

Enhanced Recovery After Surgery and Radical Cystectomy: A Systematic Review and Meta-Analysis

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Introduction: Enhanced recovery after surgery (ERAS) protocols aim to optimize patient recovery after major surgery. Our study was to examine the evidence of the effectiveness of interventions designed to improve patient outcomes after radical cystectomy.

Design: Systematic review and meta-analysis.

Data Sources: PubMed, Medline, Embase, Cochrane from January 2005 to January 2021 without language restrictions.

Eligibility Criteria: Randomized and non-randomized controlled studies implementing ERAS measuring its interventions on rates of postoperative complications, 30-day readmission, length of stay (LOS) and bowel function after radical cystectomy.

Data Extraction and Synthesis: Two members of the investigating team independently selected studies and evaluated bias using the Cochrane collaboration tool. Meta-analysis of all comparative studies used inversed-weighted, fixed- effects models and random effects models to pool results. Publication bias was graphically assessed using contour-enhanced funnel plots and the Egger's test of funnel plot symmetry.

Results: Fifteen studies were included in our meta-analysis; we observed that ERAS decreased the time for the first bowel movement (standardized mean difference [SMD]: -1.30, 95% CI -1.90 to -0.70, $P < 0.00001$) and shortened the length of stay (LOS) ([SMD]: -0.49, 95% CI -0.77 to -0.20, ($P < 0.00001$)); however, 30-day readmission (risk ratio [RR]: 0.97, 95% [CI] 0.73 to 1.28, $P = 0.52$) and the overall postoperative complication rate (risk ratio [RR]: 0.98, 95% confidence interval [CI]: 0.88 to 1.09, $P = 0.41$) showed no significant difference.

Keywords: enhanced recovery after surgery, radical cystectomy, length of stay, post-operative complications

Introduction

Bladder cancer has a high incidence and is associated with high morbidity and mortality.¹ Radical cystectomy (RC) is the gold standard treatment for high-risk grade non-muscle invasive bladder tumor and muscle invasive bladder cancer (MIBC).² RC is a complex urological procedure and is associated with poor recovery, often requiring readmission and lengthy hospital stay. Complications are attributed to the patient population who are generally the elderly presenting with comorbidities (eg, coronary artery disease, atherosclerosis, and cerebrovascular accidents). In the past decades, the perioperative management of RC patients has evolved. In the conventional care, some patients were led down a course of interventions that were based on surgical or anesthesia dogma rather than evidence-based studies. Different routines of care such as bowel preparations and

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preoperative fasting often increase the patient's physical and emotional stress. The systemic release of stress hormones and inflammatory mediators by the central nervous system can be detrimental after major operations, leading to rapid deconditioning and suboptimal outcomes of patients.³ There is no single element by itself to counteract this physiological cascade but rather a series of care pathways to help minimize this response subsequently improving the outcome of the surgery. In the late 1990s, the concept of ERAS was first introduced under the name of fast track recovery to study the effect of the surgical stress response on open colorectal surgery.⁴ It was in 2000 in Denmark that the idea was coined into ERAS evidenced-based perioperative clinical pathways that consider the factors contributing to morbidity and proactively apply measures to reduce or eliminate them.⁵ The application of evidence-based medicine has helped halve the rate of postoperative complications and reduce LOS.⁶ In recent years, many studies have recognized and approved the benefits of ERAS, and it began gaining traction in other surgical specialties such as pancreatic, gynecology and urology.⁷ ERAS pathways for cystectomy patients have tremendous clinical value and several studies have been published on the matter; however, noticeable differences exist in the effect of ERAS protocols and perioperative outcomes.^{8–21}

Considering the lack of consistency in study results, as well as the absence of experimental data from high-quality randomized controlled trials (RCT), we conducted a systematic review and meta-analysis to determine the clinical effectiveness of ERAS pathways versus standard care on various perioperative outcomes of interest after RC.

Methods

Study Selection

In accordance with the PRISMA guidelines 2020 and Cochrane handbook for systemic reviews of interventions,^{22,23} we conducted a systematic literature search from January 2005 to January 2021 based on databases including PubMed, Medline, Embase and the Cochrane Library without language restrictions. Search terms or keywords used included bladder cancer, enhanced recovery after surgery and radical cystectomy. The following Medical Subject Headings (MESH) terms were used: “Enhanced Recovery After Surgery” [Mesh] OR “Postoperative Care” [Mesh] OR “Recovery of Function” [Mesh] OR “Enhanced Recovery” [tw] OR “fast track

protocol*” [tw] OR “eras protocol*” [tw] AND “Cystectomy” [Mesh] OR “Urinary Bladder Neoplasms” [Mesh] OR “Cystectomy” [tw] OR “Bladder tumor*” [tw] OR “bladder cancer” [tw] OR “Radical cystectomy” [tw] AND “Postoperative Complications” [Mesh] OR “length of stay” [tw] OR “injury” [tw] OR “ileus” [tw] OR “incontinence” [tw] OR “shock” [tw]. We also checked the reference lists of all related articles to ensure literature saturation.

