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UROLOGY - REVIEW

Total parenteral nutrition versus early enteral nutrition after cystectomy: a meta-analysis of postoperative outcomes

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Abstract

Background This study aimed to systematically summarize and analyze the current evidence regarding the effect of total parenteral nutrition (TPN) versus early enteral nutrition (EEN) on postoperative outcomes of cystectomy.

Methods A comprehensive search of online databases was conducted to identify comparative studies on the postoperative outcomes of patients receiving TPN and EEN after cystectomy. Our subsequent meta-analysis followed the PRISMA Protocol and the Cochrane Handbook.

Results Five studies with 556 participants were included for meta-analysis. EEN was shown to have a significant effect on reducing the overall complications (odds ratio (OR) 0.52, 95% confidence interval (CI) 0.37–0.75, $P<0.01$) and infectious complications (OR 0.32, 95% CI 0.21–0.49, $P<0.01$) compared with TPN. Additionally, EEN saved €614–€3120 in costs compared to TPN. There were no significant differences between TPN and EEN groups regarding mortality rate (OR 0.47, 95% CI 0.06–3.51, $P=0.46$), the incidence of postoperative ileus (OR 0.90, 95% CI 0.55–1.47, $P=0.68$), length of hospital stay (mean difference (MD) 2.12, 95% CI −0.15 to 4.40, $P=0.07$), or time to resume a full diet (MD 1.31, 95% CI −1.15 to 3.77, $P=0.30$).

Conclusion EEN was found to have a significant effect on reducing infectious complications and costs compared with TPN treatment after cystectomy. Remarkably, EEN had no significant impact on mortality incidence, postoperative ileus, length of hospital stay, or the time to resumption of full diet.

Keywords Cystectomy · Parenteral nutrition · Enteral nutrition · Meta-analysis

Background

Radical cystectomy followed by urinary diversion remains the gold standard for treatment of localized muscle-invasive bladder cancer. However, radical cystectomy is an extensive surgical procedure associated with overall complication rates of 26–78% and mortality rates of 1.0–4.0% [1, 2]. Protein depletion as a sign of postoperative catabolism that rapidly appears after cystectomy, and total parenteral nutrition (TPN) is often part of postoperative routine care irrespective of pre- or post-malnutrition status [3]. A significant benefit to the use of TPN has not been demonstrated, and TPN potentially is associated with immune system impairment, high blood glucose, intestinal mucosal atrophy, and catheter-related bloodstream infections [4, 5].

Early enteral nutrition (EEN) by oral intake or enteral feeding with a nasojejunal tube has proved to be safe and effective as part of gastrointestinal surgery recovery in several meta-analyses, and has gained wide acceptance due to

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the avoidance of infections through the catheter, intestinal mucosal integrity protection, and lower costs [6–8]. However, these lines of evidence for gastrointestinal surgery may not be directly applicable to radical cystectomy because of the need for a urinary diversion, ureteroenteric anastomosis, and large pelvic dissection in this type of surgery [9]. The aim of this study was to summarize and analyze the current data regarding the impact of TPN versus EEN on postoperative outcomes after cystectomy.

Methods

The protocol of this meta-analysis was registered in advance at the International Prospective Register of Ongoing Systematic Reviews (registration number: CRD42018093901) [10]. The protocol followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) 2015 checklist and the Cochrane Handbook [11].

Objective

This systematic review and meta-analysis aimed to determine the effect of TPN versus EEN on postoperative outcomes of cystectomy, thus supporting evidence-based clinical decision-making about nutritional support. The primary outcomes of this study were incidence of perioperative mortality, overall complications, infectious complications, and postoperative ileus (POI). The secondary outcomes included length of hospital stay (LOS) after cystectomy, time needed to resume a full diet after cystectomy and economic cost.

Data source and search strategy

A comprehensive literature search was performed on October 2018 to identify randomized controlled trials (RCTs) and observational studies comparing the postoperative outcomes of patients receiving TPN and EEN after cystectomy. PubMed, EMBASE, LILACS, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched using the strategy outlined in Supplementary Table S1. No limits were applied regarding publishing language and conference abstracts as well as reference lists of relevant studies were also searched for additional candidate articles.

Inclusion and exclusion criteria

Two members (SXZ, YPX) independently assessed the eligibility of candidate articles for inclusion. Included studies met the following criteria: (a) studies comparing TPN and EEN after cystectomy, (b) indications for cystectomy could be oncological or non-oncological diseases, (c) cystectomy with different types of urinary diversions (ileal conduit, Indiana pouch, orthotopic ileal neobladder, ureterocutaneostomy) were available, (d) at least one of the main outcomes mentioned previously. Case reports, reviews, and duplicate publications were excluded. Disagreements about whether an article should be included was resolved by discussion with a third reviewer (JJZ).

