Enhanced recovery after surgery on multiple clinical outcomes

Umbrella review of systematic reviews and meta-analyses

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Abstract

Background: Previously, many meta-analyses have reported the impact of enhanced recovery after surgery (ERAS) programs on many surgical specialties.

Objectives: To systematically assess the effects of ERAS pathways on multiple clinical outcomes in surgery.

Design: An umbrella review of meta-analyses.

Date sources: PubMed, Embase, Web of Science and the Cochrane Library.

Results: The umbrella review identified 23 meta-analyses of interventional study and observational study. Consistent and robust evidence shown that the ERAS programs can significantly reduce the length of hospital stay (MD: −2.349 days; 95%CI: −2.349 to −1.958) and costs (MD: −639.064; 95%CI: −933.850 to −344.278) in all the surgery patients included in the review compared with traditional perioperative care. The ERAS programs would not increase mortality in all surgeries and can even reduce 30-days mortality rate (OR: 0.40; 95%CI: 0.23 to 0.67) in orthopedic surgery. Meanwhile, it also would not increase morbidity except laparoscopic gastric cancer surgery (RR: 1.49; 95%CI: 1.04 to 2.13). Moreover, readmission rate was increased in open gastric cancer surgery (RR: 1.92; 95%CI: 1.00 to 3.67).

Conclusion: The ERAS programs are considered to be safe and efficient in surgery patients. However, precaution is necessary for gastric cancer surgery.

Abbreviations: AMSTAR = a measurement tool to assess systematic reviews, CI = confidence interval, ERAS = enhanced recovery after surgery, GRADE = Grading of Recommendation Assessment, Development and Evaluation, OR = odds ratio, RR = relative ratio.

Keywords: enhanced recovery after surgery, enhanced recovery after surgery, meta-analyses, surgery, umbrella review

1. Introduction

Enhanced recovery after surgery (ERAS) programs are multi-disciplinary, multimodal care pathway aimed to optimize the management of perioperative period, reduce surgical stress response and accelerate patient recovery, which was proposed initially by professor Henrik Kehlet in 1997, also known as fast track surgery (FTS).† The ERAS pathways involving in preoperative period, intraoperative period and postoperative period consist of pre-admission counseling, nutritional screening/support, medical optimization of chronic disease, no routine use of mechanical bowel preparation, no prolonged fasting, carbohydrate treatment, antibiotic prophylaxis, thrombosis prophylaxis, pre-anesthetic sedative medication (no routine use), minimally invasive surgical techniques, standardized anesthesia protocol, restrictive use of surgical site drains, remove nasogastric tubes early, avoidance of salt and water overload, maintenance of normal temperature, early intake of oral fluids and solids, early removal of urinary catheters and intravenous fluids, prevention of nausea and vomiting, multimodal approach to opioid-sparing pain control, early mobilization, prepare for early discharge.

The ERAS pathways were initially trialed in colorectal surgery† and then were rapidly introduced in other specialties in the next few years, including liver, gastric, orthopedic,
pancreatic, urology, breast, esophageal, bariatric and other surgeries.\textsuperscript{[2]} The majority of studies have reported that the ERAS can reduce the total length of hospital stay (LOS) and cost of hospitalization, improve the quality of life (QOL) and patient satisfaction by reducing the insulin resistance and inflammatory reaction caused by surgery.\textsuperscript{[5–12]} Besides, the secondary outcomes including return of gastrointestinal function, time to first diet, post-operative pain score,\textsuperscript{[6]} operation time,\textsuperscript{[9,10]} blood loss,\textsuperscript{[2,10]} and nutritional status\textsuperscript{[6]} were also improved. The ERAS pathway was originally used for elective surgery, recently, some articles have shown that it is safe and feasible in emergency surgery.\textsuperscript{[13,14]} After two decades of development, more and more publications have been published to study the safety and effectiveness of the ERAS program in surgical patients, and many guidelines or consensus have been reached for multiple surgical sub-specialties.\textsuperscript{[15–19]}

Considering the superiority of the ERAS programs, it has been widely used in many surgical specialties worldwide.\textsuperscript{[20]} However, is this beneficial to all surgery? Obviously, it is not clear yet. For example, in some studies, the morbidity and readmission would be increased with the ERAS programs for gastric cancer surgery.\textsuperscript{[21,22]} It is necessary to determine the effects of ERAS on the multiple clinical outcomes of different procedures. Therefore, we systematically investigated the evidence of ERAS in clinical outcomes and conducted the umbrella review to determine the pros and cons of ERAS for all procedures.

2. Methods

2.1. Umbrella review methods

An umbrella review is the review of existing systematic reviews and/or meta-analyses, which can provide important information that can be used by decision makers in healthcare to systematically understand a topic area.\textsuperscript{[23]} We conducted an umbrella review to evaluate the impact of enhanced recovery after surgery (ERAS) for all kinds of surgical patients. The article did not require ethical approval because it was a systematic review and did not involve patients.

2.2. Literature search

We systematically searched the PubMed, Embase, Web of Science and Cochrane Library from the inception to March 21, 2019, to identify systematic review and meta-analyses of observational studies and randomized controlled trials (RCTs) which examined the effects of ERAS on clinical outcomes for surgery people. We used the following search strategy: ("enhanced recovery\textsuperscript{a}" OR "fast track\textsuperscript{b}" OR "ERAS") and ("systematic review\textsuperscript{a}" OR "meta-analysis\textsuperscript{c}"), and the terms were truncated for all fields, which following the SIGN guidance recommended search terms for systematic reviews and meta-analyses.\textsuperscript{[24]} We also searched the reference lists of eligible articles and relevant clinical guidelines. Two researchers reviewed the identified records independently and screened eligible studies by a three step parallel reviews of title, abstract and full text based on the predefined inclusion and exclusion criteria. Disagreements were settled by consensus or discussion with a third researcher.