Inclusion Criteria and Exclusion Criteria

Two members of the investigative team (M.P. and Z.J.W.) independently assessed the eligibility of the articles for inclusion in the study and discussed inconsistencies until consensus was obtained. The PICO method was used to define and search for potentially eligible studies.

- P (population): Patients undergoing RC.
- I (intervention): At least one element of ERAS protocols.
- C (comparison): Standard care/conventional therapy/Non-ERAS.
- O (outcomes of interest): At least one of the following; LOS, time to passage of first stool, readmission, overall complications; Clavien–Dindo classification and postoperative ileus (POI),

Studies that met one of the following criteria were excluded:

- (1) The inclusion criteria were not met or no outcomes of interest were reported.
- (2) Duplicate publications, non-comparative studies, case reports, editorial articles and reviews.

Data Extraction

One reviewer (M.P.) independently screened and extracted data from full-texts, citations, and protocols using standardized data collection forms that contained fields for authors, publication year, country, study design, matching variables (age, gender, body mass index, American society of Anesthesiology score, history of previous surgery, clinical staging, operation type, diversion type, operation time, estimated blood loss), and outcomes of interest. The outcomes of interest were as follows: length of hospital stay, time to first passage of stool, rate of 30-day readmission, and overall complications. The overall incidence of complications was classified within the Clavien–Dindo Classification and postoperative ileus. Disagreements between the two reviewers were resolved through discussion.

Quality Assessment

M.P. independently used the Cochrane risk-of-bias tool, RoB tool, in Review Manager software (<https://community.cochrane.org/help/tools-and-software/revman-5>) to assess the risk of bias of RCTs (Figure 1), and there were concerns about risk of bias for the majority of studies. The domains of assessment included (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); (7) other bias (such as funding sources). Z.J.W. independently rated the level of evidence of the included studies using the Oxford Centre for Evidence-Based Medicine.²⁴

Statistical Analysis

For studies that reported continuous data as median and range, we estimated the mean and standard deviation (SD) using the method described by Wan et al.²⁵ The continuous variables were described as the difference in mean values and the 95% confidence interval (CI) between ERAS and Non-ERAS. The dichotomous outcomes were analyzed by calculating the risk ratio (RR). The meta-analysis was performed using the RevMan 5.4 software.²⁶ An inverse-weighted, fixed-effects meta-analysis was performed. The multiple interventions that constitute ERAS make the assumptions of a fixed-effect meta-analysis (all studies in the meta-analysis share one true effect size across all included studies) unlikely; therefore, the degree of heterogeneity between studies was assessed using the chi-square test ($P < 0.10$) and the I^2 statistic with values $> 50\%$ regarded as being significant heterogeneity. A random-effects meta-analysis was used when significant heterogeneity was found between studies. We performed sensitivity analyses on recent publication 2015 or later and overall high-risk bias. To assess for publication bias, we used the RStudio coding software (RStudio Team. (2020). RStudio: Integrated Development Environment for R. Boston)²⁷ to create contour-enhanced funnel plots and applied the Egger's test of funnel plot symmetry.²⁸

Characteristics of Included Studies

The database search yielded 317 records after duplication removal; we screened 306 records, from which we retrieved 54 full-text records and included 12 studies.^{8–10,12–17,20,21,29}

Moreover, we performed a citation and reference search and included three additional studies.^{11,18,19} Fifteen studies that met the inclusion criteria were identified (Figure 2); only 1 study¹⁸ was a retrospective RCT and the 14 others were prospective cohort studies. A total of 1853 participants were included, of which 953 were grouped as ERAS and 900 as control. The characteristics of each study are summarized in Table 1. The different ERAS elements between each study are summarized in Table 2.

Results

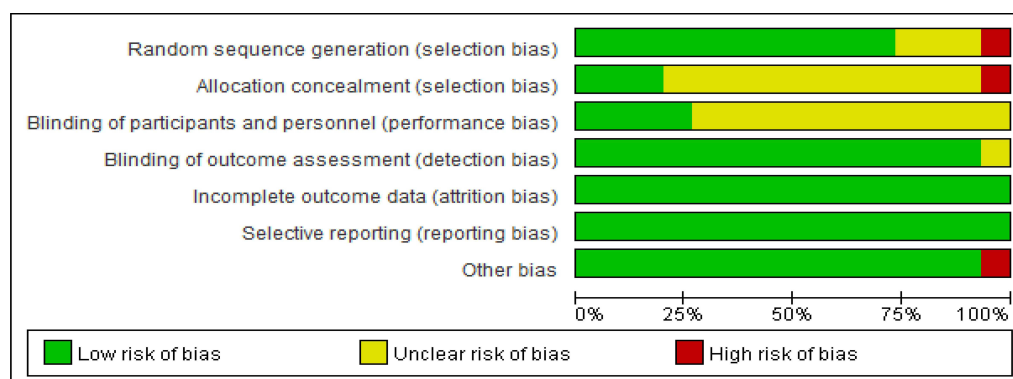
The majority of studies focused on the length of stay and overall complications. Studies were conducted in diverse country settings including the United States (two), Italy (two) and one each in India, South Korea, Greece, Sweden, Belgium, Canada, Denmark, England, Egypt and Romania. One included study was retrospective,¹⁸ 13 was prospective randomized control cohort,^{8–11,13–17,19–21,29} and one study was non-randomized prospective cohort.¹² Time-to-first defecation was recorded across 10 studies,^{8–10,14,16,17,19–21} and 30d readmission rate was assessed from 8 studies.^{9,11,13–15,17,21,29}

Length of Stay

Pooled data analysis from 13 studies,^{8–12,14,15,17–21,29} showed that the ERAS group was associated with shorter length of stay compared to the Non-ERAS group. SMD = -0.49 , 95% CI: -0.77 to -0.20 . Heterogeneity: $\text{Chi}^2 = 78.18$, $df = 12$ ($P < 0.00001$); $I^2 = 85\%$ (Figure 3) the random-effects model was used. Participants = 1471.

