## Application of Enhanced Recovery After Surgery Pathways in Patients Undergoing Laparoscopic Cholecystectomy With and Without Common Bile Duct Exploration

A systematic review and meta-analysis

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**ABSTRACT:** Many researchers have implemented enhanced recovery after surgery (ERAS) pathways for laparoscopic cholecystectomy (LC) and found it effective over conventional care. This review investigates the efficacy and safety of such pathways compared to conventional practices. PubMed Central/Medline, Scopus, Ovid and clinicaltrials. gov were searched using relevant keywords to identify studies in which ERAS pathways for LC were compared to conventional pathways. The primary outcome was length of stay (LOS) from the day of surgery and the secondary outcomes were pain scores, postoperative nausea/vomiting (PONV), readmissions (within 30 days after surgery), complications (medical and surgical), time to first flatus and cost. Out of 590 articles identified, six studies (n = 1,489 patients) fulfilled the inclusion criteria and were used for qualitative and quantitative analysis. On pooled analysis, LOS, time to first flatus, PONV and pain scores were significantly less in the ERAS group than in the conventional one, while readmission and complications were comparable in both groups.

*Keywords:* Cholecystectomy; Enhanced Recovery After Surgery; Laparoscopy; Meta-Analysis; Perioperative Care; Systematic Review.

APAROSCOPIC CHOLECYSTECTOMY (LC) IS A minimally invasive surgical procedure performed in patients with acute or chronic cholecystitis, symptomatic cholelithiasis, biliary dyskinesia, acalculous cholecystitis, gallstone pancreatitis and gallbladder masses or polyps. Over the years, LC has been established as a safe procedure that facilitates early recovery compared to the open cholecystectomies that used to be performed earlier. However, the usual problems with LC are postoperative nausea/vomiting (PONV) and acute postoperative pain, which can interfere with the early discharge process. It can also contribute to respiratory and cardiovascular events postoperatively.<sup>1</sup>

Enhanced recovery after surgery (ERAS) pathways are patient-centred, evidence-based pathways developed by multidisciplinary teams for a surgical specialty and facility culture to reduce the patient's surgical stress response, optimise their physiologic function and facilitate recovery.<sup>2</sup> ERAS pathways involve evidencebased preoperative, intraoperative and postoperative pathways and have demonstrated faster patient recovery, early feeding and mobilisation, early discharge from the hospital and better patient satisfaction.<sup>3,4</sup> The conventional pathway was employed in the era before ERAS and involved a preoperative fasting of six hours or more, mandatory bowel preparation, extended postoperative nil by mouth (at times till the following day), retention of tubes *in situ* (nasogastric tube, Foley catheter), limited use of short-acting medications (opioids, muscle relaxants) and intraoperative warming of patients, extended hospital stays, no strict postoperative mobilisation policies and opioid-based postoperative analgesia.

Several researchers have investigated the advantages and efficacy of implementing ERAS pathways in patients undergoing LC.<sup>5-11</sup> These studies compared ERAS pathways with a conventional approach in relation to various outcomes, such as length of stay (LOS) in the hospital, pain scores, surgical site infections (SSI), readmission rate (RR) and the timing of flatus passage, as well as adverse effects, such as PONV. Although ERAS pathways are being used in many centres with variable compliance, there is no clarity regarding whether the pathways are providing favourable postoperative outcomes and improved patient care.

The present systematic review and meta-analysis (SRMA) was conducted to compare the efficacy and advantages of implementing ERAS pathways with those of conventional pathways in adult patients undergoing LC.

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## Methods

#### SEARCH STRATEGY AND CRITERIA

The protocol for this systematic review was registered with PROSPERO, an international prospective register of systematic reviews (registration number: CRD42022358554). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and the Cochrane Handbook for Systematic Reviews of Interventions were followed for this SRMA.<sup>12</sup> PubMed Central/Medline (National Library of Medicine, Bethesda, USA), the Cochrane Reviews Library (Cochrane, London, UK), Scopus (Elsevier, Amsterdam, The Netherlands), Ovid and clinicaltrials.gov databases (National Library of Medicine) were searched for studies published between 2000 and July 2022. The language was restricted to English. The search approach used the following keywords: 'ERAS' or 'enhanced recovery after surgery' or 'fast track surgery' and 'laparoscopic cholecystectomy'.

# STUDY SELECTION AND DATA EXTRACTION

The present study covered research comparing ERAS routes with conventional pathways in adult patients undergoing LC and studies comparing at least two ERAS pathway components with conventional pathways were taken into consideration. Studies that compared only one pathway and those that lacked a control group were excluded. Case reports, editorials, commentaries, reviews, publications with only abstracts and all other types of publications, such as theses and dissertations, were disregarded.

The titles and abstracts were separately reviewed by two of the authors (AN and HHM) and duplicates were removed. The final list of studies to be included was chosen after consideration by both the authors, who also read the complete texts. Any disagreements or inconsistencies were settled by a third author (NB). For studies in which data were not reported in the results or were not available in supplementary files, the corresponding author was contacted via email with a request for providing the necessary information to assess the study's suitability for analysis. Conference abstracts without sufficient details regarding study design or data were excluded from analysis.

Two of the authors gathered pertinent data, including author details, publication dates, sample size, age, gender and various ERAS route components. Studies that had less than two ERAS outcomes were excluded. The outcomes compared between the ERAS pathways and conventional care pathways were operative time, the timing of oral feeds, LOS (after surgery), readmission (within 30 days of surgery) and complications. The complications could be surgical (leak, surgical site infection) or medical (fever, sepsis, pneumonia). Any disagreements or inconsistencies were settled by a third author (NB).

#### METHODOLOGICAL QUALITY ASSESSMENT

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2) was used to assess the methodological quality and risk of bias of the included trials.<sup>13</sup> Six categories were taken into consideration for bias assessment: bias due to randomisation, bias due to deviation from intended intervention, bias due to missing data, bias due to outcome measurement, bias due to selection of reported result and overall bias. The quality of randomised trials was assessed independently by two of the authors (AN and NB) based on the Jadad score.<sup>14</sup>

#### META-ANALYSIS

After a qualitative review, a quantitative review of articles with quantitative statistical data was performed. All the studies that directly compared the outcomes between ERAS protocols and conventional care pathways in patients who underwent LC were included in the quantitative meta-analysis.

