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Enhanced recovery program versus traditional care after hepatectomy

A meta-analysis

Le Li, MD*, Jinming Chen, MD, Zhonghua Liu, MD, Qiang Li, MD, Ying Shi, MD

Abstract

To assess the safety and efficacy of enhanced recovery after surgery (ERAS) as compared with the traditional care in patients undergoing liver surgery and optimization of enhanced recovery programs.

Literature, until August 2016, was searched to identify the comparative studies evaluating preoperative hospital stay time, complications, and C-reactive protein (CRP). Pooled odds ratios (OR) or weighted mean differences (WMDs) were calculated with either the fixed or random effect model.

These studies included a total of 524 patients: 254 treated with ERAS and 270 with traditional care. The postoperative recovery time and length of hospital stay were significantly better than the control group (WMD −2.72; 95% confidence interval [CI] −3.86 to −1.57; WMD −2.67; 95% CI −3.68 to −1.65, respectively). The overall complications, grade I, and Grand II–V complications were significantly favorable to the ERAS group (OR, 0.45 [95% CI, 0.30–0.67]; OR, 0.55 [95% CI, 0.31–0.98]; OR, 0.49 [95% CI, 0.32–0.76], respectively). The concentration of CRP in the control group was significantly higher than that in the ERAS group on postoperative day 5 (WMD −21.68; 95% CI −29.30 to −14.05). Time to first flatus (WMD −0.93; 95% CI −1.41 to −0.46) was significantly shortened in the ERAS group.

The evidence indicates that ERAS following liver surgery is safe, effective, and feasible. Therefore, further are essential for optimizing the ERAS protocols.

Abbreviations: ω-3 PUFAs = Omega-3 polyunsaturated fatty acid, CI = confidence interval, CRP = C-reactive protein, CVP = central venous pressure, ERAS = enhanced recovery after surgery, ERP = enhanced recovery programs, HCC = hepatocellular carcinoma, IIVCC = infrahepatic inferior vena cava clamping, OR = odds ratios, PEM = protein-energy malnutrition, RCTs = randomized controlled trials, WMDs = weighted mean differences.

Keywords: enhanced recovery after surgery, hepatectomy, meta-analysis

1. Introduction

Liver cancer is an increasing global concern owing to the spread of hepatitis B and C infections, as well as, the rise in the rates of alcohol abuse and non-alcoholic steatohepatitis.[1–3] The optimal treatment for hepatocellular carcinoma (HCC) is liver transplantation; however, hepatectomy is yet the key approach for HCC. The surgical complications led to a 10% rate of mortality and a considerable morbidity during early liver resection in HCC.[3] The rates of mortality <5% can be achieved due to improvements in patient selection, early diagnosis, preoperative and postoperative management, surgical technique, and development of new technologies.[4] However, the morbidity rates remain high at 15% to 50%.[5]

More than 20 years after the pioneering studies[6] and a few years after the publication of several randomized studies, cohort studies, and meta-analyses proved the efficacy of enhanced recovery programs (ERP) with respect to reduction of morbidity and short hospital stay.[7,8] ERP aimed to minimize the pain and stress during and after surgery in order to decrease the organ dysfunction and morbidity, enhance recovery, enable early hospital discharge, and improve cost effectiveness. ERP was initially evaluated within the framework of colorectal surgery. However, indications have rapidly extended to other specialties in gastrointestinal (bariatric, pancreatic, gastric, esophageal), orthopedic, thoracic, urologic, gynecological, and cardiovascular surgery.[9–15]

Formal guidelines for enhanced recovery after surgery (ERAS) in liver surgery have not yet been published. Therefore, we conducted a meta-analysis on the available literature in order to assess the safety and efficacy of ERAS in comparison with the traditional care in patients undergoing liver surgery. In addition, ERP was also analyzed for further optimization.

2. Methods

This work does not contain any studies involving human participants or animals performed by any of the authors. Therefore, the ethical approval was not necessary.

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The Hepatobiliary Surgery, Chifeng Municipal Hospital, Chifeng, Inner Mongolia Autonomous Region, China.

* Correspondence: Le Li, The Hepatobiliary Surgery, Chifeng Municipal Hospital, Chifeng, 024000, Inner Mongolia Autonomous Region, China (e-mail: ll200001@126.com).