Complications

The overall complications were defined as high-grade, low-grade (Clavien–Dindo classification) and POI. The overall complication rate across 12 studies^{9–15,17–21} showed that ERAS did not reduce the risk of complications with 44.3% of patients in the ERAS group against 44.79% of patients in the Non-ERAS group. Furthermore, pooled data from the fixed-effects model detected no significant difference between the two groups: RR = 0.98, 95% CI: 0.88–1.09, with low heterogeneity observed between studies: $\text{Chi}^2 = 11.37$, $df = 11$ ($P = 0.41$); $I^2 = 3\%$ (Figure 4) participants = 1507.



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Adamakis 2011	+	-	?	?	+	+	+
Bansal 2019	+	+	+	+	+	+	+
Choi 2011	+	?	?	+	+	+	+
Collins 2016	+	?	?	+	+	+	+
Declercq 2015	-	?	?	+	+	+	+
Deibert 2016	+	?	+	+	+	+	+
Ercolino 2019	?	?	?	+	+	+	+
Fress 2017	?	?	?	+	+	+	+
Jensen 2015	+	+	?	+	+	+	+
Lee CT 2014	+	+	?	+	+	+	-
Lin.T 2017	+	?	?	+	+	+	+
Maffezzini 2007	?	?	+	+	+	+	+
Mukthar 2013	+	?	?	+	+	+	+
Seham.M 2019	+	?	+	+	+	+	+
Vlad 2020	+	?	?	+	+	+	+

Figure I The risk of bias summary of included studies.

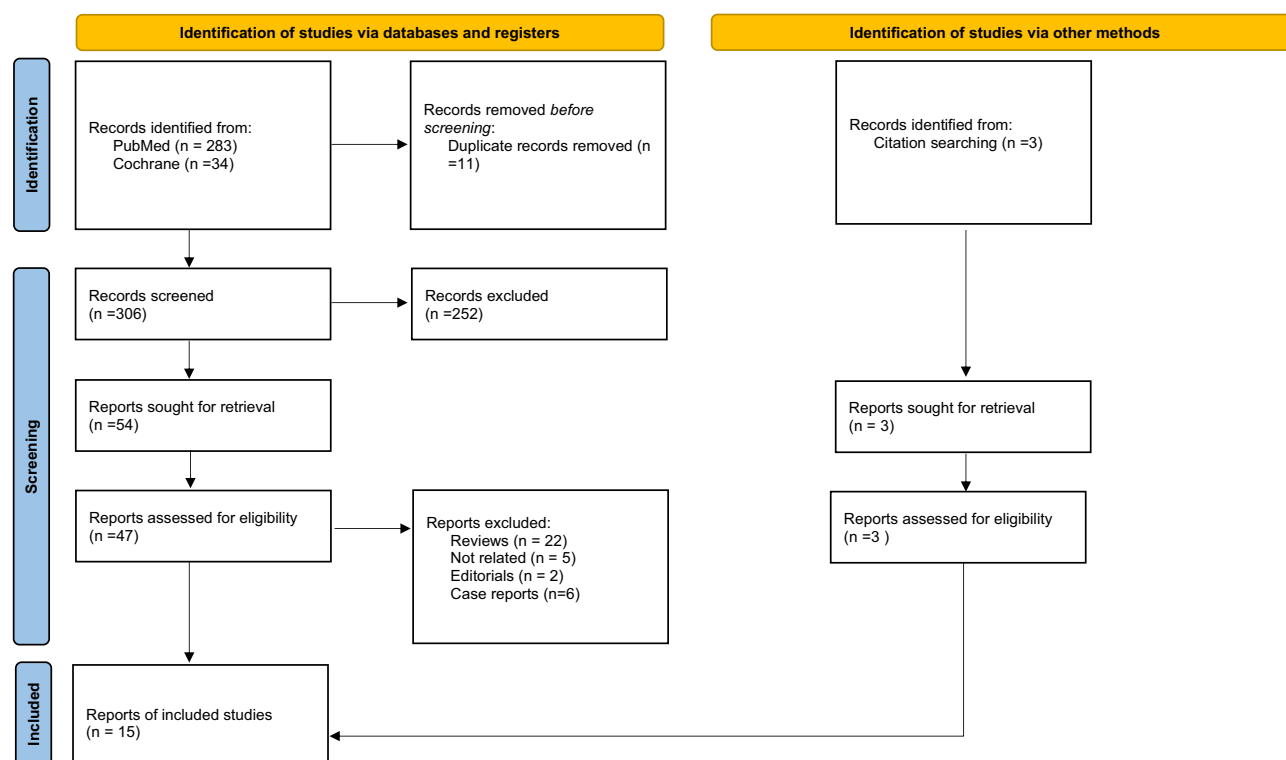


Figure 2 Flowchart of literature selection process.