#### STATISTICAL ANALYSIS

The Mantel-Haenszel technique was used to assess dichotomous variables, and the risk ratio with the associated 95% confidence interval (CI) was determined. For units-unified continuous variables, the mean difference (MD) with the accompanying 95% CI was determined using the inverse variance approach. The continuous variables in mean and standard deviation were used for analysis. In case the values were presented as median and interquartile range (IQR), the median could be used as mean and the difference of IQR divided by 1.35 would give the standard deviation. The heterogeneity between studies was evaluated using the I<sup>2</sup> statistic, which was defined as follows: 0-40%: might not be important; 30-60%: may represent moderate heterogeneity; 50-90%: may represent significant heterogeneity; and 75-100%: considerable heterogeneity.<sup>15</sup> Review Manager Version 5.4.1 (Cochrane Collaboration, Software Update, Oxford, UK) was used for analysis.<sup>16</sup> The results were compared with the random effects model and fixed effects model, and the reliability of the combined results was eventually analysed according to the consistency degree of the results. When P > 0.01 and  $I^2$  <50%, the fixed effects model was used, and when *P* 

<0.01 and I<sup>2</sup> >50%, the random effects model was used for meta-analysis. In the event that at least 10 studies were included in the meta-analysis, it was decided to construct a funnel plot to determine if there was a publication bias.

## Results

#### RESULTS OF THE LITERATURE SEARCH

PubMed Central/Medline, the Cochrane Reviews Library, Scopus, Ovid and clinicaltrials.gov databases were searched for randomised controlled trials comparing ERAS pathways with conventional care pathways in patients undergoing LC. A total of 590 articles were identified by searching the abovementioned databases and registries. After removing duplicates and articles that were not relevant to the present study, 15 articles were identified for scrutiny. A total of 10 studies were considered eligible, of which four studies were excluded-study with no control group (n = 1), review article (n = 1), article with an active control group (n = 1) and unrelated primary and secondary outcomes (n = 1). Finally, six studies we included for analysis, which comprised a total of 1,489 patients (560 in ERAS group and 929 in control group) [Figure 1]. The corresponding author of one of the studies was contacted twice with a request for relevant data that was not available in the results but was described in the methodology. As the authors did not receive any reply from them, the study was excluded from analysis.17





#### STUDY CHARACTERISTICS

Out of the six studies selected, four studies compared ERAS pathways implemented for LC with conventional pathways.<sup>5–7,10</sup> The remaining two studies involved ERAS pathway implementation in common bile duct (CBD) exploration done along with LC, which was compared to LC with CBD exploration using conventional pathways.<sup>9,11</sup> Therefore, the pooled data of all six studies were analysed initially, following which they were divided into two groups: LC with ERAS and LC-CBD exploration with ERAS.9,11 The study by Kamel et al. had four groups: laparoscopic cholecystectomy-conventional, laparoscopic cholecystectomy-ERAS, open cholecystectomy-conventional and open cholecystectomy-ERAS.7 Each group comprised 20 patients, with a total sample size of 80. For pooled analysis, that study used 40 patients: 20 in laparoscopic cholecystectomy-conventional and 20 in laparoscopic cholecystectomy-ERAS.<sup>7</sup> The summary of all the studies included in the analysis is presented in Table 1.

#### RISK OF BIAS

The risk of bias within the trials according to RoB2 is shown in Figure 2. The summary plot of quality assessment is shown in Figure 3. Bias from the randomisation process was low in four studies and high in two studies.<sup>5–7,9–11</sup> Bias due to deviations from intended interventions (allocation concealment) was high in five studies,<sup>5-7,9,10</sup> and no information was available for one study.<sup>11</sup> Bias arising due to missing outcome data was low in four studies,5,6,9,10 and no information was available for two studies.<sup>7,11</sup> Bias in the measurement of outcome was low in three studies,<sup>6,7,9</sup> high in one and not known in two studies.<sup>5,10,11</sup> Bias arising due to the selection of reported result was low in one study and not known in five studies.<sup>5–7,9–11</sup> The overall bias was low in two studies and high in four studies.<sup>5-7,9-11</sup> The average modified Jadad score calculated was approximately 4, which is suggestive of the average quality of the studies included in the analysis.

#### PRIMARY OUTCOMES

#### Meta-analysis: LOS

LOS data were available for all six studies.<sup>5,6,9–11</sup> There were 560 patients in the ERAS group and 929 patients in the control group. On pooled analysis, the LOS of the ERAS group was found to be significantly shorter than that of the control group (MD = -31.37 [95% CI: -54.69–-8.05; P = 0.008]). A random effect model was applied (Tau<sup>2</sup> = 650.63, Chi<sup>2</sup> = 650.66, df = 4; P

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Authors and year of publication	Country	Type of study	Number of patients	Primary outcome	Secondary outcome	Conclusions
Wang <i>et al.</i> <sup>11</sup> (2017)	China	Randomised controlled trial	45 (22 -fast track, 23 - conventional)	Clinical indicators between both groups	Postoperative comfort	Fast-tracking improves patient satisfaction, postoperative quality of life without increases in complications
Akhtar <i>et al.</i> <sup>6</sup> (2020)	Pakistan	Randomised controlled trial	147 (73 - ERAS group, 74 -conventional group)	LOS hospital and cost of hospitalisation	Opioid use, surgical recovery scores	Reduction in LOS and total cost although post- discharge recovery scores were similar
Zhang <i>et al.</i> <sup>9</sup> (2020)	China	Retrospective cohort study	445 (148 - ERAS group, 297 - traditional group)	Comparison of stress response, postoperative complications and rehabilitation	Demography	Use of ERAS reduces stress response and postoperative complications and accelerates postoperative rehabilitation
Kamel <i>et al.</i> <sup>7</sup> (2021)	Egypt	Randomised controlled trial	80 (40 in each group)	LOS (hospital and ICU)	Postoperative pain score, passage of first flatus, postoperative nausea	There was decrease in postoperative hospitalisation with lower complications and little chance of readmission
Nechay <i>et al.</i> <sup>5</sup> (2021)	Russia	Randomised, prospective, non-blinded controlled trial	189 (88 - ERAS, 101 -control)	LOS postoperative	Readmission, postoperative pain, peristalsis recovery	There was improved postoperative recovery and reduced hospital stay in patients with ERAS without any increase in the rate of complications or re- admissions
Demouron <i>et</i> <i>al</i> . <sup>10</sup> (2022)	France	Two-step multicentre study: 1 <sup>st</sup> = feasibility study, 2 <sup>nd</sup> = case control study	623 (209 -ERAS, 414 -conventional)	LOS	Morbidity rate, readmission and reoperation rate	ERAS implementation for LC is feasible, effective and safe for patients

