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Meta-analyses

The effects of early enteral nutrition on mortality after major emergency abdominal surgery: A systematic review and meta-analysis with Trial Sequential Analysis

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SUMMARY

Background: Early oral or enteral nutrition (EEN) has been proven safe, tolerable, and beneficial in elective surgery. In emergency abdominal surgery no consensus exists regarding postoperative nutrition standard regimens. This review aimed to assess the safety and clinical outcomes of EEN compared to standard care after emergency abdominal surgery.

Methods: The review protocol was performed according to the Cochrane Handbook and reported according to PRISMA. Clinical outcomes included mortality, specific complication rates, length of stay, and serious adverse events. Risk of bias was assessed by Cochrane risk of bias tool and Downs and Black. GRADE assessment of each outcome was performed, and Trial Sequential Analysis was completed to obtain the Required Information Size (RIS) of each outcome.

Results: From a total of 4741 records screened, a total of five randomized controlled trials and two non-randomized controlled trials were included covering 1309 patients. The included studies reported no safety issues regarding the use of EEN. A significant reduction in the mortality rate of EEN compared with standard care was seen (OR 0.59 (CI 95% 0.34–1.00), $I^2 = 0\%$). Meta-analyses on sepsis and postoperative pulmonary complications showed non-significant tendencies in favor of EEN compared with standard care. GRADE assessment of all outcomes was evaluated 'low' or 'very low'. Trial Sequential Analysis revealed that all outcomes had insufficient RIS to confirm the effects of EEN.

Conclusion: EEN after major emergency surgery is correlated with reduced mortality, however, more high-quality data regarding the optimal timing and composition of nutrition are needed before final conclusions regarding the effects of EEN can be made.

1. Introduction

Postoperative management after major abdominal emergency surgery has traditionally included a decompressing nasogastric tube and avoidance of oral food or liquids until the postoperative ileus has passed due to concerns of abdominal distension, nausea, vomitus, and fear of pulmonary aspiration [1]. However, clinical trials do not support this practice and in elective surgical settings increasing awareness of the importance of initiating early enteral nutrition after surgery has been raised [2,3]. Several meta-analyses in both lower and upper elective gastrointestinal surgery have indisputably concluded that early enteral nutrition is tolerable, safe, leads to higher patient satisfaction, and shorter postoperative length of stay [4–6]. ERAS guidelines, including early initiation of oral intake after surgery, are widely adopted in elective settings and have also been proven safe, feasible, and advantageous in emergency settings [7]. The current ERAS guideline elements after elective colonic resections recommend preoperative nutritional screening and optimization, as well as postoperative early intake of oral fluids and solids [8].

Major emergency abdominal surgery is characterized by a substantial degree of postoperative morbidity and mortality [9,10] due to the underlying pathophysiology, the often septic conditions, and the surgically induced neuro-humeral stress [11]. In emergency surgical settings, preoperative nutritional optimization is obviously not applicable due to the urgent nature of the conditions and recommendations of timing, safety, and clinical consequences of early enteral nutrition (EEN) after emergency abdominal surgery remains unclear. The purpose of this review was to systematically

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assess the clinical outcomes and safety of EEN after major emergency abdominal surgery.

2. Methods

This systematic review was planned according to a prospective online protocol at Center for Open Science (DOI 10.17605/OSF.IO/RGKP5) [12] and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13]. Cochrane Handbook of Systematic Reviews was used as guidance [14].

2.1. Study eligibility criteria

We included clinical randomized and non-randomized studies according to the predefined PICO(S) (Table 1) and excluded the following study types: editorials, case reports, narrative reviews, meeting abstracts, and letter-to-editors. EEN was defined as nutrition delivered either by oral intake or by tube (nasogastric, nasoenteric, or feeding jejunostomy). No restrictions were made regarding the date of publication. We only included published studies with data available (no submitted or in press publications). We anticipated that the majority of reported clinical outcomes would be short-term or in-hospital, however, no limitations regarding the duration of follow-up were applied.

All outcomes would preferably be compared between intervention nutritional groups and standard care groups and if possible stratified by follow-up in short-term (<30 days from index surgical procedure), mid-term (30 days – six months from index surgical procedure), and long term (>six months from index surgical procedure).

2.2. Literature search, study identification, and study selection process

A systematic literature search was completed on April 6th, 2020 in MEDLINE, SCOPUS, and Embase databases adhering to the PRISMA guidelines [13]. Grey literature was supplemented via the Opengrey database [15]. The search strategy was developed in combination with a professional medical research librarian. The MEDLINE search strategy is provided (Appendix 1). We supplemented the literature search from the reference lists of the included studies as well as by citation tracking as earlier described [16]. Related narrative and systematic reviews were not included but were examined for possible relevant references.

The potentially relevant records were transferred to the online screening tool Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) [17], where duplicates were removed and title/abstract screening was conducted. For records deemed not eligible for exclusion, the full-text version was recovered and evaluated in detail. Each step of the screening and selection process was performed independently by two authors and consulted by a third author when necessary. Any differences were settled by discussion.

