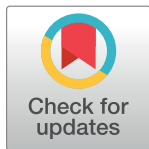# Enhanced recovery after surgery protocol in oesophageal cancer surgery: Systematic review and meta-analysis

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Abstract

Background

Enhanced Recovery After Surgery (ERAS) protocol are well established in many surgical disciplines, leading to decrease in morbidity and length of hospital stay. These multi-modal protocols have been also introduced to oesophageal cancer surgery. This review aimed to evaluate current literature on ERAS in oesophageal cancer surgery and conduct a meta-analysis on primary and secondary outcomes.

Methods

MEDLINE, Embase, Scopus and Cochrane Library were searched for eligible studies. We analyzed data up to May 2016. Eligible studies had to contain four described ERAS protocol elements. The primary outcome was overall morbidity. Secondary outcomes included length of hospital stay, specific complications, mortality and readmissions. Random effect meta-analyses were undertaken.

Results

Initial search yielded 1,064 articles. Thorough evaluation resulted in 13 eligible articles which were analyzed. A total of 2,042 patients were included in the analysis (1,058 ERAS group and 984 treated with traditional protocols). Analysis of overall morbidity as well as complication rate did not show any significant reduction. Non-surgical complications and pulmonary complications were significantly lower in the ERAS group, RR = 0.71 95% CI 0.62–0.80, $p < 0.00001$ and RR = 0.75, 95% CI 0.60–0.94, $p = 0.01$, respectively. Meta-analysis on length of stay presented significant reduction Mean difference = -3.55, 95% CI -4.41 to -2.69, p for effect<0.00001.

Conclusions

This systematic review with a meta-analysis on ERAS in oesophageal surgery indicates a reduction of non-surgical complications and no negative influence on overall morbidity. Moreover, a reduction in the length of hospital stay was presented.

Introduction

In the late 1990s Kehlet et al. published a series of papers on fast-track multimodal programme in colorectal surgery, which has been shown to reduce complications and shorten the length of stay (LOS) [1–3]. Subsequently, this idea evolved into a multidisciplinary instrument commonly known as Enhanced Recovery after Surgery (ERAS). This instrument integrates several perioperative elements which are now recognized as the ERAS protocol. Currently there are a number of official Guidelines published by the ERAS Society. Several meta-analyses comprising other surgical disciplines documented the benefits of ERAS [4–6]. According to Urbach et al., ERAS philosophy involves a multidisciplinary team of surgeons, anaesthetists, nurses, dieticians and physiotherapists who aim to improve the quality of care by integrating evidence-based knowledge into clinical practice [7].

So far, the evidence on the use of ERAS programmes in oesophageal surgery is sparse. There are no official ERAS guidelines and the number of papers documenting the benefits of modern multimodal perioperative care is limited. Nonetheless, it has been suggested that the majority of general principles used in gastrointestinal surgery may be applicable [8–10]. Therefore, the reports published include most of the perioperative elements widely used in other types of surgery and additionally comprise other procedure-specific items. Unfortunately, there is no unified protocol for oesophageal surgery, therefore the types and the number of items varies, depending on the surgical unit that implements the multidisciplinary perioperative protocol. Although there are several studies documenting the feasibility of ERAS in oesophageal surgery, the material on this matter is still scarce. Our study aimed to systematically evaluate and conduct a meta-analysis of the available evidence on ERAS pathways compared with traditional perioperative care patients undergoing oesophagectomy for cancer.

Material

Search strategy

A search was conducted by two researchers (MPe and MPi) in May 2016 of Medline, Embase, Pubmed, OVID, and the Cochrane library covering a period from January 1996 to May 2016 with language restricted to English, and using the search terms: "oesophagus", "oesophagectomy", "oesophageal resection", "esophagus", "esophagectomy", "esophageal resection" "Ivor-Lewis" and combinations of these with: "fast track", "enhanced recovery", "clinical pathway", "critical pathway", "multimodal perioperative", "perioperative protocol" using the Boolean operators "AND" and "OR". Reference lists of relevant publications were assessed for additional references. Furthermore, bibliographies from other systematic reviews or meta-analyses on the subject were searched.

A paper was included when: the study concerned adult patients who underwent oesophagectomy for malignancy, the study described an enhanced recovery programme with at least four different perioperative elements and the study reported at least the overall complication rate and the length of stay. The papers included had to be either a randomized controlled trial

(RCT) or a comparative study with a control group. All criteria mentioned above were required to enrol a study for further evaluation. The exclusion criteria were: the study described a single intervention in perioperative care, the study was a review, guidelines, single group studies, or the study was not in English.

Two researchers (MPi and MPe) identified and selected citations from the search independently. In the event of uncertainties relating to inclusion, a third reviewer was consulted (PiMał) until consensus was reached. Data from the included studies were further extracted independently by the two researchers. Randomized as well as nonrandomized studies were eligible as long as they met the inclusion criteria. The Jadad scale was used for the quality assessment of the RCTs, which contained randomization (0–2 points), blinding of the studies (0–2 points) and withdrawals (0–1 point). Observational studies were evaluated by the Newcastle–Ottawa Scale (NOS), which consists of three factors: patient selections, comparability of the study groups and assessment of outcomes. Missing data were obtained by contacting the authors of the respective studies. The study risk of bias was assessed using the ROBINS-I tool (Risk Of Bias In Non-randomized Studies—of Interventions) developed by the Cochrane Collaboration.

Outcome measures

The primary outcome measure of this systematic review was overall morbidity. Secondary outcome measures were surgical complications specifying anastomotic leakage and non-surgical complications specifying pulmonary complications. Additionally, postoperative mortality, the length of hospital stay and the readmission rate were measured.

Statistical analysis

The analysis was performed using RevMan 5.3 (freeware from the Cochrane Collaboration). Statistical heterogeneity and inconsistency were measured using Cochran's Q tests and I2, respectively. Qualitative outcomes from individual studies were analysed to assess individual and pooled risk ratios (RR) with pertinent 95% confidence intervals (CI) favouring the ERAS treatment over non-ERAS, and by means of the Peto fixed-effects method in the presence of low or moderate statistical inconsistency ($I^2 \leq 10\%$), and by means of a random-effects method (which better accommodates clinical and statistical variations) in the presence of high statistical inconsistency ($I^2 > 10\%$). When a study included medians and interquartile ranges, we calculated the mean ± SD using a method proposed by Hozo et. al. [11]. Weighted mean differences (WMD) with 95% CI are presented for quantitative variables using the inverse variance random-effects method. Statistical significance was observed with two-tailed 0.05 level for hypothesis and with 0.10 for heterogeneity testing, while unadjusted p-values were reported accordingly. This study was performed according to the Preferred Reporting Items for Systematic reviews (PRISMA) guidelines (S1 Table) and MOOSE consensus statement [12].

Results

The initial reference search yielded 1,064 articles. After removing 142 duplicates, 922 articles where evaluated through titles and abstracts. This produced 53 papers suitable for full-text review. Finally, we enrolled 1 RCT and 12 comparative studies with a total of 2,042 patients (1,058 ERAS and 984 traditional protocols) (Table 1)[13–26].

Author Shewale was contacted to acquire additional information regarding complications. The flowchart of the literature search and study selection is summarized in Fig 1. Protocol elements described in each study are presented in Table 2.

Table 1. Study characteristics and quality assessment.