#### Table 1: Characteristics of the included studies

ERAS = enhanced recovery after surgery; LOS = length of stay; ICU = intensive care unit; LC = laparoscopic cholecystectomy.





Α	ERAS		Co	ntrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean SD	Total	Mean	SD	Total V	Veight	IV, Random, 95% Cl	IV, Random, 95% CI	
Demouron et al.10 (2022	)74.4 0	209	120	0	414		Not estimable		
Wang et al. <sup>11</sup> (2017)	194.4 40.8	22	278.4	81.6	23	13.9%	-84.00 (-121.4546.55)	<b>←</b>	
Kamel <i>et al.</i> 7 (2020)	28.8 9.84	20	37.2	16.56	20	21.2%	-8.40 [-16.84, 0.04]		
Nechay <i>et al.</i> 5 (2021)	24 18.14	88	45	20	101	21.5%	-21.00 [-26.44, -15.56]		
Akhtar et al.6 (2020)	28.93 9.55	73	40.54	11	74	21.7%	-11.61 [-14.94, -8.28]	+	
Zhang et al.9 (2020)	83.76 3.36	148	133.68	5.76	297	21.7%	-49.92 [-50.77, -49.07]	•	
Total (95% CI)		560			929 1	00.0%	-31.37 [-54.69, -8.05]		
Heterogeneity: Tau <sup>2</sup> = 6	i50.63; Chi <sup>z</sup> =	650.66,	-50 -25 0 25 50	n					
Test for overall effect: Z	= 2.64 (P= 0.	008)	Favours (experimental) Favours (control)	5					
В	ERAS		Contro	bl			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weigh	t M-H	I, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
Akhtar <i>et al.</i> <sup>6</sup> (2020)	3	73	6	74	37.7%	6 0	).51 [0.13, 1.95]		
Demouron et al.10 (2022	) 3	209	14	414	59.4%	6 0	).42 [0.12, 1.46]		
Kamel <i>et al.</i> 7 (2020)	0	20	0	20			Not estimable		
Nechay <i>et al.</i> <sup>5</sup> (2021)	1	88	0	101	2.9%	6 3.	44 [0.14, 83.34]		_
Wang <i>et al</i> . <sup>11</sup> (2017)	0	22	0	23			Not estimable		
T-1-1/05W 00					400.00		54 F0 00 4 077		
Total (95% CI)	_	412		632	100.09	6 0	.54 [0.23, 1.27]		
Total events			20						
Heterogeneity: Chi*:	= 1.45, df = 2	P = 0	1.48); I*=	0%			0.01	0.1 1 10	100
Test for overall effect	t Z = 1.41 (A	2 0.16	i)				F	avours [experimental] Favours [control]	
C	CDAC.		6	-			Mana Difference	Maan Difference	
Study or Subgroup	Moan SD	Total	Moan	en .	Total M	Voiaht	Wedit Difference	W Pandom 05% Cl	
Kernel at al 7 (0000)	1.2 5.20	20	7.2.1	2 60	20 4	17.206	6.001.12.42.0.421	iv, Kandoni, 554 Ci	
Kamel <i>et al.</i> ' (2020)	167 //	20	20.7	5.00	20	75.0%	-0.00[-12.43, 0.43]		
Nechay at $a^{5}$ (2017)	22 8 88	99	20.7	1.11	101 1	25.570	-13.00 [-10.00, -3.32]	-	
Thang et al 9 (2020)	10.36 0.00	148	23.84	0.08	207	20.4%	-4.48 [-4.50 -4.46]		
211ang 02 al. (2020)	13.30 0.1	140	23.04	0.00	201 1	30.470	-4.40 [-4.50, -4.40]	_	
Total (95% CI)		278			440 1	00.0%	-6.56 [-10.64, -2.48]	•	
Heterogeneity Tau <sup>2</sup> =	14 28: Chi <sup>2</sup> =	30.73	df=3(P<	0.000	01): P= 9	90%			
retoregeneng. rete	1 1. a. V. VIII	~~		0.000					
Test for overall effect 2	Z = 3.15 (P = 1)	0.002)			01/,1 = .	00,0		-20 -10 0 10 20	
Test for overall effect 2	Z = 3.15 (P = 1	0.002)			017,1 = .			-20 -10 0 10 20 Favours [experimental] Favours [control]	
Test for overall effect: 2	Z= 3.15 (P= 1 ERAS	0.002)	Contro	bl	017,1		Risk Ratio	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio	
Test for overall effect 2 D Study or Subgroup	ERAS Events	0.002) Total	Contro	ol Total	Weigh	t M-ł	Risk Ratio I, Fixed, 95% Cl	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% Cl	
Test for overall effect 2 D Study or Subgroup Kamel <i>et al.</i> ? (2020)	Z = 3.15 (P = 1 ERAS Events 1 1	0.002) Total 20	Contro Events 3	ol Total 20	Weigh 4.5%	t <u>M-H</u> 6 0	Risk Ratio I, Fixed, 95% Cl	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% Cl	
Test for overall effect 2 D Study or Subgroup Kamel <i>et al.</i> ? (2020) Zhang <i>et al.</i> <sup>9</sup> (2020)	ERAS Events 1 6	0.002) <u>Fotal</u> 20 148	Contro Events 3 35	ol <u>Total</u> 20 297	Weigh 4.5% 35.1%	t <u>M-H</u> 6 0	Risk Ratio I, Fixed, 95% Cl 1.33 (0.04, 2.94) 1.34 (0.15, 0.80)	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% Cl	
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Test for overall effect 2 D Study or Subgroup Karnel <i>et al.</i> <sup>7</sup> (2020) Zhang <i>et al.</i> <sup>9</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Karnel <i>et al.</i> <sup>7</sup> (2020)	Z= 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11	$rac{1}{20}$ $rac{1}{20}$ $rac{1}{48}$ $rac{2}{88}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$ $rac{2}{56}$	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 1001) Co 1 <u>Mean</u> 3	ol <u>Total</u> 20 297 101 <b>418</b> 0% ontrol <u>SD</u> 1.48	Weigh 4.5% 35.1% 60.4% 100.0%	t <u>M-H</u> 6 0 6 0 6 0 6 0 <u>Veight</u> 12.3%	Risk Ratio I, Fixed, 95% CI .33 (0.04, 2.94) .34 (0.15, 0.80) .37 (0.22, 0.64) .36 (0.23, 0.56) .36 (0.23, 0.56) .0.01 F Mean Difference IV, Fixed, 95% CI -0.45 [-1.58, 0.68]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI	100
