Rapid rehabilitation effect on complications, wound infection, anastomotic leak, obstruction, and hospital re-admission for gastrointestinal surgery subjects: A meta-analysis

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Abstract
We performed a meta-analysis to evaluate the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects. A systematic literature search up to October 2021 was done and 31 studies included 4448 subjects with gastrointestinal surgery at the start of the study: 2242 of them were provided with rapid rehabilitation and 2206 were standard care. They were reporting relationships about the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects. We calculated the odds ratio (OR) with 95% confidence intervals (CIs) to assess the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects using the dichotomous method with a random- or fixed-effect model. Rapid rehabilitation had significantly lower complications (OR, 0.62; 95% CI, 0.54-0.71, \( P < .001 \)) and wound infection (OR, 0.73; 95% CI, 0.55-0.98, \( P = .03 \)) compared with standard care in subjects with gastrointestinal surgery. However, rapid rehabilitation had no significant effect on the anastomotic leak (OR, 0.90; 95% CI, 0.66-1.22, \( P = .49 \)), obstruction (OR, 0.92; 95% CI, –0.64 to 1.31, \( P = .65 \)), and hospital re-admission (OR, 0.78; 95% CI, 0.57-1.08, \( P = .13 \)) compared with standard care in subjects with gastrointestinal surgery. Rapid rehabilitation had significantly lower complications and wound infection, and had no significant effect on the anastomotic leak, obstruction, and hospital re-admission compared with standard care in subjects with gastrointestinal surgery. Further studies are required to validate these findings.

KEYWORDS
anastomotic leak, complications, gastrointestinal surgery, hospital re-admission, obstruction, rapid rehabilitation, standard care, wound infection

Lixiu Liu and Lihuang He are co-first authors; they contributed equally to this work.

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Key Messages

- we performed a meta-analysis to evaluate the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects
- rapid rehabilitation had significantly lower complications and wound infection, and had no significant effect on the anastomotic leak, obstruction, and hospital re-admission compared with standard care in subjects with gastrointestinal surgery
- further studies are required to validate these findings

1 | BACKGROUND

Rapid rehabilitation protocols have often been studied in the literature. The idea of rapid rehabilitation protocols was first recommended by a Danish surgeon, Kehlet, to decrease stress, complications, and hospital length of stay following gastrointestinal surgery. Rapid rehabilitation protocols were studied primarily in the location of elective gastrointestinal surgery. They showed, by improving and perioperative care standardisation, the hospital length of stay can be decreased from 8 to 12 days to 2 to 4 days. For the surgical management of gastrointestinal cancer illness, conservative elective gastrointestinal surgery is related to a high rate of complication (10%-45%) and a postoperative hospital length of stay (8-13 days). A higher percentage of dangerous postoperative complications are related to an extreme response to surgical stress. C-reactive protein, interleukin-6, tumour necrosis factor-α, and resting energy expenditure might act as markers for the surgical stress response severity.

To solve this problem, rapid rehabilitation protocols were established. Rapid rehabilitation protocols are established to decrease surgical stress by different surgical and anaesthetic methods to improve recovery. In a prospective study examining the value of an enhanced recovery in elective gastrointestinal surgery, it was shown that a number of the rapid rehabilitation protocols principles, for example, avoidance of prophylactic nasogastric tubes and abdominal drains, use of multimodal analgesia, and early postoperative feeding, can be used effectively in this clinical situation without increasing postoperative illness. The safety of rapid rehabilitation protocols is still conflicting. So, this meta-analysis aimed to assess the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects.

2 | METHODS

The current study was completed following a reputable protocol that was based on the meta-analysis of studies in the epidemiology statement.

2.1 | Study selection

Comprised studies were that with statistical relationship (odds ratio [OR], mean difference [MD], frequency rate ratio, or relative risk, with 95% confidence intervals [CIs]) among the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects.

Only those human studies in any language were selected. Inclusion was not limited by study size or type. Studies excluded were review articles, commentaries, and studies that did not provide a level of association. Figure 1 shows the entire study procedure. The articles were combined into the meta-analysis when the next inclusion criteria were met:

1. The study was a randomised control trial, prospective study, or retrospective study.
2. The target population was subjects with gastrointestinal surgery.
3. The intervention programme was rapid rehabilitation.
4. The study comprised comparisons between rapid rehabilitation and standard care.

Exclusion criteria were as follows:

1. Studies that did not determine the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects.
2. Studies with management other than rapid rehabilitation.
3. Studies that did not focus on the effect of comparative results.