Study	Type of study	No. of patients in study/ control group	JADAD/NOS quality score	Number of ERAS elements
Blom 2013	CS	103/78	7	14
Cao 2013	CS	55/57	8	15
Findlay 2015	CS	55/77	6	11
Ford 2014	CS	75/80	7	10
Gatenby 2015	CS	27/35	6	16
Li 2012	CS	59/47	6	9
Munitiz 2010	CS	74/74	7	11
Pan 2014	CS	40/40	8	16
Preston 2013	CS	12/12	6	11
Shewale 2015	CS	386/322	6	8
Tang 2013	CS	36/27	6	10
Wang 2015	RCT	90/90	2	12
Zhao 2014	CS	34/34	8	14

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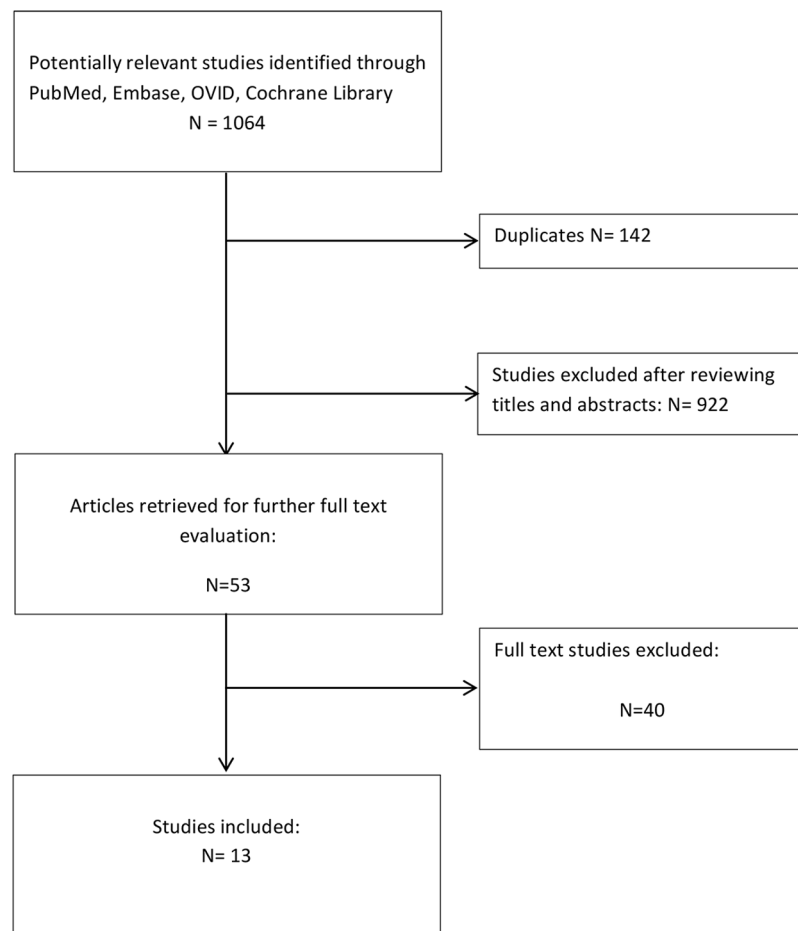
Fig 1. Study selection flow chart.

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Table 2. Protocol elements.

Study	Thrombotic prophylaxis	Anti-emetics	Urinary catheter removal	Enteral feeding	Oral feeding	Goal directed fluid therapy	Discharge planning	Dietician consult	Immediate extubation	Respiratory exercise	Preoperative counselling	Preoperative nutritional support	Carbohydrate loading	Optimized anaesthesia protocols	Multi-modal analgesia	No routine use of nasogastric tubes	Removal of chest drains	Mobilization	Prevention of hypothermia
Blom 2013	No	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Cao 2013	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Findlay 2015	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	Yes	No
Ford 2014	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	No
Gatenby 2015	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Li 2012	No	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No
Munitiz 2010	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No
Pan 2014	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preston 2013	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	No	Yes	Yes	No
Shewale 2015	No	No	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	No
Tang 2013	No	No	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No
Wang 2015	No	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhao 2014	No	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

https://doi.org/10.1371/journal.pone.0174382.t002

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Blom 2013	73	103	53	78	13.5%	1.04 [0.86, 1.27]	
Cao 2013	16	55	27	57	7.2%	0.61 [0.37, 1.01]	
Findlay 2015	38	55	47	77	12.2%	1.13 [0.88, 1.46]	
Ford 2014	48	75	42	80	11.8%	1.22 [0.93, 1.60]	
Gatenby 2015	2	9	2	16	0.9%	1.78 [0.30, 10.56]	
Li 2012	35	59	29	47	10.9%	0.96 [0.71, 1.31]	
Munitiz 2010	23	74	28	74	8.0%	0.82 [0.52, 1.29]	
Pan 2014	23	40	31	40	10.7%	0.74 [0.54, 1.02]	
Preston 2013	4	12	9	12	3.4%	0.44 [0.19, 1.05]	
Shewale 2015	147	386	174	322	14.3%	0.70 [0.60, 0.83]	
Tang 2013	6	36	7	27	2.8%	0.64 [0.24, 1.70]	
Wang 2015	6	90	17	90	3.2%	0.35 [0.15, 0.85]	
Zhao 2014	2	34	4	34	1.1%	0.50 [0.10, 2.55]	
Total (95% CI)		**1028**		**954**	**100.0%**	**0.85 [0.71, 1.01]**	
Total events	423		470				

Heterogeneity: Tau² = 0.05; Chi² = 32.65, df = 12 (P = 0.001); I² = 63%
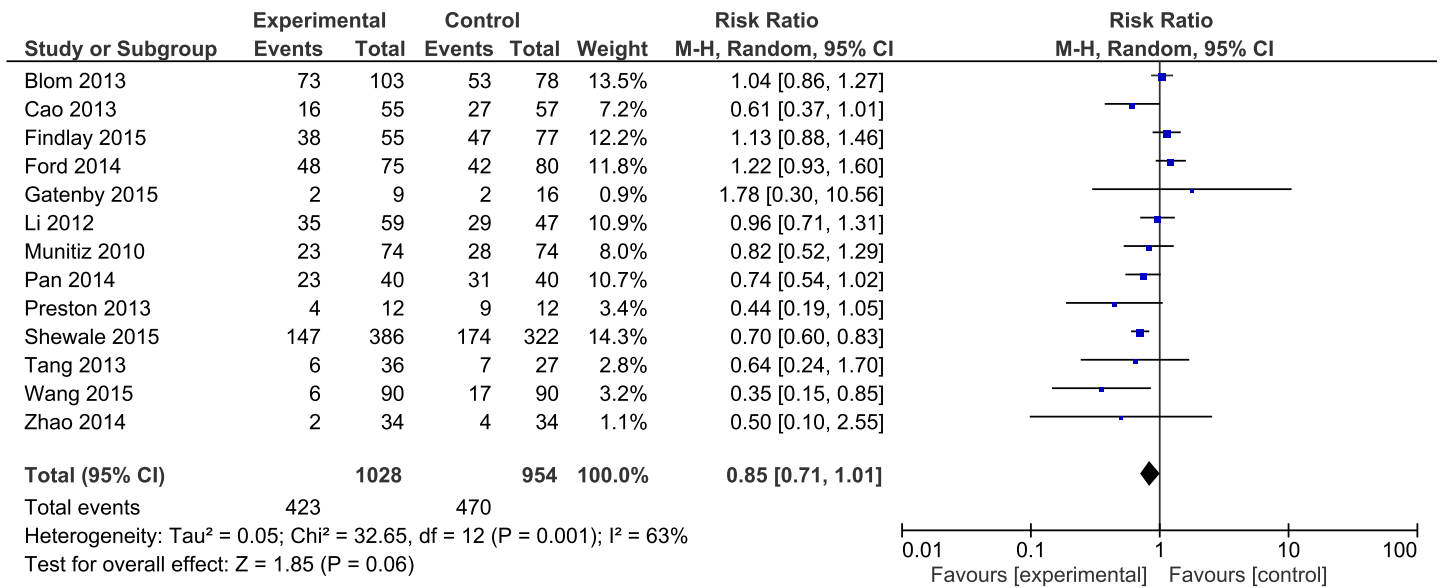Test for overall effect: Z = 1.85 (P = 0.06)

Fig 2. Pooled estimates of morbidity comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.