2.3. Data collection, data extraction, and data items

The included studies were grouped in randomized controlled trials (RCTs), confounder-controlled non-randomized trials (nRCTs) (both types eligible for quantitative analysis), and non-confounder controlled observational trials (only used narratively). No previous systematic reviews or meta-analyses have evaluated the effects on EEN after emergency abdominal surgery, so besides our predefined primary outcomes, we chose to approach the data extraction pragmatic and explorative regarding possible outcomes. We extracted study design and publication year, statistical methods, number of participants and distribution between nutritional groups, patient demographics, surgical procedures and perioperative data (the type of surgical procedure, the condition leading to surgery), type of postoperative nutrition method (timing of nutrition onset, type of nutrition), clinical outcomes and events, and risk of bias.

2.4. Assessment of methodological risk of bias

For evaluating study-level bias in the included RCTs the Cochrane risk of bias tool for randomized studies was used [14]. This evaluates studies using seven parameters and results in an evaluation for each study as *high risk*, *low risk*, or *unclear risk of bias*. For evaluating study-level bias in the included nRCTs the modified Downs and Black checklist was used, as recommended by the Cochrane non-randomized studies method group [18]. The Downs and Black checklist consists of 27 items, which covers the sections *study quality*, *external validity*, *study bias*, *confounding and selection bias*, and *study power* with a maximal score of 25 for non-randomized studies. The checklist has proven valid and reproducible among

Table 1
Participants, intervention, comparison, outcome, and study types for the included articles.

Participants (P) of interest
Adults (age 15 or higher) of both sexes undergoing major emergency abdominal surgery
Intervention (I) of interest
Early postoperative enteral nutrition or early postoperative oral nutrition as defined by study authors administered orally or via nasogastric or nasoenteric tube, or by feeding jejunostomy The timeline of early nutritional intervention was applied as defined by study authors, however, studies with onset of nutritional intervention more than 72 h after the surgical procedure were not included
Comparison (C) of interest
Standard postoperative nutritional care as defined by study authors
Outcome (O) of interest
Postoperative mortality rate Postoperative complications including overall complication rate, specific infectious complications if reported, and preferably a grading of complications by a validated complication rating system Postoperative length of stay (number of days from index surgical procedure to discharge) Adverse effects of early enteral or peroral nutrition defined as complications directly correlating to early enteral or oral nutrition
Study types (S) of interest
Clinically controlled (randomized or non-randomized) studies and prospective/retrospective observational studies published in English

reviewers [19]. The Downs and Black score were given corresponding graduation levels: *excellent* (*score 24–25*), *good* (*score 19–23*), *moderate* (*score 15–18*), *poor* (*score ≤ 14*) [20]. Justification and results of the two risk of bias tools are presented in the supplemental appendices. Risk of bias assessments were discussed until consensus and consulted by a third author when necessary.

2.5. Measures of treatment effect, heterogeneity assessment and data synthesis

All outcomes were summarized narratively, and quantitative meta-analysis of each clinical outcome was planned when studies were evaluated homogenous and at least three studies assessed an outcome. It was not considered a prerequisite that a specific clinical outcome variable was the primary outcome of the included studies. We extracted the raw data where it was not possible to extract relevant adjusted relative effects (hazard ratio, relative risk, odds ratio). Differences from included studies were considered significant at $p < 0.05$ unless otherwise stated. Meta-analyses are presented by Forest plots.

Data were entered in Review Manager v.5.3 statistical software (Nordic Cochrane Collaboration) [21]. The DerSimonian-Laird random-effects model was applied on all meta-analysis outcomes since variation due to coincidence as well as considerable clinical diversity between the studies was expected [22].

All included studies were evaluated for methodological heterogeneity (risk of bias) and clinical heterogeneity (e.g. variability in pathophysiology leading to surgery, different surgical procedures and techniques, interventional nutrition regimens, etc.) before calculation of statistical heterogeneity. Clinically acceptable homogenous studies were evaluated for between-study heterogeneity in meta-analysis by performing inconsistency I [2] statistics. Based on the I [2] statistics value, we classified heterogeneity as *low (0–25%)*, *moderate (26–50%)*, *high (51–75%)*, or *very high (>75%)*, respectively [23].

The following criteria for including non-randomized studies in quantitative synthesis were used: 1) reasonably resistant to bias (Downs and Black score ≥ 14), 2) homogenous with the RCTs regarding setup (population, intervention, comparison, outcome) and confounder control, and 3) matching of intervention and control group by relevant demographic parameters.

2.6. Assessment of quality of body of evidence

We included a between-study quality evaluation of the performed meta-analyses by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach via the GRADEpro application (GRADEpro GDT: GRADEpro Guideline Development Tool [Software], McMaster University, 2015) and by the GRADE handbook [24]. The GRADE tool uses downgrading and upgrading factors on the quality of the outcome measurements. The downgrading factors were risk of bias (compiled Downs and Black score < 14), inconsistency (statistical heterogeneity measured by the I [2] statistics), indirectness, imprecision of the effect estimate (including evaluation of Required Information Size (RIS) (see below)), and publication bias (evaluated from the funnel plot). The upgrading factors are large effect estimates (RR > 2), confounding changes of the effect estimate that lowers the effect estimate, and occurrence of a dose–response gradient.