2.3. Eligibility criteria

The included criteria were:

1. the article was a systematic review and meta-analyses or a meta-analyses of both RCTs and observational studies;
2. evaluated the effects of enhanced recovery after surgery program for surgical patients;
3. reported effect sizes-odds ratio (OR), relative risk (RR), or hazard ratio (HR) for qualitative outcomes and mean difference (MD) or standardized mean differences (SMD) for quantitative outcomes;
4. the ERAS protocols must be used in ERAS/FT group;
5. the meta-analyses investigated the effects of ERAS compared with conventional care;
6. the article must be published in English.

Systematic reviews without meta-analyses were ruled out. The meta-analyses emphasized just one protocol of the ERAS program (such as early oral feeding or early mobilization on postoperative) was excluded. If full text was unavailable, the article was excluded as well.

2.4. Data extraction

Data was extracted using a double-extraction method from each eligible study by the two investigators. We extracted data of each eligible reference and recorded the first author, year, journal of publication, and the type of surgery. Then we extracted the number of studies included in meta-analyses, study design(s) (case-control, cohort, or randomized controlled trial), the number of participants, the range of ERAS protocols in the articles and the study outcomes (length of hospital stay, mortality, complication and so on). In addition, we abstracted data from the meta-analyses of observational studies or randomized controlled trials, included metric (odds ratio, risk ratio, mean differences, standard mean difference, weighted mean difference), the summary estimates and related 95% confidence interval (CI), heterogeneity ($I^2$) and type of effect model used in the meta-analysis (fixed or random), publication bias was recorded as well. If possible, we also extracted the populations as well as the country where the study was conducted. When the article reported more than one outcome, we recorded each outcome respectively. When there was more than one paper reported the same outcomes, we would choose the updated one. If any discrepancies could not be resolved by consensus, the third researcher involved in and made the final decision.

2.5. Evaluation of quality and grading of evidence

We used the assessment of multiple systematic reviews (AMSTAR) tool to assess the methodological quality of each involved meta-analysis. The AMSTAR was a reliable and valid measurement tool to assess the quality of systematic review and meta-analyses,\textsuperscript{[25]} which was made of 11 items including a priori design, study selection and data extraction, the literature search, gray literature, the list of included and excluded studies, study characteristics, critical appraisal, formulation of conclusions, the combination of study results, publication bias, and conflicts of interest.\textsuperscript{[26]} The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)\textsuperscript{[27]} system was used to access the quality of evidence for included articles. The GRADE assorted the quality of evidence into four categories: "high", "moderate", "low", and "very low."\textsuperscript{[28]} The quality of Evidence based on RCTs or observational studies can be decreased or increased according to the study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect.\textsuperscript{[27]}
2.6. Data analysis
We extracted the outcomes of ERAS on all of the surgery patients from the identified systematic review and meta-analyses, and we recorded the summary estimates and 95% CI of each related outcomes, which was calculated by both fixed and inverse variance random effects methods, if the heterogeneity existed ($I^2 > 50\%$) between the studies, we used the random effects methods, otherwise, a fixed effects method was used. We extracted the $I^2$ metric and Egger test to measure the heterogeneity and publication bias if they were available. And if the number of studies included in the meta-analyses was more than ten, we would calculate the publication bias through Egger regression test with the original detailed data was obtainable. A $P < .1$ for Egger regression test was regarded as statistically significant publication bias. We did not reanalyze the other data or primary studied included in the meta-analyses.

3. Results

3.1. Characteristics of meta-analyses
A total of 804 publications were revealed in the systematic research, including 276 publications by PubMed, 367 publications by Web of Science, 116 publications by Embase and 45 publications by the Cochrane Library. After removing duplicates, a total of 581 articles were rested. Based on the title, abstract and full text, 55 meta-analyses were included in the umbrella review which applying our inclusion criteria. The detailed selection process was shown in Figure 1.

All of the 55 articles investigated the impact of ERAS/FTS on clinical outcomes compared with conventional care mode involved in colorectal surgery (n = 13),[31–42] liver surgery (n = 7),[43–49] gastric surgery (n = 7),[22,50–55] orthopedic surgery (n = 3),[56–58] bariatric surgery (n = 3),[59–61] urology surgery (n = 3),[62–64] breast surgery (n = 3),[65–67] esophageal surgery (n = 3),[68–70] pancreatic surgery (n = 3),[71–73] and other surgery (n = 10)[44,74–82] including gynecologic surgery,[74] abdominal aortic aneurysm repair surgery,[76] lung surgery[77] and vascular operations.[79] The most clinical results were measured in the meta-analyses are length of hospital stay (LOS)/post-operative hospital stay (PLOS) (n = 47), cost (n = 16), mortality (n = 30), morbidity (n = 34), readmission (n = 42), reoperation (n = 8) and other secondary outcomes. All the meta-analyses reported the ERAS/FTS pathways were used in observational groups and 37 of 55 specifically pointed out the number of protocols in the pathways and the range of ERAS elements applied in the articles was from 2 to 22. Full version information was available in Supplemental Table 1, http://links.lww.com/MD/E467. And we included the latest 23 meta-analyses to analyze.