Complications

Overall morbidity was reported in all included papers. Complication rates were analysed with a subsequent meta-analysis (Fig 2). There were no statistically significant differences in overall complications in ERAS group (423/1028, 41%) in comparison to patients receiving traditional care (470/954, 49%): RR = 0.85, 95% CI 0.71–1.01, *p* for effect = 0.06, *p* for heterogeneity = 0.001, I^2 = 63%.

Surgical complications and anastomotic leakage

Surgical complications were reported in 11 papers. The analysis (Fig 3) revealed no significant differences among the studied groups 176/917(19.2%) in ERAS group vs. 174/847(20.5%) in

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Blom 2013	33	103	32	78	22.2%	0.78 [0.53, 1.15]	
Cao 2013	6	55	10	57	3.8%	0.62 [0.24, 1.59]	
Findlay 2015	18	55	25	77	13.5%	1.01 [0.61, 1.66]	
Gatenby 2015	1	9	1	16	0.5%	1.78 [0.13, 25.13]	
Li 2012	8	59	5	47	3.0%	1.27 [0.45, 3.64]	
Munitiz 2010	10	74	9	74	4.7%	1.11 [0.48, 2.58]	
Pan 2014	6	40	6	40	3.1%	1.00 [0.35, 2.84]	
Preston 2013	2	12	5	12	1.6%	0.40 [0.10, 1.67]	
Shewale 2015	90	386	75	322	46.3%	1.00 [0.77, 1.31]	
Wang 2015	1	90	3	90	0.7%	0.33 [0.04, 3.14]	
Zhao 2014	1	34	3	34	0.7%	0.33 [0.04, 3.05]	
Total (95% CI)		**917**		**847**	**100.0%**	**0.92 [0.76, 1.10]**	
Total events	176		174				

Heterogeneity: Tau² = 0.00; Chi² = 5.58, df = 10 (P = 0.85); I² = 0%
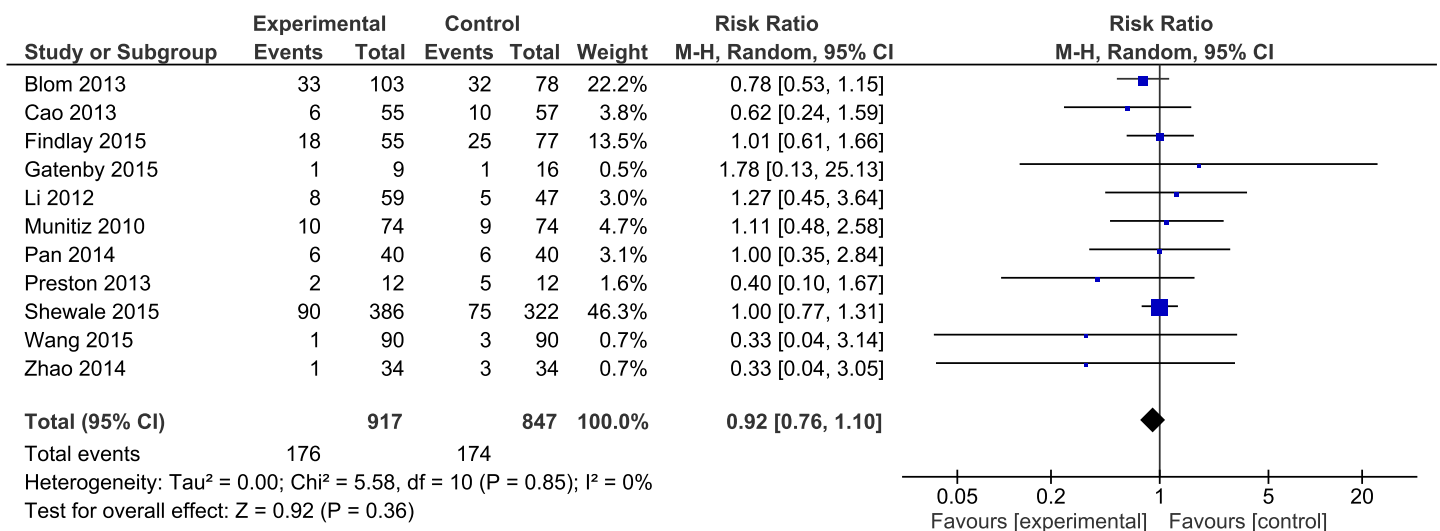Test for overall effect: Z = 0.92 (P = 0.36)

Fig 3. Pooled estimates of surgical complications comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Blom 2013	15	103	18	78	18.1%	0.63 [0.34, 1.17]	
Cao 2013	4	55	6	57	4.7%	0.69 [0.21, 2.32]	
Findlay 2015	5	55	4	77	4.3%	1.75 [0.49, 6.22]	
Ford 2014	3	75	11	80	4.5%	0.29 [0.08, 1.00]	
Gatenby 2015	0	9	0	16		Not estimable	
Li 2012	8	59	5	47	6.3%	1.27 [0.45, 3.64]	
Munitiz 2010	5	74	6	74	5.3%	0.83 [0.27, 2.61]	
Pan 2014	3	40	3	40	2.9%	1.00 [0.21, 4.66]	
Preston 2013	1	12	1	12	1.0%	1.00 [0.07, 14.21]	
Shewale 2015	49	386	45	322	49.0%	0.91 [0.62, 1.32]	
Tang 2013	3	36	3	27	3.0%	0.75 [0.16, 3.43]	
Wang 2015	0	90	0	90		Not estimable	
Zhao 2014	0	34	1	34	0.7%	0.33 [0.01, 7.91]	
Total (95% CI)		**1028**		**954**	**100.0%**	**0.83 [0.63, 1.08]**	
Total events	96		103				

Heterogeneity: Tau² = 0.00; Chi² = 6.21, df = 10 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