The GRADE tool then assesses each outcome variable to be a *very low*, *low*, *moderate*, or *high quality* outcome. Observational studies by definition initiate as low-quality due to inherent risk of bias and lack of confounder distribution between the groups.

2.7. Trial Sequential Analysis

Trial Sequential Analysis (TSA) was used to adjust for the risk of concluding based on random error, spurious overestimations (type I errors), or underestimations (type II errors) [25]. TSA provides an imprecision assessment in the GRADE system as well as the possibility to calculate the heterogeneity-adjusted required information size (RIS), which is defined as the required number of participants or events necessary in a meta-analysis to detect or reject an a priori assumed intervention effect [26,27].

The RIS was calculated by the DerSimonian-Laird TSA random-effects model. We applied the proportion rates of the standard care group for each outcome, the heterogeneity (I [2]) estimate from each meta-analysis, the assumption of a relative risk reduction of the EEN intervention effect of 20% [5,28], the assumptions of an overall type-I error of 5%, and power of 80%. Each trial was sequentially added in the TSA by publication year, which provides a timewise series of points that forms the basis of the cumulative analysis. The Lan-DeMets trial sequential monitoring boundaries based on O'Brien-Fleming alpha-spending function were applied [29], which is used to determine whether an estimated effect is convincingly large (or small) such as the conclusions are unlikely to change with more evidence. The cumulative Z-curve based on the positive or negative effect finding from each consecutive study in the meta-analysis was plotted against the monitoring boundaries. An example of a detailed interpretation of a TSA plot are explained in Fig. 3b. The concepts behind TSA and statistical rationale have earlier been described [26,30]. We used the TSA software vs.0.9.5.10.beta (www.ctu.dk/tsa) for calculations.

3. Results

The literature search yielded a total of 4778 records. Of these, a total of 145 studies were read in full-text and assessed for eligibility. Six studies were included in the review covering a total of 1309 included patients (57% males). From the reference lists of the included studies, 173 additional studies were screened against title- and abstract. 22 studies were read in full-text and assessed for eligibility. None of these were found eligible for inclusion and a total of six studies were included (Fig. 1).

Of the six studies [32–37], one study was a confounder-controlled propensity-matched cohort study [32], one study was a retrospective cohort study [33], while the remaining four studies were randomized controlled trials (RCT) [34–37]. Included studies were published from the year 1998 [36] to 2014 [32] and originating from India [34,36,37], Argentine [35], and South Korea [32,33]. A total of 491 patients were in EEN groups while 818 patients were in standard care groups. The most frequently reported outcome variable was overall number of complications, and post-operative mortality (Table 2).

Authors from a total of six studies were contacted regarding data from mixed elective/emergency populations, however without response. Meta-regression and Forest was not possible due to the limited number of included studies (<10).

3.1. Characteristics, quality and risk of bias in the included studies

The Downs and Black score for the two non-randomized studies were 19 [31] and 15 [32] corresponding to '*moderate risk of bias*'