Test for overall effect 2 <u>Study or Subgroup</u> Karnel <i>et al.</i> <sup>7</sup> (2020) Zhang <i>et al.</i> <sup>9</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) <u>Total (95% CI)</u> <u>Total events</u> Heterogeneity: Chi <sup>2</sup> = <u>Test for overall effect</u> <u>E</u> <u>Study or Subgroup</u> Karnel <i>et al.</i> <sup>7</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48	(P = 0)	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 0001) Co Mean 3 3 3	ol <u>Total</u> 20 297 101 <b>418</b> 0% ontrol <u>SD</u> 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0% Total V 20 101	t M-H 6 0 6 0 6 0 6 0 9 6 0 9 7 8 7.7%	Risk Ratio 4, Fixed, 95% Cl 1.33 (0.04, 2.94) 1.34 (0.15, 0.80) 1.37 (0.22, 0.64) 1.36 (0.23, 0.56) Mean Difference IV, Fixed, 95% Cl -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI	100
Test for overall effect 2 Study or Subgroup Kamel et al. <sup>7</sup> (2020) Zhang et al. <sup>9</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total events Heterogeneity: Chi <sup>2</sup> : Test for overall effect E Study or Subgroup Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>5</sup> (2021)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48	(P = 0)	Contro Events 3 35 43 81 1.98); I <sup>*</sup> = 0001) Co Mean 3 3	ol <u>Total</u> 20 297 101 <b>418</b> 0% ontrol <u>SD</u> 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0%	t <u>M-F</u> 6 C 6 C 6 C 6 C 6 C 6 C 6 C 7 6 O 7 7 8 7.7%	Risk Ratio 4, Fixed, 95% Cl 1.33 (0.04, 2.94) 1.34 (0.15, 0.80) 1.37 (0.22, 0.64) 36 (0.23, 0.56) 0.01 F Mean Difference IV, Fixed, 95% Cl -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI	100
Test for overall effect 2 Study or Subgroup Kamel et al. <sup>7</sup> (2020) Zhang et al. <sup>9</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS <u>Mean SD</u> 2.55 2.11 2 1.48	(P = 0) (P = 0)	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 1001) Co Mean 3 3	ol <u>Total</u> 20 297 101 <b>418</b> 0% ontrol <u>SD</u> 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0% Total V 20 101 4 101 4	t <u>M-H</u> 6 C 6 C 6 C 6 C 6 V <u>eight</u> 12.3% 87.7%	Risk Ratio 4, Fixed, 95% CI 1.33 (0.04, 2.94) 1.34 (0.15, 0.80) 1.37 (0.22, 0.64) 3.36 (0.23, 0.56) Mean Difference IV, Fixed, 95% CI -0.45 (-1.58, 0.68) -1.00 (-1.42, -0.58) -0.93 (-1.33, -0.54)	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI	100
Test for overall effect 2 D Study or Subgroup Kamel et al. <sup>7</sup> (2020) Zhang et al. <sup>9</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = E Study or Subgroup Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI) Heterogeneity: Chi <sup>2</sup> =	Z= 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (P	$rac{1}{10002}$ $rac{1}{20}$ $rac{1}{148}$ $ ac{256}{256}$ $ ac{1}{1000}$ $ ac{1}{1000}$	Contro Events 3 43 81 1.98); F = 10001) Co Mean 3 3 3 7); F = 0%	ol Total 20 297 101 418 0% mtrol SD 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0% 70tal V 20 101 4 121 1	t M-H 6 C 6 C 6 C 6 C 6 C 6 C 6 V 6 0 7 87.7% 87.7%	Risk Ratio 4, Fixed, 95% Cl 1.33 [0.04, 2.94] 1.34 [0.15, 0.80] 1.37 [0.22, 0.64] 1.36 [0.23, 0.56] Mean Difference IV, Fixed, 95% Cl -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI	100
Test for overall effect 2 D <u>Study or Subgroup</u> Kamel <i>et al.</i> <sup>7</sup> (2020) Zhang <i>et al.</i> <sup>6</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) <u>Total (95% CI)</u> Total events Heterogeneity: Chi <sup>2</sup> = <u>Test for overall effect</u> Kamel <i>et al.</i> <sup>7</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) <u>Total (95% CI)</u> Heterogeneity: Chi <sup>2</sup> = Test for overall effect.	Z= 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (P Z = 4.61 (P	$\begin{array}{c} \hline 0.002) \\ \hline \hline 0.002) \\ \hline 20 \\ 148 \\ 88 \\ 256 \\ \hline 0.000 \\ \hline 0.0000 \\ \hline$	Contro Events 3 43 81 1.98); I <sup>P</sup> = 0001) Co <u>Mean</u> 3 3 3 7); I <sup>P</sup> = 0%	ol Total 20 297 101 418 0% mtrol SD 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0%	t M-H 6 C 6 C 6 C 6 C 6 C 6 C 6 C 6 C 6 C 7 87.7%	Risk Ratio 4, Fixed, 95% Cl 1.33 [0.04, 2.94] 1.34 [0.15, 0.80] 1.37 [0.22, 0.64] 3.36 [0.23, 0.56] Mean Difference IV, Fixed, 95% Cl -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI -2 -1 0 1 2 Favours [experimental] Favours [control]	100
Test for overall effect 2 D Study or Subgroup Kamel et al. <sup>7</sup> (2020) Zhang et al. <sup>6</sup> (2020) Nechay et al. <sup>6</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>6</sup> (2021) Total (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect.	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (V Z = 4.61 (P <	0.002) Total 20 148 88 256 20 20 20 20 20 20 20 20 20 20	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 10001) Co Mean 3 3 7); I <sup>2</sup> = 0% 1)	ol Total 20 297 101 418 0% sp 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0% 100.0%	t <u>M-H</u> 6 C 6 C 6 C 6 C 6 O 7 8 7.7%	Risk Ratio I, Fixed, 95% Cl .33 [0.04, 2.94] .34 [0.15, 0.80] .37 [0.22, 0.64] .36 [0.23, 0.56] Mean Difference IV, Fixed, 95% Cl -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 iavours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI -2 -1 0 1 2 Favours [experimental] Favours [control]	100