0.01 0.1 1 10 100
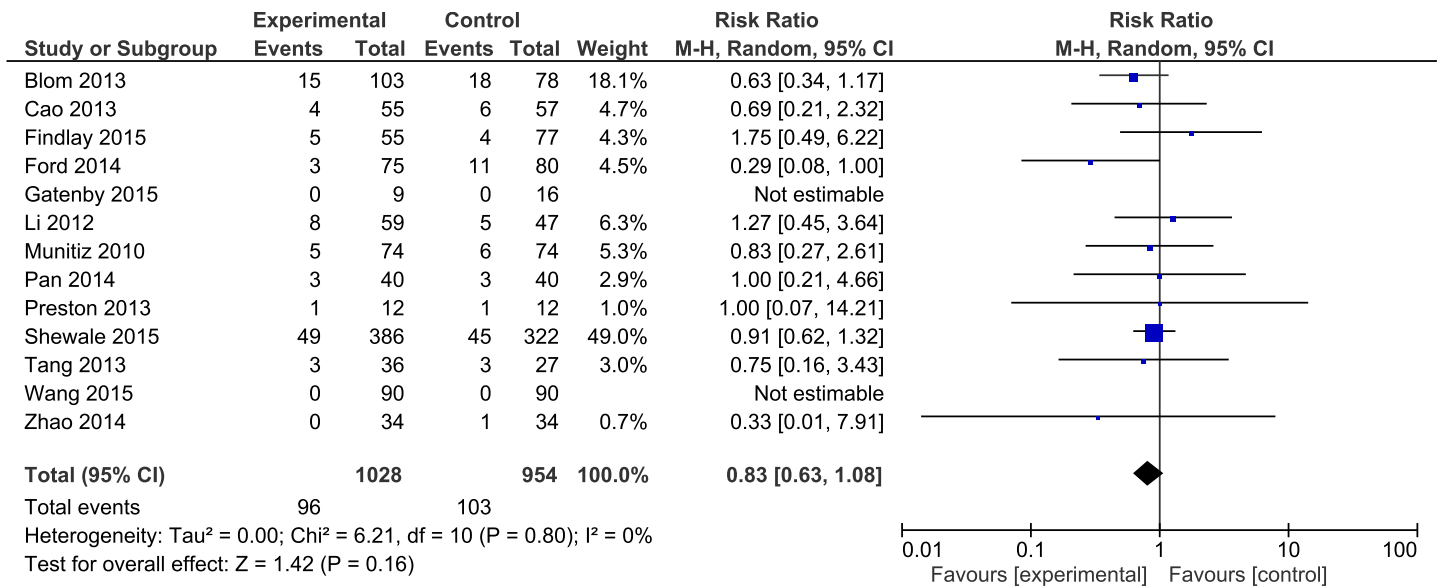Favours [experimental]   Favours [control]

Fig 4. Pooled estimates of anastomotic leakage comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.

https://doi.org/10.1371/journal.pone.0174382.g004

control group: RR = 0.92, 95% CI 0.76–1.1), *p* for effect = 0.36, *p* for heterogeneity = 0.85, $I^2 = 0\%$.

Anastomotic leakage was reported in all papers. The analysis (Fig 4) showed no significant variations among the studied groups 96/1028(9.3%) in ERAS group vs. 103/954(10.8%) in control group: RR = 0.83, 95% CI 0.63–1.08), *p* for effect = 0.16, *p* for heterogeneity = 0.80, $I^2 = 0\%$.

Non-surgical complications and pulmonary complications

Non-surgical complications were reported in 10 papers. Findlay et. al did not report the general number of non-surgical complications, while describing particular complications in detail. Due to the fact that some patients had multiple complications it is impossible for us to assess the number of patients with non-surgical complications, thus excluding this paper from analysis. The analysis (Fig 5) showed significant differences among the studied groups 240/853 (28.1%) in ERAS group vs. 297/754 (39.4%) in control group: RR = 0.71, 95% CI 0.62–0.80, *p* for effect < 0.00001, *p* for heterogeneity = 0.94, $I^2 = 0\%$.

Pulmonary complications were reported in 11 papers. The analysis (Fig 6) showed significant differences among the studied groups 175/917(19.1%) in ERAS group vs. 213/847(25.2%) in control group: RR = 0.75, 95% CI 0.60–0.94, *p* for effect = 0.01, *p* for heterogeneity = 0.26, $I^2 = 20\%$.

Mortality

Mortality was reported in 10 out of 13 included studies. Papers by Pan et al. and Preston et al. reported no events of mortality in their material. The analysis of mortality (Fig 7) showed no significant variations among the studied groups 19/895 (2.1%) in ERAS groups vs. 24/814 (2.9%) in control groups: RR = 0.71, 95% CI, 0.38–1.33, *p* for effect = 0.28, *p* for heterogeneity = 0.75, $I^2 = 0\%$.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Blom 2013	35	103	36	78	12.5%	0.74 [0.51, 1.06]	
Cao 2013	10	55	17	57	3.4%	0.61 [0.31, 1.21]	
Li 2012	1	59	0	47	0.2%	2.40 [0.10, 57.60]	
Munitiz 2010	13	74	19	74	4.1%	0.68 [0.37, 1.28]	
Pan 2014	17	40	25	40	8.7%	0.68 [0.44, 1.05]	
Preston 2013	7	12	9	12	4.9%	0.78 [0.44, 1.39]	
Shewale 2015	151	386	176	322	64.2%	0.72 [0.61, 0.84]	
Wang 2015	5	90	14	90	1.7%	0.36 [0.13, 0.95]	
Zhao 2014	1	34	1	34	0.2%	1.00 [0.07, 15.34]	
Total (95% CI)		**853**		**754**	**100.0%**	**0.71 [0.62, 0.80]**	
Total events	240		297				

Heterogeneity: Tau² = 0.00; Chi² = 2.93, df = 8 (P = 0.94); I² = 0%
Test for overall effect: Z = 5.34 (P < 0.00001)

0.01 0.1 1 10 100
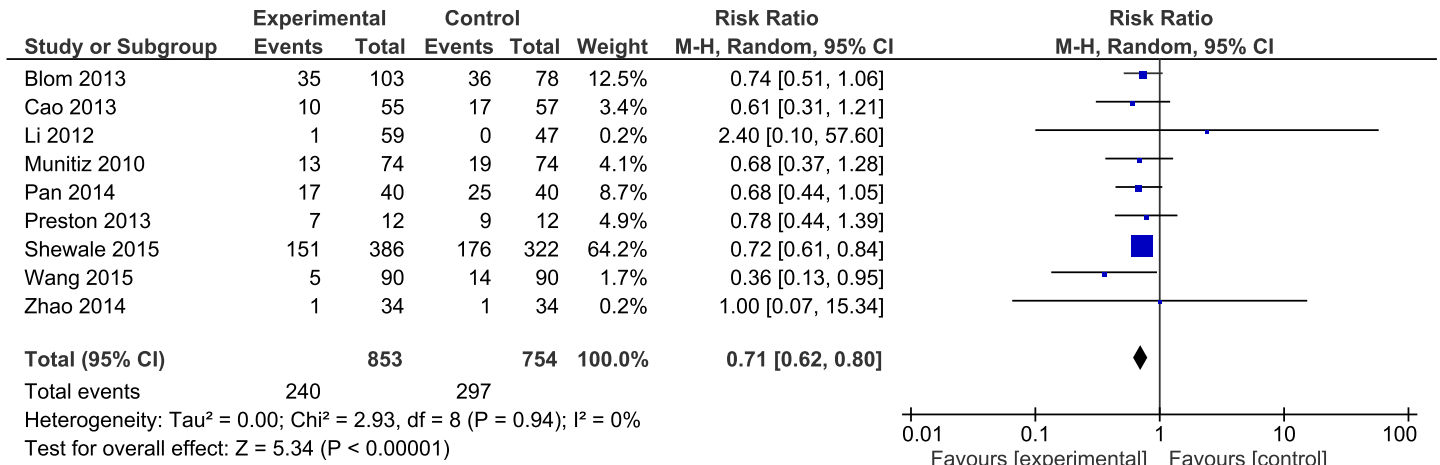Favours [experimental] Favours [control]

Fig 5. Pooled estimates of non-surgical complications comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.