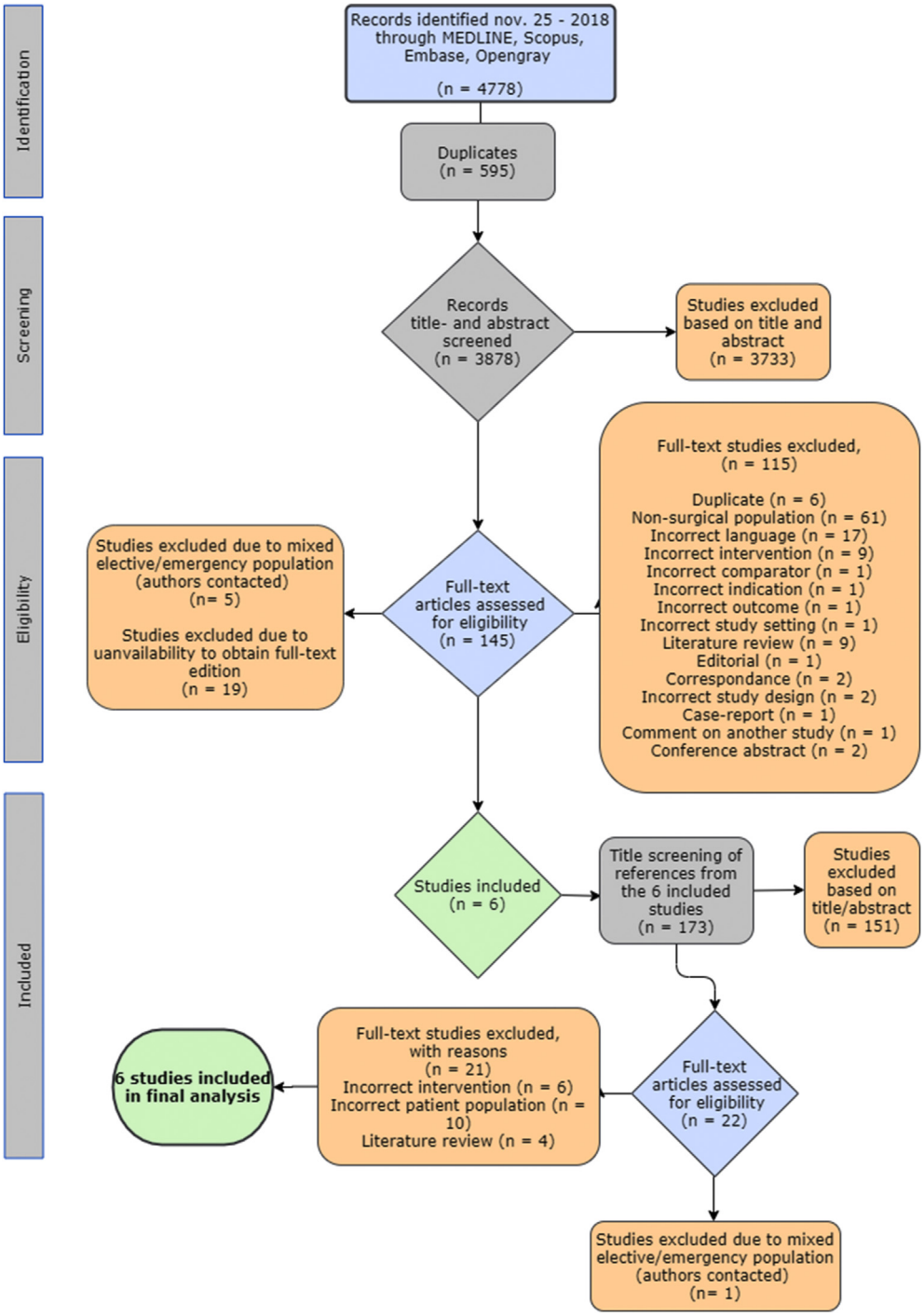

Fig. 1. PRISMA flow diagram. A literature search was performed in MEDLINE, Embase, SCOPUS, and Opengray databases. After removing duplicates and after screening of title and abstracts a total of 145 articles were read in full-text and of those were six studies included in the systematic review.

(Appendix 3). The four RCTs differed in the risk of bias, and there was a general issue with blinding of patients, blinding of personnel, and blinding of outcome assessment (Appendix A3).

3.2. Interventions and co-interventions

According to the inclusion criteria of the review, all patients in the EEN groups received nutrition earlier than the patients in the control groups. Timewise, this intervention varied between soft or liquid oral intake, and the administration route differed by oral intake, nasogastric tube, nasoenteric tube, or feeding jejunostomy. In the included studies, the timing of EEN was started on post-operative day (POD) 1 or earlier in three of six studies [33–35], and within 48 h after surgery at the latest in the remaining three studies [31,32,36]. All studies described EEN compared to standard care, however, with variations between the setups