Bowel Function

Time-to-first bowel movement was lower in the ERAS group regardless of the diversion type used. Moreover, pooled data from the random-effects model across 10 studies pointed towards a faster return to bowel function in the ERAS group: SMD= -1.30 95% but CI: -1.90 to 0.70. Heterogeneity: $\chi^2 = 185.97$, $df = 9$ ($P < 0.00001$); $I^2 = 95\%$ (Figure 5) participants =1216.

Readmissions

In general, ERAS did not significantly reduce the probability of patients being readmitted after RC. Moreover, 15.7% of the patients in the ERAS group were readmitted within 30 d compared with 15.3% of the patients in the Non-ERAS group. Pooled data from the fixed-effects model showed no significant difference between the two groups' 30-day readmission rate': RR =0.97, 95% CI: 0.73–1.28, and there was statistical heterogeneity between studies: $\chi^2 = 6.14$, $df = 7$ ($P = 0.52$); $I^2 = 0\%$, (Figure 6) participants=1077.

Sensitivity Analysis and Publication Bias

This sensitivity analysis that removes studies with potential bias found no significant changes. To examine small study and publication bias, we used contour-enhanced funnel plots (Figure 7). Visual inspection of the funnel plots indicates possible bias. To further investigate the possibility of bias, we conducted an Egger test for funnel plot asymmetry, and the results are shown in Table 3. With these collective findings, we therefore can conclude that our results are with minimal publication bias.

Discussion

The study demonstrated that the implementation of ERAS protocols for patients undergoing radical cystectomy quickens the return of bowel function and shortens the length of hospitalization. No significant difference in readmission and complication rates were noted. Urologists have been slow to adopt ERAS despite evidence from colorectal literature showing ERAS protocols lead to improved outcomes.^{30,31} The key principles of the ERAS

Table 1 Characteristics of Each Study

First Author, Year	Country	Study Type	ERAS/Non-ERAS	Variable Outcomes	Level of Evidence
Bansal et al, ⁹ 2020	India	Prospective	27/27	[1,2,3,4,6,7,9,10]	3b
Choi et al, ¹⁴ 2010	South Korea	Prospective	30/30	[1,2,3,4,6,7,8,9,10]	2b
Adamakis et al, ⁸ 2010	Greece	Prospective	22/21	[1,2,3,5,8,9,10]	2b
Collins et al, ¹⁵ 2016	Sweden	Prospective	135/86	[1,2,3,4,5,6,8]	3b
Declercq et al, ¹⁶ 2015	Belgium	Prospective	46/48	[1,2,3,6,7,8,9,10]	3b
Deibert et al, ¹⁷ 2016	USA	Prospective	50/52	[2,4,6,7,8,9,10]	3b
Ercolino et al, ¹⁸ 2019	Italy	Prospective	75/116	[1,2,3,6,7,8,9]	3b
Frees et al, ²⁹ 2017	Canada	Prospective	10/13	[1,2,3,4,7,8,9,10]	2b
Jensen et al, ¹⁹ 2014	Denmark	Prospective	50/57	[1,2,3,4,6,7,8,9]	3b
Lee et al, ²⁰ 2014	USA	Prospective	143/137	[1,2,3,6,7,8,9,10]	3b
Lin et al, ²¹ 2017	China	Prospective	144/145	[1,2,3,6,7,8,9,10]	3b
Maffezzini et al, ¹⁰ 2007	Italy	Retrospective	71/40	[1,2,4,6,8,9]	3b
Mukhtar et al, ¹¹ 2013	England	Prospective	51/26	[1,2,3,4,5,6,7,8,9]	3b
Moeen et al, ¹² 2019	Egypt	Prospective	54/57	[1,2,3,4,6,7,8,9,10]	3b
Vlad et al, ¹³ 2020	Romania	Prospective	45/45	[1,2,3,4,6,7,8,9,10]	3b

Notes: Includes the number of patients in ERAS group against the number of patients in the Non-ERAS group. 1) age, 2) gender, 3) body mass index (BMI), 4) American Society of Anesthesiology (ASA) Score, 5) history of previous surgery, 6) clinical stage, 7) operation type, 8) diversion type, 9) operation time, 10) estimated blood loss.