Length of hospital stay

The mean length of hospital stay (LOS) was reported in all papers and in all of them it included the primary LOS (excluding potential readmissions). When all papers were included in the analysis, a high heterogeneity (>84%) was observed. A subsequent subgroup analysis revealed 2 studies, Cao et. al and Findlay et. al, which generated most of the heterogeneity. In order to reduce heterogeneity, they were excluded from meta-analysis of this outcome. There was a significant reduction in LOS in 7 papers. The mean LOS for the ERAS group was 10.76 days while for the control group it was 14.4 days. In the study by Findlay et al. the mean LOS was longer in the ERAS group [17]. The analysis (Fig 8) showed significant differences between the studied groups: Mean difference = -3.55, 95% CI -4.41 to -2.69, p for effect<0.00001, p for heterogeneity = 0.007, I^2 = 56%.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Blom 2013	35	103	36	78	21.6%	0.74 [0.51, 1.06]	
Cao 2013	6	55	11	57	5.1%	0.57 [0.22, 1.42]	
Findlay 2015	21	55	21	77	14.2%	1.40 [0.85, 2.30]	
Gatenby 2015	1	9	1	16	0.7%	1.78 [0.13, 25.13]	
Li 2012	13	59	16	47	10.0%	0.65 [0.35, 1.21]	
Munitiz 2010	10	74	17	74	8.1%	0.59 [0.29, 1.20]	
Pan 2014	7	40	5	40	4.0%	1.40 [0.48, 4.04]	
Preston 2013	3	12	8	12	4.0%	0.38 [0.13, 1.08]	
Shewale 2015	76	386	88	322	29.0%	0.72 [0.55, 0.94]	
Wang 2015	3	90	9	90	2.8%	0.33 [0.09, 1.19]	
Zhao 2014	0	34	1	34	0.5%	0.33 [0.01, 7.91]	
Total (95% CI)		**917**		**847**	**100.0%**	**0.75 [0.60, 0.94]**	
Total events	175		213				

Heterogeneity: Tau² = 0.02; Chi² = 12.42, df = 10 (P = 0.26); I² = 20%
Test for overall effect: Z = 2.56 (P = 0.01)

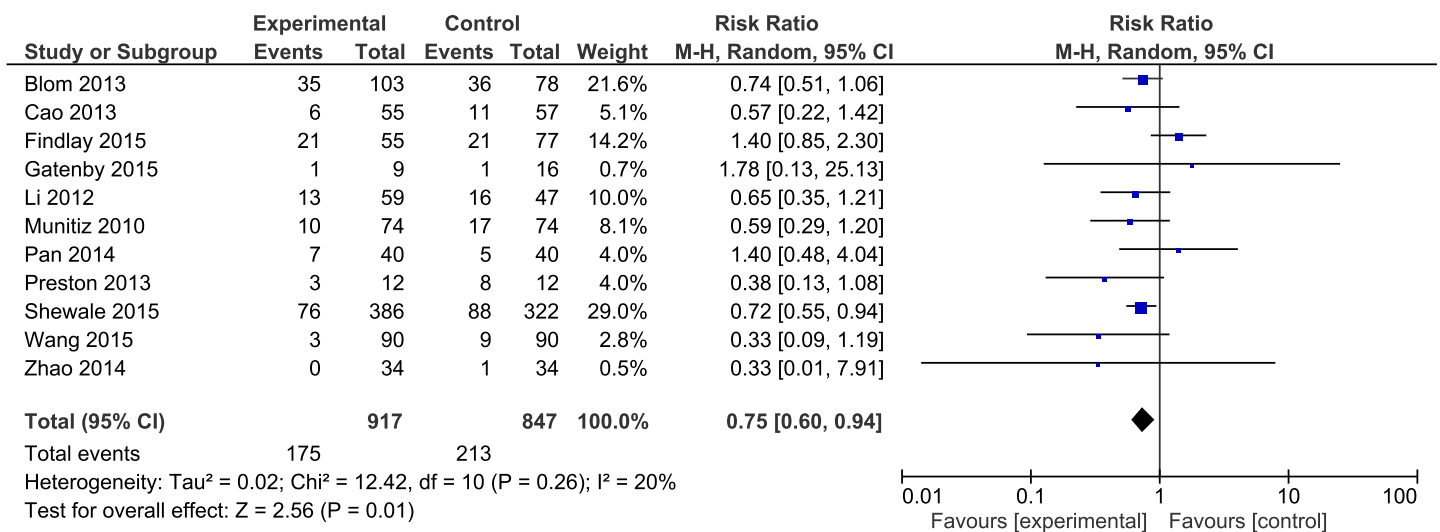0.01 0.1 1 10 100
Favours [experimental] Favours [control]

Fig 6. Pooled estimates of pulmonary complications comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.
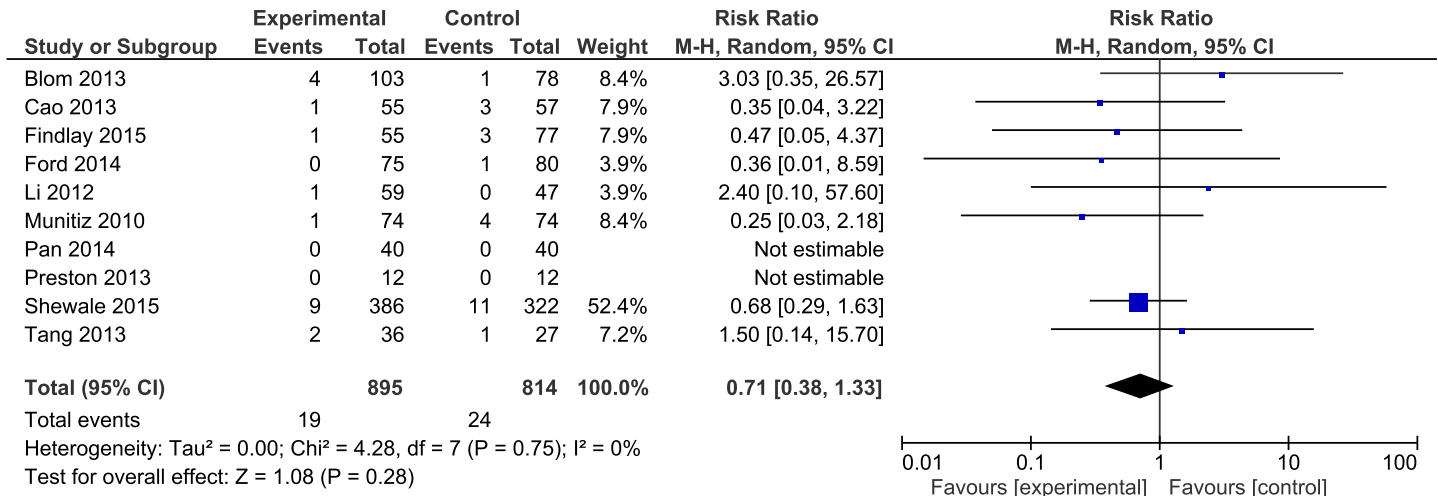
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Blom 2013	4	103	1	78	8.4%	3.03 [0.35, 26.57]	
Cao 2013	1	55	3	57	7.9%	0.35 [0.04, 3.22]	
Findlay 2015	1	55	3	77	7.9%	0.47 [0.05, 4.37]	
Ford 2014	0	75	1	80	3.9%	0.36 [0.01, 8.59]	
Li 2012	1	59	0	47	3.9%	2.40 [0.10, 57.60]	
Munitiz 2010	1	74	4	74	8.4%	0.25 [0.03, 2.18]	
Pan 2014	0	40	0	40		Not estimable	
Preston 2013	0	12	0	12		Not estimable	
Shewale 2015	9	386	11	322	52.4%	0.68 [0.29, 1.63]	
Tang 2013	2	36	1	27	7.2%	1.50 [0.14, 15.70]	
Total (95% CI)		895		814	100.0%	0.71 [0.38, 1.33]	
Total events	19		24				

Heterogeneity: Tau² = 0.00; Chi² = 4.28, df = 7 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)

Fig 7. Pooled estimates of mortality comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.