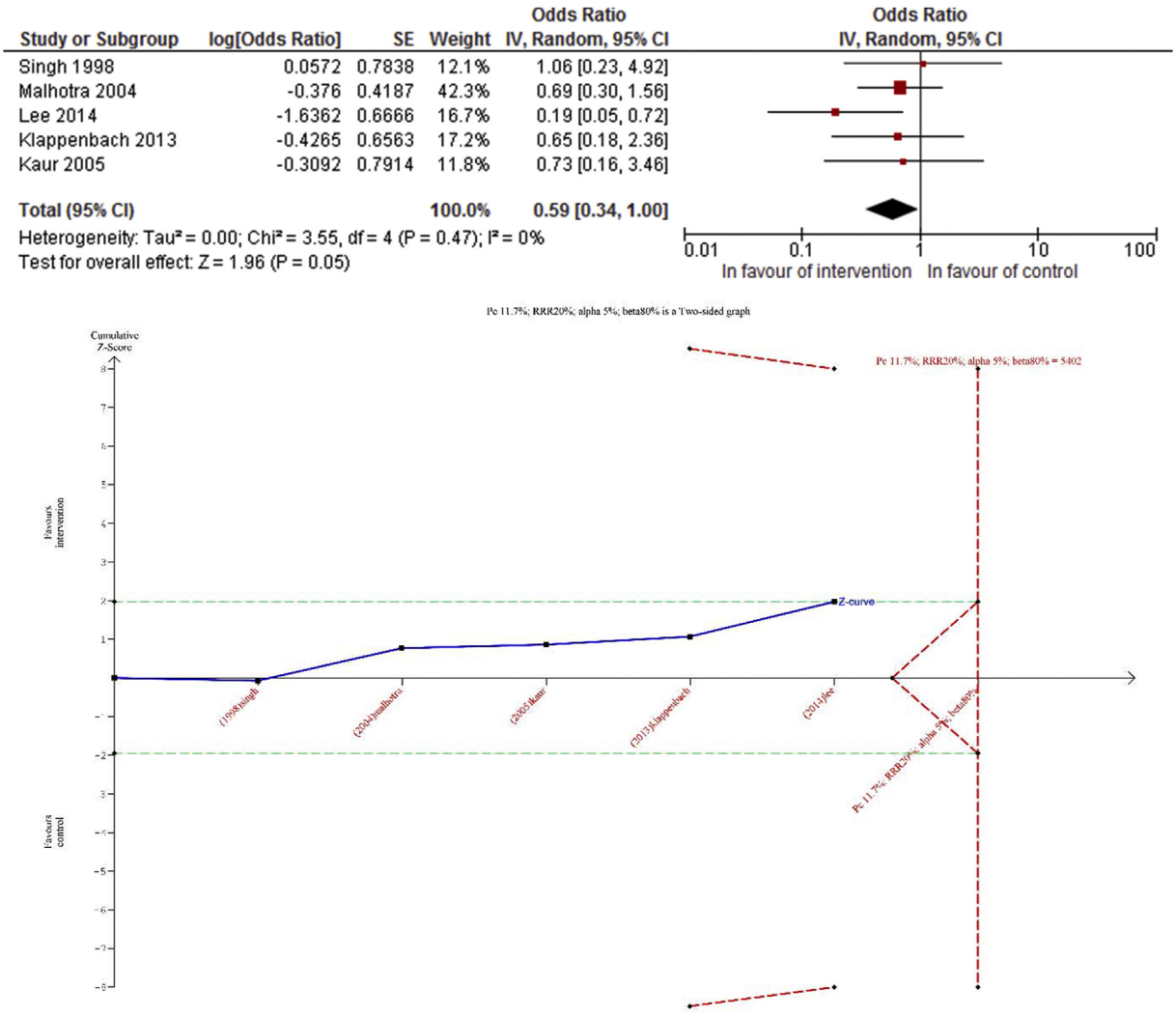

Fig. 2. Meta-analysis of early enteral nutrition (EEN) compared to standard care on mortality (A) and Trial Sequential Analysis (B). **A:** Meta-analysis of the effect of early enteral nutrition (EEN) compared to standard care on mortality after emergency abdominal surgery. **B:** Trial Sequential Analysis (TSA) plot for all-cause mortality. The TSA was based on five trials, which is the meta-analysed effect of early enteral nutrition (EEN) versus standard care on risk of mortality (Fig. 3). The TSA parameters were the proportion rate in the control group of 11.7%, an assumed relative risk reduction of 20%, heterogeneity (I [2]) of 0%, alpha 5%, and beta 80%. The y-axis indicates favor of either benefit of EEN (positive direction) or harm of EEN (negative direction). The blue cumulative z-curve was constructed using a DerSimonian-Laird random-effects model and the studies were depicted in consecutive order by publication year. The horizontal green dotted lines represent the conventional boundaries for benefit or harm according to $p = 0.05$. The red dotted lines represent the trial sequential boundaries for benefit (positive), harm (negative), or futility (middle triangular area). A total of 736 patients were included in the analysis and a total of 5402 patients were needed in order to obtain the Required Information Size (RIS). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

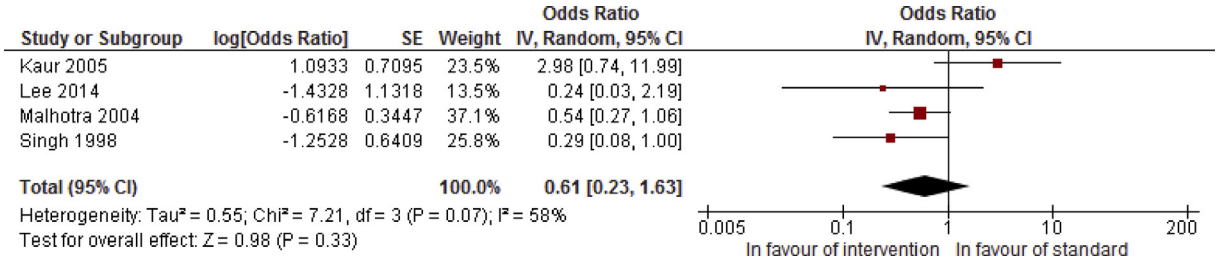

Fig. 3. Meta-analysis of the effect of early enteral nutrition (EEN) compared to standard care on development of sepsis after emergency abdominal surgery.

(Appendix 2). In the standard care groups, the majority of studies awaited bowel function until oral intake. Stratifying outcomes in short-term, mid-term, and long-term was not possible. The demographic details of the included studies are shown in Appendix 2. It is noted that the median age of the patients in the included studies originating from India and Argentine [33–36] was very low, which could point towards differences in study-design and health-care setup.

Table 2
Distribution of outcomes between the included studies.