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2.1. Publication search

We searched MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for literature until August 2016. The search terminology included perioperative care, preoperative care, postoperative care, convalescence, ERAS, fast track, enhanced recovery, and enhanced rehabilitation combined with liver, hepatic, hepato-, resection, segmentectomy, and hepatectomy. To ensure a complete meta-analysis, we used a maximally sensitive search for randomized controlled trials (RCTs). Language restrictions were not applied.

2.2. Data extraction and quality assessment

Data were extracted by 2 independent observers using standardized forms. The recorded data included the number of patients, ERP, preoperative length of hospital stay, complications, readmissions, and C-reactive protein. The quality of all the selected articles was ranked according to the score of the randomized controlled clinical trial quality evaluation standard.

2.3. Inclusion and exclusion criteria

Studies selected for the meta-analysis fulfilled the following inclusion criteria: the study evaluated ERAS in comparison with the conventional care in adult patients undergoing elective open or laparoscopic liver surgery; the outcome measures included complications and duration of hospital stay; the study was an RCT; studies compared the ERAS programs with conventional care and described an ERAS program with a minimum of 7 items in the ERAS groups. The following exclusion criteria were applied: the study was not an RCT; the study did not compare ERAS with conventional care; the study reported on emergency, non-elective, or transplantation surgery; the study consisted of unpublished data with only the abstract presented at a national or international meeting.

2.4. Statistical analysis

Meta-analyses were conducted using odd ratios (ORs) for dichotomous outcomes, and weighted mean differences (WMDs) were used for continuous outcomes. Pooled estimates were presented with 95% confidence intervals (CIs). If the included studies provided medians and interquartile ranges, the mean ± Standard Deviation (SD) was calculated according to the method described by Hozo et al.[16] When heterogeneity was found to be statistically significant ($P<.05$ or $I^2>50\%$), a random effects model was applied.[17] Conversely, a fixed effects model was adopted to calculate the pooled ORs or WMDs. Funnel plots were generated to determine the presence of publication bias. In the event that a study presented significant heterogeneity, sensitivity analyses assessed the effect of SDs from medians and interquartile ranges in poor quality studies on the overall results. We further identified the sources of heterogeneity and assessed the robustness and consistency of the statistical techniques used in the present study. For all other comparisons, statistical significance was defined by $P<.05$, and all tests were 2-tailed. All statistical analyses were performed using the Review Manager (RevMan; http://tech.cochrane.org/) software, version 5.3 from the Cochrane Collaboration.

2.5. Publication bias

A funnel plot was used to evaluate the bias. The asymmetry in the funnel plot of trial size against treatment effect was used to assess the risk of bias.

3. Results

3.1. Study characteristics

In total, 862 records were retrieved from the initial literature search. After the removal of duplicates (179 records), we identified 683 records by screening the titles and abstracts. Six hundred seventy one articles were excluded; thus, 12 articles remained for further evaluation. Subsequently, 7 articles were excluded after full-text reading, including 3 that had <7 ERAS items and 4 were non-randomized controlled trials. Lu et al[18] demonstrated that the ERP reduced the time of anesthesia and controlled the duration of operation, which could artificially affect the postoperative results. In addition, the present study was only single-blind, and hence, we excluded the article by Lu et al from the analysis. Eventually, 4 RCTs were included in the meta-analysis (Fig. 1).[19–22]

The trials were spanned over a period from 2013 to 2016. A total of 254 patients underwent liver resection according to an ERAS protocol, and 270 were managed on a conventional care pathway after liver resection. The majority of the operations were conducted for benign diseases, colorectal liver metastases, or HCC. The participants' characteristics are summarized in Table 1. All the studies explicitly described an ERAS protocol. The individual components utilized and rates of adherence to the protocol are displayed in Table 2.

3.2. Postoperative hospital stay

3.2.1. The length of postoperative hospital stay. The meta-analysis (all trials reported these data) showed a significant difference favorable to the ERAS group (WMD −2.72; 95% CI −3.86 to −1.57; $P<.00001$), with certain heterogeneity (Table 3).

3.2.2. Time to function recovery. The meta-analysis (3 trials reported these data) showed a significant difference favorable to the ERAS group (WMD −2.67; 95% CI −3.68 to −1.65; $P<.00001$), with certain heterogeneity.

3.3. Complications

3.3.1. The overall complications. The meta-analysis (all trials reported these data) showed a significant difference and was favorable to the ERAS group (OR, 0.45 [95% CI, 0.30–0.67]; $P<.0001$), with no evidence of significant heterogeneity (Fig. 2).