In the latest meta-analysis, ERAS pathways can significantly reduce the morbidity (RR: 0.620; 0.545 to 0.704),[61] LOS (MD: −2.349; −2.740 to −1.958),[4] hospital cost (MD: −639.06; −933.85 to −344.28)[4] and shorten the time to first flatus (MD: −13.119; −17.980 to −8.257)[4] for surgery patients, while have no impacts on mortality and readmissions.[4] However, the results were different among diverse surgical specialties.

3.2. ERAS on colorectal cancer
Consistent evidence indicated that the ERAS pathways can significantly reduce the LOS, PLOS, morbidity and enhance the recovery of bowel functions. Morbidity was decreased by 34% compared with conventional care (RR: 0.66; 0.54 to 0.80).[3] And the reduction in LOS were 2.6 days (−3.2 to −2.0),[73] PLOS were 2.0 days (−2.52 to −1.48),[75] cost were $1003.790 (−1872.567 to −135.012),[10] time to first flatus and defecation were shortened by 1 day as well.[42] Similar results were found in laparoscopic surgery.[37] In addition, inflammatory response indicators were attenuated with the ERAS pathways, C-reactive protein (CRP), Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels on POD 3 to POD 5 were reduced significantly.[37] Results were shown in Table 1.

3.3. ERAS on orthopedic surgery
Evidence shown that the mortality and morbidity of orthopedic surgery have been significantly reduced by 60% and 30% (RR: 0.40, 0.23 to 0.67; 0.70, 0.64 to 0.78; respectively).[57] Moreover, meta-analyses indicated that a decrease in LOS of 2.03 (−2.64 to −1.42)[56] days, PLOS of 0.85 (−1.24 to −0.45)[58] days in those patients treated with ERAS pathways for joint arthroplasty. Most importantly, Oswestry Disability Index and transfusion rate were decreased as well, but not for readmission.[37] The detailed results were shown in Table 2.

3.4. ERAS on gastric surgery
Compared with traditional care, LOS was significantly reduced by 2.47 days (WMD: 2.27, 3.06 to −1.89).[22] PLOS were decreased 1.85 (−2.35 to −1.35)[52] and 2.65 (−4.01 to −1.29)[53] days both in open and laparoscopic approach. The cost,[52] time to first flatus[54] and inflammatory response[22] were also reduced. However, the readmission was increased (RR: 1.95; 95% CI: 1.03 to 3.67).[22] Mortality and morbidity were comparable between ERAS and traditional pathways. The detailed results were shown in Table 3.

3.5. ERAS on other surgeries
The data indicated that ERAS pathways can significantly reduce LOS and PLOS compared with traditional care. And the reduction of LOS were 3.75 days (−5.13 to −2.36) in cystectomy,[64] 3.55 days (−4.42 to −2.69) in esophageal cancer surgery,[69] 3.5 days (−5.8 to −1.4) in vascular operations,[79] 3.17 days (−3.99 to −2.35) in liver surgery,[49] 3.05 days (−4.87 to −1.23) in abdominal gynecologic surgery,[74] and 1.58 days (−1.99 to −1.18) in breast reconstruction.[66] There are also some articles shown the reduction of PLOS, in pancreatic surgery, it was shorter 4.45 days (−5.99 to −2.91)[72] than traditional groups, 4.17 days (−5.72 to −2.61) in pancreaticoduodenectomy,[73] and 2.72 days (−3.86 to −1.57) in hepatectomy.[44] Meta-analysis shown a significant reduction in the total cost of hospital for upper gastrointestinal surgery,[81] liver surgery[47] and non-colorectal surgery[62] compared with control groups. ERAS pathways can reduce the rate of morbidity in bariatric,[19] cystectomy,[64] liver surgery,[47] lung cancer surgery[77] and pancreatic surgery.[72] The detailed information was shown in the Supplement Table 1, http://links.lww.com/MD/E467.

3.6. Heterogeneity of included outcomes
Among the 146 outcomes of 23 meta-analyses, about 15.0% did not report the value of $I^2$, and we did not conduct the $I^2$ statistic
for assessment of heterogeneity because of the lack of available data. For the other outcomes, 35.0% had low heterogeneity with \( I^2 < 25\% \), and 26.7% had very high heterogeneity, with \( I^2 > 75\% \). About 23.3% had moderate-to-high heterogeneity with \( I^2 \) range from 25% to 75%. The heterogeneity in the individual studies included meta-analyses was affected by many factors such as the participation, type of surgery, duration of follow-up, the number of ERAS protocols used in the study and the endpoints of ERAS in each primary study.

3.7. Publication bias of included outcomes

Of the total of 146 outcomes, about 41.8% did not report the publication bias, and we did not conduct the Egger regression test for these outcomes because the data were unavailable or the study was too small. For the remaining outcomes with assessment of publication bias, 20.5% were evaluated with Egger regression test and 37.7% were evaluated with funnel plots. In Egger’s regression test, 22 of those reported the \( P \) value, 18 outcomes with the \( P > .1 \), 4 outcomes with the \( P < .1 \), and 8 outcomes were
reported as no publication bias. In funnel plots, 7 outcomes were reported had high risk of publication bias, 11 outcomes were reported had low risk of publication bias and 37 outcomes were reported as no publication bias. The statistical evidences of publication bias were shown in LOS and mortality for gastric cancer surgery, and mortality and post-operative paralytic ileus for cystectomy with ERAS pathway.