Abbreviation: ERAS, enhanced recovery after surgery.

model are evidence-based and include preoperative counseling, preoperative nutrition, omission of mechanical bowel preparation (MBP), limiting preoperative fasting, carbohydrate loading (non-diabetic patients), standardized analgesic regimens, fluid management, prevention of hypothermia and deep venous thrombosis, minimally invasive approach, antimicrobial prophylaxis, prevention of POI, early mobilization and early oral diet.³² The standardized pathways are designed to achieve optimum outcome from major surgeries and provide the necessary measures to attain such goals. Two studies did not omit MBP,^{11,18} all studies implemented early mobilization, early removal of NG tube, early oral feeding and pain management. The other pathways varied among studies for instance some studies show that ERAS pathways can shorten LOS,^{10,11,29} whereas others do not,^{8,15,20} most studies highlight the effect of ERAS pathways on reducing time to recovery of bowel function,^{9,10,14,17,29} with the exception of one⁸;

some studies demonstrate that ERAS protocols reduce readmission rates,^{14,21,33} yet three studies did not^{11,15,29}; some studies concluded that the standardized protocol reduces the overall complications^{9,12,19–21}; however some studies showed no change in morbidity.^{13,14,18} The differences in pathways most certainly raise the question about which elements to universally adopt, but the focus of this study was to assess whether their implementations have any clinical impact. Our study showed the importance in adopting the ERAS protocols to improve perioperative outcomes of RC patients compared to a traditional approach and that the multimodal nature of ERAS is better than individually focusing on a single element within it. A recent umbrella review of 23 meta-analyses across multiple surgical specialties including urology (3) by Zhang et al³⁴ showed strong evidence that ERAS pathways can reduce LOS and cost without increasing morbidity and readmission. Despite these positive results, we need to

Table 2

First Author, Year	Adamakis et al, 2010	Bansal et al, 2020	Choi et al, 2010	Collins et al, 2016	Declercq et al, 2015	Deibert et al, 2016	Ercolino et al, 2019	Frees et al, 2017	Jensen et al, 2014	Lee et al, 2014	Lin et al, 2017	Maffezzini et al, 2007	Mukhtar et al, 2013	Moeen et al, 2019	Vlad et al, 2020
Patient counseling and education	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓
MBP omission	✓	✓	×	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
Limited preoperative fasting	✓	✓	×	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓
Carbohydrate loading	✓	✓	×	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓
Antibiotics prophylaxis	×	✓	×	×	✓	✓	×	✓	✓	×	✓	✓	×	✓	✓
Venous thrombosis prevention	✓	✓	×	✓	×	✓	✓	✓	✓	×	✓	×	✓	✓	✓
EDA	✓	✓	×	✓	✓	✓	×	✓	✓	×	×	✓	✓	✓	✓
Minimal invasive approach	×	×	✓	✓	✓	✓	×	×	✓	✓	✓	×	✓	×	✓
GDFT	×	×	×	✓	✓	×	×	✓	✓	×	✓	×	✓	✓	✓
Prevention of hypothermia	✓	×	×	✓	✓	×	✓	✓	✓	×	✓	✓	✓	×	×
Early removal of NG tube	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pain management	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Early mobilization	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

(Continued)

Table 2 (Continued).

First Author, Year	Adamakis et al, 2010	Bansal et al, 2020	Choi et al, 2010	Collins et al, 2016	Declercq et al, 2015	Deibert et al, 2016	Ercolino et al, 2019	Frees et al, 2017	Jensen et al, 2014	Lee et al, 2014	Lin et al, 2017	Maffezzini et al, 2007	Mukhtar et al, 2013	Moeen et al, 2019	Vlad et al, 2020
Early oral intake	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Early removal of UC	X	✓	X	✓	✓	X	✓	X	✓	✓	✓	X	✓	✓	✓
POI prevention	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	X	X	X	✓
Total ERAS elements	12	13	7	15	15	12	12	14	16	8	15	9	14	13	14

Abbreviations: MBP, mechanical bowel preparation; EDA, epidural anesthesia; GDFT, goal-directed fluid therapy; NG, nasogastric; UC, urinary catheter; ✓, Included; X, Not included.