3.3.2. Grade I complications. The meta-analysis (all trials reported these data) revealed a significant difference and was favorable to the ERAS group (OR, 0.55 [95% CI, 0.31–0.98]; $P=.04$), with no evidence of significant heterogeneity.

3.3.3. Grade II–V complications. The meta-analysis (all trials reported these data) showed a significant difference that was favorable to the ERAS group (OR, 0.49 [95% CI, 0.32–0.76]; $P=.001$), with no evidence of significant heterogeneity.

3.4. Readmissions

The meta-analysis (3 trials reported these data) showed no statistical differences (OR, 1.16 [95% CI, 0.38–3.54]; $P=.08$).

3.5. C-reaction protein (CRP) concentration

3.5.1. Postoperative day 1. The meta-analysis (2 trials reported these data) showed that there was no statistics (WMD −6.67; 95% CI −16.25–2.91; $P=.17$).

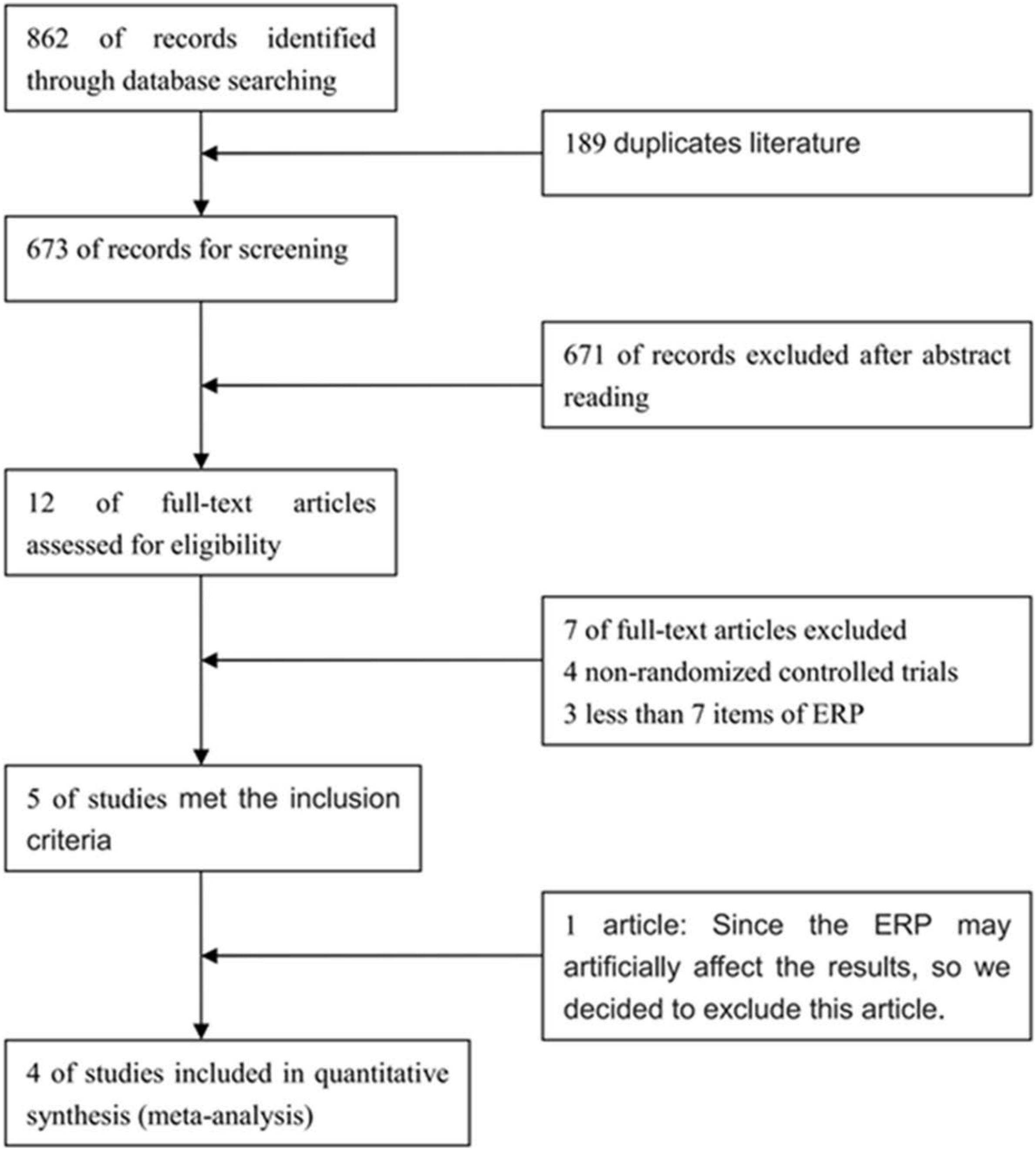

Figure 1. Identification of studies for inclusion.