Test for overall effect 2 D Study or Subgroup Kamel et al. <sup>7</sup> (2020) Zhang et al. <sup>9</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect. F	Z= 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (P Z = 4.61 (P <	0.002) Total 20 148 88 256 2 (P = 0 20 88 108 P= 0.37 0.0000	Contro Events 3 35 43 81 1.98); I <sup>*</sup> = 10001) Contro Contro	ol Total 20 297 101 418 0% ntrol <u>SD</u> 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0% 100.0%	t <u>M-H</u> 6 C 6 C 6 C 6 C 6 O 8 O 87.7%	Risk Ratio <u>I, Fixed, 95% CI</u> .33 [0.04, 2.94] .34 [0.15, 0.80] .37 [0.22, 0.64] .36 [0.23, 0.56] Mean Difference <u>IV, Fixed, 95% CI</u> -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54] Risk Ratio	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 iavours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI -2 -1 0 1 2 Favours [control] Risk Ratio	100
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Test for overall effect 2 Study or Subgroup Karnel <i>et al.</i> <sup>7</sup> (2020) Zhang <i>et al.</i> <sup>9</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Karnel <i>et al.</i> <sup>7</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) Total (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect: F Study or Subgroup Akhtar <i>et al.</i> <sup>6</sup> (2020)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (P Z = 4.61 (P < ERAS Events 1 3	Total         1           20         148           28         256           2         <0.002	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 10001) Contro Events 4 4 4	ol <u>Total</u> 200 297 101 <b>418</b> 0% mtrol <u>SD</u> 1.48 1.48 1.48 0l <u>Total</u> 74	Weigh 4.5% 35.1% 60.4% 100.0% <u>Total V</u> 20 101 121 121 1 <u>Weight</u> 9.7%	t <u>M-H</u> 6 C 6 C 6 C 6 C 6 C 6 C 6 C 6 C 6 0 87.7% 00.0%	Risk Ratio 4, Fixed, 95% Cl 1.33 [0.04, 2.94] 1.34 [0.15, 0.80] 1.37 [0.22, 0.64] 1.36 [0.23, 0.56] Mean Difference IV, Fixed, 95% Cl -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54] Risk Ratio 1, Fixed, 95% Cl 1.76 [0.18, 3.28]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI -2 -1 0 1 2 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI	100
Test for overall effect 2 Study or Subgroup Kamel <i>et al.</i> ? (2020) Zhang <i>et al.</i> <sup>6</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Kamel <i>et al.</i> <sup>7</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) Total (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Akhtar <i>et al.</i> <sup>6</sup> (2020) Kamel <i>et al.</i> <sup>7</sup> (2020)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (P Z = 4.61 (P < ERAS Events 1 3 3	Total         1           20         148           28         256           2 (P = 0         20           1 Total         20           7 Total         73           20         20	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 0001) Contro Events 4 4 4	ol <u>Total</u> 20 297 101 <b>418</b> 0% ontrol <u>\$D</u> 1.48 1.48 1.48 ol <u>Total</u> 74 20	Weigh 4.5% 35.1% 60.4% 100.0% Total V 20 101 3 121 1 Weight 9.7% 9.8%	I         M-H           6         C           6         C           6         C           6         C           6         C           6         C           6         C           6         C           6         C           6         C           6         C           6         C           00.0%         I           1         T           6         C	Risk Ratio 4, Fixed, 95% CI 1.33 [0.04, 2.94] 1.34 [0.15, 0.80] 1.37 [0.22, 0.64] 3.36 [0.23, 0.56] Mean Difference IV, Fixed, 95% CI -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54] Risk Ratio 1, Fixed, 95% CI 1.76 [0.18, 3.28] 1.75 [0.19, 2.93]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI -2 -1 0 1 2 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI	100