2.2 | Identification

A protocol of search plans was arranged based on the PICOS principle, and we defined it as follow: P (population): subjects with gastrointestinal surgery; I (intervention/exposure): rapid rehabilitation; C (comparison): rapid rehabilitation and standard care; O (outcome): complications, wound infection, anastomotic leak, obstruction, and hospital re-admission; and S (study design): no limit. First, we
performed a systematic search of Embase, PubMed, Cochrane Library, OVID, and Google scholar till October 2021, by a blend of keywords and related words for rapid rehabilitation, gastrointestinal surgery, standard care, complications, wound infection, anastomotic leak, obstruction, and hospital re-admission as shown in Table 1. All selected studies were grouped in an EndNote file, duplicates were removed, and the title and abstracts were reviewed to remove studies that did not show any association about the effect of rapid rehabilitation on the outcomes of care for subjects with gastrointestinal surgery. The remaining studies were studied for associated information.

2.3 | Screening

Data were shortened depending on the following; study-related and subject-related properties onto a homogeneous form as follow: the primary author last name, study period, country, publication year, the studies region and type of the population, and design of the study; the total number of subjects, demographic data, and clinical and treatment properties. In addition, the evaluation period is related to measurement, quantitative technique and qualitative technique of assessment, source of information, outcomes’ evaluation, and statistical analysis of MD or relative risk, with 95% CI of relationship.13

If a study fit for inclusion depended on the abovementioned principles, data were extracted separately by two authors. In case of dissimilarity, the corresponding author gives a final choice. When there were different data from one study based on the evaluation of the relationship between the effects of rapid rehabilitation compared with standard care on the outcomes of care for subjects with gastrointestinal surgery, we extracted them separately. The risk of bias in these studies: each study was appraised using two authors who separately evaluated the procedural quality of the nominated studies. The ‘risk of bias tool’ from the RoB 2: A studied Cochrane risk of bias tool for randomised trials was used to measure procedural quality. In terms of the evaluation criteria, each study was valued and consigned to one of the next three risks of bias: low: if all quality standards were met, the study was considered to have a low risk of bias; unclear: if one or more of the quality standards were partly met or unclear, the study was considered to have a moderate risk of bias; or high: if one or more of the standards were not met, or not comprised, the study was considered to have a high risk of bias. Any discrepancies were addressed by reviewing the original article.
The search strategy for each database

| Database        | Search strategy                                                                 |
|-----------------|---------------------------------------------------------------------------------|
| PubMed          | #1 ‘rapid rehabilitation’[MeSH Terms] OR ‘gastrointestinal surgery’[All Fields] OR ‘standard care’[All Fields] |
|                 | #2 ‘complications’[MeSH Terms] OR ‘rapid rehabilitation’[All Fields] OR ‘wound infection’[All Fields] OR ‘anastomotic leak’[All Fields] OR ‘obstruction’[All Fields] OR ‘hospital re-admission’[All Fields] |
|                 | #3 #1 AND #2                                                                    |
| Embase          | ‘rapid rehabilitation’/exp OR ‘gastrointestinal surgery’/exp OR ‘standard care’/exp |
|                 | #2 ‘complications’/exp OR ‘ICBG’/exp OR ‘wound infection’/exp OR ‘anastomotic leak’/exp OR ‘obstruction’/exp OR ‘hospital re-admission’/exp |
|                 | #3 #1 AND #2                                                                    |
| Cochrane Library | #1 (rapid rehabilitation):ti,ab,kw OR (gastrointestinal surgery):ti,ab,kw OR (standard care):ti,ab,kw (Word variations have been searched) |
|                 | #2 (complications):ti,ab,kw OR (wound infection):ti,ab,kw OR (anastomotic leak):ti,ab,kw OR (obstruction):ti,ab,kw OR (hospital re-admission):ti,ab,kw (Word variations have been searched) |
|                 | #3 #1 AND #2                                                                    |

2.4 | Eligibility

The chief result concentrated on the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects. An evaluation of the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects was extracted to make a summary.

2.5 | Inclusion

Sensitivity analyses were limited only to studies showing the association of the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects. For subgroup and sensitivity analysis, we performed a comparison between rapid rehabilitation and standard care.

2.6 | Statistical analysis

We computed the odds ratio (OR) and 95% confidence interval (CI) by the dichotomous technique with a fixed- or random-effect model. We calculated the I² index, and the I² index was between 0% and 100%. When the I² index was around 0%, 25%, 50%, and 75%, it refers to no, low, moderate, and high heterogeneity, respectively. If the I² was >50%, we used the random-effect model; if it was <50%, we used the fixed-effect model. We used stratifying the original calculation per result category as defined before the subgroup analysis. A P value for differences among subgroups of <.05 reflected statistically significant. Studies bias was measured quantitatively using the Egger regression test (studies bias is present if P ≥ .05), and qualitatively, by visual examination of funnel plots of the logarithm of odds ratios against their standard errors. The entire P values were two-tailed. Reviewer manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to perform all measurements and graphs.