3.5.2. Postoperative day 3. The meta-analysis (2 trials reported these data) demonstrated no statistical differences (WMD −22.43; 95% CI −66.53–21.67; P = .32).

3.5.3. Postoperative day 5. The meta-analysis (2 trials reported these data) showed that the experimental group of ERAS was significantly lesser than the control group (WMD −21.68; 95% CI −29.30–14.05; P < .0001), with no evidence of significant heterogeneity.

3.6. Duration to first flatus

The meta-analysis (2 trials reported these data) showed that the experimental group of ERAS was significantly shorter than the control group (WMD −0.93; 95% CI −1.41 to −0.46; P = .0001), with no evidence of significant heterogeneity.

3.7. Sensitivity analysis and publication bias

The complication, postoperative hospital stay, readmissions, CRP concentration, and duration to first flatus following ERAS or control in hepatectomy were calculated by both fixed-effect and random-effect models. The results obtained by both the methods were similar, and the combined results were highly reliable. Moreover, the results of subgroup analysis were also in agreement (laparoscopic and open liver surgery).

The funnel plots of the study results were shown in Fig. 3. The funnel plots on overall complications following ERAS versus

Table 1

Characteristics of included trials.

		Number of patients		Age (y), Mean ± SD/ mean (range)		Sex (male/female)		Liver pathology						ASA scores I/II/III	
								HCC		Metastases		Surgical approach	Follow-up (mo)		
Study	Group	ERAS	Control	ERAS	Control	ERAS	Control	ERAS	Control	ERAS	Control			ERAS	Control
Liang et al[22]	Random	80	107	53.4 ± 13.5	55.5 ± 12.8	37/43	50/57	38	46	9	6	Laparoscopic	1	35/45/0	49/58/0
He et al[21]	Random	48	38	56.3 ± 16.3	60.4 ± 20.7	22/26	18/20	11	8	20	16	Laparoscopic	5	10/26/2	12/24/2
Jones et al[20]	Random	46	45	64 (27–83)	67 (27–84)	31/15	23/22	–	–	45	36	Open	1	0/43/3	2/38/5
Ni et al[19]	Random	80	80	48.4 ± 15.6	50.1 ± 21.8	66/14	59/21	71	76	–	–	Open	Unstated	76/4/0	78/2/0

ASA = American society of Anesthesiologists, ERAS = enhanced recovery after surgery, HCC = hepatocellular carcinoma.

control after hepatectomy showed symmetry, which did not indicate a significant publication bias.

4. Discussion

The present meta-analysis evaluated the effects of ERAS programs in comparison with the conventional care in patient recovery after liver surgery. The primary outcome parameters reflect the safety and efficacy of the intervention, which is always the greatest concern in clinical practice.

The length of stay is not an ideal index to judge the success of an ERAS program. Because, several factors make the patients able to or keen to stay in the hospital.[23] Functional recovery, which offered the modest reporting of recovery milestones, was

Table 2

Enhanced recovery programs of included trial.

