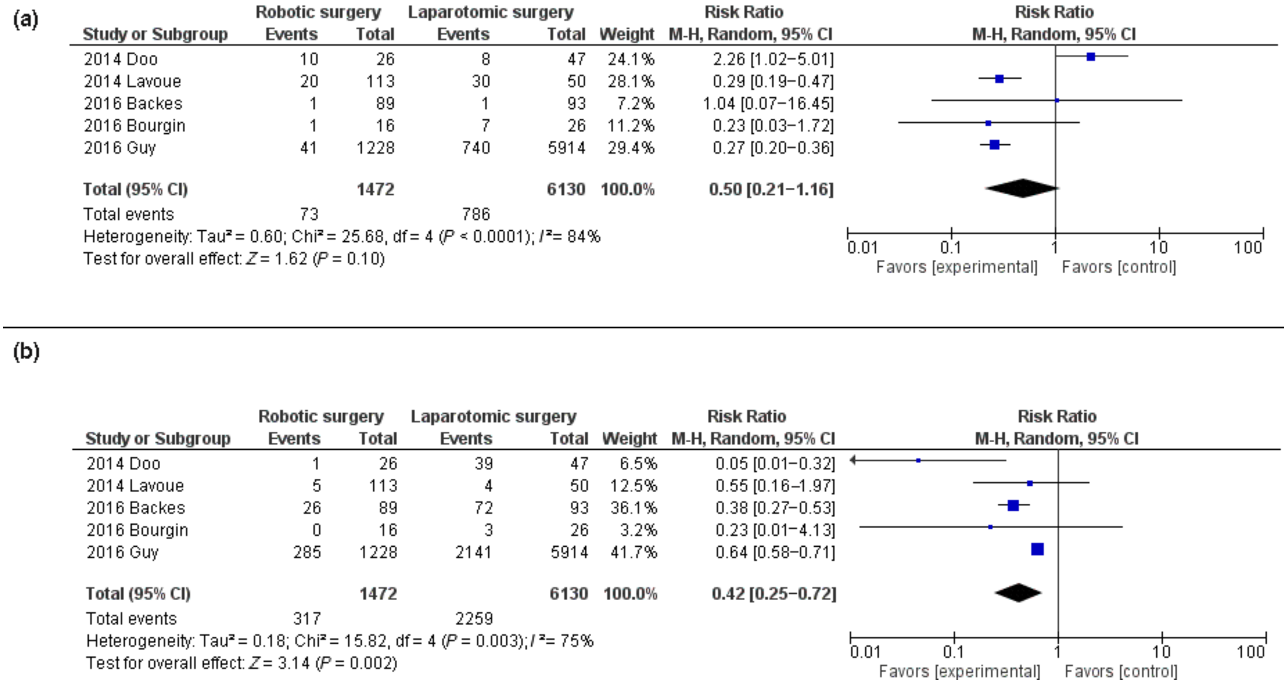

FIGURE 6 Forest plot of individual studies and pooled relative risk for overall complications in robotic surgery and laparotomic surgery groups of patients treated for endometrial cancer stratified for severity of complications as (a) minor complications and (b) major complications [Colour figure can be viewed at wileyonlinelibrary.com]

Moreover, such findings might be relevant to elderly patients requiring surgery for other diseases, either benign or malignant.

However, several limitations may affect our findings. First, a limitation may be the retrospective design of the included studies. After the Laparoscopic Approach to Cervical Cancer (LACC) Trial,[48] limitations related to retrospective design have been highlighted in drawing conclusions. Therefore, despite the quality of the included studies being high (as shown by the assessment of risk of bias within studies), further prospective studies are necessary to confirm these findings. Second, data from the included studies did not allow comparisons about survival outcomes among the surgical approaches. For these outcomes, further studies assessing this subset of EC patients are needed. Third, data from the included studies did not allow us to stratify analysis based on the extension of surgical staging for EC nor on the FIGO stage of EC. However, no significant difference was reported in the included studies between robotic and laparotomic groups.

In conclusion, robotics might be recommended as a viable alternative to the laparotomic approach for elderly patients with EC because it significantly decreases the risk of overall and peri-operative complications (mainly major complications), and the length of stay in hospital when compared with laparotomic surgery for treatment and staging of elderly patients with EC. Moreover, the decrease in risk of overall complications is greater with increasing patient age.

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[Correction added on 07-May-2022, after first online publication: CRUI-CARE funding statement has been added.]

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

AR conception, protocol, data analysis, manuscript preparation, results interpretation, disagreement resolutions; AT conception, protocol, data analysis, manuscript preparation, results interpretation, disagreement resolutions; DR protocol, study selection, data extraction, risk of bias assessment, manuscript preparation, results interpretation; DB protocol, study selection, data extraction, risk of bias assessment, manuscript preparation, results interpretation; MV protocol, study selection, data extraction, risk of bias assessment, manuscript preparation, results interpretation; PV protocol, manuscript preparation, results interpretation, disagreement resolutions; MG protocol, manuscript revision, results interpretation, disagreement resolutions, supervision; PC protocol, manuscript revision, results interpretation, disagreement resolutions, supervision; LI protocol, manuscript revision, results interpretation, disagreement resolutions, supervision; AM conception, protocol, manuscript revision, results interpretation, disagreement resolutions, supervision; RS conception, protocol, manuscript revision, results interpretation, disagreement resolutions, supervision.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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