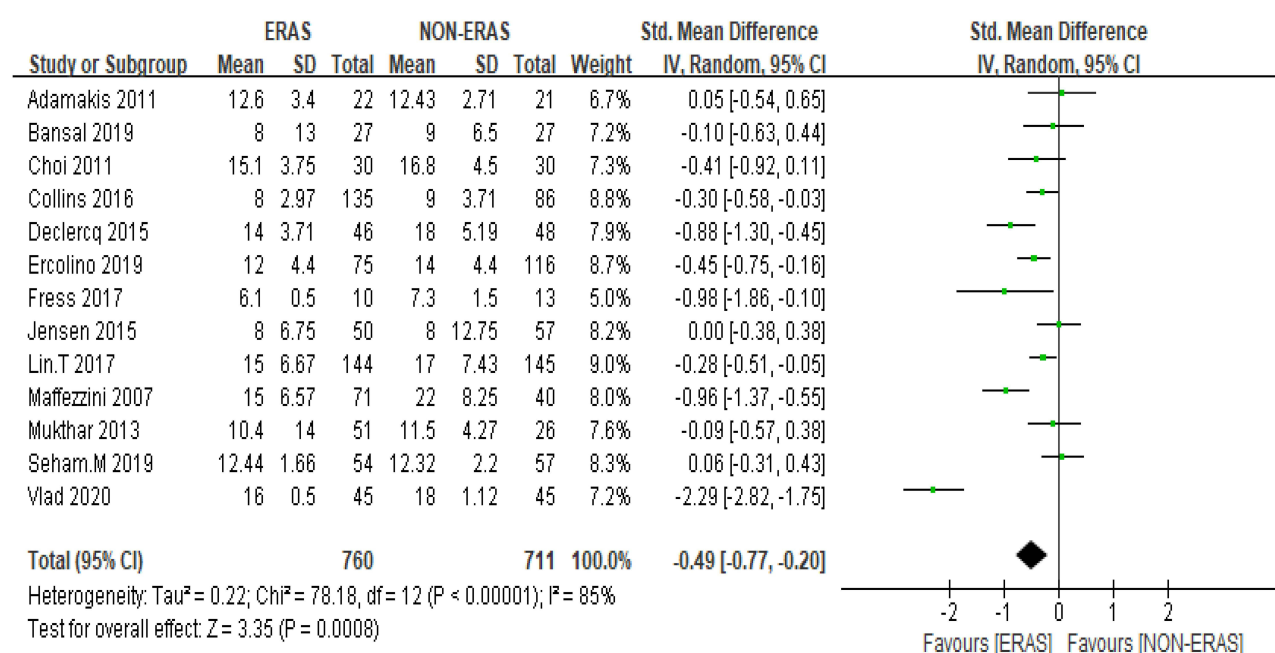


Figure 3 Forest plot displaying a random-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on length of stay after cystectomy. Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; SMD, standardized mean difference.

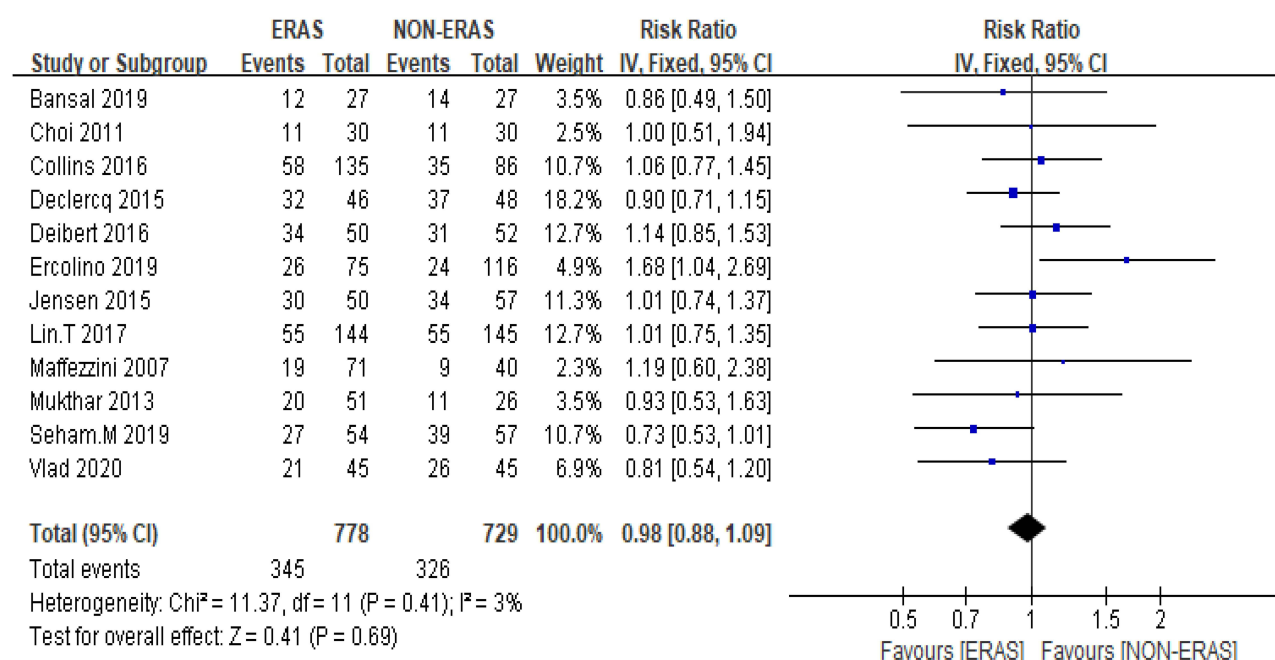


Figure 4 Forest plot displaying a fixed-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on complication rates after cystectomy.

Abbreviations: CI, confidence interval; RR, risk ratio.