30-day readmission rate

Data on the readmission rate were present in 10 included articles. The analysis established no differences in the readmission rate (Fig 9) between the ERAS group 100/917 (10.9%) and the control group 75/836 (9.0%): RR = 1.18, 95% CI 0.89–1.56, p for effect = 0.25, p for heterogeneity = 0.99, I^2 = 0%.

Discussion

This systematic review, based on 1 RCT and 12 comparative studies enrolling 1,982 patients—1,028 in the ERAS group and 954 in the traditional care group, documents the feasibility and
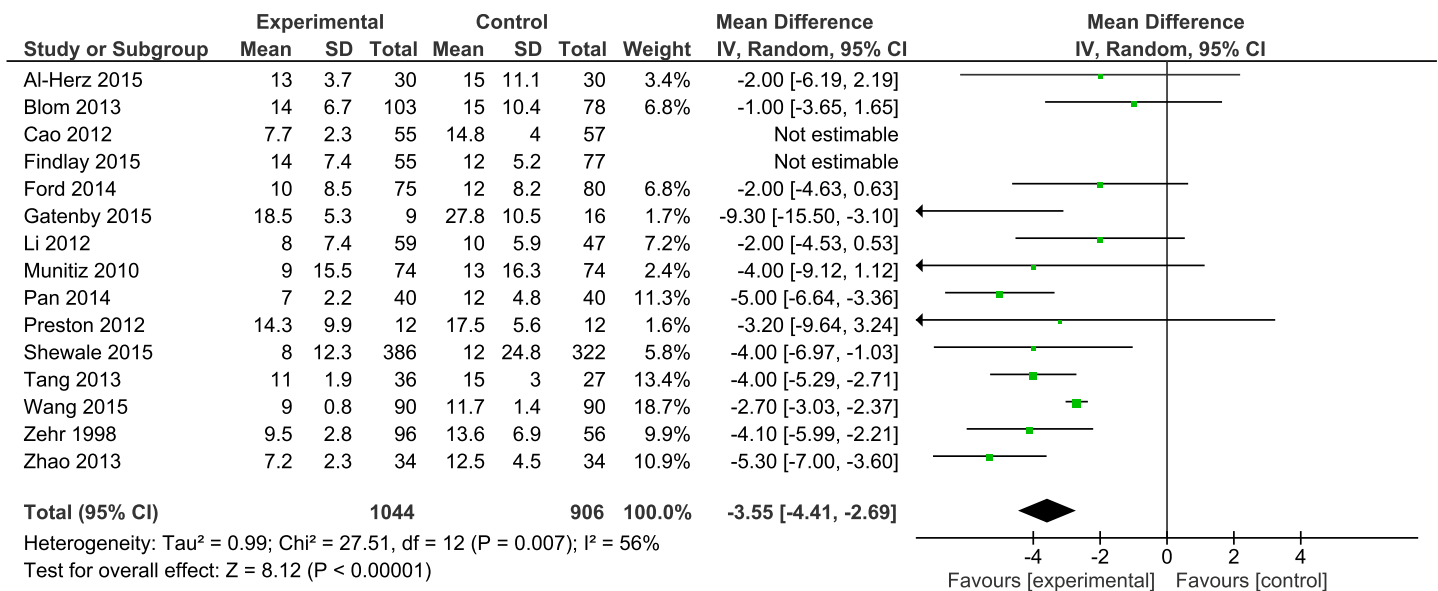
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Al-Herz 2015	13	3.7	30	15	11.1	30	3.4%	-2.00 [-6.19, 2.19]	
Blom 2013	14	6.7	103	15	10.4	78	6.8%	-1.00 [-3.65, 1.65]	
Cao 2012	7.7	2.3	55	14.8	4	57		Not estimable	
Findlay 2015	14	7.4	55	12	5.2	77		Not estimable	
Ford 2014	10	8.5	75	12	8.2	80	6.8%	-2.00 [-4.63, 0.63]	
Gatenby 2015	18.5	5.3	9	27.8	10.5	16	1.7%	-9.30 [-15.50, -3.10]	
Li 2012	8	7.4	59	10	5.9	47	7.2%	-2.00 [-4.53, 0.53]	
Munitiz 2010	9	15.5	74	13	16.3	74	2.4%	-4.00 [-9.12, 1.12]	
Pan 2014	7	2.2	40	12	4.8	40	11.3%	-5.00 [-6.64, -3.36]	
Preston 2012	14.3	9.9	12	17.5	5.6	12	1.6%	-3.20 [-9.64, 3.24]	
Shewale 2015	8	12.3	386	12	24.8	322	5.8%	-4.00 [-6.97, -1.03]	
Tang 2013	11	1.9	36	15	3	27	13.4%	-4.00 [-5.29, -2.71]	
Wang 2015	9	0.8	90	11.7	1.4	90	18.7%	-2.70 [-3.03, -2.37]	
Zehr 1998	9.5	2.8	96	13.6	6.9	56	9.9%	-4.10 [-5.99, -2.21]	
Zhao 2013	7.2	2.3	34	12.5	4.5	34	10.9%	-5.30 [-7.00, -3.60]	
Total (95% CI)			1044			906	100.0%	-3.55 [-4.41, -2.69]	

Heterogeneity: Tau² = 0.99; Chi² = 27.51, df = 12 (P = 0.007); I² = 56%
Test for overall effect: Z = 8.12 (P < 0.00001)

Fig 8. Pooled estimates of length of hospital stay comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.
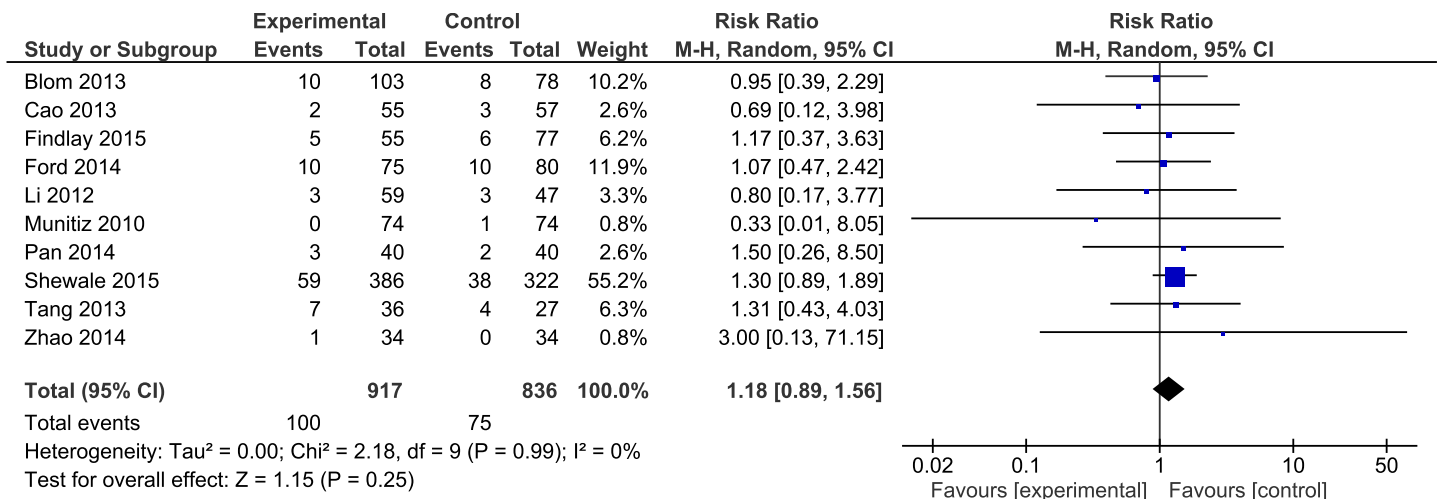
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Blom 2013	10	103	8	78	10.2%	0.95 [0.39, 2.29]	
Cao 2013	2	55	3	57	2.6%	0.69 [0.12, 3.98]	
Findlay 2015	5	55	6	77	6.2%	1.17 [0.37, 3.63]	
Ford 2014	10	75	10	80	11.9%	1.07 [0.47, 2.42]	
Li 2012	3	59	3	47	3.3%	0.80 [0.17, 3.77]	
Munitiz 2010	0	74	1	74	0.8%	0.33 [0.01, 8.05]	
Pan 2014	3	40	2	40	2.6%	1.50 [0.26, 8.50]	
Shewale 2015	59	386	38	322	55.2%	1.30 [0.89, 1.89]	
Tang 2013	7	36	4	27	6.3%	1.31 [0.43, 4.03]	
Zhao 2014	1	34	0	34	0.8%	3.00 [0.13, 71.15]	
Total (95% CI)		**917**		**836**	**100.0%**	**1.18 [0.89, 1.56]**	
Total events	100		75				

Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 9 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.15 (P = 0.25)

0.02   0.1   1   10   50
Favours [experimental]   Favours [control]

Fig 9. Pooled estimates of readmission rate comparing enhanced recovery after surgery versus standard care. CI confidence interval, df degrees of freedom.

potential benefits of ERAS protocol in oesophageal cancer surgery. The subsequent meta-analysis of results showed a general reduction of LOS with no significant influence on surgical morbidity. Moreover, it showed a reduction in overall non-surgical and pulmonary complications. Surgical complications and anastomotic leakage rate were not affected. Also, mortality and readmission rates did not vary between groups. This suggests that multimodal modern perioperative care can be also safe in this type of surgery.

The efficacy of ERAS protocol in gastrointestinal surgery was confirmed in the previously published systematic reviews regarding colorectal, pancreatic, gastric or liver surgery [4–6,27]. These studies showed the reduction of LOS and an additional decrease in the complication rate. The number of studies with control groups regarding the application of ERAS protocol in oesophageal surgery is limited. In our literature research we came upon only one systematic review by Gemmill et al., published in 2015 [28]. This review included 11 studies, none of which was a RCT, with no subsequent meta-analysis, thus the quality of evidence was rather limited. On the contrary, our review provides a meta-analysis performed on the analysed data. However, it comprises of comparative studies and only one RCT, which obviously limits the quality of evidence.

All previous systematic reviews, regarding other surgical disciplines, showed a significant decrease in overall morbidity, mostly by decreasing non-surgical morbidity [4–6]. We did not demonstrate a reduction of overall complication rates between the groups in our review, however lack of high quality studies limits the potential evidence in this matter. Oesophageal resections are considered technically demanding, involving more than one operating field (abdominal, thoracic and cervical). Therefore, the morbidity associated with this procedure is relatively high, which was also confirmed in our review. Apart from surgical complications, high non-surgical morbidity has been reported. Interestingly, our analysis showed that standardized multimodal perioperative care may positively influence non-surgical complications. With no influence on surgical adverse events we may assume that the introduction of multimodal modern perioperative care programmes could possibly be considered as safe and beneficial. However, this statement is limited by the inconsistency of how complications were reported in the studies subject to analysis.

A common belief in the surgical world is that while ERAS shortens LOS, it inevitably leads to an increase in the readmission rate. We have shown that LOS in ERAS patients was indeed

significantly shorter, but it did not affect readmissions. It was significantly shorter in 6 of 13 studies. This is may very well serve as another implication of potential safety of this type of perioperative care after oesophageal resections. Shorter LOS with non-surgical morbidity reduction and no influence on surgical complications allows us to imply that ERAS protocol improves general functional recovery. It is generally believed that modern perioperative care diminishes postoperative stress response, thus allowing faster convalescence [29]. Currently it is emphasized that a full functional recovery, rather than the postoperative hospital stay, is considered as the main goal of perioperative care [30].

The general quality of the papers included is limited. Only one analysed study was RCT with rather low quality (Jadad score 2 points), whereas the remaining were cohort studies. In order to fully assess the feasibility and potential of ERAS protocol in oesophageal surgery, more randomized trials of high quality are required.

Also, a very important aspect should be raised. Although guidelines for perioperative care in other types of surgery have been officially published by the ERAS Society, such a document for oesophageal resections does not exist. This results in a significant diversity of perioperative protocol items. While analysing the articles included we have identified at least 19 protocol elements that may be included in future guidelines. It is not surprising that none of the studies used all of these items. Their number varied between 8 and 16, which clearly demonstrates the inadequacy of the protocols described. Another issue is the interpretation of particular protocol elements in the studies included. Even though some protocols used similar items, its rendition varied, thus making it difficult to compare. For instance, chest drains were removed between postoperative day (POD) 2 and 6, patients were mobilized between POD 0 and 2, oral feeding was introduced between POD 1 and 6. In some protocols there were items which have been previously shown inappropriate or even harmful in modern perioperative care (use of nasogastric tubes, no immediate extubation, etc.). Whereas some of the programmes report using antithrombotic prophylaxis, some do not mention this element at all, yet it is difficult to comprehend that this element would not be considered conservative protocols. All of this demonstrates that it is difficult to fully assess the ERAS principles of early feeding, quick mobilization, appropriate analgesia and stress response reduction in most of the included studies. Moreover, protocol compliance was only reported by Ford et al, Li et al., Blom et al., Findlay et al. and Munitiz et al, [13,17,18,20,21]. This is important since many papers link adherence to the protocol with post-operative outcomes [31]. Due to the lack of data in other studies, it is impossible to determine the compliance rate in this review. The variability in both the number and the type of ERAS items implemented did not permit reliable subgroup analyses to identify which items might be more effective. We did not find a link between the number of the protocol elements implemented and the efficacy of the protocol. However, it has to be underlined that full evaluation may only be possible in future studies, based on unified standardised protocols or guidelines with additional information on adherence to each protocol element. Another limitation to this study is the variability of the used surgical techniques. Studies were not homogenous in this aspect and this may present a bias to our results. In most papers, types of surgery and approach used (open/minimally invasive) were usually not reported precisely. Therefore, a subgroup analysis or even a simple comparison between studies could not have been performed due to lack of necessary data. The heterogeneity of the studies, a different number of protocol elements, the lack of ERAS compliance and no unified stratification of morbidity classification prevent us from making strong conclusions about ERAS in oesophageal surgery. Although the present meta-analysis adds substantial evidence for the use of ERAS protocol in oesophageal surgery, further high quality trials are needed to fully assess its feasibility and safety.

Conclusions

This systematic review with a meta-analysis on ERAS in oesophageal surgery indicates a reduction of non-surgical complications and no negative influence on overall morbidity. Moreover, a reduction in the length of hospital stay was presented. All analysed papers were of low quality with a high risk of bias, thus rendering limited level of evidence from these results. Therefore, further research with high quality RCTs is required to fully assess the feasibility of modern perioperative care protocols in oesophageal surgery. They may well serve as references for the forthcoming ERAS guidelines for perioperative care in oesophageal surgery.

