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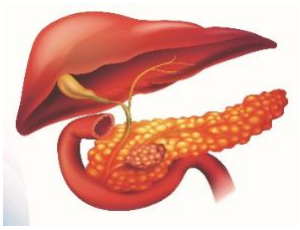
ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΚΑΡΚΙΝΟΣ ΠΑΓΚΡΕΑΤΟΣ-από το Α ως το Ω»



Μεταπτυχιακή Διπλωματική Εργασία

"ΕΝΙΣΧΥΜΕΝΗ ΑΝΑΡΡΩΣΗ ΜΕΤΑ ΑΠΟ ΠΑΓΚΡΕΑΤΟΔΩΔΕΚΑΔΑΚΤΥΛΕΚΤΟΜΗ – ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΚΑΙ ΜΕΤΑ-ΑΝΑΛΥΣΗ''

υπό

ΔΕΣΠΟΙΝΑ ΛΙΟΤΗΡΗ

Αναισθησιολόγου

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«ΚΑΡΚΙΝΟΣ ΠΑΓΚΡΕΑΤΟΣ-από το Α ως το Ω»

Λάρισα, 2023

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Τίτλος εργασίας στα αγγλικά:

ENHANCED RECOVERY AFTER PANCREATODUODENECTOMY – SYSTEMATIC REVIEW AND META-ANALYSIS

ΕΥΧΑΡΙΣΤΙΕΣ

Η εκπόνηση της συγκεκριμένης διπλωματικής εργασίας δεν θα ήταν εφικτή χωρίς την πολύτιμη συμβολή κάποιων σπουδαίων ανθρώπων τους οποίους θα ήθελα να ευχαριστήσω ιδιαιτέρως.

Κατ' αρχήν θα ήθελα να ευχαριστήσω όλους τους διδάσκοντες στο μεταπτυχιακό πρόγραμμα «Καρκίνος Παγκρέατος – από το Α ως το Ω» γιατί με τις διδασκαλίες τους άνοιξαν νέους δρόμους σκέψης και γνώσης που με βοήθησαν να προσανατολιστώ στη δική μου ερευνητική πορεία.

Τις θερμές μου ευχαριστίες θα ήθελα να εκφράσω στην κυρία Ελένη Αρναούτογλου, η οποία ως επιβλέπουσα καθηγήτρια με βοήθησε στην ολοκλήρωση της εργασίας με την επιστημονική της καθοδήγηση και τις εποικοδομητικές της υποδείξεις.

Επίσης, ευχαριστώ πολύ τον καθηγητή και διευθυντή του προγράμματος μεταπτυχιακών σπουδών κύριο Δημήτριο Ζαχαρούλη που με εμπιστεύθηκε στην επιλογή θέματος και με στήριξε με αμείωτο ενδιαφέρον καθ' όλη τη διάρκεια της ερευνητικής διαδικασίας. Με τη διδασκαλία του και τη συνεχή καθοδήγησή του αποτέλεσε για εμένα πηγή άντλησης δύναμης, υπομονής και επιμονής που με βοήθησαν να ολοκληρώσω τη συγκεκριμένη εργασία.

Θα ήθελα επίσης να ευχαριστήσω τον επίκουρο καθηγητή κύριο Δημήτριο Συμεωνίδη για την πολύτιμη συμπαράστασή του ως μέλος της τριμελούς επιτροπής.

Επιπλέον ιδιαίτερες ευχαριστίες θα ήθελα να απευθύνω στον καθηγητή κύριο Αλέξανδρο Μπρότη για την άριστη συνεργασία που είχαμε, και τη συνεχή υποστήριξη και ανεκτίμητη βοήθειά του.

Τέλος, θα ήθελα να εκφράσω πόσο ευγνώμων νοιώθω απέναντι στους γονείς μου Γεώργιο και Ελένη Λιοτήρη, που με την απέραντη αγάπη και κατανόησή τους, αποτέλεσαν για εμένα σημαντικό ηθικό στήριγμα σε όλα τα βήματα της ερευνητικής μου πορείας.

‘’Όρθιος, λοιπόν, να στέκεις, όχι να σε ορθώνουν άλλοι’’

Μάρκος Αυρήλιος,

Τα εις Εαυτόν

Περίληψη

Εισαγωγή

Τα προγράμματα ενισχυμένης μετεγχειρητικής ανάρρωσης (Enhanced Recovery after Surgery, ERAS) βασίζονται στην αποδεικτική ιατρική και αποσκοπούν στη μείωση του χειρουργικού στρες και στη βελτίωση της έκβασης των χειρουργημένων ασθενών. Στόχος της συγκεκριμένης μελέτης ήταν να συγκρίνει την ασφάλεια και την βραχυπρόθεσμη έκβαση των ασθενών που υποβάλλονται σε παγκρεατοδωδεκαδακτυλεκτομή (ΠΔ) και ακολουθούν τα πρωτόκολλα ERAS σε σχέση με τη συμβατική φροντίδα.

Μεθοδολογία

Πραγματοποιήσαμε μια διεξοδική συστηματική ανασκόπηση της βιβλιογραφίας σε 5 ιατρικές βάσεις δεδομένων και αναζητήσαμε μελέτες που συγκρίνουν τα πρωτόκολλα ERAS με τη συμβατική ιατρική φροντίδα σε ενήλικες ασθενείς που υποβάλλονται σε ΠΔ. Έγινε εξαγωγή δεδομένων σχετικά με τις μετεγχειρητικές επιπλοκές, το χρόνο νοσηλείας, τις επανεισαγωγές, και το χρονικό διάστημα μέχρι την έναρξη της χημειοθεραπείας. Υπολογίσαμε pooled relative risk (RR) και standardized mean difference (SMD) με τη χρήση fixed- ή random effects μοντέλο μετα-ανάλυσης. Ο ρόλος τροποποιητικών παραγόντων, όπως η χειρουργική τεχνική, η ήπειρος προέλευσης της μελέτης, και το είδος της μελέτης μελετήθηκαν με τη χρήση meta-regressions.

Αποτελέσματα

Συμπεριλάβαμε 22 μελέτες και συνολικά 4043 ασθενείς με βάση τα κριτήρια επιλεξιμότητας. Η εφαρμογή των πρωτοκόλλων ERAS είχε ως αποτέλεσμα μικρότερο χρονικό διάστημα μέχρι την έναρξη χημειοθεραπείας (SMD: -0.69; 95% CI: -0.88 to -0.5) και λιγότερες επιπλοκές (RR: 0.83; 0.75 to 0.91), ιδιαίτερα Clavien-Dindo (CD) grade 1 και 2 επιπλοκές (RR: 0.82; 0.72 to 0.92), και χαμηλότερα ποσοστά καθυστερημένης γαστρικής κένωσης (ΚΓΚ, RR: 0.69; 0.52 to 0.93) και μετεγχειρητικού παγκρεατικού συριγγίου (ΜΠΣ, RR: 0.76; 0.66 to 0.89). Τα πρωτόκολλα ERAS δεν επηρέασαν τον κίνδυνο για CD 3 and 4 επιπλοκές (RR: 1.00; 0.72 to 1.38), μετεγχειρητική αιμορραγία μετά παγκρεατεκτομή (ΜΑΜΠ, RR: 0.88; 0.67 to 1.14), επανεισαγωγή (RR: 1.01; 0.84 to1.21), και θάνατο (RR: 0.81; 0.54 to 1.22). Η ήπειρος προέλευσης της μελέτης ήταν τροποποιητικός παράγοντας στο ρόλο

των πρωτοκόλλων ERAS στις CD 1 and 2 επιπλοκές (p= 0.047) και στο ΜΠΣ (p=0.02).

Συμπεράσματα

Η εφαρμογή των πρωτοκόλλων ERAS στην ΠΔ ελαττώνει την πιθανότητα για ελάσσονες μετεγχειρητικές επιπλοκές, ΚΓΚ, και ΜΠΣ, χωρίς να επηρεάζει τον κίνδυνο για μείζονες επιπλοκές, επανεισαγωγή και θάνατο. Το ερώτημα που χρήζει περαιτέρω έρευνα είναι εάν τα πρωτόκολλα ERAS επηρεάζουν επίσης την ογκολογική έκβαση μέσω της πιο γρήγορης ανάρρωσης και έναρξης χημειοθεραπείας.

Λέξεις-Κλειδιά: ενισχυμένη μετεγχειρητική ανάρρωση, παγκρεατοδωδεκαδακτυλεκτομή, συστηματική ανασκόπηση, μετα-ανάλυση

Abstract

Introduction

Enhanced recovery after surgery (ERAS) is an evidence-based perioperative care model that aims to attenuate surgical stress and improve postoperative outcomes. We aimed to compare the safety and short-term outcomes of ERAS with standard care for patients undergoing pancreatoduodenectomy (PD) based on literature published following the first publication of ERAS guidelines for PD.

Methodology

To achieve our objective, we thoroughly searched five medical databases for studies that compared ERAS to standard care in adult patients undergoing PD. We analyzed the data on readmissions, length of hospitalization, time to chemotherapy, and postoperative complications. We used a fixed- or random-effects model meta-analysis to summarize the pooled relative risk (RR) and the standardized mean difference (SMD) estimates. Additionally, we examined the role of modifiers, such as operative technique, study origin, and study design, using meta-regressions.

Results

Our analysis included 22 studies involving 4043 patients. ERAS was associated with a shorter time to chemotherapy (SMD: -0.69; 95% CI: -0.88 to -0.5) and fewer complications (RR: 0.83; 0.75 to 0.91), particularly Clavien-Dindo (CD) grade 1 and 2 complications (RR: 0.82; 0.72 to 0.92), delayed gastric emptying (DGE, RR: 0.69; 0.52 to 0.93), and postoperative fistulae (POPF, RR: 0.76; 0.66 to 0.89). However, ERAS did not affect the risk for CD 3 and 4 complications (RR: 1.00; 0.72 to 1.38), post-pancreatectomy hemorrhage (PPH, RR: 0.88; 0.67 to 1.14), readmission (RR: 1.01; 0.84 to 1.21), and death (RR: 0.81; 0.54 to 1.22). We also found that the continent of origin was an effect moderator in the role of ERAS in CD 1 and 2 complications ($p= 0.047$) and POPF ($p=0.02$).

Conclusions

In conclusion, implementing ERAS principles in PD may decrease minor complications, DGE, and POPF without affecting the risk for significant complications, readmission rate, and mortality. ERAS may also play a role in oncological outcomes by accelerating recovery and time to chemotherapy, an essential issue for future research.

Keywords: Enhanced recovery after surgery; Pancreatoduodenectomy; Systematic review; Meta-analysis

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General part

Chapter 1 Introduction

1.1 Pancreatic cancer and surgery

Pancreatic cancer (PC) is currently the twelfth most common cancer in the world.[1] Unfortunately, the incidence of this cancer is increasing rapidly, and by 2030, it is projected to be the second leading cause of cancer-related deaths (as shown in Figure 1).[2] Despite significant research efforts to understand the tumor's molecular biology and natural history, there have been no significant clinical advances, and the prognosis remains generally poor.[3] One of the biggest hurdles in addressing PC is that it is usually a systemic disease by the time it is diagnosed, and there are no specific symptoms or early screening methods to aid in early detection. The tumor's unique biological behavior also contributes to treatment resistance, making progress challenging.[3,4]