3.8. Results of AMSTAR and GRADE assessment

In the 23 meta-analyses, the median AMSTAR score was 8.5 out of 11 (range 6.0–10.5, interquartile range 7.5–9). Studies that did not assess heterogeneity and publication bias were marked as lower scores. After assessing the quality of evidences with the GRADE, about 28.8% were rated as “very low”, 47.2% were rated as “low” and 24.0% rated as “moderate”, none was rated as “high” quality. As for the “low” and “very low” quality of evidences, most of them had a risk of publication bias, inconsistency or imprecision. Table 4 shows detailed information about AMSTAR score and GRADE evaluation.

4. Discussion

4.1. Main findings and interpretation in light of evidence

We identified 23 meta-analyses in our umbrella review to systematically evaluate the impacts of ERAS programs on clinical outcomes for all surgery. We summarized the existing evidence of ERAS in various operations and then drawn a conclusion. As the result shown that ERAS is beneficial to all surgery, which can
reduce LOS and cost without increasing morbidity, mortality or readmission for colorectal, liver, gastric, orthopedic, bariatric, urology, breast, esophageal, pancreatic, gynecologic, lung, abdominal aortic aneurysm repair surgery and vascular operations. What is more, the complication rates were reduced in pancreatic surgery, colorectal surgery, cystectomy, lung cancer surgery, liver surgery and bariatric surgery. While in gastric surgery, the morbidity and readmission rates were increased when compared with conventional care.

We used the AMSTAR to assess the methodological quality of included meta-analyses, and GRADE to assess the quality of outcomes in each study. In the most recent 23 meta-analyses with 146 outcomes, about 60.9% of the meta-analyses had an AMSTAR score of more than 8, and 76.0% of the outcomes were graded as “low” or “very low”. The high AMSTAR score of meta-analyses did not related to high quality of outcomes in each study and participants and would reduce the quality of evidence. Graded as AMSTAR score of more than 8, and 76.0% of the outcomes were included in the umbrella review indicated that ERAS pathways can significantly reduce the LOS and hospital cost for all surgery patients. As a stressor, surgery can arouse the changes of the neurohormonal system and inflammation responses resulting in major trauma to the human body. The purpose of ERAS pathways is to reduce the surgical stress which can cause organ dysfunction and proinflammatory response that result in the subsequent need for hospitalization. With the multimodal measures, operations are completed in the condition of pain-free and stress-free. Early removal of the drainage tubes and multimodal analgesia including epidural analgesia, local anesthetic and patient controlled analgesia (PCA) would enable patient early mobilization, which can avoid post-operative complications such as intestinal obstruction; early oral nutrition can reduce catabolism, limit loss of muscle function and promote recovery.

All meta-analyses included in the umbrella review indicated that ERAS pathways can significantly reduce the LOS and hospital cost for all surgery patients. As a stressor, surgery can arouse the changes of the neurohormonal system and inflammation responses resulting in major trauma to the human body. The purpose of ERAS pathways is to reduce the surgical stress which can cause organ dysfunction and proinflammatory response that result in the subsequent need for hospitalization. With the multimodal measures, operations are completed in the condition of pain-free and stress-free. Early removal of the drainage tubes and multimodal analgesia including epidural analgesia, local anesthetic and patient controlled analgesia (PCA) would enable patient early mobilization, which can avoid post-operative complications such as intestinal obstruction; early oral nutrition can reduce catabolism, limit loss of muscle function and promote recovery.

The Table 3 below presents the effect of ERAS programs on outcomes for gastric surgery.