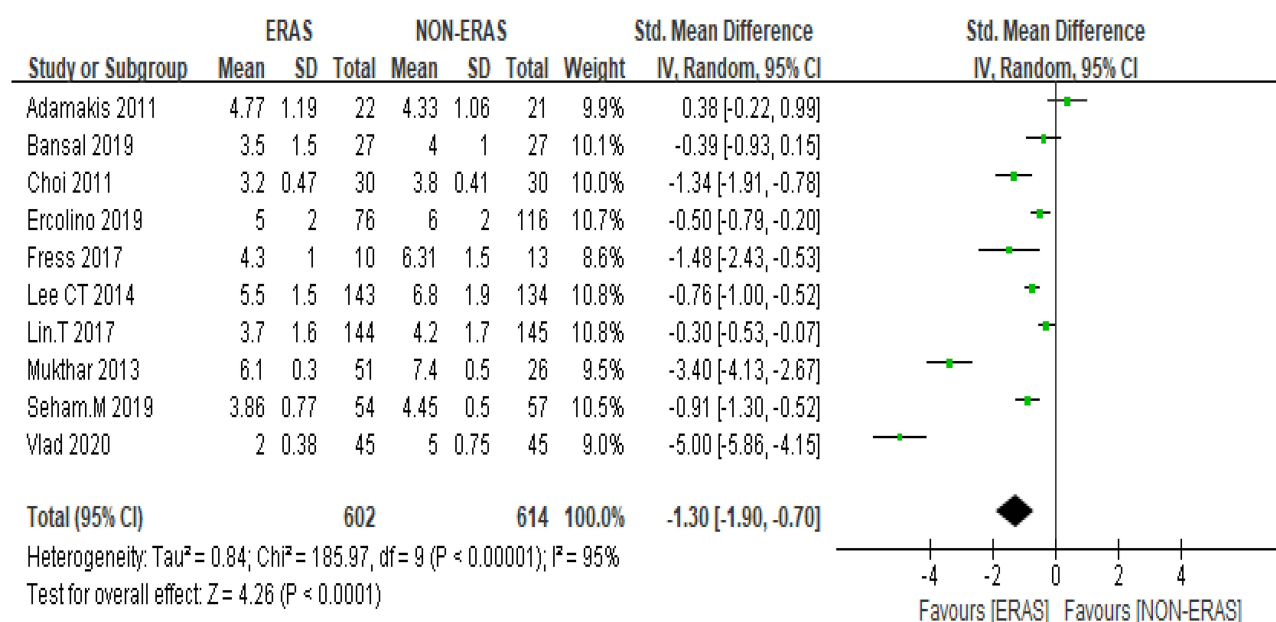


Figure 5 Forest plot displaying a random-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) on time to bowel function recovery after cystectomy. Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; SMD, standardized mean difference.

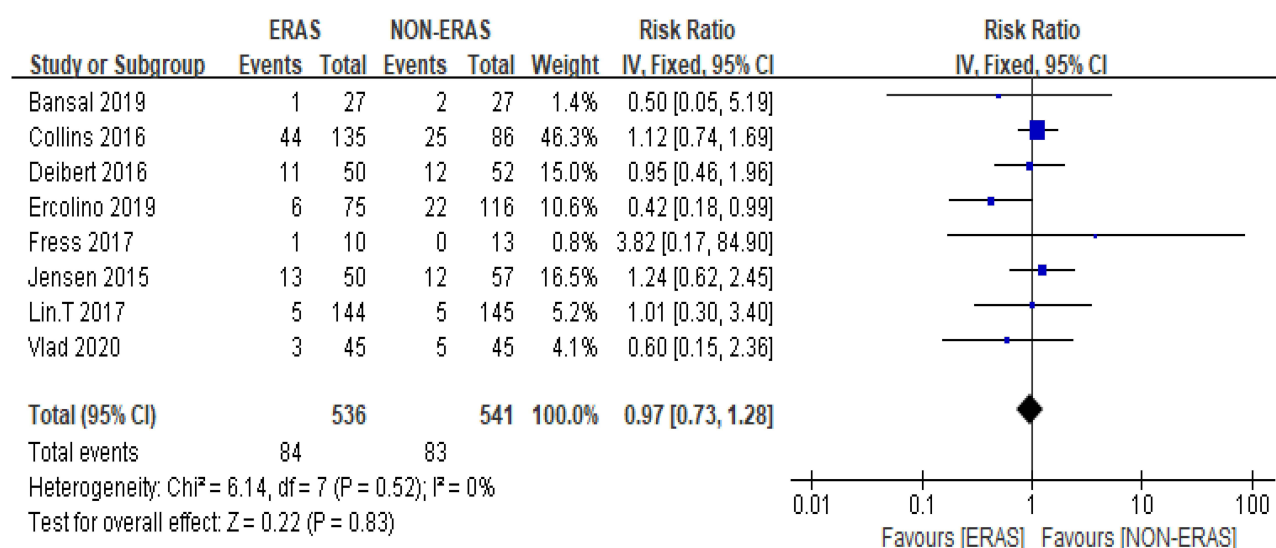


Figure 6 Forest plot displaying a fixed-effects meta-analysis of the effect of enhanced recovery after surgery (ERAS) readmission rates within 30 d after cystectomy.