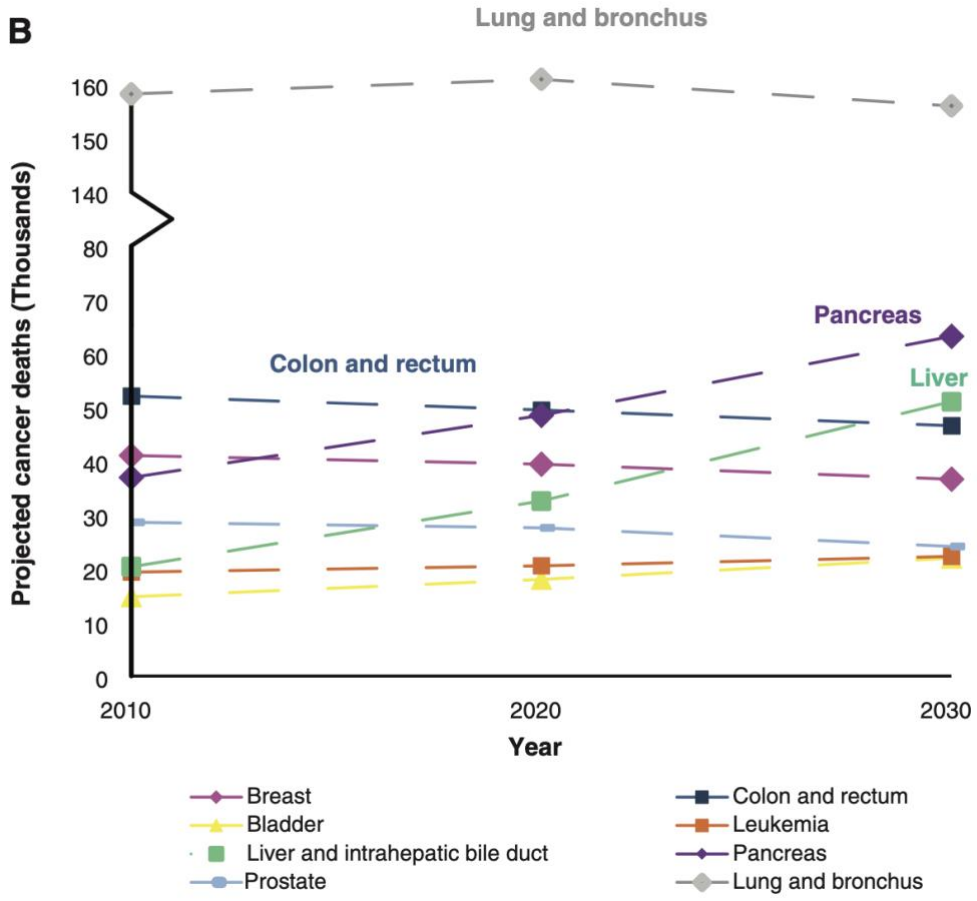


Figure 1. Projected cancer deaths of the deadliest cancers by 2030 (Rahib, 2014)

Pancreatic cancer is typically treated using multimodal therapy, which combines various treatment approaches for the best possible outcome. Surgery is a critical component of curative treatment, and chemotherapy is also essential to the overall treatment plan. For individuals with resectable pancreatic cancer, surgery is often followed by adjuvant chemotherapy, while those with borderline resectable or locally advanced disease may receive neoadjuvant chemotherapy followed by surgery.[5] Additionally, recent research indicates that select patients with metastatic disease may benefit from curative surgery, even if they were previously only offered palliative chemotherapy.[6]

Thanks to advances in chemotherapy and surgical techniques, patients have improved treatment options and better prognoses. More patients undergo surgery rather than conservative management, significantly increasing survival rates over the past few decades. For instance, the 5-year survival rate after tumor resection and adjuvant therapy is now 30%.[7] Importantly, a recent study found that early detection (stage IA) can lead to a survival rate of over 80%.[8] Additionally, resection rates have increased to almost 20% for patients with potentially resectable cancer, while over 50% of those with borderline resectable and locally advanced disease can undergo surgery after neoadjuvant therapy.[7]

Pancreatic surgery is a highly complex and technically challenging procedure that can cure the disease. However, it is still considered a high-risk surgery despite significant advances in surgical techniques, training, and perioperative care that have reduced mortality rates from almost 30% three decades ago to less than 3% today. Unfortunately, such surgery-specific complications as delayed gastric emptying (DGE), postoperative pancreatic fistula (POPF), and post-pancreatectomy hemorrhage (PPH) can still occur, resulting in a high morbidity rate of up to 60%.[9,10] These complications can significantly delay recovery and become life-threatening if not adequately treated.

Although modern surgical techniques are designed to minimize tissue trauma and utilize minimally invasive approaches, even the most experienced surgeons can encounter complications during surgery. However, by addressing modifiable risk factors such as smoking, alcohol consumption, diabetes, hypertension, obesity, coronary artery disease, anemia, malnutrition, poor functional reserve, medications,

surgical stress response, and quality of postoperative care and rehabilitation, many postoperative complications can be avoided.[11] The term "operative risk" is multifaceted and encompasses a range of risk factors, as depicted in Figure 2.

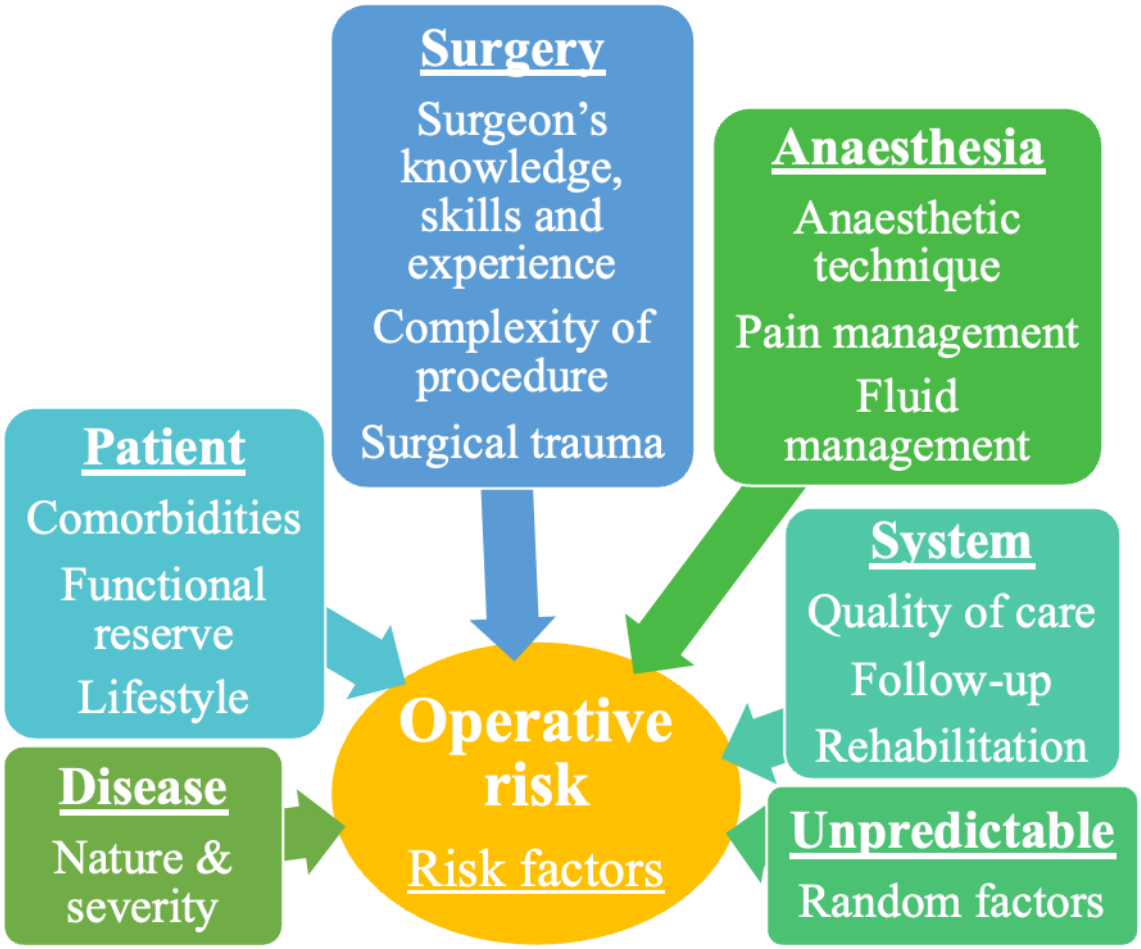


Figure 2. Risk factors for postoperative complications

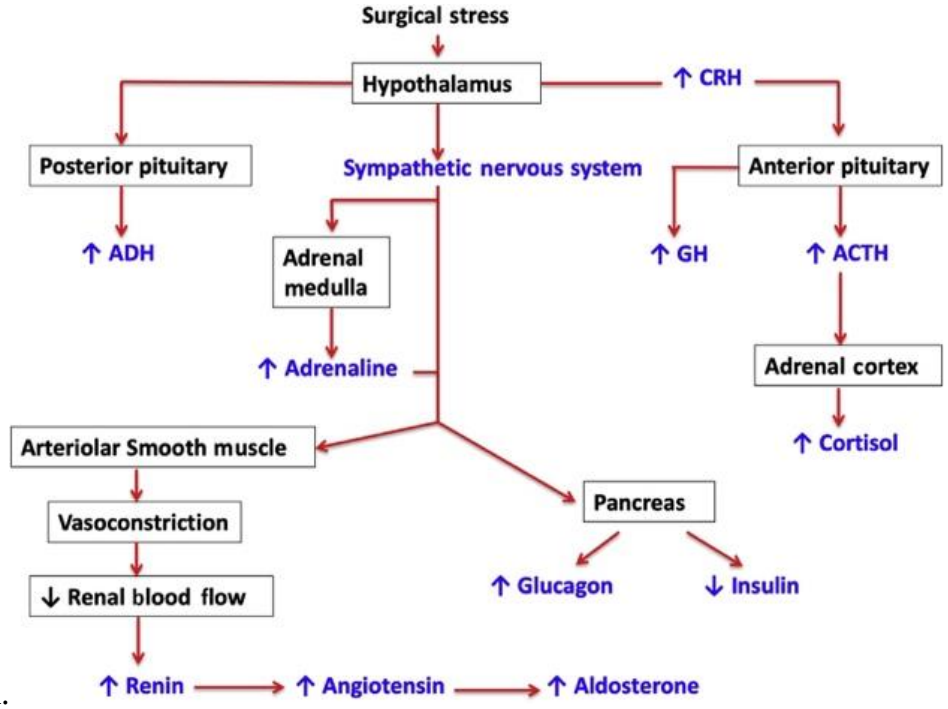
Recent research indicates that innovative perioperative care models can effectively mitigate risks and boost patient outcomes.[12] The Enhanced Recovery After Surgery (ERAS) care pathways have emerged as a promising strategy that addresses the entire perioperative process, focusing on enhancing the well-being of individuals undergoing complex surgical interventions, such as pancreatic surgery.[12,13] This novel approach aims to minimize complications and optimize the quality of care while facilitating speedier recovery and prompt return to daily activities.[13]

1.2 ERAS and pancreatic surgery

The concept of minimizing the impact of surgical stress response and improving outcomes was introduced more than thirty years ago.[14] Over the past two decades, there have been significant advancements in perioperative techniques that modify the stress response to surgery. These techniques and detailed care protocols have been proven to promote faster recovery and reduce complications.[12] In 2001, the concept of Enhanced Recovery After Surgery (ERAS) emerged, revolutionizing perioperative care. The ERAS society guidelines have since become the standard of care for various procedures. Additional information regarding these guidelines can be found at http://www.erassociety.org.[15]

The stress response to surgery is intricate, involving metabolic and inflammatory changes as shown in Figure 3.[14,16] Activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis leads to heightened cortisol and catecholamine levels, along with activation of the renin-angiotensin-aldosterone system.[16] Furthermore, tissue damage prompts the release of pro-inflammatory cytokines and acute-phase proteins.[16] Although this response is a natural way for the body to handle stress, it can impede recovery, as shown in Figure 4. The heightened organ demands during this reaction contribute to postoperative morbidity, potentially causing complications even after a successful surgery.[14]

A.



B.