Supporting information

S1 Table. PRISMA checklist.
(DOC)

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References

1. Kehlet H (1997) Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 78: 606–617. PMID: 9175983

2. Bardram L, Funch-Jensen P, Jensen P, Crawford ME, Kehlet H (1995) Recovery after laparoscopic colonic surgery with epidural analgesia, and early oral nutrition and mobilisation. Lancet 345: 763–764. PMID: 7891489

3. Kehlet H, Mogensen T (1999) Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme. Br J Surg 86: 227–230. https://doi.org/10.1046/j.1365-2168.1999.01023.x PMID: 10100792

4. Ni TG, Yang HT, Zhang H, Meng HP, Li B (2015) Enhanced recovery after surgery programs in patients undergoing hepatectomy: A meta-analysis. World J Gastroenterol 21: 9209–9216. https://doi.org/10.3748/wjg.v21.i30.9209 PMID: 26290648

5. Coolsen MM, van Dam RM, van der Wilt AA, Slim K, Lassen K, Dejong CH (2013) Systematic review and meta-analysis of enhanced recovery after pancreatic surgery with particular emphasis on

pancreaticoduodenectomies. World J Surg 37: 1909–1918. https://doi.org/10.1007/s00268-013-2044-3 PMID: 23568250

6.   Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M (2014) Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. World J Surg 38: 1531–1541. https://doi.org/10.1007/s00268-013-2416-8 PMID: 24368573

7.   Urbach DR, Baxter NN (2005) Reducing variation in surgical care. BMJ 330: 1401–1402. https://doi.org/10.1136/bmj.330.7505.1401 PMID: 15961794

8.   Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ, et al. (2015) Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. Acta Anaesthesiol Scand 59: 1212–1231. https://doi.org/10.1111/aas.12601 PMID: 26346577

9.   Thorell A, MacCormick AD, Awad S, Reynolds N, Roulin D, Demartines N, et al. (2016) Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg.

10. Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. (2013) Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS($^{®}$)) Society recommendations. World J Surg 37: 259–284. https://doi.org/10.1007/s00268-012-1772-0 PMID: 23052794

11. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5: 13. https://doi.org/10.1186/1471-2288-5-13 PMID: 15840177

12. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2008–2012. PMID: 10789670

13. Blom RL, van Heijl M, Bemelman WA, Hollmann MW, Klinkenbijl JH, Busch OR, et al. (2013) Initial experiences of an enhanced recovery protocol in esophageal surgery. World J Surg 37: 2372–2378. https://doi.org/10.1007/s00268-013-2135-1 PMID: 23807122

14. Al-Herz F, Sammour T, Milne H, Rhind B, Young M (2015) Closing the audit cycle: improving short-term outcomes of oesophagectomy in a provincial hospital. J Perioper Pract 25: 111–114. PMID: 26302592

15. Cao S, Zhao G, Cui J, Dong Q, Qi S, Xin Y, et al. (2013) Fast-track rehabilitation program and conventional care after esophagectomy: a retrospective controlled cohort study. Support Care Cancer 21: 707–714. https://doi.org/10.1007/s00520-012-1570-0 PMID: 22933129

16. Pan H, Hu X, Yu Z, Zhang R, Zhang W, Ge J (2014) Use of a fast-track surgery protocol on patients undergoing minimally invasive oesophagectomy: preliminary results. Interact Cardiovasc Thorac Surg 19: 441–447. https://doi.org/10.1093/icvts/ivu172 PMID: 24916581

17. Findlay JM, Tustian E, Millo J, Klucniks A, Sgromo B, Marshall RE, et al. (2015) The effect of formalizing enhanced recovery after esophagectomy with a protocol. Dis Esophagus 28: 567–573. https://doi.org/10.1111/dote.12234 PMID: 24835109

18. Ford SJ, Adams D, Dudnikov S, Peyser P, Rahamim J, Wheatley TJ, et al. (2014) The implementation and effectiveness of an enhanced recovery programme after oesophago-gastrectomy: a prospective cohort study. Int J Surg 12: 320–324. https://doi.org/10.1016/j.ijsu.2014.01.015 PMID: 24486931

19. Gatenby PA, Shaw C, Hine C, Scholtes S, Koutra M, Andrew H, et al. (2015) Retrospective cohort study of an enhanced recovery programme in oesophageal and gastric cancer surgery. Ann R Coll Surg Engl 97: 502–507. https://doi.org/10.1308/003588415X14181254789880 PMID: 26414360

20. Li C, Ferri LE, Mulder DS, Ncuti A, Neville A, Lee L, et al. (2012) An enhanced recovery pathway decreases duration of stay after esophagectomy. Surgery 152: 606–614; discussion 614–606. https://doi.org/10.1016/j.surg.2012.07.021 PMID: 22943844

21. Munitiz V, Martinez-de-Haro LF, Ortiz A, Ruiz-de-Angulo D, Pastor P, Parrilla P (2010) Effectiveness of a written clinical pathway for enhanced recovery after transthoracic (Ivor Lewis) oesophagectomy. Br J Surg 97: 714–718. https://doi.org/10.1002/bjs.6942 PMID: 20187171

22. Preston SR, Markar SR, Baker CR, Soon Y, Singh S, Low DE (2013) Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer. Br J Surg 100: 105–112. https://doi.org/10.1002/bjs.8974 PMID: 23161343

23. Shewale JB, Correa AM, Baker CM, Villafane-Ferriol N, Hofstetter WL, Jordan VS, et al. (2015) Impact of a Fast-track Esophagectomy Protocol on Esophageal Cancer Patient Outcomes and Hospital Charges. Ann Surg 261: 1114–1123. https://doi.org/10.1097/SLA.0000000000000971 PMID: 25243545

24. Tang J, Humes DJ, Gemmil E, Welch NT, Parsons SL, Catton JA (2013) Reduction in length of stay for patients undergoing oesophageal and gastric resections with implementation of enhanced recovery packages. Ann R Coll Surg Engl 95: 323–328. https://doi.org/10.1308/003588413X13629960046039 PMID: 23838493

25. Zhao G, Cao S, Cui J (2014) Fast-track surgery improves postoperative clinical recovery and reduces postoperative insulin resistance after esophagectomy for esophageal cancer. Support Care Cancer 22: 351–358. https://doi.org/10.1007/s00520-013-1979-0 PMID: 24068549

26. Wang JY, Hong X, Chen GH, Li QC, Liu ZM (2015) Clinical application of the fast track surgery model based on preoperative nutritional risk screening in patients with esophageal cancer. Asia Pac J Clin Nutr 24: 206–211. https://doi.org/10.6133/apjcn.2015.24.2.18 PMID: 26078236

27. Beamish AJ, Chan DS, Blake PA, Karran A, Lewis WG (2015) Systematic review and meta-analysis of enhanced recovery programmes in gastric cancer surgery. Int J Surg 19: 46–54. https://doi.org/10.1016/j.ijsu.2015.05.021 PMID: 26004350

28. Gemmill EH, Humes DJ, Catton JA (2015) Systematic review of enhanced recovery after gastro-oesophageal cancer surgery. Ann R Coll Surg Engl 97: 173–179. https://doi.org/10.1308/003588414X14055925061630 PMID: 26263799

29. Pędziwiatr M, Kisialeuski M, Wierdak M, Stanek M, Natkaniec M, Matłok M, et al. (2015) Early implementation of Enhanced Recovery After Surgery (ERAS®) protocol—Compliance improves outcomes: A prospective cohort study. Int J Surg 21: 75–81. https://doi.org/10.1016/j.ijsu.2015.06.087 PMID: 26231994

30. Aahlin EK, von Meyenfeldt M, Dejong CH, Ljungqvist O, Fearon KC, Lobo DN, et al. (2014) Functional recovery is considered the most important target: a survey of dedicated professionals. Perioper Med (Lond) 3: 5.

31. Pędziwiatr M, Pisarska M, Kisielewski M, Matłok M, Major P, Wierdak M, et al. (2016) Is ERAS in laparoscopic surgery for colorectal cancer changing risk factors for delayed recovery? Med Oncol 33: 25. https://doi.org/10.1007/s12032-016-0738-8 PMID: 26873739