Test for overall effect 2 D <u>Study or Subgroup</u> Kamel <i>et al.</i> <sup>7</sup> (2020) Zhang <i>et al.</i> <sup>6</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) <u>Total (95% CI)</u> Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E <u>Study or Subgroup</u> Kamel <i>et al.</i> <sup>7</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021) <u>Total (95% CI)</u> Heterogeneity: Chi <sup>2</sup> = Test for overall effect: F <u>Study or Subgroup</u> Akhtar <i>et al.</i> <sup>6</sup> (2020) Kamel <i>et al.</i> <sup>7</sup> (2020) Nechay <i>et al.</i> <sup>5</sup> (2021)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (P Z = 4.61 (P ERAS Events 1 3 3 6	rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal rotal r	Contro Events 3 35 43 81 1.98); F = 10001) Contro Events 4 4 4 4 5	ol Total 20 297 101 418 0% ntrol <u>SD</u> 1.48 1.48 1.48 1.48	Weigh 4.5% 35.1% 60.4% 100.0% Total V 20 101 121 121 121 121 121 9.7% 9.8% 11.4%	t         M-H           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           7         87.7%           00.0%         1           1         1           6         0           6         0           6         0           6         0	Risk Ratio 4, Fixed, 95% CI 1.33 [0.04, 2.94] 1.34 [0.15, 0.80] 1.37 [0.22, 0.64] 1.36 [0.23, 0.56] Mean Difference IV, Fixed, 95% CI -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54] Risk Ratio 4, Fixed, 95% CI 1.76 [0.18, 3.28] 1.75 [0.19, 2.93] .38 [0.44, 4.36]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI -2 -1 0 1 2 Favours [experimental] Favours [control]	
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Test for overall effect 2 D Study or Subgroup Kamel et al. <sup>7</sup> (2020) Zhang et al. <sup>6</sup> (2020) Nechay et al. <sup>8</sup> (2021) Total (95% CI) Total events Heterogeneity. Chi <sup>2</sup> =: Test for overall effect E Study or Subgroup Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>8</sup> (2021) Total (95% CI) Heterogeneity. Chi <sup>2</sup> =: Test for overall effect. F Study or Subgroup Akhtar et al. <sup>6</sup> (2020) Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>8</sup> (2021) Zhang et al. <sup>9</sup> (2020) Demouron et al. <sup>10</sup> (2022)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (U Z = 4.61 (P < ERAS Events 1 3 3 6 5 ) 8	0.002) Total 1 20 148 88 256 2 (P = 0 20 20 20 88 108 P= 0.37 0.0000 Total 1 73 20 88 148 225 148 20 148 20 108 20 20 20 20 20 20 20 20 20 20	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 10001) Contro Events 4 4 5 12 31	ol Total 207 101 418 0% mtrol <u>SD</u> 1.48 1.48 1.48 1.48 74 20 101 297 414	Weight 4.5% 35.1% 60.4% 100.0% 100.0% 101 % 121 1 Weight 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7% 9.7%	I         III           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           7         87.7%           00.0%         1           1         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0           6         0	Risk Ratio I, Fixed, 95% CI I.33 [0.04, 2.94] I.34 [0.15, 0.80] I.37 [0.22, 0.64] I.36 [0.23, 0.56] Mean Difference IV, Fixed, 95% CI -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54] Risk Ratio I, Fixed, 95% CI I.76 [0.18, 3.28] I.76 [0.19, 2.93] I.38 [0.44, 4.36] I.84 [0.30, 2.33] I.53 [0.25, 1.14]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI -2 -1 0 1 2 Favours [control]	100
Test for overall effect 2 D Study or Subgroup Kamel et al. <sup>7</sup> (2020) Zhang et al. <sup>6</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect E Study or Subgroup Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>5</sup> (2021) Total (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect. F Study or Subgroup Akhtar et al. <sup>6</sup> (2020) Kamel et al. <sup>7</sup> (2020) Nechay et al. <sup>5</sup> (2021) Zhang et al. <sup>6</sup> (2020) Demouron et al. <sup>10</sup> (2022)	Z = 3.15 (P = 1 ERAS Events 1 1 6 14 21 = 0.03, df = 2 t Z = 4.48 (P ERAS Mean SD 2.55 2.11 2 1.48 0.80, df = 1 (U Z = 4.61 (P < ERAS Events 1 3 3 6 5 ) 8	0.002) Total   20 148 88 256 2 (P = 0 20 20 20 20 20 20 20 20 20 2	Contro Events 3 35 43 81 1.98); I <sup>2</sup> = 10001) Contro Events 4 4 5 12 31	ol <u>Total</u> 207 101 418 0% ontrol <u>SD</u> 1.48 1.48 1.48 1.48 01 <u>Total</u> 74 207 414 006	Weigh 4.5% 35.1% 60.4% 100.0% 100.0% 101 % 101 % 121 1 Weigh 9.7% 9.8% 11.4% 19.5% 49.6%	Veight           12.3%           00.0%           12.3%           00.0%           1           1           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0	Risk Ratio <u>I, Fixed, 95% CI</u> .33 [0.04, 2.94] .34 [0.15, 0.80] .37 [0.22, 0.64] .36 [0.23, 0.56] Mean Difference IV, Fixed, 95% CI -0.45 [-1.58, 0.68] -1.00 [-1.42, -0.58] -0.93 [-1.33, -0.54] Risk Ratio <u>I, Fixed, 95% CI</u> .75 [0.19, 2.93] .38 [0.44, 4.36] .84 [0.30, 2.33] .53 [0.25, 1.14] 73 [0.46, 1.47]	-20 -10 0 10 20 Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI 0.1 1 10 avours [experimental] Favours [control] Mean Difference IV, Fixed, 95% CI Favours [experimental] Favours [control] Risk Ratio M-H, Fixed, 95% CI -2 -1 0 1 2 Favours [control]	100
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**Figure 3:** Forest plot of comparison of (A) LOS between ERAS group and conventional group, (B) readmissions between ERAS group and conventional group, (C) first flatus between ERAS group and conventional group, (D) PONV between ERAS group and conventional group, (E) 24-hrs pain score between ERAS group and conventional group and (F) LOS between ERAS group and conventional group.