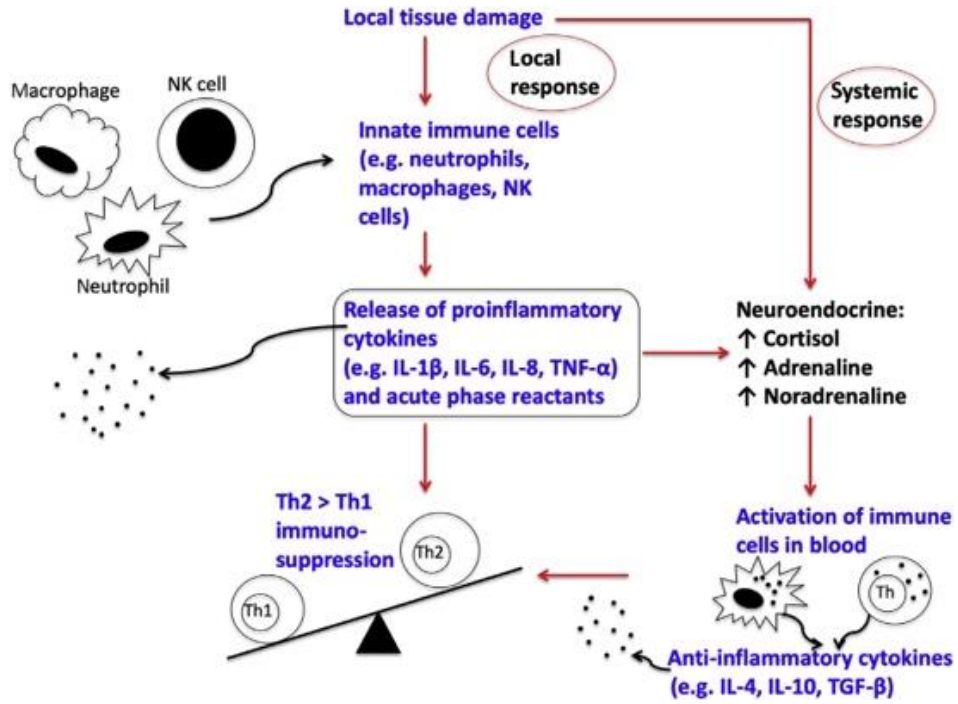


Figure 3. Surgical stress response (Cusack, 2020)

A. Activation of hypothalamus, sympathoadrenal, and sympathoadrenal responses

B. Inflammatory-immune response

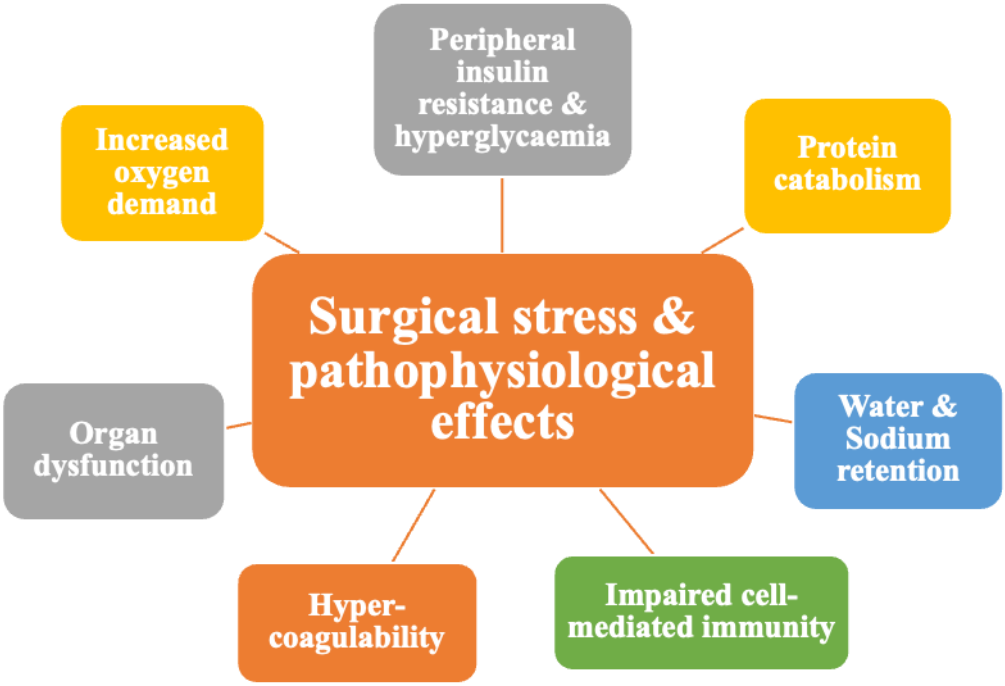


Figure 4. Surgical stress response and pathophysiological effects

In 2001, Professor Henrik Kehlet of the University of Copenhagen established the first ERAS study group.[12] Their goal was to enhance surgical outcomes by challenging the traditional methods of postoperative management that involved extended bed rest and fasting. The group tested protocols, organized symposia, and collaborated with national health ministries to develop ERAS.[12] Combining new evidence-based best practices in perioperative care, ERAS protocols and guidelines were created for various surgical procedures. Initially, there was skepticism worldwide, but numerous publications verified the positive impact of ERAS on patient outcomes across various surgical specialties.[12,13,15] Recently, Professor Kehlet was granted the prestigious BJS Society Award to acknowledge his innovative ERAS protocols, which have transformed clinical practice in multiple fields of surgery and elevated the quality of life for patients globally.[17]

Enhanced Recovery After Surgery (ERAS) pathways are a series of evidence-based interventions to minimize surgical stress throughout the perioperative period - from preoperative to intraoperative and postoperative, as shown in Figure 5. ERAS protocols involve various professionals, including surgeons, anesthesiologists, nurses,

and physiotherapists, who work together towards a common goal of achieving a fast and quality recovery without complications.

To achieve this, ERAS initiatives prioritize preoperative optimization and patient education, early removal of catheters and drains, and multimodal opioid-sparing analgesia with early oral intake and mobilization. These approaches have been shown to improve recovery quality and reduce hospital stay, complications, and costs.[12] However, it is crucial to note that choices made during one period may affect outcomes in the following period. For instance, inadequate pain control may delay mobilization and increase the risk of thromboembolic events, chest infections, muscle wasting, and weakness, leading to a vicious cycle of morbidity.

Therefore, success in the improvement process requires a multimodal and multidisciplinary approach. ERAS pathways rely on coordinated teamwork among professionals who focus on their specific roles and work together towards a common goal.

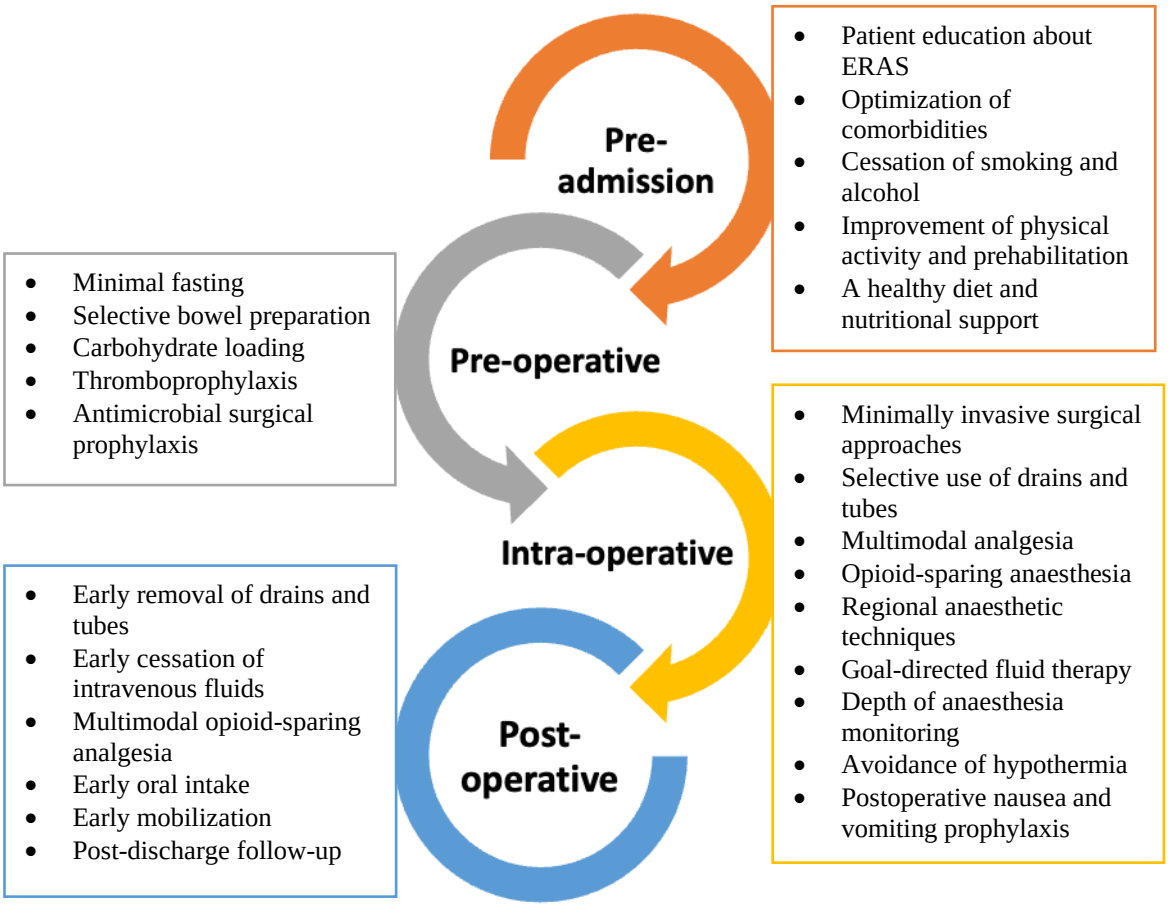


Figure 5. Typical ERAS program elements

The ERAS Society released its first pancreatoduodenectomy (PD) guideline in 2012.[18] A recent meta-analysis discovered that using ERAS during PD can lead to reduced complication rates and shorter hospital stay compared to traditional care.[19] In 2019, an updated guideline with 27 recommendations (as seen in Table 1) was published.[20] While implementing all these guidelines can be challenging, research indicates that achieving a compliance rate of 70% or higher can result in better outcomes.[21] This can prove challenging in PD, especially concerning managing postoperative drains, nasogastric tubes, and oral feeding.

Table 1. Summary of updated ERAS guidelines for PD (Melloul, 2019)	E	R
1. **Preoperative counseling** Dedicated multimedia preoperative counseling decreases fear and anxiety and improves outcomes.	M	W
2. **Prehabilitation** A preoperative program with exercise, nutrition & anxiety reduction may reduce postoperative complications and preserve function.	M	S
3. **Preoperative biliary drainage** Preoperative biliary drainage should be avoided unless necessary (bilirubin > 250 mol/l, cholangitis, pruritus, neoadjuvant treatment), as it increases postoperative complications.	H	S
4. **Preoperative smoking and alcohol consumption** Four weeks of smoking cessation prior to surgery reduces respiratory and wound healing complications. Preoperative alcohol cessation for heavy drinkers reduces postoperative complications.	M H	S S
5. **Preoperative nutrition** 5% weight loss is a significant predictor of complications. Preoperative nutritional intervention is recommended for >15% weight loss or BMI <18.5.	H	S
6. **Perioperative oral immunonutrition**	H	S

It is not recommended due to a lack of unbiased evidence.		
7. **Preoperative fasting and treatment with carbohydrates** Fasting should be limited to 6h for solids and 2h for liquids (if no risk factors exist). Carbohydrate loading is safe and positively affects metabolic conditioning, insulin resistance, thirst, and anxiety.	M M	S S
8. **Pre-anaesthetic medication** Long-acting anxiolytics should be avoided due to concerns about postoperative cognitive dysfunction. Pre-anesthetic multimodal non-opioid analgesic administration (paracetamol, NSAIDS, and gabapentinoid) reduces the need for postoperative opioids and their side effects.	M	S
9. **Anti-thrombotic prophylaxis** Chemical and mechanical thromboprophylaxis is recommended to commence 2-12 hours preoperative and continue for 4 weeks after surgery.	H	S
10. **Antimicrobial prophylaxis and skin preparation** Single-dose iv antibiotics should be administered less than 60 min before skin incision and repeated intraoperative depending on drug half-life and surgery duration. Postoperative antibiotics are not recommended for prophylaxis and should be given only for therapeutic purposes. Intraoperative biliary culture should be sent for all patients with endobiliary stents. Alcohol-based skin preparation and wound protectors may help reduce the SSI rate.	H M	S S
11. **Epidural analgesia** A mid-thoracic epidural is recommended for open PD due to its metabolic effects and positive impact on intestinal function and the respiratory system.	M	S
12. **Postoperative iv and po analgesia**	M	S