	Liang et al[22]	He et al[21]	Jones et al[20]	Ni et al[19]
Day before surgery	Perioperative education, including mobilization and dietary goals; no routine bowel preparation; normal oral nutrition	Presurgery education; avoid laxatives	Information and education, including mobilization and dietary goals; oral nutritional supplements; carbohydrate drink	Preoperative education; no preanesthetic medication; normal oral nutrition until midnight and no bowel preparation
Day of surgery	Carbohydrate drinks until 2 h before surgery (250 mL); combined tracheal intubation and general anesthesia, local anesthesia (0.2% ropivacaine); no nasogastric tube or removed as early as possible; less abdominal drain used	Reduced the fasting time to 2 h, preoperative oral glucose administration, antibiotic prophylaxis, nausea, and vomiting prophylaxis and prevention of hypothermia; gastric tube or drainage tube will not be routinely	Standard anesthesia protocol and surgical management; thoracic epidural for postoperative analgesia; all patients extubated and taken to level 2 high-dependency unit	Carbohydrate drinks up to 2 h before surgery; mid-thoracic epidural analgesia (local anesthetic + low-dose opioid), combined tracheal intubation and general anesthesia; nasogastric tube removed as early as possible after surgery; restricted fluid regimen during surgery; minimal use of abdominal drain
Postoperative day 0	Drink water 6 h after surgery; restricted intravenous fluid 2000–2500 mL; pain control: patient-controlled intravenous analgesia + 40 mg ParecoxibNa (Dynastat) i.v. every 12 h	Water intake began at 4 h after surgery and liquid diet restored 12 h after surgery; fluid infusion should be restricted to <2500 mL/d	Eat and drink normally; oral nutritional supplements; goal-directed fluid therapy for 6 h to optimize stroke volume; LiDCO (Cambridge, UK) rapid™—250 mL colloid boluses; chest physiotherapy	
Postoperative day 1	Oral nutritional supplements (liquid); mobilization twice daily; urinary catheter removed; reduce intravenous fluid	Urinary catheter removed; daily review of discharge criteria; intravenous fluids discontinued; analgesia—thoracic epidural; nutritional care; glucose control; mobilization (twice daily)	Physiotherapy/mobilization twice daily; stop i.v. maintenance fluid; oral nutritional supplements; eat and drink normally	Continue portable epidural analgesia or with fentanyl transdermal system; patients drink approximately 5 mL liquid; patients mobilize out of bed at least 4 times/d; start laxative
Postoperative day 2	Stop intravenous anesthetics and use oral Tramadol or Celecoxib; oral semiliquid diet; stop maintenance intravenous fluid; mobilization 4 times daily; removal central venous catheter; removed abdominal drainage tube if volume of drainage <30 mL	Daily review of discharge criteria; intravenous fluids discontinued; analgesia—thoracic epidural; nutritional care; glucose control; mobilization (twice daily)	Diamorphine 3 mg via epidural; epidural removed in the morning, or stopped and capped off if INR ≥1.5; regular oral analgesics and oral morphine as needed; physiotherapy/mobilization twice daily; urinary catheter removed 4 h after epidural; removal of surgical drains (if appropriate); central venous catheter removed; blinded assessment of discharge criteria	Removal of urinary catheter; removal of drainage of peritoneal cavity; enforced mobilization; continue portable epidural analgesia or with fentanyl transdermal system; patients drink at least 1000 mL liquid
Postoperative day 3 (+4)	Stopped anesthetics if pain controlled well; normal mobilization; normal diet; discharge criteria checked	Daily review of discharge criteria; analgesia—thoracic epidural; nutritional care; glucose control; mobilization (twice daily)	Physiotherapy/mobilization twice daily; blinded assessment of discharge criteria	Stopped epidural analgesia; continue mobilization; normal diet; discharge criteria verified

Table 3

Summary of the comparison between ERAS versus conditional care in hepatectomy.

		Results				
Variables	**No. of studies furnishing data**	**ERAS**	**Control**	**OR (95% CI)/WMD (95%)**	***P* value**	I^2
Postoperative hospital stay, d	4 [19–22]	5.87	8.73	−2.72 [−3.86, −1.57]	<.00001	77%
Time to function recovery, d	3 [19,20,22]	4.4	7.01	−2.67 [−3.68, −1.65]	<.00001	85%
Complications rates						
The overall complications	4 [19–22]	21.26%	37.78%	0.45 [0.30, 0.67]	<.0001	0%
Grand I complications	4 [19,22]	8.27%	13.70%	0.55 [0.31, 0.98]	=.04	0%
The Grade II–V complications	4 [19–22]	16.54%	28.89%	0.49 [0.32, 0.76]	=.001	0%
Readmissions rates	3 [20,21,22]	3.45%	3.16%	1.16 [0.38–3.54]	=.08	0%
C-reaction protein concentration						
Postoperative day 1	2 [19,22]	37.1	44.1	−6.67 [−16.25, 2.91]	=.17	41%
Postoperative day 3	2 [19,22]	88.45	110.85	−22.43 [−66.53, 21.67]	=.32	95%
Postoperative day 5	2 [19,22]	46.1	67.35	−21.68 [−29.30, −14.05]	<.0001	0%
Duration to first flatus (days)	2 [19,21]	2.15	3.15	−0.93 [−1.41, −0.46]	=.0001	0%

CI=confidence interval, ERAS=enhanced recovery after surgery, OR=odds ratios, WMDs=weighted mean differences.

assessed in the present studies frequently. This study showed that the durations of postoperative recovery time and hospital stay were significantly better than the control group, indicating the effectiveness of ERAS.