Data collection and data extraction

Two members (SXZ, JJZ) independently extracted data and assessed the quality of presented evidence. Data were extracted to fill pre-designed forms containing the following items: first author, publication date, country, study design, patient clinicopathological characteristics, details of TPN and EEN regimen, as well as postoperative outcomes of interest. The level of evidence in the included studies was rated according to the criteria provided by the Oxford Centre for Evidence-Based Medicine guidelines [12]. Means and standard deviations were calculated using the method described by Wan et al. [13] when studies presented continuous data with median and range or interquartile range. For studies that only reported means and p-values, the standard deviation was calculated using the method described by the Cochrane handbook [11]. The methodological quality of the included retrospective and prospective non-randomized case–control studies were assessed using the Newcastle–Ottawa Scale [14], and prospective RCTs were assessed by the Jadad Scale [15].

Data synthesis and analysis

Statistical analysis was performed following the principles of the Cochrane Handbook for Systematic Reviews of Interventions. Additionally, Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) was used for meta-analysis. Heterogeneity among the included studies was assessed using Cochran Q and inconsistency index (I^2) statistics [16]. I^2 values > 50% were considered to represent substantial heterogeneity. Pooled estimates were calculated by employing a fixed-effect model for $I^2 \leq 50\%$, and a random-effect model for $I^2 > 50\%$. As stated in our protocol, publication bias was assessed by visual inspection of asymmetry with Begg's funnel plot if more than ten studies were included for a particular outcome [10, 11]. Sensitivity analysis was performed by restricting the analysis to studies with low risk of bias. $P < 0.05$ was considered statistically significant.

Results

The flow of literature through the assessment process is shown in Fig. 1. There were 429 articles identified without duplication by comprehensive electronic databases search.

Finally, five studies published between 2011 and 2015, which enrolled a total of 556 participants, were assessed as suitable for inclusion in this analysis. This sample comprised of two prospective RCTs, and three retrospective case–control studies [4, 17–20]. The characteristics of included studies are summarized in Table 1.

Primary outcomes

Perioperative mortality data were provided in three studies; however, overall analysis revealed no difference in mortality between patients in the EEN and TPN groups (Fig. 2a, 1.28% versus 0.56%, OR 0.47, 95% CI 0.06–3.51, $P=0.46$, $I^2=0\%$).

Overall complication rate was reported in all included studies. As shown in Fig. 2b, EEN was associated with a significant decrease in the incidence of overall complications compared with TPN (44.61% vs. 56.45%, OR 0.52, 95% CI 0.37–0.75, $P<0.01$, $I^2=35\%$).

Infectious complication rate was assessed in all included studies. The incidence of infectious complication was significant lower in the EEN group, in which 16.36% of patients had infectious complications compared to 33.80% of patients in the TPN group (Fig. 2c, OR 0.32, 95% CI 0.21–0.49, $P<0.01$, $I^2=42\%$).

While data regarding POI were available in four studies, there was no statistically significant difference between the groups regarding the incidence of POI (Fig. 2d, 15.38% vs. 14.40%, OR 0.90, 95% CI 0.55–1.47, $P=0.68$, $I^2=34\%$).

Secondary outcomes

Length of hospital stay was reported in four studies. Pooled results revealed no statistically significant difference