3 | RESULTS

A total of 1021 distinctive studies were found, of which 31 studies (between 2003 and 2021) satisfied the inclusion criteria and were comprised in the study. The 32 studies included 4448 subjects with gastrointestinal surgery at the start of the study: 2242 of them were provided with rapid rehabilitation and 2206 were standard care. All studies evaluated the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects.

The study size ranged from 25 to 597 subjects with gastrointestinal surgery at the beginning of the study. The information of the 31 studies is shown in Table 2. Twenty-nine studies reported data stratified to the complications, 19 studies reported data stratified to the wound infection, 19 studies reported data stratified to anastomotic leak, 12 studies reported data stratified to the obstruction, and 16 studies reported data stratified to the hospital re-admission.

Rapid rehabilitation had significantly lower complications (OR, 0.62; 95% CI, 0.54-0.71, P ≤ .001) with low heterogeneity (I² = 37%), and wound infection (OR, 0.73; 95% CI, 0.55-0.98, P = .03) with no heterogeneity (I² = 8%) compared with standard care in subjects with gastrointestinal surgery as shown in Figures 2 and 3.

However, rapid rehabilitation had no significant effect on the anastomotic leak (OR, 0.90; 95% CI, 0.66-1.22, P = .49) with no heterogeneity (I² = 0%), obstruction (OR, 0.92; 95% CI, 0.64 to 1.31, P = .65) with no heterogeneity (I² = 0%), and hospital re-admission (OR, 0.78; 95% CI, 0.57-1.08, P = .13) with low heterogeneity (I² = 26%) compared with standard care in
Studies stratified analysis that adjusted for ethnicity, and age was not completed because no studies stated or adjusted for these influences. Depending on the visual assessment of the funnel plot as well as on quantitative measurement by the Egger regression test, there was no sign of publication bias \( (P = .88) \). Yet, the majority of the included studies were of low procedural quality because of their small sample size. All studies did not have selective reporting bias, and no study had incomplete outcome data and selective reporting.

### DISCUSSION

This meta-analysis study based on 31 studies included 4448 subjects with gastrointestinal surgery at the start of the study: 2242 of them were provided with rapid rehabilitation and 2206 were standard care. Rapid rehabilitation had significantly lower complications and wound infection compared with standard care in subjects with gastrointestinal surgery. However, rapid rehabilitation had no significant effect on the anastomotic leak, obstruction, and hospital re-admission compared with standard care in subjects with gastrointestinal surgery.
FIGURE 2  Forest plot of the complications in subjects with gastrointestinal surgery with rapid rehabilitation compared with the standard care

FIGURE 3  Forest plot of the wound infection in subjects with gastrointestinal surgery with rapid rehabilitation compared with the standard care
Yet, the analysis of results must be done with attention because of the low sample size of most of the selected studies found for the meta-analysis, 16 out of 31 studies with less than 100 subjects as sample size, recommending the necessity for additional studies to confirm these findings or perhaps to significantly impact confidence in the effect assessment.

The safety of rapid rehabilitation protocols after gastrointestinal surgery has been well discussed internationally. The latest analysis confirmed that male gender, pre-operative education, counselling, anaesthetics, early postoperative oral nutrition, and care quality were possible complications risk factors after gastrointestinal resection. Also, many studies have shown a high risk of anastomotic leaks in men compared with women because 10.1% of the men needed reoperation for anastomotic leak compared with 3.3% of women. Pre-operative education and counselling are vital factors for rapid rehabilitation protocols. It is essential to present the detailed management programme, rapid rehabilitation protocols' different steps, and related procedures, and decrease the psychological pressure to help subjects understand and organise the rapid rehabilitation protocols. Better collaboration of subjects can bring better results of rapid