	Number of complications	Sepsis	Pulmonary complications	Wound dehiscence	Lenght of stay	ICU	Mortality
Lee (2014) [33]		+	+	+			+
Lee (2014) [34]							
Kaur (2005) [35]		+	+				+
Klappenbach (2013) [36]			+				+
Singh (1998) [37]		+	+	+			+
Malhotra (2004) [38]		+	+	+			+

Grey: indicates outcome not reported.

Blue: indicates outcome is reported.

+ indicates study included in relevant meta-analysis.

3.3. The effect of EEN on mortality

Mortality was reported in all six studies, hereof four RCTs [33–36], one confounder-controlled propensity-matched cohort study [31], and one retrospective observational study [32] including a total of 1247 patients. Timing from surgery to mortality was not specified further. The single study that did not meet the criteria for meta-analysis [32], rather unlikely found zero mortality rates in both EEN and standard care groups.

The meta-analysis on the remaining five studies [31,33–36] included 736 patients (369 in EEN groups, 367 in control groups) and found a reduction in mortality in EEN (26/369 (7%)) compared with the standard care (43/367 (11.7%)) (OR 0.59 (CI 95% 0.34–1.00), I^2 = 0%) (Fig. 2A). TSA revealed a RIS of 5402 meaning that 13.6% of the required data was included and that further 4666 patients should be included before the RIS would be obtained (OR 0.59 TSA-adjusted CI 95% (0.07–5.17)) (Fig. 2B). The body of evidence was assessed "low" by GRADE due to serious

Table 3
Summary of findings of meta-analysis outcomes.

Summary of findings					
Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects[e]	
				Risk with standard postoperative nutritional care	Risk difference with early postoperative peroral or enteral nutrition
Mortality	736 (5 RCTs) [33,36,37,39,41][a]	⊕⊕◯◯ LOW[b,c]	**OR 0.59** (0.34–1.00)	117 per 1.000	**45 fewer per 1.000** (74 fewer to 0 fewer)
Postoperative sepsis	441 (4 RCTs) [33,37,39,41],[a]	⊕◯◯◯ VERY LOW[b,c,d]	**OR 0.61** (0.23–1.63)	232 per 1.000	**76 fewer per 1.000** (167 fewer to 98 more)
Postoperative pulmonary complications	441 (4 RCTs) [33,37,39,41],[a]	⊕◯◯◯ VERY LOW[b,c,d]	**OR 0.54** (0.23–1.25)	273 per 1.000	**104 fewer per 1.000** (193 fewer to 46 more)
Wound dehiscence	341 (3 RCTs) [33,37,39],[a]	⊕⊕◯◯ LOW[b,c]	**OR 0.70** (0.33–1.51)	106 per 1.000	**29 fewer per 1.000** (68 fewer to 46 more)

GRADE evidence assessments.
- *High certainty:* We are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate certainty:* We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low certainty:* Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- *Very low certainty:* We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] The included studies consist of randomized controlled trials and one propensity matched cohort study.
[b] Risk of bias due to unclear risks of allocation concealment and lack of blinding of outcomes assessment. Furthermore, risk of bias due to non-blinding of personnel or patients.
[c] The Required Information Size (RIS) of the outcome was not met.
[d] Confidence intervals of the meta-analysis showed minimal overlap, test for heterogeneity was significant, and the I^2 (%) value of the meta-analysis was considered high.
[e] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio.

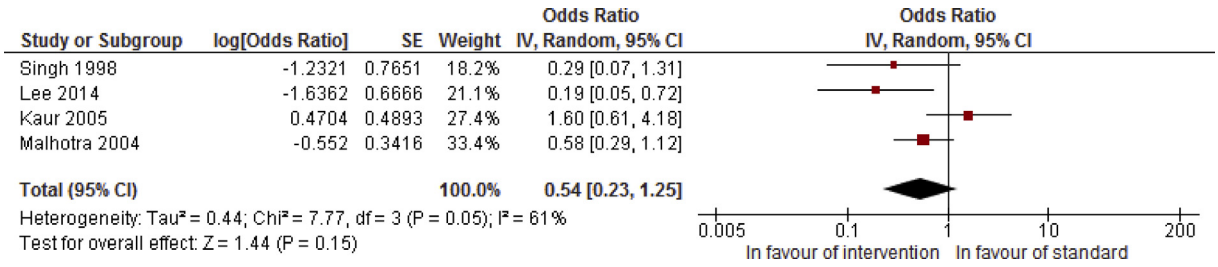

Fig. 4. Meta-analysis of the effect of early enteral nutrition (EEN) compared to standard care on development of postoperative pulmonary complications after emergency abdominal surgery.

risk of bias and imprecision down-grade due to lack of achieved RIS (Table 3).

3.4. The effect of EEN on postoperative complication rate

All six studies reported data on the overall complication rate [31–36], however, it was chosen not to perform a meta-analysis on the overall complication rate since the reporting of overall complications between the groups and the specific distribution of complications between the groups were insufficiently reported. Data regarding postoperative development of sepsis, development of postoperative pulmonary complications (PPCs), and fascial dehiscence were extractable from the included studies, why meta-analyses were performed on these three outcomes. Five studies [31–34,36] found a reduced overall complication rate and major complication rate in favor of EEN compared to standard care. One study found no difference in complication rates between the groups [35].