Abbreviations: CI, confidence interval; RR, risk ratio.

exercise caution in interpreting these findings, there are limitations that cannot be ignored. The primary limitation is the limited number of RCT studies. Only two studies were blinded, all studies had at least an unclear bias in one

domain. Another limitation was that we did not perform a subgroup analysis based on the operation type and diversion type, we grouped all patients implementing the ERAS protocols under one group, which may also introduce

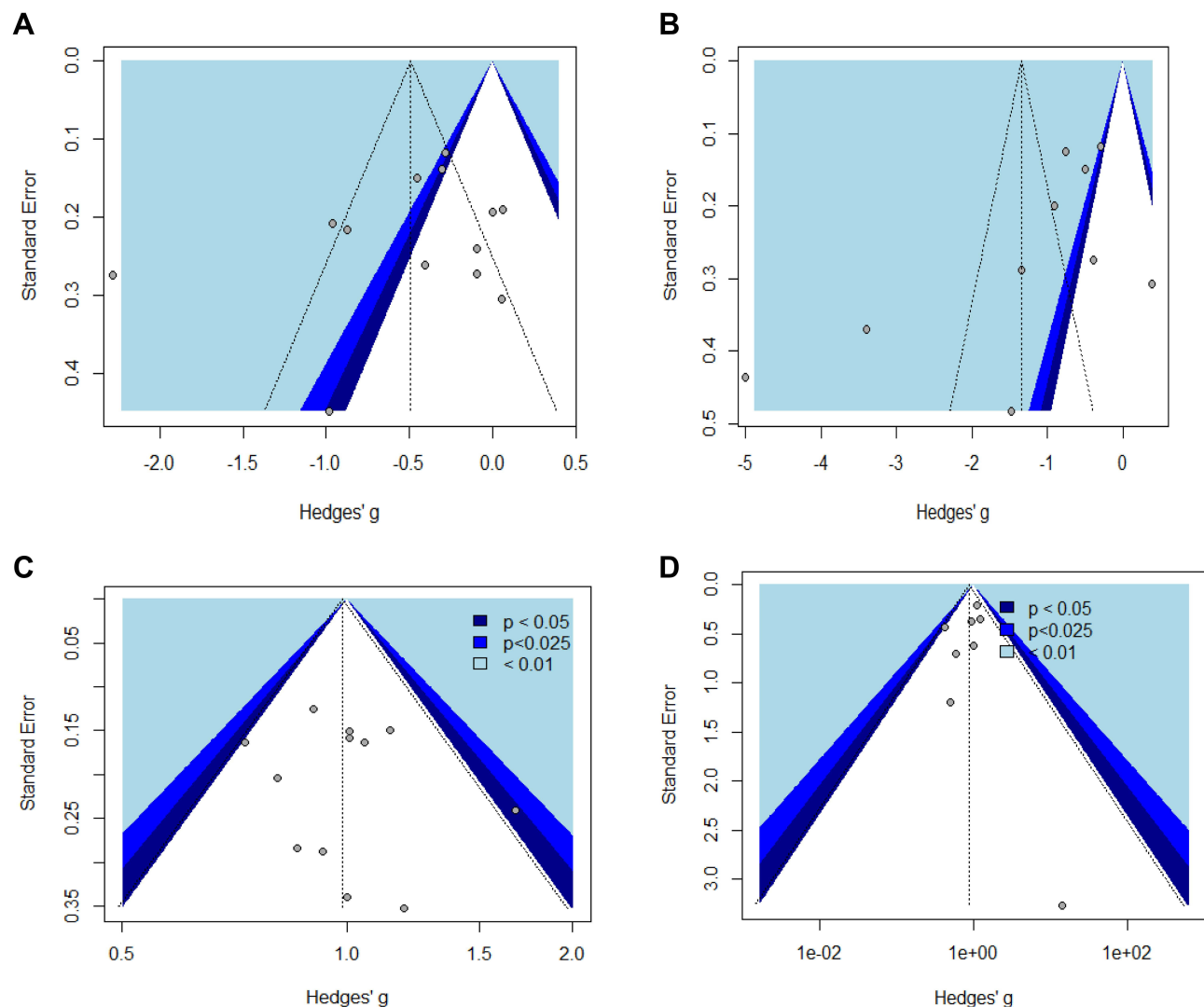


Figure 7 Contour-enhanced funnel plots for (A). Length of stay (B). bowel function (C). rate of complications (D). 30d readmission.

biased results. The publication bias was assessed by visual interpretation of funnel plots and Egger's test for funnel plot symmetry. Lastly, health economics and quality of life

were not included in our study due to lack of data. Despite these limitations, pooled data displayed the clinical efficacy of ERAS. Our findings indicated that ERAS

Table 3 Eggers' Test

Outcomes	P-Intercept	95% CI	t value	P value
LOS	-2.143	[-6.43 to 2.14]	-0.981	0.347
Bowel movement	-5.88	[-11.28 to -0.48]	-2.135	0.065
Overall complications	0.57	[-1.34 to 2.54]	0.602	0.560
30d-readmission	-0.37	[-1.65 to 0.92]	-0.564	0.593

Abbreviations: LOS, length of stay, CI, confidence interval.

protocols on perioperative outcomes of radical cystectomy provide a better improvement of the length of hospital stay and early rehabilitation of gastrointestinal function. Moreover, ERAS protocols did not increase the risk of adverse events, when compared with conventional protocols. These data have important clinical significance and we believe that our study further contributes to the body of evidence that supports the clinical value of ERAS in an effort to improve patients' outcomes in the cystectomy population.

Author Contributions

Study concept and design: Peerbocus, Wang.

Acquisition of data: Peerbocus.

Analysis and interpretation of data: Peerbocus, Wang.

Critical revision of the manuscript for important intellectual content: Wang.

Statistical analysis: Peerbocus.

Supervision: Wang.

Other: None.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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