**Figure 4:** Group 1 forest plot of comparison of (**A**) length of stay between enhanced recovery after surgery (ERAS) group and conventional group, (**B**) readmissions between ERAS group and conventional group, (**C**) time of first flatus between ERAS group and conventional group, (**C**) post-operative nauseal vomiting between ERAS group and conventional group, (**E**) pain scores between ERAS group and conventional group and (**F**) complications between ERAS group and conventional group.

<0.00001;  $I^2 = 99\%$ ), which was suggestive of a high level of heterogeneity [Figure 3A].

#### Group One

LOS data for group one were available for four studies.<sup>5–7,10</sup> There were 390 patients in the ERAS group and 609 patients in the control group. On pooled

analysis, the LOS of the ERAS group was found to be significantly shorter than that of the control (MD = -13.97 [CI: -20.99--6.95; P = 0.008]). A random effect model was applied (Tau<sup>2</sup> = 29.79, Chi<sup>2</sup> = 9.94, df = 2, P = 0.007, I<sup>2</sup> = 80%), which was suggestive of a significant heterogeneity [Figure 4A].



**Figure 5:** Group 2 forest plot of comparison of (**A**) length of stay between enhanced recovery after surgery (ERAS) group and conventional group and (**B**) time to first flatus between ERAS group and conventional group.

#### Group Two

In group two, two studies reported LOS.<sup>9–11</sup> There were 170 patients in the ERAS group and 320 patients in the control group. On pooled analysis, the LOS was found to be significantly shorter in the ERAS group when compared to the control group (MD = -61.61 [CI: -93.31--29.90; P = 0.0001]). A random effect model was applied (Tau<sup>2</sup> = 398.05, Chi<sup>2</sup> = 3.18, df = 1, P = 0.07, I<sup>2</sup> = 69%), which was suggestive of significant heterogeneity [Figure 5A].

#### SECONDARY OUTCOMES

#### Meta-analysis: Readmissions

Data on readmissions were reported by five studies.<sup>5–7,10,11</sup> There were 412 patients in the ERAS group and 632 patients in the control group. On pooled analysis, the readmission was found to be comparable in both groups (relative risk [RR] = 0.54 [95% CI: 0.23–1.27; P = 0.16]). A fixed effect model was applied (Chi<sup>2</sup> = 1.45, df = 2, P = 0.48, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 3B].

In group one, four studies reported the data on readmissions.<sup>5–7,10</sup> There were 390 patients in the ERAS group and 609 patients in the control group. On pooled analysis, the readmission was found to be comparable in both groups (RR = 0.53 [95% CI: 0.22–1.27; P = 0.15]). A fixed effect model was applied (Chi<sup>2</sup> = 1.47, df = 2, P = 0.48, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 4B]. None of the studies in group two reported data on readmissions.

#### Meta-analysis: Time to first flatus

The data on time to first flatus were reported by four studies.<sup>67,9-11</sup> There were 278 patients in the ERAS group and 440 patients in the control group. On pooled analysis, the time to first flatus was found to be significantly less in patients with ERAS implementation than in the control group (MD =

-6.56 [95% CI: -10.64–-2.48; P = 0.002]). A random effect model was applied (Tau<sup>2</sup> = 14.28, Chi<sup>2</sup> = 30.73, df = 3, P < 0.00001, I<sup>2</sup> = 90%), which was suggestive of significant heterogeneity [Figure 3C].

In group one, the data on time to first flatus were reported by two studies.<sup>5,7</sup> There were 278 patients in the ERAS group and 440 patients in the control group. On pooled analysis, the time to first flatus was found to be significantly less in patients with ERAS implementation than in the control group (MD = -3.49 [95% CI: -6.10--0.89, P = 0.009]). A random effect model was applied (Chi<sup>2</sup> = 0.70, df = 1, P = 0.40, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 4C].

In group two, two studies reported the data on time to first flatus.<sup>9,11</sup> There were 170 patients in the ERAS group and 320 patients in control group. On pooled analysis, the time to first flatus was found to be significantly less in the ERAS group when compared to the control group (MD = -8.60 [95% CI: -16.94--0.25; P = 0.04]). A random effect model was applied (Tau<sup>2</sup> = 35.10, Chi<sup>2</sup> = 30.33, df = 1, P < 0.00001, I<sup>2</sup> = 97%), which was suggestive of considerable heterogeneity [Figure 5B].

#### Meta-analysis: PONV

The data on PONV were reported by three studies.<sup>5.7,9</sup> There were 256 patients in the ERAS group and 418 patients in the control group. On pooled analysis, the number of PONV events was found to be significantly less in the ERAS group when compared to the control group (RR = 0.36 [95% CI: 0.23–0.56; P < 0.00001]). A fixed effect model was applied (Chi<sup>2</sup> = 0.03, df = 2, P = 0.98, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 3D].

In group one, the data on PONV was reported by two studies.<sup>5,7</sup> There were 108 patients in the ERAS group and 121 patients in the control group. On pooled analysis, the number of PONV events was found to be significantly less in the ERAS group when compared to the control group (RR = 0.26 [95% CI: 0.13–0.50; P < 0.0001]). A fixed effect model was applied (Chi<sup>2</sup> = 0.02, df = 1, P = 0.90, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 4D]. The studies in group two did not report data on PONV.

#### Meta-analysis: Pain scores

The comparison of postoperative pain scores was reported by two studies.<sup>5,7</sup> There were 108 patients in the ERAS group and 121 patients in the control group. On pooled analysis, the pain scores were found to be lower in the ERAS group than in the control group (MD = -0.93 [95% CI: -1.33--0.54; *P* <0.00001]). A fixed effect model was used (Chi<sup>2</sup> = 0.80, df = 1, *P* = 0.37, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 3E].

In group one, the comparison of postoperative pain scores was reported by two studies.<sup>5,7</sup> There were 108 patients in the ERAS group and 121 patients in the control group. On pooled analysis, the pain scores were found to be lower in the ERAS group than in the control group (MD = -1.07 [95% CI: -1.46--0.67; P < 0.00001]). A fixed effect model was used (Chi<sup>2</sup> = 0.79, df = 1, P = 0.38, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 4E]. The studies in group two did not report pain scores.

#### Meta-analysis: Complications

The data on postoperative complications were reported by five studies.<sup>5–7,9,10</sup> There were 530 patients in the ERAS group and 906 patients in the control group. Pooled analysis revealed that the complications were comparable in both the groups (RR = 0.73 [95% CI: 0.46–1.17; P = 0.19]). A fixed effect model was used (Chi<sup>2</sup> = 1.91, df = 4, P = 0.75, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 3F].

In group one, the data on postoperative complications were reported by four studies.<sup>5–7,10</sup> There were 382 patients in the ERAS group and 609 patients in the control group. Pooled analysis revealed that the complications were comparable in both the groups (RR = 0.69 [95% CI: 0.39–1.20; P = 0.19]). A fixed effect model was used (Chi<sup>2</sup> = 1.85, df = 3, P = 0.60, I<sup>2</sup> = 0%), which was without heterogeneity [Figure 4F]. The studies in group two did not report any complications.