| First author | Year | Outcomes | Population | No. of studies in MA | Type of studies in MA | Participants in MA | Metric of MA | Effects mode | Effect size (95% CI) | I² (%) | Publication bias | ERAS Elements |
|--------------|------|----------|------------|----------------------|----------------------|-------------------|-------------|--------------|---------------------|--------|---------------|---------------|
| Beamish      | 2015 | LOS      | NR         | 13                   | RCT,5 CS             | 1561              | WMD         | REM          | -1.10 (-1.56 to -0.65) | 93.0   | NR            |               |
| Beamish      | 2015 | Morbidity| NR         | 13                   | RCT,5 CS             | 1596              | OR           | FEM          | 0.83 (0.66 to 1.00)    | 51.0   | NR            |               |
| Ding, J      | 2017 | Blood loss| NR         | 8                    | RCT,6                | 635               | WMD         | FEM          | -1.80 (-7.71 to 4.12)  | 9.0    | NR            | 11.3          |
| Ding, J      | 2017 | Cost      | NR         | 6                    | RCT,5                | 64               | OR           | FEM          | -9.41 (-14.0 to -4.89) | 9.0    | NR            | 11.3          |
| Ding, J      | 2017 | CRP       | NR         | 5                    | RCT,3               | 282               | WMD         | REM          | -19.46 (-21.74 to -17.18) | 73.0   | NR            | 11.3          |
| Ding, J      | 2017 | Duration of foley catheter| NR | 2 | RCT,5 | 107 | SMD | REM | -1.30 (-3.30 to 0.70) | 95.0 | NR | 11.3 |
| Ding, J      | 2017 | IL-6      | NR         | 3                    | RCT,3               | 191               | WMD         | FEM          | -32.16 (-33.86 to -30.46) | 95.0   | NR            | 11.3          |
| Ding, J      | 2017 | Mortality | NR         | 8                    | RCT,5               | 801               | OR           | REM          | 1.31 (0.76 to 2.27)    | 71.0   | NR            | 11.3          |
| Ding, J      | 2017 | Operation time | NR | 6 | RCT,5 | 635 | WMD | FEM | -2.88 (-6.21 to 0.48) | 0.0    | NR            | 11.3          |
| Ding, J      | 2017 | PLOS      | NR         | 8                    | RCT,5               | 801               | WMD         | REM          | -1.85 (12.35 to -1.35) | 69.0   | NR            | 11.3          |
| Ding, J      | 2017 | Readmission| NR         | 6                    | RCT,5               | 635               | FEM          | REM          | 3.42 (1.43 to 2.51)    | 0.0    | NR            | 11.3          |
| Ding, J      | 2017 | Time to first status | NR | 7 | RCT,3 | 740 | WMD | REM | -17.04 (-23.64 to -10.43) | 81.0   | NR | 11.3 |
| Li, Z.Y      | 2017 | Time to start diet | China,Korea | 2 | RCT,2 | 188 | WMD | REM | -0.97 (-2.27 to 0.33) | 61.0   | NR |                |
| Li, Z.Y      | 2017 | PLOS      | China, Korea| 4 | RCT,4 | 274 | WMD | REM | -2.169 (-3.05 to -1.26) | 65.0   | NR |                |
| Li, Z.Y      | 2017 | Cost      | China, Korea| 3 | RCT,3 | 191 | WMD | REM | -4.72 (-6.88 to -2.55) | 72.0   | NR |                |
| Li, Z.Y      | 2017 | Ambulation time | China,Korea | 5 | RCT,5 | 315 | OR | REM | 0.63 (0.37 to 1.09) | 43.0   | NR |                |
| Li, Z.Y      | 2017 | Ambulation time | China,Korea | 2 | RCT,2 | 188 | WMD | REM | -0.97 (-2.27 to 0.33) | 61.0   | NR |                |
| Li, Z.Y      | 2017 | CRP       | China, Korea| 5 | RCT,5 | 315 | OR | REM | 0.63 (0.37 to 1.09) | 43.0   | NR |                |
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| Li, Z.Y      | 2017 | Mortality | China, Korea| 3 | RCT,3 | 191 | WMD | REM | -4.72 (-6.88 to -2.55) | 72.0   | NR |                |
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CC = cohort study, CI = confidence interval, CRP = C-reactive protein, ERAS = enhanced recovery after surgery, FEM = fixed effects model, IL-6 = Interleukin-6, INF-a = tumor necrosis factor-α, LOS = length of hospital stay, MA = meta-analysis, MD = mean difference, NR = not report, OR = odds ratio, PLOS = postoperative length of hospital stay, POD = postoperative day, RCT = randomized control trial, REM = random effects model, RR = relative risk, SMD = standardized mean difference, WMD = weighted mean differences.
Table 4
Results of AMSTAR and GRADE.