A postoperative multimodal opioid-sparing analgesia strategy is recommended (paracetamol, lidocaine infusion, ketamine, dexmedetomidine).		
13. **Wound catheter and TAP block** Instead of epidural, alternative locoregional anesthetic techniques such as continuous wound infiltration through a preperitoneal catheter or TAP blocks are recommended for open PD.	H	S
14. **PONV prophylaxis** Patients should receive a combination of two or more antiemetics depending on the risk factors.	M	S
15. **Avoiding hypothermia** Inadvertent hypothermia is associated with wound infections, cardiac complications, bleeding, immunosuppression, delayed post-anesthetic recovery, and higher mortality. Active warming measures should be initiated before the induction of anesthesia and should continue into the intraoperative and postoperative periods to maintain temperature above 36 °C.	H	S
16. **Postoperative glycemic control** Postoperative hyperglycemia is associated with adverse clinical outcomes, such as: SSI, POPF, DGE, LOS, and re-admission. Recommended perioperative treatments that reduce insulin resistance without causing hypoglycemia are preoperative carbohydrate loading, minimal period of fasting, continuous epidural analgesia for postoperative pain, early feeding, and mobilization).	M	S
17. **Nasogastric intubation** Nasogastric tubes should be removed before the end of anesthesia because there is no evidence to support their routine maintenance after surgery.	M	S
18. **Fluid balance** Excessive fluid administration causes interstitial fluid shift and bowel wall edema, triggering an inflammatory response with decreased	M	S

anastomotic stability. Avoidance of fluid overload and implementation of goal-directed fluid therapy strategies improve outcomes.		
19. **Perianastomotic drainage** Due to conflicting evidence on a no-drain approach in pancreatic surgery, a more conservative approach is recommended with the routine placement of drains but early removal at 72 h if amylase content in the drain is low on POD1 (low risk for POPF when drain amylase value is less than 5000 U/L on POD1).	H	S
20. **Somatostatin analogues** Not recommended due to lack of validated trial results.	W	W
21. **Urinary drainage** The urinary catheter should be removed as soon as the patient is independently mobilized.	L	S
22. **Delayed gastric emptying (DGE)** There is conflicting evidence regarding modification of surgical technique and the risk for DGE. DGE is most commonly secondary and related to postoperative complications such as POPF and intra-abdominal infections. There are no acknowledged preventive strategies, however, timely diagnosis and management may reduce the duration of DGE. In persisting DGE, better outcomes are achieved when artificial nutrition, either parenteral or enteral, is started within 10 days of operation.	L	S
23. **Stimulation of bowel movement** Chewing gum is a simple and safe measure to accelerate bowel recovery (3 times a day, for 30–60 min). Alvimopan and mosapride appear to improve ileus. Metoclopramide, bromopride and other drugs such as ghrelin receptor antagonists, dihydroergotamine and neostigmine, and erythromycin appear to have no effect in postoperative ileus and their routine used is not justified.	M M L	W W W

24. **Postoperative artificial nutrition** Early normal diet according to tolerance is safe and feasible, even in the presence of DGE or pancreatic fistula. When intake of less than 60% of energy requirements for 7-10 days is expected, artificial postoperative nutrition should be considered. The enteral route should be preferred. Either combined parenteral nutrition or total parenteral nutrition has been suggested as alternatives when enteral nutrition is not feasible.	M	S
25. **Early and scheduled mobilization** Bed rest and immobilization are associated with muscle atrophy, thromboembolic and respiratory complications, insulin resistance and delayed and complicated recovery. Early mobilisation from the day of surgery should be encouraged.	L	S
26. **Minimally invasive surgery** Laparoscopic PD should only be performed in highly experienced, high-volume centers, and only within strict protocols. Safety is still a concern. Currently, there is insufficient evidence to assess Robot-Assisted PD and it cannot be recommended. Prospective studies from high-volume centers are needed.	M L	S W
27. **Audit** Regular audits and feedback are essential to improve compliance and outcome.	M	S

E, Evidence level: L, Low; M, Moderate; H, High; R, Recommendation grade; W, Weak; S, Strong; BMI, Body Mass Index; NSAIDS, Non-steroidal anti-inflammatory drugs; TAP, Transversus Abdominis Plane; PONV, Postoperative nausea, and vomiting; SSI, Surgical site infection; POPF, Postoperative pancreatic fistula; DGE, Delayed gastric emptying; LOS, Length of stay; POD, Postoperative day.

Specific part

Chapter 2 Methodology

2.1 Aim of the Systematic Review

Our study aims to compare the effectiveness and safety of ERAS versus conservative management for patients undergoing PD.

Our primary outcome of interest is the incidence of complications, with secondary outcomes including minor and major complications, DGE, POPF, PPH, readmission rates, length of hospital stay (LOS), time to start adjuvant chemotherapy, and overall postoperative 30-day mortality.

2.2 Inclusion/exclusion criteria

Table 2 summarizes the inclusion and exclusion criteria for our meta-analysis.

Table 2. PICOT criteria for our current meta-analysis

Study Component	Inclusion	Exclusion
Participants	Adult patients (>18 years of age) undergoing elective open PD	Paediatric population
Intervention	ERAS clinical pathway	Peripheral and total pancreatectomies, laparoscopic, emergency, or palliative PDs, and studies implementing fewer than 9 ERAS items
Comparator	Standard care	Paucity of data
Outcomes	Complications, DGE, POPF, PPH, Readmissions, LOS, time to Chemotherapy, and mortality	Paucity of data
Study Design	RCTs or observational studies (prospective or retrospective)	In vitro studies, animal studies, case reports, and underpowered comparative studies (<10 patients per treatment group)
Publication	Studies published in English in peer reviewed journals	Abstracts, editorials, letters, duplicate publications of the same study which do not report on different outcomes, White

		papers, narrative and systematic reviews, and articles identified as preliminary reports when results are published in later versions, non-English studies
Timing	Studies published from January 2013 to date	Older studies published before the publication of the first ERAS guidelines for PD (2012)

2.3 Study design and Search Strategy

Study design

Our current meta-analysis was designed following the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA) to address our research questions.[22] Furthermore, it was registered in PROSPERO (CRD42023432293).[23] We prospectively designed the search methods, eligibility criteria, and data extraction process. No patient informed consent or IRB/ethics committee approval was required, as our study was based on published records.

Search strategy

Two authors (DL and AD) conducted a thorough search across five databases, namely MEDLINE, Scopus, Web of Science, Cochrane, and EBSCO, to identify studies that reported on the safety and effectiveness of ERAS in patients undergoing PD. We did not perform a registry search, nor did we search multiple databases. We did not search the grey literature or the "health data" on Google. We used the following terms, including synonyms in all potential fields: "ERAS" OR "enhanced recovery after surgery" OR "fast track recovery" OR "accelerated recovery" AND "open pancreaticoduodenectomy" OR "duodenopancreatectomy" AND "complications" OR "length of stay" OR "time to chemotherapy" OR "delayed gastric emptying" OR "postoperative hemorrhage" OR "post pancreatectomy fistula" OR "readmissions" OR "deaths" OR "mortality" in any possible combination and form. The search period extended from 2013 until June 2023. The last search in all databases occurred on the 1st of July, 2023. No search filters were used. The references of eligible studies were searched for additional relevant citations, and duplicates were manually removed.

Eligibility criteria

We searched for randomized controlled trials (RCTs) and observational studies comparing the ERAS (intervention arm) to standard care (control arm) in adult patients (>18 years of age) undergoing elective open PD and reporting at least one outcome of interest. We focused on studies written in English and published in peer-reviewed journals during the last ten years (2013-2023). On the other hand, we excluded i) underpowered studies (< 10 participants per arm) and studies with inappropriate study design (non-comparative studies, Reviews, Meta-analyses, Editorials), ii) inappropriate population (pediatric population), iii) inadequate or inappropriate intervention (peripheral and total pancreatectomies, laparoscopic, emergency, or palliative PDs), iv) studies implementing fewer than 9 ERAS items, and v) studies published in other languages than English.

2.4 Data extraction and Quality assessment

Data extraction

Each study was identified by the first author's name and publication year. The following data were collected: 1) the study's hosting country, 2) the study type, 3) the size of the patient sample and baseline demographic characteristics, 4) the type of the surgical procedure, 5) the number of complications, including DGE, POPF, PPH, and death, 6) the length of hospitalization, and 7) the time to chemotherapy. Notably, we registered the reported complications according to the Clavien-Dindo grading.[24] When relevant summary data were provided in median and range, we estimated the mean and standard deviations whenever data were not skewed according to Shi et al. and Luo et al.[25, 26, 27]

Risk of bias assessment

Two review authors (DL and AB) were individually involved in the quality assessment. Any disagreement between the review authors was resolved after discussion with the senior author (EA). The risk of bias was assessed according to the Cochrane risk-of-bias tools RoB-2 and ROBINS (I) for randomized and observational studies.[28,29] The former tools identify bias from the selection process, deviations from the intended interventions, attrition, measurement, classification, and selective result

reporting. The assessment was performed both at the study level and the meta-analysis level. The results were visualized in traffic-light plots and weighted bar plots of the distribution of risk-of-bias judgments within each bias domain for the primary outcome using the online app Robvis.[30] The overall body of evidence was graded according to the GRADE recommendations based on the study design of all eligible studies, the risk of bias, inconsistency, indirectness, publication bias, the magnitude of effect, dose-response relationship, and screening for confounding factors.[31]

2.5 Definitions

Postoperative complications were defined as any complication within 30 days from surgery, and their severity was graded according to the Clavien-Dindo classification system. [24] Complications were divided into minor (Grades I and II) and major complications (Grades III and IV).

DGE was defined according to the International Study Group of Pancreatic Surgery (ISGPS) as the requirement or re-insertion of NGT after the third postoperative day or inability to tolerate oral diet by the seventh postoperative day.[32] There are three grades of DGE (A, B, C) as defined by ISGPS according to severity.[32]

POPF was defined according to the International Study Group for Pancreatic Fistula (ISGPF) as drain output of any measurable volume on or after the third postoperative day with amylase content greater than three times the upper normal serum value.[33] There are three grades of POPF (A, B, C) as defined by ISGPF based on severity.[33]

PPH was also defined, according to the ISGPS guidelines, as early (<24 hours) or late (>24 hours) intraluminal or extraluminal, and mild, moderate, or severe hemorrhage post-PD.[34] There are three grades of PPH according to severity and clinical impact.[34]

The length of hospital stay referred to the time from the date of surgery to the date of discharge.

Readmission was defined as a readmission within 30 days of discharge.

Time to chemotherapy referred to the time from the date of surgery to the date of start of chemotherapy.

Mortality was defined as death within 30 days of surgery.

2.6 Statistical analysis

The event incidence for each arm was pooled after a proportion meta-analysis. The two treatment arms were compared using the relative risk (RR) and its 95% confidence interval as the pooled estimate. A fixed- or random-effects model was fitted to the data according to statistical heterogeneity. Heterogeneity was studied using the Q-test and the Higgins I^2 statistic. We searched for potential sources of heterogeneity after eyeballing the Baujat plots. The sensitivity analysis of our results was carried out by re-running our meta-analysis, having excluded one study at a time. A meta-regression and a subgroup analysis studied the effect of moderators (continent, study design, and type of surgery) on the overall effect. We detected potential sources of publication bias using the Beggs test. We used the fragility index and a cumulative analysis to study the robustness of our results. Likewise, the net benefit of the intervention was calculated using numbers needed-to-treat (NNT) based on the RR. The results were plotted using forest and funnel plots. The statistical analysis was carried out using an R statistical environment. Statistical significance was set at 0.05, and we used a continuity correction of 0.5 for complications associated with zero events.

Chapter 3 Results

3.1 Study selection

After eliminating any duplicates, both DL and AD conducted separate evaluations of the article titles and abstracts to determine their relevance. Our current literature search identified 455 unique articles. After reading the title and abstract, we excluded 408 articles and sought the full text of the remaining 47 studies. We could not retrieve five articles, and after reading the full text of the gathered studies, we excluded 25 other irrelevant studies. We excluded studies with inadequate descriptions of surgical techniques and those without extractable data. If multiple techniques were studied, we included studies reporting complication data for each technique separately. After reading through the reference list of the collected articles, five more studies were discovered. Ultimately, 22 articles formed the basis of our systematic review and meta-analysis.[35-56] Any disagreement between the two reviewers was resolved through discussion with the senior author, EA. The study selection process is outlined in a PRISMA flowchart according to the PRISMA 2020 statement (Figure 6).[22]

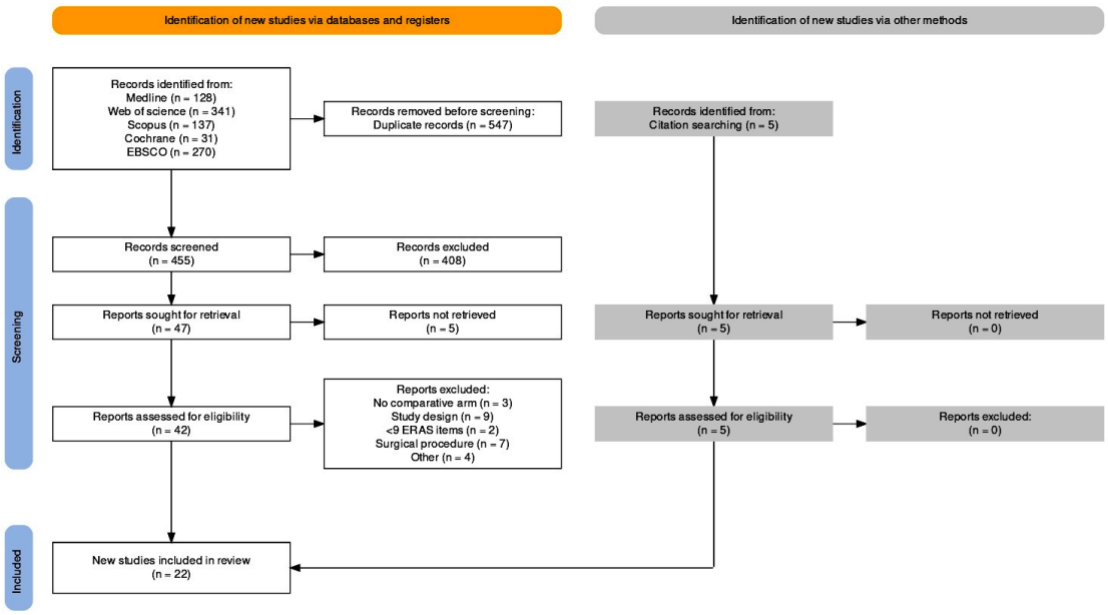


Figure 6. PRISMA Flowchart of the study selection process

3.2 Patient selection

Twenty-two comparative studies with 2063 patients in the ERAS group and 1980 patients in the comparator arm fulfilled our eligibility criteria.[35-56] There were four

RCTs and 18 observational studies from 2013 to 2022. Asia, Europe, and the US contributed ten, nine, and three studies. The reported surgical intervention was pylorus-preserved PD (PPPD) in three studies and Whipple in four, whereas it was either PPPD or Whipple in five studies and mixed (PPPD, Whipple, or Stomach preserved PD [SPPD]) in 2 articles and not specified PD in the remaining seven articles. The mean patients' age ranged from 51 to 77 years across studies, and the male-to-female ratio was 1.26 and 1.3 for the ERAS and control groups. Table 3 summarizes the basic study characteristics of our eligible studies. Table 4 displays the ERAS items implemented in each study.