### Table 1

| Study or Subgroup | Rapid rehabilitation | Standard care | Odds Ratio | Odds Ratio |
|------------------|----------------------|---------------|------------|------------|
|                  | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI Year | M-H, Fixed, 95% CI |
| Basse, 2005      | 1      | 30    | 0      | 30    | 0.6%   | 3.10 [0.12, 79.23] 2005  |
| Khoo, 2007       | 1      | 35    | 3      | 35    | 2.4%   | 0.31 [0.03, 3.17] 2007  |
| King, 2008       | 1      | 41    | 0      | 19    | 0.8%   | 1.44 [0.06, 37.10] 2008 |
| Muller, 2009     | 1      | 76    | 2      | 75    | 2.3%   | 0.49 [0.04, 5.48] 2009  |
| Ionescu, 2009    | 1      | 48    | 1      | 48    | 1.2%   | 1.00 [0.06, 16.48] 2009 |
| Faiz, 2009       | 9      | 161   | 1      | 50    | 1.1%   | 2.90 [0.36, 23.48] 2009 |
| Hübner, 2010     | 0      | 36    | 1      | 31    | 1.9%   | 0.28 [0.01, 7.09] 2010  |
| van Bree, 2011   | 1      | 36    | 1      | 36    | 1.1%   | 1.00 [0.06, 16.63] 2011 |
| Garcia-Botello, 2011 | 4       | 61    | 6      | 58    | 6.8%   | 0.61 [0.16, 2.36] 2011  |
| Vlug, 2011       | 15     | 193   | 13     | 207   | 13.6%  | 1.26 [0.58, 2.72] 2011  |
| Wang, 2011       | 4      | 106   | 2      | 104   | 2.3%   | 2.00 [0.36, 11.18] 2011 |
| Ren, 2012        | 5      | 299   | 5      | 298   | 5.8%   | 1.00 [0.29, 3.48] 2012  |
| Veenhof, 2012    | 2      | 36    | 4      | 35    | 4.5%   | 0.46 [0.08, 2.67] 2012  |
| Lemanu, 2013     | 2      | 40    | 2      | 38    | 2.3%   | 0.95 [0.13, 7.09] 2013  |
| Jia, 2014        | 3      | 117   | 2      | 116   | 2.3%   | 1.50 [0.25, 9.15] 2014  |
| Vignali, 2016    | 23     | 162   | 25     | 135   | 27.5%  | 0.73 [0.39, 1.33] 2016  |
| Maggio, 2017     | 8      | 130   | 10     | 133   | 10.9%  | 0.91 [0.31, 2.11] 2017  |
| Ostermann, 2019  | 5      | 75    | 5      | 75    | 5.9%   | 1.00 [0.28, 3.61] 2019  |
| Tesauro, 2021    | 2      | 47    | 9      | 126   | 5.5%   | 0.58 [0.12, 2.78] 2021  |

Total (95% CI) 1729 1649 100.0% 0.90 [0.66, 1.22] 1729 1649 100.0% 0.90 [0.66, 1.22]

Total events 88 92

Heterogeneity: $\chi^2 = 7.03, df = 18 (P = .99); I^2 = 0%$

Test for overall effect: $Z = 0.70 (P = .49)$

**Figure 4** Forest plot of the anastomotic leak in subjects with gastrointestinal surgery with rapid rehabilitation compared with the standard care.

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**Figure 5** Forest plot of the obstruction in subjects with gastrointestinal surgery with rapid rehabilitation compared with the standard care.
rehabilitation protocols. The solid meal and fluid gastric emptying time are 6 hours and 2 hours, respectively.\textsuperscript{50} Reasonable activity after surgery might enhance recovery and decrease complications. The subjects should be stimulated to have a liquid meal 2 hours before the operation in place of fasting. It has been reported that pre-operative oral carbohydrate is safe and can efficiently decrease complications.\textsuperscript{51,52} The role of regional anaesthesia or epidural in rapid rehabilitation protocols should be stressed. Postoperative epidural analgesia can avoid stress-induced neurological, endocrinological, and homeostatic variations or the blocking of the sympathetic nerve-related surgical stress response, decrease postoperative complications, eg, nausea, vomiting, and enteroparalysis, increase early ambulation, recover intestinal function, and shorten hospital stay after resection of gastrointestinal cancer.\textsuperscript{45,53,54} Early postoperative oral nutrition is a vital part of rapid rehabilitation protocols. Food consumption can encourage gastrointestinal peristalsis, and quick feeding in the first 24 hours after surgery stimulates obstruction recovery. It has been shown that early postoperative oral nutrition reduces catabolism and possibly reduces infectious complications.\textsuperscript{46,55} Rapid rehabilitation protocols can increase the subjects’ rehabilitation after gastrointestinal cancer surgery better than standard care plans, so benefiting surgery, anaesthesia, pain treatment, physical treatment, and social work. The main effort of rapid rehabilitation protocols is the pre-operative education of subjects to let them understand the entire strategy and the objective of each phase. So, it is essential to obtain collaboration from nurses. The pathophysiological mechanisms in postoperative obstruction are still not completely understood; nevertheless, the latest studies have stressed the importance of the intestinal muscularis inflammation following the handling during surgery.\textsuperscript{56-58}