| Type of surgery       | Author                          | Year | Outcomes                      | AMSTAR | Grade   |
|-----------------------|---------------------------------|------|-------------------------------|--------|---------|
| AAA repair surgery    | Gurgel, S. J. T. et al          | 2014 | Mortality                     | 7.0    | Very low|
| AAA repair surgery    | Gurgel, S. J. T. et al          | 2014 | Morbidity                     | 7.0    | Very low|
| Bariatric surgery     | Ahmed Ola S, et al              | 2018 | LOS                           | 6.0    | Low     |
| Bariatric surgery     | Ahmed Ola S, et al              | 2018 | Mortbidity                    | 6.0    | Low     |
| Bariatric surgery     | Ahmed Ola S, et al              | 2018 | Operative time                | 6.0    | Low     |
| Bariatric surgery     | Ahmed Ola S, et al              | 2018 | Cost                          | 6.0    | Low     |
| Breast surgery        | Offodile, et al                 | 2019 | LOS                           | 7.5    | Very low|
| Breast surgery        | Offodile, et al                 | 2019 | Major complications           | 7.5    | Very low|
| Breast surgery        | Offodile, et al                 | 2019 | Reatmissions                  | 7.5    | Very low|
| Breast surgery        | Offodile, et al                 | 2019 | Post-operative hematomas      | 7.5    | Very low|
| Breast surgery        | Offodile, et al                 | 2019 | Post-operative infections     | 7.5    | Very low|
| Colorectal surgery    | Greer, N. L. et al              | 2018 | LOS                           | 7.0    | Very low|
| Colorectal surgery    | Greer, N. L. et al              | 2018 | Mortality                     | 7.0    | Low     |
| Colorectal surgery    | Greer, N. L. et al              | 2018 | Readmissions                  | 7.0    | Low     |
| Colorectal surgery    | Greer, N. L. et al              | 2018 | Surgical site infection       | 7.0    | Low     |
| Colorectal surgery    | Zhuang, C. L. et al             | 2013 | PLOS                          | 8.5    | Low     |
| Colorectal surgery    | Zhuang, C. L. et al             | 2013 | LOS                           | 8.5    | Moderate|
| Colorectal surgery    | Zhuang, C. L. et al             | 2013 | Readmissions                  | 8.5    | Moderate|
| Colorectal surgery    | Zhuang, C. L. et al             | 2013 | Mortbidity                    | 8.5    | Low     |
| Colorectal surgery    | Zhuang, C. L. et al             | 2013 | Time to first flatus          | 8.5    | Moderate|
| Colorectal surgery    | Zhuang, C. L. et al             | 2013 | Time to first defecation      | 8.5    | Moderate|
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | PLOS                          | 9.0    | Moderate|
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | Time to first flatus          | 9.0    | Moderate|
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | Time to first defecation      | 9.0    | Moderate|
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | Morbidity                     | 9.0    | Moderate|
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | Readmissions                  | 9.0    | Low     |
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | Mortbidity                    | 9.0    | Low     |
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | IL-6 POD 1                    | 9.0    | Low     |
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | IL-6 POD 3                    | 9.0    | Low     |
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | IL-6 POD 5                    | 9.0    | Low     |
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | CRP POD1                      | 9.0    | Low     |
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | CRP POD3                      | 9.0    | Low     |
| Colorectal surgery-lap| Ni, Xiaofei, et al              | 2019 | CRP POD5                      | 9.0    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Operation time                | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Blood loss                    | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | No. of lymph nodes removed    | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Time to first flatus          | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Time to regular diet          | 8.5    | Moderate|
| Cystectomy            | Xiao, J. et al                  | 2019 | LOS                           | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Mortbidity                    | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Readmission rates             | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Reopenations                  | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Morbidity                     | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Paralytic ileus               | 8.5    | Low     |
| Cystectomy            | Xiao, J. et al                  | 2019 | Cardiovascular complication   | 8.5    | Very low|
| Cystectomy            | Xiao, J. et al                  | 2019 | Wound dehiscence              | 8.5    | Very low|
| Gastrectomy           | Ding, Jie, et al                | 2017 | Blood loss                    | 10.0   | Moderate|
| Gastrectomy           | Ding, Jie, et al                | 2017 | Operation time                | 10.0   | Moderate|
| Gastrectomy           | Ding, Jie, et al                | 2017 | PLOS                          | 10.0   | Low     |
| Gastrectomy           | Ding, Jie, et al                | 2017 | Cost                          | 10.0   | Low     |
| Gastrectomy           | Ding, Jie, et al                | 2017 | Time to first flatus          | 10.0   | Moderate|
| Gastrectomy           | Ding, Jie, et al                | 2017 | Duration of Foley catheter    | 10.0   | Low     |
| Gastrectomy           | Ding, Jie, et al                | 2017 | CRP                           | 10.0   | Low     |
| Gastrectomy           | Ding, Jie, et al                | 2017 | IL-6                          | 10.0   | Moderate|
| Gastrectomy           | Ding, Jie, et al                | 2017 | Reatmissions                  | 10.0   | Moderate|
| Gastrectomy           | Ding, Jie, et al                | 2017 | Morbidity                     | 10.0   | Low     |
| Gastrectomy-Lap       | Li, Zhengyan, et al             | 2017 | PLOS                          | 8.5    | Low     |
| Gastrectomy-Lap       | Li, Zhengyan, et al             | 2017 | Cost                          | 8.5    | Very low|
| Type of surgery          | Author                  | Year | Outcomes                  | AMSTAR | Grade   |
|-------------------------|-------------------------|------|---------------------------|--------|---------|
| Gastrectomy-Lap         | Li, Zhengyan. et al     | 2017 | Morbidity                 | 8.5    | Moderate|
| Gastrectomy-Lap         | Li, Zhengyan. et al     | 2017 | Readmissions              | 8.5    | Low     |
| Gastrectomy-Lap         | Li, Zhengyan. et al     | 2017 | Time to first flatus       | 8.5    | Very low|
| Gastrectomy-Lap         | Li, Zhengyan. et al     | 2017 | Ambulation time            | 8.5    | Very low|
| Gastrectomy-Lap         | Li, Zhengyan. et al     | 2017 | Time to start diet        | 8.5    | Very low|
| Gastrectomy-Lap         | Li, M. Z. et al         | 2018 | PLOS                      | 10.0   | Moderate|
| Gastrectomy-Lap         | Li, M. Z. et al         | 2018 | Time to first flatus       | 10.0   | Moderate|
| Gastrectomy-Lap         | Li, M. Z. et al         | 2018 | Cost                      | 10.0   | Moderate|
| Gastrectomy-Lap         | Li, M. Z. et al         | 2018 | Morbidity                 | 10.0   | Low     |
| Gastric cancer          | Beamish. et al          | 2015 | LOS                       | 8.5    | Very kw |
| Gastric cancer          | Beamish. et al          | 2015 | Mortality                 | 8.5    | Low     |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | LOS                       | 8.5    | Low     |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | Mortbidity                | 8.5    | Low     |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | Readmissions              | 8.5    | Low     |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | Time to return function   | 8.5    | Moderate|
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | Cost                      | 8.5    | Moderate|
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | Mortality                 | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | CRP POD1                  | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | CRP POD3/4                | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | CRP POD7                  | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | IL-6 POD 1                | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | IL-6 POD 3/4              | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | IL-6 POD 7                | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | TNFα POD1                 | 8.5    | Very kw |
| Gastric cancer surgery  | Wee, I. J. Y. et al     | 2019 | TNFα POD3/4               | 8.5    | Very kw |
| Gynecologic surgery     | de Groot, J. J. et al   | 2016 | LOS                       | 8.0    | Low     |
| Gynecologic surgery     | de Groot, J. J. et al   | 2016 | Morbidity                 | 8.0    | Low     |
| Joint arthroplasty      | Deng, Q. F. et al       | 2018 | Mortality                 | 9.5    | Moderate|
| Joint arthroplasty      | Deng, Q. F. et al       | 2018 | Postoperative transfusions| 9.5    | Low     |
| Joint arthroplasty      | Deng, Q. F. et al       | 2018 | Postoperative ROM         | 9.5    | Low     |
| Joint arthroplasty      | Deng, Q. F. et al       | 2018 | Readmissions              | 9.5    | Low     |
| Joint arthroplasty      | Deng, Q. F. et al       | 2018 | Mortality                 | 9.5    | Moderate|
| Joint arthroplasty      | Deng, Q. F. et al       | 2018 | LOS                       | 9.5    | Low     |
| Liver resection         | Wang, Cheng. et al      | 2017 | Mortbidity                | 9.0    | Low     |
| Liver resection         | Wang, Cheng. et al      | 2017 | LOS                       | 9.0    | Low     |
| Liver resection         | Wang, Cheng. et al      | 2017 | Readmissions              | 9.0    | Very kw |
| Liver resection         | Wang, Cheng. et al      | 2017 | Mortality                 | 9.0    | Very kw |
| Liver resection         | Wang, Cheng. et al      | 2017 | Time to bowel function recovery | 9.0 | Low |
| Liver resection         | Wang, Cheng. et al      | 2017 | cost                      | 9.0    | Low     |
| Liver resection         | Wang, Cheng. et al      | 2017 | blood loss                | 9.0    | Very kw |
| Liver resection         | Wang, Cheng. et al      | 2017 | Transfusion Rate          | 9.0    | Very kw |
| Liver resection         | Zhao, Yiyang. et al     | 2017 | LOS                       | 7.5    | Moderate|
| Liver resection         | Zhao, Yiyang. et al     | 2017 | Time to first flatus       | 7.5    | Low     |
| Liver resection         | Zhao, Yiyang. et al     | 2017 | Morbidity                 | 7.5    | Low     |
| Lung cancer             | Li, S. et al            | 2017 | Morbidity                 | 10.5   | Moderate|
| Lung cancer             | Li, S. et al            | 2017 | Mortality                 | 10.5   | Low     |
| Lung cancer             | Li, S. et al            | 2017 | Pulmonary complications   | 10.5   | Moderate|
| Lung cancer             | Li, S. et al            | 2017 | Surgical complications   | 10.5   | Moderate|
| Lung cancer             | Li, S. et al            | 2017 | Cardiovascular complications | 10.5 | Low |
| Noncolorectal surgery   | Visioni, Anthony. et al | 2018 | LOS                       | 8.0    | Moderate|
| Noncolorectal surgery   | Visioni, Anthony. et al | 2018 | Mortbidity                | 8.0    | Low     |
| Noncolorectal surgery   | Visioni, Anthony. et al | 2018 | Readmissions              | 8.0    | Low     |
| Noncolorectal surgery   | Visioni, Anthony. et al | 2018 | Time to first flatus       | 8.0    | Moderate|
| Noncolorectal surgery   | Visioni, Anthony. et al | 2018 | Cost                      | 8.0    | Moderate|
| Orthopedic surgery      | Hu, Z. C. et al         | 2019 | Mortality                 | 9.5    | Very kw |
| Orthopedic surgery      | Hu, Z. C. et al         | 2019 | Readmissions              | 9.5    | Very kw |
| Orthopedic surgery      | Hu, Z. C. et al         | 2019 | Mortality                 | 9.5    | Very kw |
| Orthopedic surgery      | Hu, Z. C. et al         | 2019 | ODI                       | 9.5    | Very kw |
| Pancreatic surgery      | Ji, H. B. et al         | 2018 | Pancreatic fistula         | 9.0    | Low     |
| Pancreatic surgery      | Ji, H. B. et al         | 2018 | DGE                       | 9.0    | Low     |
now on, more than 20 countries have put the ERAS pathways into use. In addition, many countries have published the local guidelines of ERAS. Therefore, implementation of ERAS programs has been a common way to deal with patients with colorectal surgery.