Table 3. The table displays for each included study the citation, country, study design, sample size, number of ERAS items implemented, and outcomes assessed

Study author (year)	Country	Study design	Sample size	Number of ERAS Items	Outcomes assessed									
			ERAS/ control		Complications	CD 1-2	CD 3-4	DGE	POPF	PPH	LOS	Readmissions	Deaths	Time to ChemoX
Abu Hilal (2013)	UK	case-control study	20/24	17	√	√	√	√	√	√	√	√	√	-
Braga (2014)	Italy	case-control study	115/115	19	√	√	√	√	√	√		√	√	-
Coolsen (2014)	The Netherlands	case-control study	86/97	17	√	√	√	√	√	√		√	√	-
Kobayashi (2014)	Japan	case-control study	100/90	11	√	-	-	√	√	√	√	√	√	-
Pillai (2014)	India	case-control study	20/20	10	√	-	-	√	√	√		√	√	-
Joliat (2015)	Switzerland	case-control study	74/87	21	√	√	√	√	√	-		-	√	-
Williamsson (2015)	Sweden	case-control study	50/50	16	√	√	√	√	√	√		√	√	-
Parteli (2016)	Italy	case-control study	22/66	17	√	√	√	√	√	-		√	√	-
Zouros (2016)	Greece	case-control study	75/50	16	√	√	√	√	√	√	√	√	√	-
Aviles (2016)	USA	case-control study	40/140	20	-	-	-	√	√	-		√	√	-
Dai (2017)	China	case-control study	68/98	13	√	√	√	√	√	√		√	√	-
Deng (2017)	China	RCT	76/83	14	-	-	-	√	√	√	√	√	√	√
Su (2017)	China	case-control study	31/31	12	√	√	√	√	√	√		√	√	-
Van der Kolk (2017)	The Netherlands	case-control study	95/52	20	-	-	√	√	-	-		√	√	-
Hwang (2019)	Korea	RCT	138/138	25	√	√	√	-	√	√		√	√	-
Lavu (2019)	USA	RCT	37/39	10	√	-	-	√	√	-		√	√	√
Takagi (2019)	Japan	RCT	37/37	19	√	√	√	√	√	√	√	√	√	-
Li (2020)	China	case-control study	203/141	12	√	-	-	√	√	√		√	√	√
Lof (2020)	UK	case-control study	250/125	16	√	-	-	-	√	√		√	√	-
Zhu (2020)	China	case-control study	64/69	16	-	-	-	√	√	√	√	√	√	-
Kim (2021)	Korea	case-control study	352/318	9	√	-	-	√	√	√	√	√	√	-
Takchi (2022)	USA	case-control study	110/110	11	√	-	-	√	√	-		√	√	-

Table 4. ERAS items implemented in each included study.

	ERAS ITEMS as per updated 2019 ERAS guidelines for PD																									
STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	**TOTAL ITEMS**
Abu Hilal et al	√						√		√	√		√	√	√	√		√	√	√	√	√	√	√	√	√			17
Braga et al	√		√		√	√	√	√	√	√	√	√		√	√		√	√	√	√	√			√	√			19
Coolsen et al	√						√	√	√	√	√	√		√	√		√	√	√	√	√	√	√		√			17
Kobayashi et al	√		√		√	√	√		√	√							√		√	√				√				11
Pillai et al	√									√	√			√			√		√		√	√		√	√			10
Joliat et al	√				√		√	√	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√		√	21
Williamsson et al	√						√		√	√	√	√		√		√	√		√	√	√	√	√	√	√			16
Parteli et al	√		√					√	√	√	√				√	√	√	√	√	√	√	√		√	√			17
Zouros et al	√		√				√	√	√	√	√			√	√		√	√	√	√	√		√		√			16
Aviles et al	√			√	√		√		√	√	√	√		√	√	√	√	√	√		√	√	√	√	√		√	20
Dai et al	√		√				√		√	√	√				√		√	√	√		√			√	√			13
Deng et al	√						√	√	√	√		√		√	√		√	√	√	√	√				√			14
Su et al	√						√	√	√	√	√	√		√			√	√						√	√			12
Van der Kolk et al	√	√			√		√		√	√	√	√		√	√	√	√	√	√	√	√	√		√	√		√	20
Hwang et al	√		√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		√	25
Lavu et al	√								√			√					√	√	√		√		√		√			10
Takagi et al	√	√			√	√	√	√	√	√	√	√			√	√	√	√	√		√	√			√			19
Li et al	√		√				√				√	√			√		√		√				√	√	√			12
Lof et al	√						√	√	√			√	√	√	√		√	√	√	√	√				√		√	16
Zhu et al	√	√			√		√		√	√	√				√		√	√	√	√	√	√			√			16
Kim et al							√		√	√		√					√		√		√			√				9
Takchi et al									√		√	√		√			√	√	√		√			√	√			11
TOTAL STUDIES	20	3	7	2	8	3	18		20	18	16	17	3	14	15	7	22	17	21	13	19	11	9	15	20	0	5	

Risk of bias

The overall risk of bias in the 18 observational studies, according to ROBINS-I, was moderate (75%) to high (25%) (Figure 7). More specifically, there was a potential for a severe risk of bias due to confounding, reaching as high as 25%, while there was a moderate risk from missing data (100%) and deviation from the intended interventions (75%). Regarding the RCTS, the RoB-2 tool identified serious concerns for risk of bias in 25% of the available evidence, mainly attributed to bias attributed to the potential deviations from the intended interventions (Figure 8). The quality of evidence according to the GRADE recommendations is shown in Table 5.

Figure 7. Risk of bias assessment of non-randomized studies using the ROBINS-I tool.

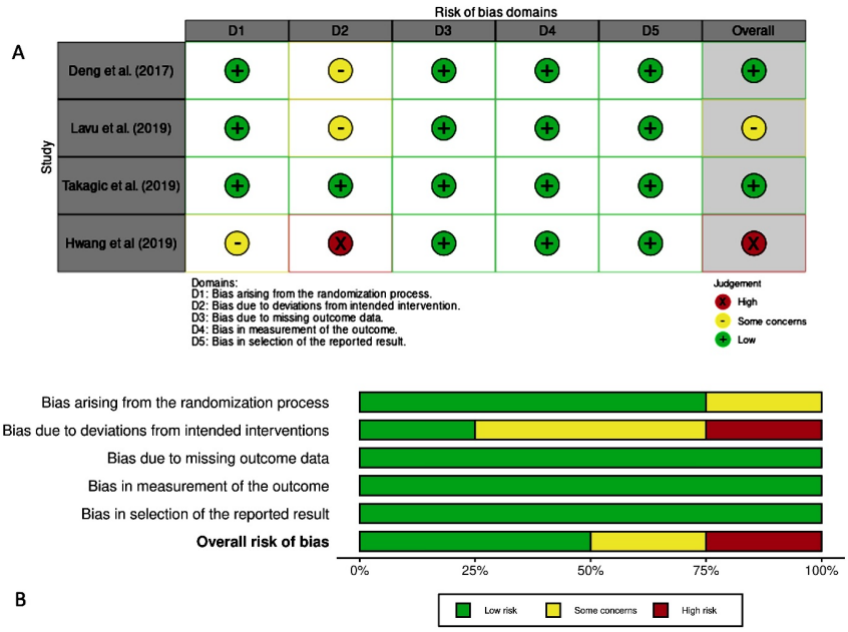


Figure 8. Risk of bias assessment of randomized studies using the RoB-2 tool.

Table 5. GRADE of the Evidence table

Parameter	Starting Grade	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Magnitude of effect	Dose response	Confounding factors	Final grade	
Complications	4	1	0	0	0	0	0	0	1	4	⊕⊕⊕⊕
CD 1-2	4	1	0	0	0	0	0	0	0	3	⊕⊕⊕
CD 3-4	4	1	1	0	0	0	0	0	0	2	⊕⊕
DGE	4	1	1	0	0	0	0	0	0	2	⊕⊕
POPF	4	1	1	0	0	0	0	0	1	3	⊕⊕⊕
PPH	4	1	1	0	1	0	0	0	0	1	⊕
Readmissions	4	1	1	0	0	0	0	0	0	2	⊕⊕
Deaths	4	1	1	0	1	0	0	0	0	1	⊕
LOS (days)	4	1	1	0	1	0	0	0	0	1	⊕
Time to ChemoX	4	1	1	0	1	0	0	0	0	1	⊕

CD, Clavien-Dindo; DGE, Delayed gastric emptying; POPF, Postoperative pancreatic fistula; PPH, Postpancreatectomy hemorrhage; LOS, Length of hospital stay; ChemoX, Chemotherapy

3.3 Synthesis of Outcomes

Overall Complications

Eighteen studies reported overall postoperative complications (Figure 9). In total, 989 and 1080 complications occurred in the ERAS and control groups, corresponding to a proportion incidence of 52% (44%-59%) and 66% (57% - 73%), respectively. In the presence of significant heterogeneity (63%), the random-effect models showed that the ERAS pathway was associated with fewer complications (RR 0.83; 95% CI: 0.75 – 0.91). The Beggs test did not identify significant concerns about publication bias (p=0.198). The studies by Takchi et al. and Dai et al. contributed the most to the statistical heterogeneity according to the Baujat plots.[45, 56] After excluding each study and re-running the meta-analysis, the pooled RR were 0.82 (0.77-0.86) and 0.86 (0.81-0.91), respectively. The meta-regression showed that the effect varied according to the continent of the study origin (p=0.047). Indeed, the RR was more profound in studies from Asia (0.74; 0.66 – 0.84), marginal in studies from Europe (0.91; 0.83 – 0.99), and not significant in studies from the US (0.95; 0.58 – 1.56). The present results are robust and originate from high-quality evidence with a fragility index as high as 29 (Table 6). At the same time, the NNT to avoid a single complication using ERAS is as low as 9 (6 to 18).