The ERAS patients presented a significant reduction in overall morbidity. Simultaneously, the Grade I and Grade II–V complications were significantly favorable to the ERAS group. However, the rates of readmission were not statistically significant; thus, the ERAS program can be designated as safe.

The levels of serum CRP were used to evaluate the surgical stress response.[24] The meta-analysis showed that although the comparison is not statistically significant on postoperative days 1 and 3, the CRP concentration in the control group was significantly higher than that in the ERAS group on postoperative day 5, thereby indicating that ERAS regulates the postoperative inflammation.

We also compared the duration to first flatus, which is commonly assessed by recovery bowel function. The experimental group of ERAS was found to be superior to the control group, which could be attributed to no bowel preparation and less fasting time preoperative, early mobilization and feeding postoperative.

In 2005 and 2009, the consensus guidelines of ERAS programs were developed and modified by a group of colorectal surgeons.[25,26] However, there is no similar guideline in liver surgery. The current analysis revealed that the ERAS programs were heterogeneous in all the included articles. Therefore, optimization of the ERAS programs is imperative. We found that the following areas may optimize the ERAS programs to facilitate recovery.

4.1. Family support

Family support was a very big element while considering early discharge. Early discharge was thinked with trepidation and apprehension regarding patients with limited family support. Patients with sick family members, other family commitments, and those living alone were often concerned about the actual care arrangements at home, especially during early discharge.[27]

4.2. Preoperative nutritional assessment and adjustment

Malnutrition was found in 17% to 46% of patients in general surgery.[28] Several studies have shown that protein-energy malnutrition (PEM), an imbalance between the needs and expenditure of an organism, significantly impairs the postoperative course and increases morbidity,[29–31] especially infectious complications, and postoperative mortality.[32] Moreover, the surgical stress increases metabolic needs and releases cytokines, which worsen anorexia and muscle wasting. Thus, malnutrition leads to increased postoperative complications, and surgical stress worsens malnutrition.

4.3. Type of incision

Two systematic reviews[33,34] demonstrated that the "long transverse incision" group harbored fewer postoperative pulmonary complications, short- and long-term wound complications and postoperative pain than the "long longitudinal incisions" group in the gastrointestinal and abdominal aortic surgeries. Similarly, concerning a mini-incision approach for locally advanced colonic cancer, a transverse incision seems to be

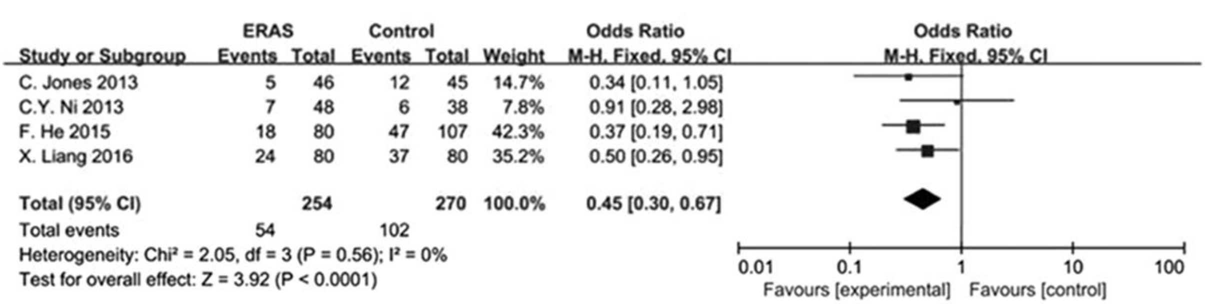

Figure 2. Forest plot: the overall complications by ERAS versus conventional care after hepatectomy. ERAS=enhanced recovery after surgery.