Five studies evaluated postoperative development of sepsis [31–33,35,36], of which four studies [31,33,35,37] were included into a meta-analysis including 440 patients, which found a tendency towards lower sepsis rate in the EEN group (36/221 (16.3%)) compared to the standard care group (51/220 (23.2%)), but did not obtain significance (OR 0.61 (CI 95% 0.23–1.63), $I^2 = 58\%$) (Fig. 3). TSA analysis revealed that only 7.7% (440/5704) of RIS was obtained (OR 0.61 TSA-adjusted CI 95% 0.23–1.63). The body of evidence was by GRADE determined "very low" due to downgrading by the risk of bias, inconsistency, and imprecision (Table 3).

Five studies evaluated postoperative pulmonary complications (PPC) [31–33,35,36], and four studies were included into a meta-analysis including 441 patients, which found a tendency towards lower rate of postoperative pulmonary complications in the EEN group (40/221 (18.1%)) compared to the standard care group (60/220 (27.3%)), however without obtaining significance (OR 0.54 (CI 95% 0.23–1.25), $I^2 = 61\%$) (Fig. 4). TSA analysis revealed that 7.2% (441/6104) of RIS was accrued in the analysis (OR 0.54 TSA adjusted 95% CI (0.23–1.25)). The body of evidence was by GRADE determined "very low" (Table 3).

Four studies evaluated postoperative wound dehiscence [31–33,35], hereof three studies including 341 patients could enter a meta-analysis, which found a tendency towards a lower wound dehiscence rate in the EEN group (13/171 (7.6%)) compared to the standard care group (18/170 (10.6%)), however without obtaining significance (OR 0.70 (CI 95% 0.33–1.51), $I^2 = 0\%$) (Fig. 5). TSA on the three included studies revealed that 5.6% (341/6029) of RIS was accrued in the analysis (OR 0.70 TSA adjusted CI 95% (0.33–1.47)). The body of evidence was by GRADE determined "low" (Table 3).

3.5. The effect of early enteral or peroral nutrition on postoperative length of stay (LOS) and ICU admission

A total of five studies including a total of 797 patients described postoperative LOS [31–34,36]. It was not possible to perform a meta-analysis as the results were presented heterogeneously in the included studies, however, all of the studies reported shorter LOS favoring EEN compared to the standard care group.

Postoperative ICU admission and the duration of ICU admission did not point in a clear direction when stratified by EEN. One nRCT reported that ICU admission was higher in the EEN group (30/44 (68%)) vs. the standard care group (23/40 (57.5%)) [32], one study found that the mean ICU stay was shorter in the EEN group (1.6 days) than standard care group (2.1 days) [36], while the last study found that the EEN group had more ICU free postoperative days (27 days) vs. standard care group (25 days) [31].

3.6. Safety of EEN

All of the included studies concluded that EEN was reported feasible and safe despite that none of the studies were designed to evaluate the safety of EEN. Two studies reported non-significant higher rates of minor complications in the EEN group such as abdominal distension, vomiting, and diarrhea [35,36]. One of the included studies [33] found that the rate of postoperative pulmonary event was higher in the EEN group (17 vs. 14), and attributed this to esophageal tubes, which could impair coughing.

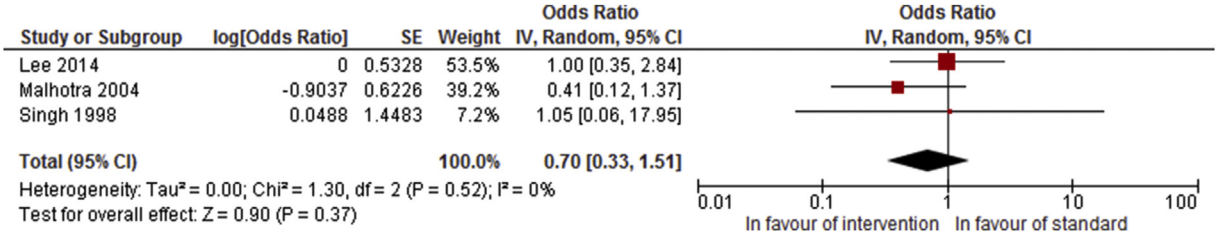

Fig. 5. Meta-analysis of the effect of early enteral nutrition (EEN) compared to standard care on development of wound dehiscence after emergency abdominal surgery.

4. Discussion

In this systematic review, we found that early oral or enteral nutrition (EEN) after major emergency abdominal surgery was associated with a lower mortality rate compared to standard care. Furthermore, we found non-significant tendencies in favor of EEN towards a lower overall complication rate, a lower sepsis rate, a lower rate of postoperative pulmonary complications, and a lower rate of wound dehiscence compared to patients receiving standard care. However, Trial Sequential Analysis on all outcomes revealed that the required information sizes were not obtained, thus final conclusions cannot be drawn regarding the true positive or negative effects of EEN after major emergency abdominal surgery. EEN was not reported to be associated with serious adverse effects.