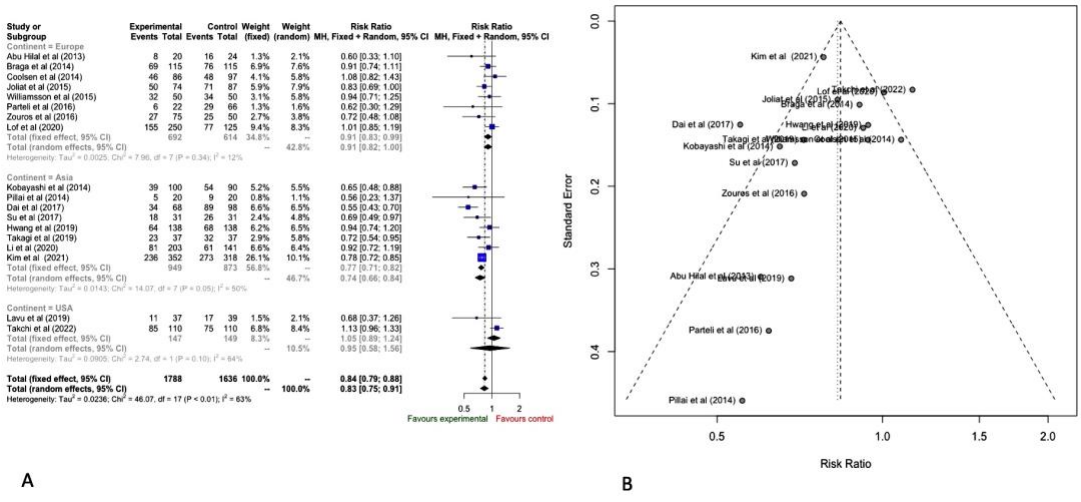


Figure 9. A. Forest plot demonstrating overall postoperative complications in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

Table 6. Results with a summary of the evidence

	GRADE	Studies	Events / Total		Proportion meta-analysis		Comparative meta-analysis			Meta-regression			Robustness	NNT
		k	ERAS group	Control group	Pooled % (ERAS)	Pooled % (Control)	Pooled RR	Heterogeneity (I^2, %)	Publication bias (Begg's test, p)	Type of Surgery	Study design	Continent	Fragility index	
Complications	⊕⊕⊕⊕	18	989/1788	1080/1636	0.52 (0.44; 0.59)	0.66 (0.57; 0.73)	0.83 (0.75; 0.91)*	63.1	0.198	0.240	0.831	0.047*	29	9 (6; 18)
CD 1-2	⊕⊕⊕	11	251/716	345/793	0.35 (0.29; 0.42)	0.43 (0.31; 0.56)	0.82 (0.72; 0.92)*	3	0.436	0.6549	0.719	0.215	10	12 (8; 30)
CD 3-4	⊕⊕	12	150/811	173/845	0.18 (0.11; 0.28)	0.19 (0.14; 0.25)	1.00 (0.72; 1.38)	56	0.945	0.1579	0.554	0.328	26	3333 (18; -13)
DGE	⊕⊕	20	254/1675	369/1717	0.14 (0.1; 0.20)	0.24 (0.16; 0.35)	0.69 (0.52; 0.93)*	73	0.112	0.803	0.439	0.651	7	12 (4; 50)
POPF	⊕⊕⊕	21	260/1968	339/1928	0.13 (0.11; 0.17)	0.16 (0.13; 0.21)	0.76 (0.66; 0.89)*	23	0.319	0.05*	0.365	0.02*	4	24 (16; 50)
PPH	⊕	16	104/1685	101/1486	0.06 (0.05; 0.07)	0.07 (0.06; 0.08)	0.88 (0.67; 1.14)	0	0.829	0.852	0.66	0.345	11	114 (43; -98)
Readmissions	⊕⊕	21	208/1989	204/1893	0.06 (0.03; 0.10)	0.07 (0.05; 0.11)	1.01 (0.84; 1.21)	0	0.528	0.280	0.811	0.373	12	-1404 (68; -52)
Deaths	⊕	22	39/2063	47/1980	0.02 (0.01; 0.03)	0.02 (0.01; 0.03)	0.81 (0.54; 1.22)	0	0.36	0.316	0.819	0.146	9	275 (112; -233)
	GRADE	K	Total		Pooled mean (ERAS)	Pooled mean (Control)	SMD	Heterogeneity (I^2, %)	Publication bias (Begg's test, p)	Type of Surgery	Study design	Continent	Fragility index	NNT
LOS (days)	⊕	7	723	671	16.6 (12.2; 19.9)	19.7 (16.5; 22.9)	-0.56 (-0.26; 0.01)	95	NA#	0.474	0.627	0.895	NA	NA
Time to ChemoX	⊕	2	258	200	53.6 (50.7; 55.4)	67.9 (65; 70.87)	-0.69 (-0.88; -0.5)*	0	NA	NA	NA	NA	NA	NA

RR, risk ratio; SMD, standardized mean difference; NA, not applicable; NNT, numbers need to treat; POPF, postoperative fistula; DGE, delayed gastric emptying; PPH, post-pancreatectomy hemorrhage; LOS, length of stay, ChemoX, chemotherapy
#, k >10;
*, statistical significant result

Minor complications CD 1-2

CD grade 1 and 2 complications were reported in 11 studies (Figure 10). In total, 252 and 345 CD 1 and 2 complications occurred in the ERAS and control groups, corresponding to a proportion incidence of 35% (29%-42%) and 43% (31% - 56%), respectively. In the absence of significant heterogeneity (3%), the fixed-effect models showed that the ERAS pathway was associated with fewer CD 1 and 2 complications (RR 0.82; 95% CI: 0.72 – 0.92). The Beggs test did not identify significant concerns about publication bias (p=0.436). The studies by Abu Hilal et al. and Dai et al. mainly contributed to the statistical heterogeneity according to the Baujat plots.[35, 45] After excluding these studies and re-running the meta-analysis, the pooled RR was 0.80 (0.71-0.91) and 0.85 (0.74-0.97), respectively. The meta-regression did not identify any effect modifier among the studied parameters. The present results are robust and originate from moderate-quality evidence with a fragility index as high as 10. At the same time, the NNT to avoid a single CD 1 and 2 complication using ERAS is as low as 12.

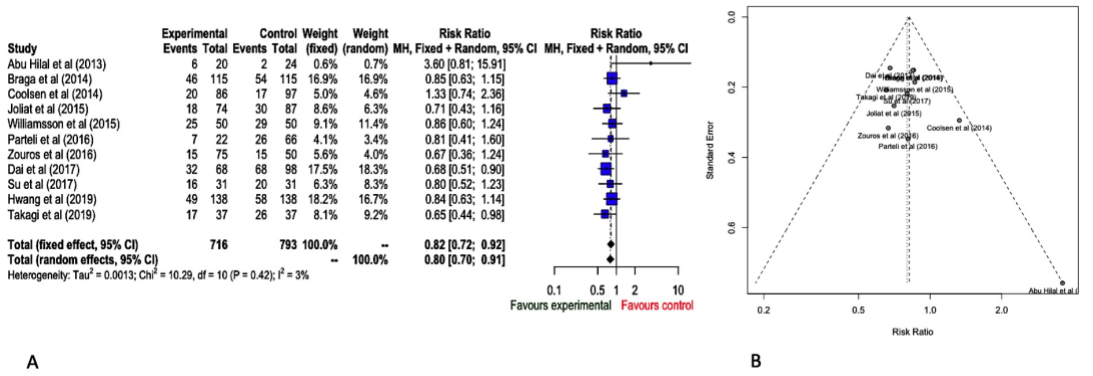
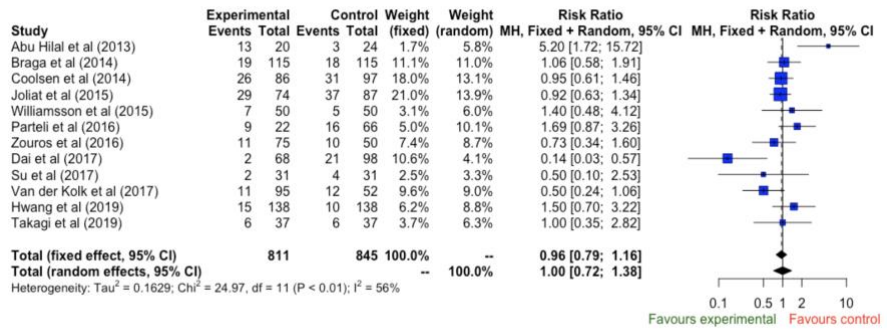


Figure 10. A. Forest plot demonstrating postoperative complications CD 1 and 2 in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

Major complications CD 3-4

CD grade 3 and 4 complications were reported in 12 studies (Figure 11). In total, 150 and 173 CD 3 and 4 complications occurred in the ERAS and control groups, corresponding to a proportion incidence of 18% (11%-28%) and 19% (14% - 25%), respectively. In the presence of significant heterogeneity (56%), the random-effect models showed that the ERAS pathway was not associated with fewer CD 3 and 4 complications (RR 1.00; 0.72 - 1.38). The Beggs test did not identify significant concerns about publication bias (p=0.945). The studies by Abu Hilal and Dai et al. contributed the most to the statistical heterogeneity according to the Baujat plots.[35, 45] After excluding these studies and re-running the meta-analysis, the pooled RR was 0.88 (0.73-1.08) and 1.05 (0.87 – 1.28), respectively. The meta-regression did not identify any effect modifier among the studied parameters. The present results are relatively robust and originate from high-quality evidence with a fragility index as high as 26. At the same time, the NNT to avoid a single CD 3 and 4 complication using ERAS is as high as 3333.



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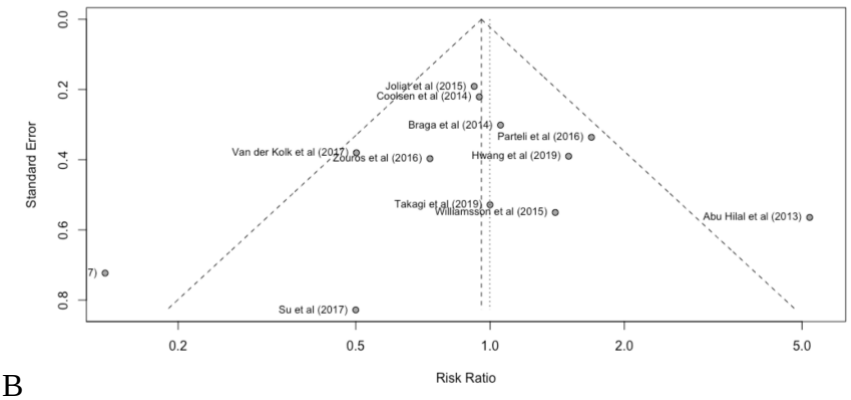

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Figure 11. A. Forest plot demonstrating postoperative complications CD 3 and 4 in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

DGE

DGE was reported in 20 studies (Figure 12). In total, 254 and 369 cases presented DGE in the ERAS and control groups, corresponding to a proportion incidence of 14% (1%-20%) and 24% (16% - 35%), respectively. In the presence of significant heterogeneity (73%), the random-effect models showed that the ERAS pathway was associated with fewer DGE (RR 0.69; 0.52 – 0.93). The Beggs test did not identify significant concerns about publication bias (p=0.112). The study by Van der Kolk et al. contributed the most to the statistical heterogeneity according to the Baujat plots.[48] After excluding this study and re-running the meta-analysis, the pooled RR was 0.78 (0.67-0.91). The meta-regression did not identify any effect modifier among the studied parameters. The present results originate from low-quality evidence and are

characterized by a fragility index of 7. At the same time, the NNT to prevent a patient from DGE using ERAS is as low as 12.

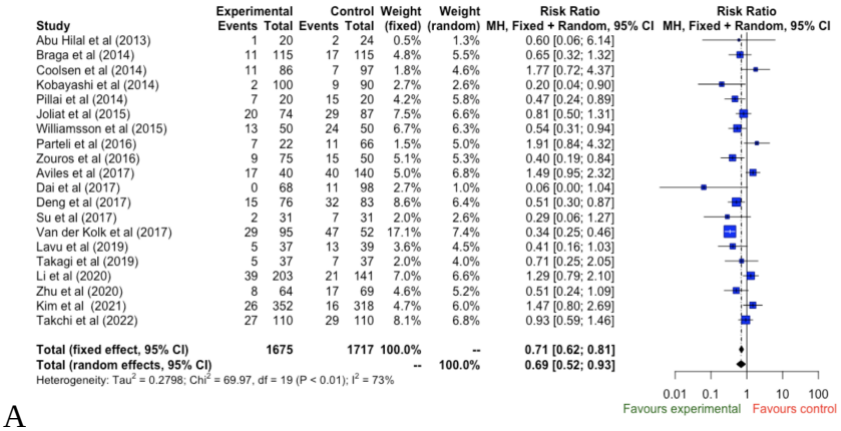
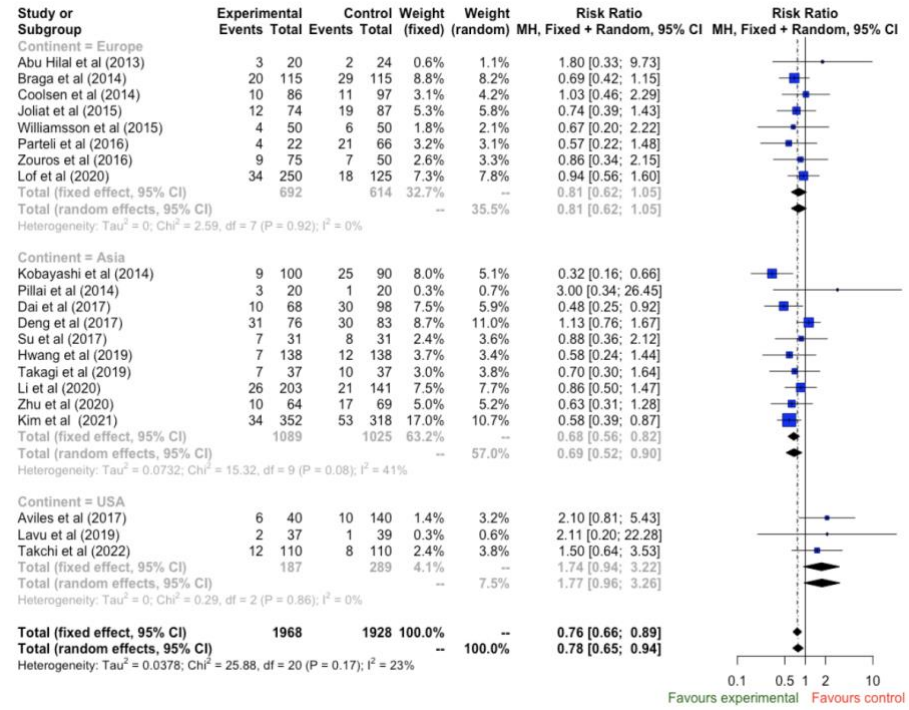