The ERAS programs were most beneficial to orthopedic surgery including total hip arthroplasty (THA) and spinal surgery. The ERAS can reduce the LOS, cost, and blood loss and can also decrease the rates of morbidity, mortality and readmission. In THA and TKA, the prevalence of complications was 24.5% in ERAS group whilst 36.9% in the traditional group. In addition, the rate of readmission for THAs performed under the ERAS pathway was almost one-third of that of traditional care.

What is more, the 30-days and 90-days morbidity were reduced both in THA and TKA, and the reduction is 0.5% to 0.1% (P = 0.02, 0.8% to 0.2%, (P = 0.01), respectively. The reason was that the ERAS programs can decrease the post-operative myocardial infarction (MI). In the study including 6000 consecutive procedures, the 30-day rate of MI was reduced from 0.9% in the conventional group to 0.4% in ERAS group. Although the ERAS group had a higher prevalence of co-morbidities such as hypertension, ischemic heart disease, chronic obstructive pulmonary disease (COPD) and type-2 diabetes, cardiac ischemic events were lesser in the postoperative compared with traditional group. In the latest paper, the morbidity was also reduced in the postoperative compared with traditional surgery.

In gastric cancer surgery, ERAS programs would increase the readmission rates in open surgery. Another study also found that the readmission was 19% in ERAS and 5% in the traditional group for elderly gastric cancer open surgery. The reason of readmission is postoperative complications including nausea and vomiting, gastric retention, intestinal obstruction, and delayed convalescence resulting in higher readmission.