### Discussion

This SRMA demonstrates the advantages of the implementation of ERAS pathways in patients undergoing LC. Adhering strictly to ERAS protocols can result in a reduced LOS after LC, reduced time to first flatus after surgery, less PONV and better pain scores in the postoperative period without

CBD exploration and reduced LOS and reduced time to first flatus with CBD exploration. This could lead to better patient satisfaction, lower cost of treatment and hospitalisation and early initiation of oral diet. However, the pooled analysis did not find any significant decrease in the rate of postoperative complications and readmissions after the patients' discharge. To the best of the authors' knowledge, this is the first SRMA comparing the perioperative outcomes of LC with the implementation of ERAS pathways and that with conventional pathways.

Several researchers have applied ERAS pathways to various laparoscopic abdominal surgeries successfully. In a systematic review conducted by Li et al., where the authors analysed articles from January 1990 to October 2017, 34 comparative studies (15 randomised controlled studies and 19 non-randomised controlled studies) were identified and data involving 3,615 patients (1,749 in the ERAS group and 1,866 in the control group) were analysed.18 On analysing the pooled data, the authors concluded that ERAS is safe, effective and when combined with laparoscopic surgery leads to a faster postoperative recovery without increasing RR and perioperative mortality. In another SRMA conducted by Ni et al., the authors analysed the efficacy and safety of ERAS implementation in laparoscopic digestive system surgery.<sup>19</sup> The authors identified 25 randomised controlled trials comprising a total of 2,219 patients. On pooled analysis, they concluded that ERAS implementation led to faster postoperative rehabilitation, shorter LOS and less postoperative complication rates.

The website of ERAS Society does not provide any specific guidelines for LC per se. However, researchers have adhered to the key pathways of ERAS and conducted several studies that compared postoperative outcomes of ERAS implementation with those of conventional pathways. In a prospective, randomised, non-blinded clinical trial in patients undergoing LC for acute cholecystitis, Nechay et al. compared the outcomes of LC in patients with ERAS pathways to outcomes in those with conventional pathways (88 patients in the ERAS group and 101 patients in the conventional pathways group).<sup>5</sup> The authors concluded that the implementation of ERAS pathways improved postoperative recovery and reduced LOS in patients undergoing LC without increasing the rate of complications or readmissions. Akhtar et al. randomised 150 patients undergoing LC (75 in the ERAS group and 75 in the conventional pathways group).6 On analysis, the authors concluded that the implementation of ERAS pathways led to reduced LOS and lower cost of treatment with comparable recovery scores on discharge, day three and day 10.

Kamel et al. compared the perioperative outcomes in patients undergoing LC with ERAS pathways to outcomes in those with traditional care pathways.7 They concluded that patients in ERAS pathways had reduced LOS, fewer complications and lower RR. In another study by Yu et al., the authors enrolled 200 patients undergoing LC into two groups: 100 in the fast-track group with continuous postoperative care and 100 in the routine care group.8 They compared surgical stress levels, postoperative recovery (time to first exhaust, time to first meal, time taken to get out of bed, LOS), complications, SF-36 scores after discharge and overall satisfaction in both groups. On analysis, the authors concluded that fast-track pathways reduced overall level of surgical stress, accelerated the recovery process, reduced complications, improved the quality of life of patients significantly and afforded greater satisfaction. Zhang et al.'s retrospective cohort study involved 445 patients undergoing LC with CBD exploration with ERAS pathways and conventional pathways.9 They compared stress response index, postoperative complication rate and postoperative rehabilitation between the two groups. On analysis, the authors concluded that incorporating ERAS pathways led to less complications, earlier rehabilitation and reduced stress response. Demouron et al. conducted a study in patients with acute calculous cholecystitis undergoing LC and analysed patients following ERAS and conventional pathways (209 in ERAS and 414 in conventional pathways).<sup>10</sup> Although ERAS pathways had reduced LOS, the morbidity rate, mortality rate, RR and reoperation rate were comparable. Wang et al. randomised 45 patients undergoing LC (23 in conventional pathways and 22 in ERAS pathways).<sup>11</sup> They concluded that time to ambulation, time to first flatus passage and LOS were significantly shorter with ERAS pathways.

Udayasankar et al. randomised 50 patients undergoing elective LC into two equal groups (25 patients in each group) and compared postoperative recovery between ERAS pathways and the conventional approach.<sup>20</sup> They concluded that patients in the ERAS group had reduced anxiety, hunger, thirst and fatigue and enhanced overall perioperative comfort when compared to those in the conventional care group. Yeh et al. retrospectively reviewed data of 250 paediatric patients who underwent LC with and without ERAS implementation.<sup>21</sup> The authors concluded that ERAS implementation facilitated single-day discharge with less complications and without readmissions or emergency department visits. All these studies thus highlight the advantages of ERAS pathway implementation for LC over conventional care.

The present SRMA had several limitations, including the fact that prospective RCTs were few, overall sample size was small and outcomes were inconsistent. In group two studies, only LOS and time to first flatus were reported. Therefore, there was no uniformity in the reporting of outcomes in the two groups. Many essential components of ERAS pathways, especially the preoperative pathways that involve optimisation of the medical conditions and intraoperative pathways that include anaesthesia management (multimodal analgesia, PONV, fluid management, intraoperative warming), were not reported and compared in several studies. There was heterogeneity in the quantitative analysis of several variables, which could be attributed to the different study designs, variable sample size and inconsistent reporting and analysis of data.

## Conclusion

Implementation of ERAS pathways in patients undergoing LC can facilitate reduced LOS in hospital after surgery, lower pain scores, early bowel activity and less PONV when compared to patients undergoing LC using only conventional perioperative pathways, with reduced LOS and early time to first flatus in patients undergoing LC with CBD exploration. Further welldesigned studies need to be conducted to compare various preoperative and intraoperative pathways, including postoperative opioid consumption, which has not been addressed in previous studies.

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