Figure 12. A. Forest plot demonstrating DGE in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

POPF

POPF was reported in 21 studies. In total, 260 and 339 cases presented POPF in the ERAS and control groups, corresponding to a proportion incidence of 13% (11%-17%) and 16% (13% - 21%), respectively. In the absence of significant heterogeneity (23%), the fixed-effect models showed that the ERAS pathway was associated with fewer POPF (RR 0.76; 0.66 – 0.89). The Beggs test did not identify significant concerns about publication bias (p=0.319). The studies by Kobayashi et al. and Aviles et al. contributed the most to the statistical heterogeneity according to the Baujat plots.[38, 44] After excluding these studies and re-running the meta-analysis, the pooled RR was 0.80 (0.69-0.93) and 0.75 (0.64 – 0.87). The meta-regression identified that the type of surgery (p=0.05) and the continent of study origin (p=0.02) were among the effect estimate modifiers. Indeed, the beneficial effect of ERAS was evident in

studies with mixed interventions (0.60; 0.48-0.76) but not with Whipple PD (0.96; 0.62-1.44) or PPPD (0.86; 0.64-1.28). Likewise, studies from Asia reported fewer cases of POPF using ERAS (0.68; 0.52-0.82). However, this beneficial effect of ERAS was not observed in studies from Europe (0.81; 0.62-1.05) and the US (1.77; 0.94-3.22). The present results originate from a moderate quality of evidence and are characterized by a fragility index of 4. At the same time, the NNT to prevent a patient from POPF using ERAS is 24.



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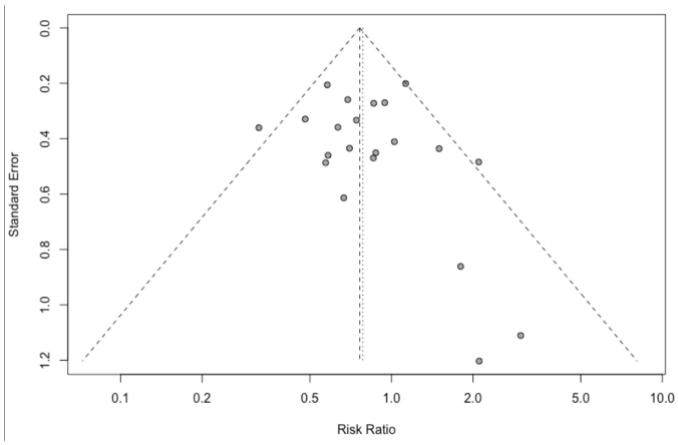
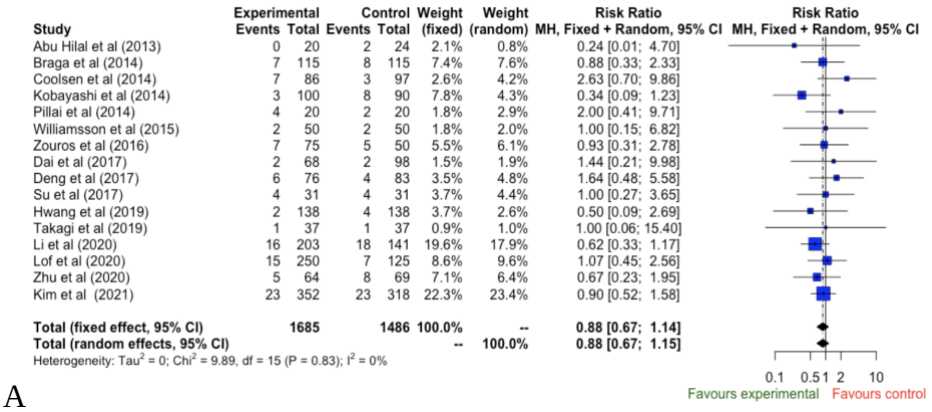


B

Figure 13. A. Forest plot demonstrating POPF in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

PPH

PPH was reported in 16 studies (Figure 14). 104 and 101 cases presented PPH in the ERAS and control groups, corresponding to a proportion incidence of 6% (5%-7%) and 7% (6% - 8%), respectively. In the absence of significant heterogeneity (0%), the fixed-effect models showed that the ERAS pathway was not associated with fewer PPH (RR 0.88; 0.67 - 1.14). The Beggs test did not identify significant concerns about publication bias (p=0.829). According to the Baujat plots, the studies by Coolsen et al. and Kobayashi et al. contributed the most to the statistical heterogeneity.[37, 38] The pooled RR, after excluding these studies and re-running the meta-analysis, was 0.83 (0.63-1.09) and 0.92 (0.7 – 1.21). The meta-regression did not identify any effect modifier among the studied parameters. The present results originate from very low-quality evidence and are characterized by a fragility index of 11. At the same time, the NNT to prevent a patient from PPH using ERAS is as high as 114.



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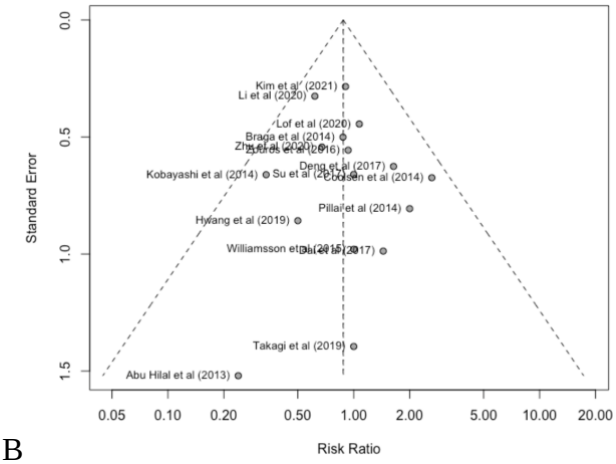
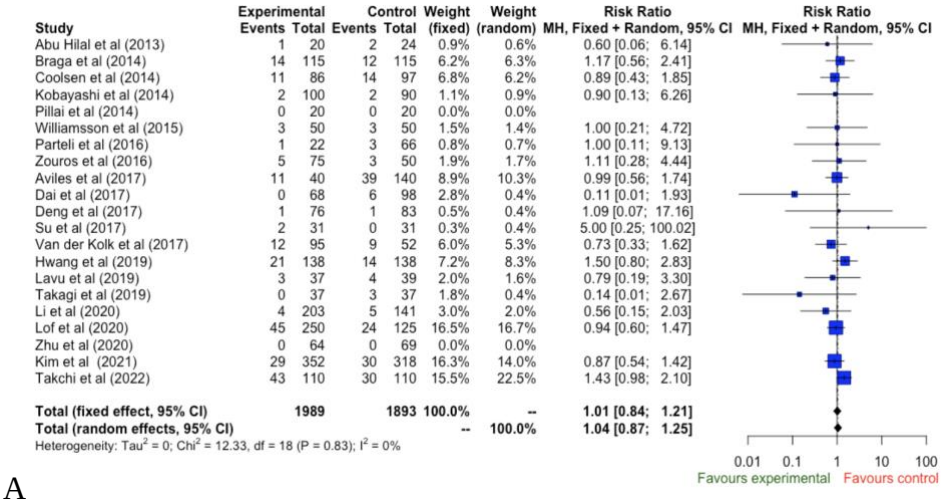


B

Figure 14. A. Forest plot demonstrating PPH in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

Readmissions

Twenty-one articles studied the re-admission rate after pancreatic resection surgery. In total, 208 and 204 cases required re-admission in the ERAS and control groups, corresponding to a proportion incidence of 6% (3%-10%) and 7% (5% - 11%), respectively. In the absence of significant heterogeneity (0%), the fixed-effect models showed that the ERAS pathway was not associated with fewer re-admissions (RR 1.01; 0.84 - 1.21). The Beggs test did not identify significant concerns about publication bias (p=0.528). According to the Baujat plots, the study by Tackhi et al. contributed the most to the statistical heterogeneity.[56] After excluding this study and re-running the meta-analysis, the pooled RR was 0.93 (0.76-1.14). The meta-regression did not identify any effect modifier among the studied parameters. The present results were extracted from low-quality evidence and characterized by a fragility index 12. At the same time, the NNT to prevent a patient from readmission using ERAS is as high as 275.



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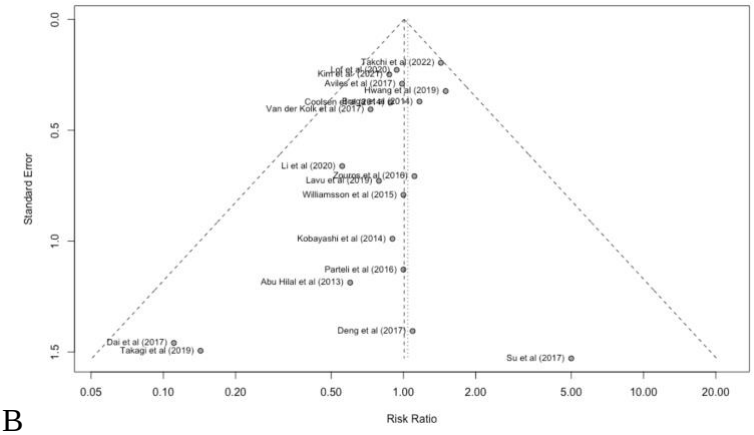
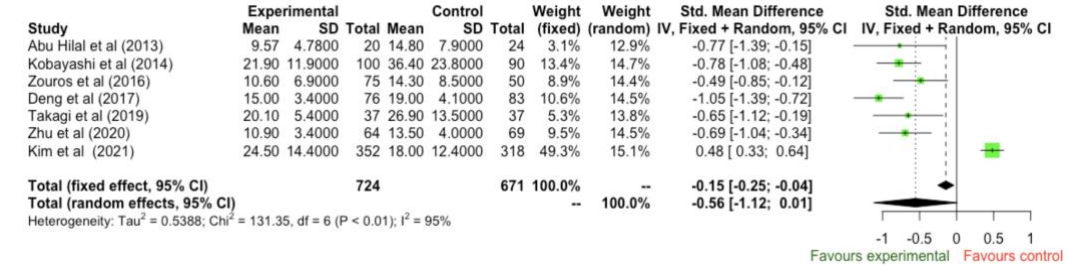


B

Figure 15. A. Forest plot demonstrating readmissions in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

Length of hospitalization

All studies provided data on LOS (Figure 16). However, 17 studies described the LOS in terms of median and range or IQR values. Among them, in 15 studies, the data were significantly skewed away from normality, and thus, it was not appropriate to apply the normal-based method for data transformation. Only seven articles provided data amenable to quantitative synthesis on the LOS after pancreatic resection surgery. The pooled mean hospital stay was 16.6 days (95% CI 12.2 – 19.9) and 19.7 (16.5 – 22.9) using ERAS and the standard of care, respectively. According to our meta-analysis, and in the presence of significant statistical heterogeneity (95%), the standardized mean difference in LOS was -0.56 (-0.26; 0.01) and did not differ between the two groups at a significant level. After eyeballing the funnel plot, we concluded that there was no significant risk of publication bias. According to the Baujat plots, the study by Kim et al. contributed the most to the statistical heterogeneity.[55] Notably, after excluding this study and re-running the meta-analysis, the pooled SMD was -0.76 (-0.91; -0.60) and changed in favor of the ERAS group. The meta-regression did not identify any effect modifier among the studied parameters. The present results were extracted from very low-quality evidence.