Table 4 (continued).

| Type of surgery       | Author          | Year | Outcomes                      | AMSTAR | Grade  |
|-----------------------|-----------------|------|-------------------------------|--------|--------|
| Pancreatic surgery    | Ji, H. B. et al | 2018 | Morbidity                     | 9.0    | Low    |
| Pancreatic surgery    | Ji, H. B. et al | 2018 | Abdominal infection           | 9.0    | Low    |
| Pancreatic surgery    | Ji, H. B. et al | 2018 | PLOS                          | 9.0    | Moderate |
| Pancreatic surgery    | Ji, H. B. et al | 2018 | Mortality                     | 9.0    | Moderate |
| Pancreatic surgery    | Ji, H. B. et al | 2018 | Readmissions                  | 9.0    | Moderate |
| Pancreatic surgery    | Ji, H. B. et al | 2018 | Reoperation                   | 9.0    | Moderate |
| Surgery               | Lau, C. S. et al| 2017 | LOS                           | 7.0    | Low    |
| Surgery               | Lau, C. S. et al| 2017 | Readmissions                  | 7.0    | Very low |
| Surgery               | Lau, C. S. et al| 2017 | Cost                          | 7.0    | Very low |
| Surgery               | Lau, C. S. et al| 2017 | Morbidity                     | 7.0    | Very low |
| Surgery               | Lau, C. S. et al| 2017 | Time to first flatus           | 7.0    | Very low |
| Surgery               | Lau, C. S. et al| 2017 | Mortality                     | 7.0    | Very low |
| UGI surgery           | Siotos, C. et al| 2018 | Morbidity for gastrectomy     | 7.5    | Low    |
| UGI surgery           | Siotos, C. et al| 2018 | Morbidity                     | 7.5    | Low    |
| UGI surgery           | Siotos, C. et al| 2018 | Time to first flatus           | 7.5    | Very low |
| UGI surgery           | Siotos, C. et al| 2018 | PLOS                          | 7.5    | Low    |
| UGI surgery           | Siotos, C. et al| 2018 | Reoperations                  | 7.5    | Very low |
| UGI surgery           | Siotos, C. et al| 2018 | Cost                          | 7.5    | Very low |
| Vascular operations   | McGingile, K. L. et al | 2019 | Time to regular diet          | 6.0    | Very low |
| Vascular operations   | McGingile, K. L. et al | 2019 | LOS                           | 6.0    | Moderate |

AAA = abdominal aortic aneurysm, AMSTAR = a measurement tool to assess systematic reviews, CRP = C-reactive protein, DGE = delayed gastric emptying, ERAS = enhanced/recovery after surgery, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, IL-6 = Interleukin-6, INF-a = tumor necrosis factor-a, LOS = length of hospital stay, NR = not report, ODI = Oswestry disability index, PLOS = postoperative length of hospital stay, POD = postoperative day, ROM = range of motion, UGI = upper gastrointestinal.

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care with laparoscopic surgery for gastric cancer. However, there was a higher morbidity in the laparoscopic gastric cancer surgery with ERAS programs in this umbrella review. And there was inconsistent evidence. Hu et al.\(^{[59]}\) evaluated the safety and effectiveness of ERAS combined with laparoscopic gastrectomy for gastric cancer found that there were 12 post-operative complications in ERAS group while 8 in the control group. As for elderly patient, morbidity in ERAS group was 11 while in control group was 6.\(^{[100]}\) But in another two RCTs, morbidity was similar between ERAS and traditional groups.\(^{[97,101]}\) The same result was found in a meta-analysis, which included 6 RCTs aimed to compare fast-track recovery with conventional recovery strategies in laparoscopic radical gastrectomy.\(^{[53]}\) Maybe there were other reasons for the result in this umbrella review, for instance, heterogeneity and publication bias of the included studies. Whether morbidity with the ERAS pathways would be increased need further study in high quality studies.

### 4.2. Strengths and limitations

There was several strength in this study. This umbrella review systematically evaluated the effects of ERAS pathway in multiple clinical outcomes for all kinds of surgeries included the latest evidence in each surgical specialty. And we found that the ERAS programs were not beneficial to all the surgeries, for example, readmission and morbidity would be increased for gastric cancer surgery, so precaution is necessary for gastric cancer surgery with ERAS programs. However, there were also many limitations in this umbrella review. First, only the study published in English was included, other studies would be ignored. Secondly, the conclusion depended on the meta-analyses, some individual studies which have been missed might have minor influence on our findings, because the meta-analyses we selected was the most recent one with the highest number of studies included. Thirdly, a number of meta-analyses put emphasis on gastrointestinal surgery, just a few studies involved in the thoracic or vascular surgery. Fourthly, compliance or ERAS components used in each study were different, which would have an impact on the effectiveness of ERAS. Fifthly, in these publications included in meta-analyses, many of data derived from cohort studies rather RCT, and even in RCT, blindness is impossible due to the nature of intervention,\(^{[70]}\) and maybe the study populations were small or highly selected result in lacking external validity.\(^{[102]}\) Finally, it was uncertain whether the evidence-based experience of colorectal surgery can be fully used in other operations.\(^{[21,102]}\)

### 5. Conclusions

In a conclusion, the ERAS programs are safe, feasible and efficient in most surgeries, especially for orthopedic surgery. However, it is necessary to take measures to prevent adverse events when adopting ERAS pathways for gastric cancer surgery especially in older patients. And more RCT is needed to justify the feasibility and effectiveness for those patients.

### Author contributions

Yong Zhou, and Ka Li conceived and designed the study; Zhang Xingxia, Jie Yang Xinrong Chen collected the data; Zhang Xingxia, Xinrong Chen and Liang Du analyzed and interpreted the data; Zhang Xingxia wrote the manuscript; Yong Zhou provided critical revisions; and all authors approved the final version of the manuscript.

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