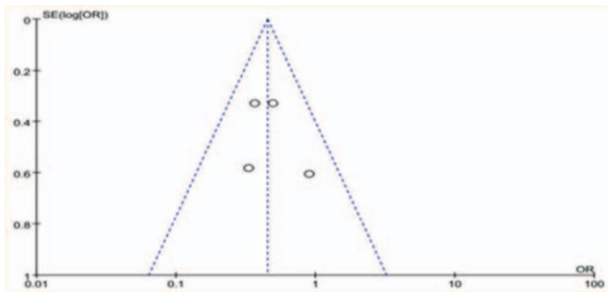

Figure 3. Funnel plot: the overall complications by ERAS versus conventional care after hepatectomy. ERAS = enhanced recovery after surgery.

advantageous with respect to minimal invasiveness and early recovery as compared with the longitudinal incision. The mechanism underlying less pain after a transverse incision is a 2-sided approach. First, it could potentially avoid cutaneous somatic nerve injuries. In addition, the approach did not divide the rectus abdominis muscle and retracted it laterally, also avoiding relevant nerve injuries. Second, compared with the longitudinal incision, a transverse incision might decrease the tension on the wound itself as demonstrated in human and animal studies, leading to less pain.[34,35]

4.4. Incision suture

Evidence-based medicine concluded that continuous sutures of midline incision were beneficial as compared with interrupted sutures owing to lower incidence of incisional hernia and time saving, and therefore strongly recommended.[36,37] The continuous suture minimized the number of knots and an evenly distributed tension across the suture line,[38] which was associate with an equivalent or lower rate of an incisional hernia and decreased operation time.[39] In liver resection with transverse or oblique incisions, no difference was confirmed in the short-term and long-term wound complications between continuous and interrupted sutures. However, the continuous sutures significantly saved time and healed than interrupted layered sutures.[40]

4.5. Infrahepatic inferior vena cava clamping (IIVCC)

The decrease in intraoperative blood loss and the need for blood transfusion were considered as principal contributors towards the decrease in morbidity and mortality.[41] The observed low blood loss and transfusion rates potentially originated from low central venous pressure (CVP) during liver transection,[42] although with the risk of various side-effects. Besides impairment of kidney function and tissue oxygenation, hypovolemic patients are at risk of circulatory instability, especially in the case of unexpected intraoperative hemorrhage. IIVCC were significantly less than the low CVP in total blood loss and transection-related blood loss, albeit with fewer side-effects. The key reasons would be: IIVCC decreases CVP and controls venous backflow bleeding, and IIVCC causes fewer hemodynamic disturbances in cirrhosis patients than low CVP.[43–45]

4.6. Omega-3 polyunsaturated fatty acids (ω-3 PUFAs)

Previous studies have proved that ω-3 PUFAs effectively reduced severe hepatic steatosis and protected the liver from ischemia-reperfusion injury. The regenerative capacity and oncological outcomes await confirmatory studies in humans.[46,47]

5. Limitations of the study

As with all systematic reviews, our review is limited by the quality of the studies available for inclusion. First, the small number of RCTs prevents any meaningful meta-analysis. Second, the randomization procedure was unclear or inadequate in the trials, which could lead to selection bias. Finally, the nature of the surgical research often precludes blinding of personnel and participants in the RCT, which leads to an increased risk for both performance and measurement bias. Therefore, our pooled RR might be an overestimate of the true effect.

Furthermore, in the included articles, they had different patient eligible standards, different evaluation time, different treatment programs, different pathological types, and different discharge criteria, which can result in heterogeneity.

6. Optimized ERAS groups

6.1. Preoperative

Preoperative education, no routine bowel preparation, no routine use of nasogastric tube, preoperative nutritional assessment and adjustment, carbohydrate drinks until 2 hours before surgery (500 mL).

6.2. Intraoperative

Multimodal analgesia; less abdominal drain used; antibiotic prophylaxis, nausea, and vomiting prophylaxis and prevention of hypothermia; target guiding fluid, transverse incision; continuous sutures; reasonable blood flow control technology.

6.3. Postoperative

Multimodal analgesia; water intake began at 4 hours after surgery and liquid diet restored 12 hours after surgery; restricted intravenous fluid; the urinary catheter was removed 1 day after surgery; early activity; remove the abdominal drainage tube as soon as possible, etc.

7. Conclusion

In summary, the evidence suggested that ERAS following liver surgery is safe, effective, and feasible. Nevertheless, additional studies are essential for optimizing ERAS protocols.

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