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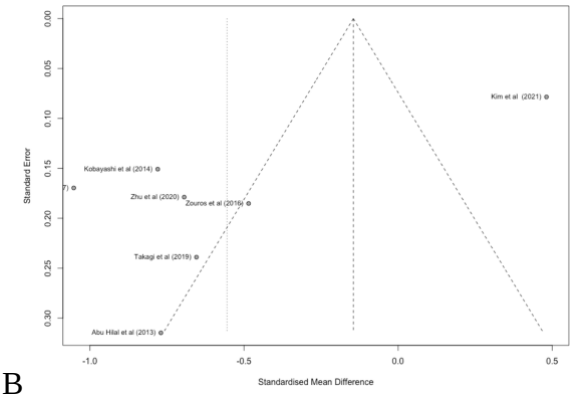

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Figure 16. A. Forest plot demonstrating LOS in terms of ERAS versus conservative management after PD. B. Funnel plot of included studies.

Time-to-chemotherapy

Two articles studied the time to chemotherapy after pancreatic resection surgery (Figure 17). The pooled mean time to chemotherapy was 53.6 days (95% CI 50.7 – 55.4 days) and 67.9 days (65 – 70.87 days) using ERAS and the standard of care, respectively. According to our meta-analysis and in the absence of significant statistical heterogeneity (0%), the standardized mean difference in the time to chemotherapy was -0.69 days (-0.88; -0.5 days) in favor of the ERAS group. Due to the small number of eligible studies, no further analysis took place. The present results were extracted from very low-quality evidence.

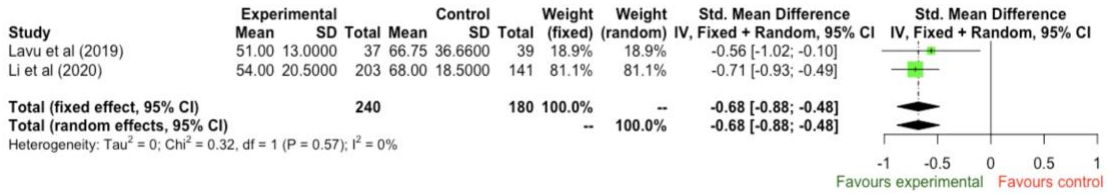

Figure 17. A. Forest plot demonstrating time to chemotherapy in terms of ERAS versus conservative management after PD.

Mortality

Twenty-two articles studied the mortality after pancreatic resection surgery. In total, 39 and 47 cases occurred in the ERAS and control groups, corresponding to a proportion incidence of 2% (1%-3%) and 2% (1% - 3%), respectively. In the absence of significant heterogeneity (0%), the fixed-effect models showed that the ERAS pathway was not associated with fewer deaths (RR 0.81; 0.54 - 1.22). The Beggs test did not identify significant concerns about publication bias (p=0.36). According to the Baujat plots, the studies by Tackhi et al. and Li et al. contributed the most to the statistical heterogeneity.[52, 56] After excluding these studies and re-running the meta-analysis, the pooled RR was 0.73 (0.48-1.13) and 0.91 (0.58-1.41). The meta-regression did not identify any effect modifier among the studied parameters. The present results originated from very low-quality evidence and are characterized by a fragility index of 9.

Chapter 4 Discussion

Overview of findings

Our recent systematic review has found twenty-two studies that compared the ERAS pathway with the standard of care for patients undergoing PD. Serial meta-analyses showed that ERAS can reduce overall and minor complications, DGE, POPF, and time to chemotherapy. Nonetheless, we have found no significant impact on the incidence of severe complications, PPH, re-admission rates, and associated mortality. Additionally, most of the studies we reviewed indicated that ERAS could reduce the duration of hospital stay after PD.

Interpretation in the context of other evidence

These results align with prior systematic reviews examining the effects of ERAS on morbidity following PD.[19, 57-62] Implementing ERAS principles lowers overall and minor complications while not causing an increase in major complications. Notably, this meta-analysis is the first to calculate the NNT for each outcome, revealing that the NNT to avoid a single complication using ERAS can be as low as 9. This finding further supports the beneficial effect of ERAS on overall morbidity. Furthermore, the study suggests that ERAS protocols can safely reduce the incidence of complications, including DGE and POPF. Such results reinforce the safety of ERAS interventions, such as early oral feeding and the prompt removal of NGT and drains, which have been controversial.

Additionally, this systematic review is the first to explore the role of ERAS in the timing of adjuvant chemotherapy following PD. Interestingly, ERAS patients were found to initiate chemotherapy 14 days sooner than patients who received conventional perioperative care. While it is essential to exercise caution in interpreting this finding due to the limited number of studies, it is of paramount clinical significance as 30% of patients do not receive adjuvant therapy following PD due to postoperative complications, early metastases, and decreased performance status.[63]

The ERAS society has established 29 guidelines for PD, as listed in Table 1.[20.] However, the protocols of the studies reviewed in our investigation included only some of these items. The most commonly implemented guidelines were preoperative counseling, antithrombotic and antimicrobial chemoprophylaxis, prevention of PONV and hypothermia, as well as multimodal analgesia, as noted in Table 4.

Postoperatively, the most frequently implemented items were removal of NGT, early oral feeding, early and scheduled mobilization, and drain and urinary catheter removal plans. Nevertheless, not all studies reported compliance with ERAS pathways. A recent meta-analysis of studies on patients undergoing PD revealed that the median overall compliance with ERAS guidelines was 65.7%, with postoperative compliance as low as 44%.[60] It was observed that morbidity was lower when compliance levels were above 50%.[60] Interestingly, low compliance in the early postoperative period, particularly poor tolerance of early oral feeding, was often linked to complications. Early identification of such patients offers a chance to intervene early and prevent further deterioration.[36, 60]

Implications for practice

Implementing ERAS programs for pancreatic surgery is a challenging task due to the complexity of the surgical procedure and the high risk of complications that may hinder the change in traditional clinical practice. Nevertheless, the findings of this review strengthen the existing evidence that ERAS pathways for PD improve safety and short-term outcomes, thus becoming the standard of care. It is crucial to encourage local initiatives to establish modern and evidence-based perioperative care models, and successful strategies should be shared across centers to foster a culture of learning from one another. To this end, we are sharing our locally adapted ERAS protocol for PD, which we recently introduced in our practice (Figure 18). Changing the culture in the complex healthcare environment is undoubtedly challenging. Nonetheless, strong leadership, teamwork, and continuous audits based on the PDSA (plan-do-study-act) theoretical framework should be the way to promote a culture of quality improvement and evidence-based practice.

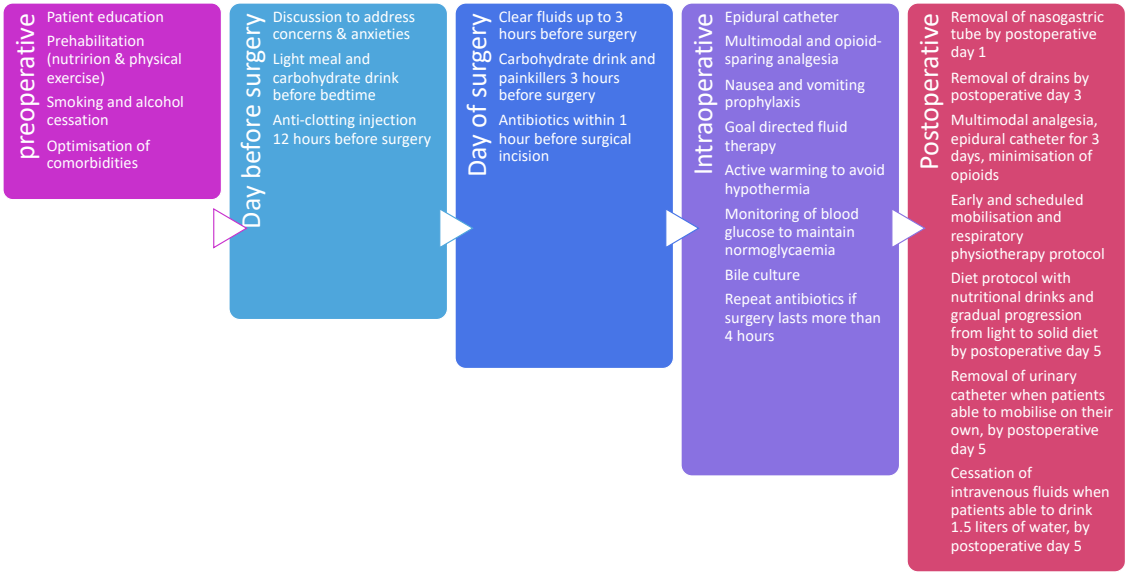

Figure 18. ERAS protocol at IASO Thessalias General Hospital

Implications for future research

While ERAS protocols have shown promise in patients undergoing PD, questions remain about their application, given the high complication rate associated with this procedure. To better understand which ERAS items, lead to positive outcomes, further research is needed, focusing on functional recovery, time for adjuvant chemotherapy, and the impact on long-term outcomes and survival.

Timely postoperative chemotherapy is crucial in increasing the chances of cure after surgery. However, the postoperative stress response leads to immunosuppression, which creates a vulnerable window of opportunity for the expansion of minimal residual disease. As a result, the patient becomes more susceptible to tumorigenesis after removing the primary tumor.[64] It is reasonable to assume that strategies such as ERAS principles that suppress stress response may protect patients against perioperative tumor growth. Another critical issue for future research is whether compliance with ERAS programs may affect oncological outcomes.

Well-designed multicenter prospective cohort studies may be more appropriate compared to RCTs. Not only does the number of interventions that comprise the ERAS pathway make randomization and blinding not feasible, but it might also be unethical to randomize patients to the control group and deny them evidence-based interventions.

In addition, future research should examine human factors and models of education, teamwork, and leadership support to facilitate the application of new perioperative care models that target the whole patient journey rather than just one intervention.

Limitations

It should be noted that the current study has certain limitations. Firstly, the analysis is based on relatively few studies, particularly those focusing on the LOS and time to chemotherapy. Secondly, the quality of evidence varies significantly among the parameters studied. Most studies were case-control studies, which may result in selection bias. Additionally, most of these studies were conducted retrospectively, which means that the accuracy of process indicators may have affected some patients. The quality of the randomized controlled trials (RCTs) was moderate due to the lack of blinding, which could introduce bias in implementation and measurement. However, applying blinding methods for the ERAS protocol is problematic. Thirdly, we identified significant statistical heterogeneity in some parameters during the meta-analysis, such as overall complications and DGE. We used several techniques, such as random-effect models and sensitivity analysis using the leave-out-one method, to search for sources of statistical heterogeneity and overcome the problem. Fourthly, the LOS and time to chemotherapy were reported using median and range values. Whenever possible, we transformed them into mean values and standard deviation. Lastly, not all studies implemented the same ERAS protocol, and the number of ERAS items used in each study varied between 9 and 25, potentially causing clinical heterogeneity. However, this is inevitable due to how clinical pathways are devised based on local clinical practices and socio-cultural needs.

Chapter 5 Conclusion

According to this review and meta-analysis, implementing ERAS principles in pancreatic surgery can lower the occurrence of overall and specific complications such as DGE and POPF while not posing any more significant risk of major complications, readmission, or mortality. ERAS is a secure and practical approach to pancreatic surgery, and it may even enhance oncological outcomes by hastening recovery and decreasing the time needed for chemotherapy. In future research, emphasis should be placed on implementation strategies and considering human

factors and cultural context to ensure the successful application of new perioperative care models.

Thesis synopsis

Implementing Enhanced Recovery After Surgery (ERAS) has proven effective in reducing surgical stress and enhancing postoperative results. In this study, we aimed to compare the safety and short-term outcomes of ERAS to standard care for patients undergoing pancreatoduodenectomy (PD) based on literature published after the first publication of ERAS guidelines for PD. We conducted a thorough literature search across five databases and identified twenty-three studies involving 4043 patients. Data on readmissions, length of hospital stay, time to chemotherapy, and postoperative complications were extracted. A meta-analysis utilizing fixed or random-effects models was conducted to summarize the pooled relative risk (RR) and the standardized mean difference (SMD) estimates. Furthermore, meta-regressions were performed to examine the impact of different modifiers, including operative technique, study origin, and study design. Our findings indicate that implementing ERAS principles in PD can reduce the incidence of minor complications, delayed gastric emptying (DGE), and postoperative fistulae (POPF) without affecting the risk for major complications, readmission rate, and mortality. The continent of origin influenced the role of ERAS in CD 1 and 2 complications and POPF. The type of surgery also impacted POPF. In conclusion, ERAS can significantly improve postoperative outcomes, expedite recovery, and reduce the time to chemotherapy for patients undergoing PD. However, further research is necessary to examine the impact of ERAS on oncological outcomes.

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