The effects of EEN on mortality has been examined in other settings than in major emergency abdominal surgery. In critically ill ICU patients, randomized multicenter trials investigating the effect of EEN vs. early parenteral nutrition did not find any correlation with mortality [37,38]. This finding was confirmed in a subsequent Cochrane review [39]. However, in a sub-group, the in-ICU mortality was significantly reduced in patients treated with EEN whereas overall hospital-mortality remained unchanged [40]. In patients with severe acute pancreatitis, a recent meta-analysis including ten randomized trials found that EEN vs. delayed onset of nutrition resulted in significantly reduced multiorgan failure and mortality in the EEN group [41]. Severe pancreatitis is characterized by a massive inflammation in high-risk patients with potential frailty and malnutrition [42], which can be a possible explanation as to why a larger effect of EEN is seen in this group compared to other clinical conditions. A lower mortality rate has also been observed in sarcopenic patients admitted with sepsis who were treated with EEN [43]. The studies included in this review did not provide frailty scores or sarcopenia evaluations on the included patients, however from other similar cohorts of patients undergoing major emergency abdominals surgery we know that up to 35% are sarcopenic [44,45]. This could be an explanation why we, in this group of high-risk emergency surgical patients, found an effect of EEN compared with standard care (OR 0.59 (CI 95% 0.34–1.00), $I^2 = 0\%$) (Fig. 2A). Furthermore, as with severe pancreatitis, high-risk emergency surgery is characterized by a massive neurohumeral response followed by an inflammatory response [46,47]. These responses are the results of sympathetic nervous activation, cell damage, and physical intraabdominal manipulation [48], which due to activation of inhibitory adrenergic nerves leads to intestinal hypo-motility (postoperative ileus) and compromised intestinal barrier [49]. The systemic manifestations of this include increased risk of pulmonary events due to neutrophil migration from the intravascular space to pulmonary alveoli [50], as well as increased risk of kidney and liver damage due to oxidative stress [51]. A possible pathophysiological explanation of the positive effects of EEN after emergency surgery is the reduction of this postoperative inflammatory phase. EEN stimulates intestinal contractility, the release of exocrine substances from the pancreas and liver, and initiates numerous endocrine and immune changes [50].

The majority of the included studies used peroral, nasogastric, or nasoenteric administrating routes where one study exclusively used postoperative feeding jejunostomy (Appendix 2). Traditionally, there have been hesitations regarding EEN due to concerns regarding the risk of complications such as small bowel ischemia and aspiration [51–53]. However, increasing evidence from ERAS programs in elective upper and lower gastrointestinal surgery [5,6,27], colorectal surgery [2,4,54], and gynecologic surgery [55] points towards safety and good patient tolerance of EEN with reduced duration of postoperative ileus and a reduction in postoperative length of stay. It should be noted that even though the included studies used different nutrition administrating routes, and that different safety aspects apply to each of these techniques, none of the studies reported serious adverse events.

This study is limited in several ways. Only a small number of studies could be included and the study failed in obtaining the RIS in all investigated outcomes. Thus, our possibilities are reduced regarding rejection or confirmation of the advantageous hypotheses of EEN after emergency abdominal surgery. Several of the studies were performed in non-western populations from India [33,35,36], Argentine [34], and South Korea [31,32], which may reduce the transferability of the findings to daily clinical practice in western populations and health care systems as patients could present with other medical challenges than are typically met in western hospitals. The populations from the included studies had very low median age and were thus somewhat incomparable with similar western-based cohorts regarding age [8,9]. Furthermore, there are a possible risk of population-overlap between two of the included studies [31,32]. All included studies had issues with bias. Throughout the studies, a mix of administration routes ranging from oral intake, over nasogastric tubes to feeding jejunostomies was seen, which increases the heterogeneity. All of the included studies reported that EEN was safe to use in emergency surgical settings despite that none of the studies were designed to evaluate the safety aspects of EEN. The strengths of this study include prospectively published protocol, the rigorous use of methodology, validated risk of bias evaluation tools, and GRADE assessed body of evidence. Furthermore, we used Trial Sequential Analysis to supplement the imprecision judgments [53], rather than just using GRADE thereby reducing the risk of false-positive or negative conclusions based on type-II errors in our meta-analyses [56].

5. Conclusion

This systematic review found sparse and heterogenous literature, however found a reduced mortality after major emergency abdominal surgery when administering early enteral or oral nutrition (EEN) compared to standard care. Tendencies towards lower overall complication rates and shorter length of stay in favor of early enteral or oral nutrition compared to standard care were also found. However, the required information sizes were not reached and given the potential to influence important clinical outcomes by the use of EEN, further well-designed and adequately powered randomized clinical trials investigating the optimal timing and nutritional composition after emergency surgery are much needed.

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Conflicts of interest

No conflicts of interest exist for any of the authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.02.050.

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