The mechanisms behind the beneficial influence of rapid rehabilitation protocols are still conflicting. Numerous cytokines, for example, interleukin-6, tumour necrosis factor-\(\alpha\), and C-reactive protein, are included in the response to surgical stress and are consequently useful serum markers for assessing the severity of surgery-induced stress.\textsuperscript{8,11} C-reactive protein is a general acute-phase protein created by the liver after trauma or inflammation. Serum C-reactive protein level is closely related to trauma and stress,\textsuperscript{39} so quantifying postoperative C-reactive protein might imitate the degree of the trauma initiated by a surgical process. Interleukin-6 is created and initiated by monocytes, macrophages, and endothelial cells in surgical trauma and stress. Interleukin-6 levels are related to the surgical trauma severity.\textsuperscript{8,11} Surgical trauma results in noticeable metabolic variations and resting energy expenditure. Also, it acts as the marker for surgical stress.\textsuperscript{12,45} The resting energy expenditure rate of subjects from the rapid rehabilitation protocols group was lower than that in the standard care group, mainly on postoperative days 1 and 3. Post-surgical complications in subjects who experienced rapid rehabilitation protocols for colorectal illnesses were managed without definite side effects or complications. Compared with standard care plans, rapid rehabilitation protocols greatly decreased complications, and no other side effects were found. Rapid rehabilitation protocols are safe and possible. We believe that rapid rehabilitation protocols are significantly beneficial over other methods for subjects after gastrointestinal cancer surgery.
This meta-analysis reported the association of the effect of rapid rehabilitation on the curative effect of gastrointestinal surgery subjects. However, other studies are needed to confirm these probable relationships. Also, additional studies are required to provide a clinically meaningful difference in the outcomes. This was suggested also in previous similar meta-analysis studies, which showed a similar effect of rapid rehabilitation and standard care in subjects with different types of surgery. The insignificant results of rapid rehabilitation in the anastomotic leak, obstruction, and hospital re-admission also need additional study and clarification because no clear reasoning was found to clarify these outcomes. Well-conducted studies are also required to measure these factors and the blend of different ages and ethnicity; because our meta-analysis study could not answer whether they are related to the outcomes. Most of the selected studies evaluated were designed and accompanied before 2013, when SPIRIT Statement was started as a protocol to assist in improving the quality of clinical trial protocols. The CONSORT Statement (2010) is a 25-item checklist and flow diagram for authors to confirm transparent reporting of randomised trials. Using the SPIRIT and CONSORT protocols and checklists when designing and reporting a randomised controlled trial will assist in confirming that all vital elements of the trial are reported. Therefore, reducing the risk of bias eventually will help increase the quality of rapid rehabilitation of randomised controlled trials. We suggest that well-designed, high-quality randomised controlled trials are required to be accomplished about the effect of rapid rehabilitation on gastrointestinal surgery subjects. Health care providers need to confirm completed studies are published to establish and document results related to the effect of rapid rehabilitation on gastrointestinal surgery subjects because published evidence should be used to lead the clinical practice.

In summary, rapid rehabilitation had significantly lower complications and wound infection compared with standard care in subjects with gastrointestinal surgery. However, rapid rehabilitation had no significant effect on the anastomotic leak, obstruction, and hospital re-admission compared with standard care in subjects with gastrointestinal surgery. Further studies are required to confirm these findings. Additional studies are essential to confirm these outcomes. More studies are essential to confirm these outcomes. Yet, the analysis of results must be done with attention because of the low sample size of most of the selected studies found for the meta-analysis, recommending the necessity for additional studies to confirm these findings or perhaps to significantly impacts confidence in the effect assessment.

### 5 CONCLUSIONS

Rapid rehabilitation had significantly lower complications and wound infection compared with standard care in subjects with gastrointestinal surgery. However, rapid rehabilitation had no significant effect on the anastomotic leak, obstruction, and hospital re-admission compared with standard care in subjects with gastrointestinal surgery. Further studies are required to validate these findings. More studies are essential to confirm these outcomes. Yet, the analysis of results must be done with attention because of the low sample size of most of the selected studies found for the meta-analysis, recommending the necessity for additional studies to confirm these findings or perhaps to significantly impacts confidence in the effect assessment.

### DATA AVAILABILITY STATEMENT

The datasets examined during the present study are obtainable from the corresponding author on reasonable request.

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