Fig. 1 PRISMA flow diagram

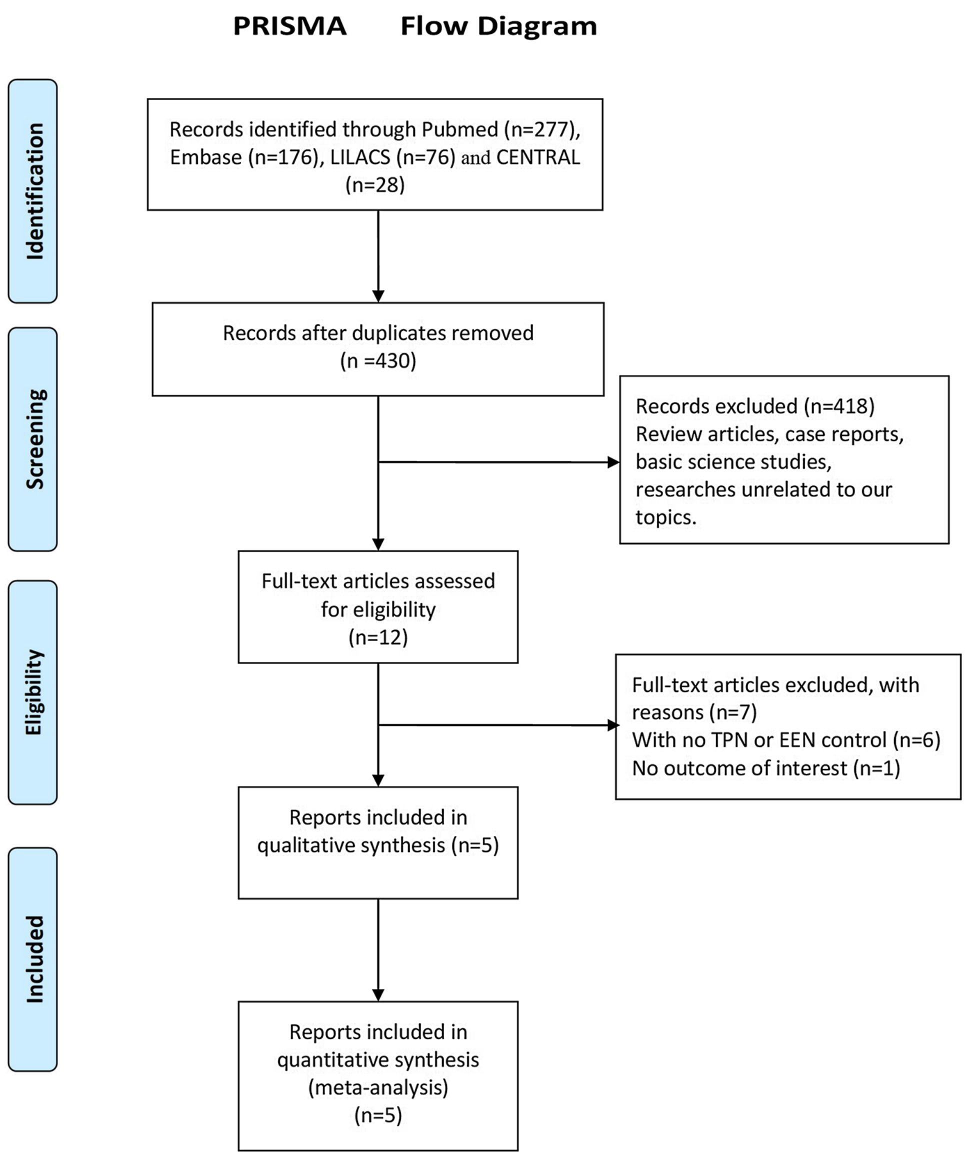

Table 1 Characteristics of included studies

Study	Country	Study period	Study design	No. of patients		LE[a]	Quality
				TPN	EEN		
Maccagnano et al. [17]	Italy	Not available	Prospective, randomized	27	19	3b	1[c]
Roth et al. [4]	Switzerland	2008.09–2011.03	Prospective, randomized	74	83	2b	2[c]
de Vries et al. [19]	Netherlands	2007.06–2008.11	Retrospective	34	51	3b	6[b]
Pham et al. [20]	USA	2002.02–2010.06	Retrospective	104	70	3b	7[b]
Declercq et al. [18]	Belgium	2009.02–2011.10	Prospective, non-randomized	48	46	3b	8[b]

[a]Using criteria provided by the Oxford Centre for Evidence-based Medicine

[b]Using Newcastle–Ottawa Scale for Cohort Study (score from 0 to 9)

[c]Using Jadad scale (score from 0 to 5)

between the treatment groups in terms of length of hospital stay (Fig. 3a, mean difference (MD) 2.12, 95% CI −0.15 to 4.40, $P=0.07$, $I^2=83\%$). However, these results should be interpreted with caution given the high heterogeneity of this estimate ($I^2=83\%$).

Resumption of a full diet after cystectomy was assessed in three studies, and no significant difference was observed between treatment groups (Fig. 3b, MD 1.31, 95% CI −1.15–3.77, $P=0.30$, $I^2=96\%$). In a case of high heterogeneity ($I^2=95\%$), an outlier study by Declercq et al. [18] was identified and overall heterogeneity decreased after removal of this study ($I^2=0\%$). There was also no significant difference in pooled estimates after removal of this study (MD 0.08, 95% CI −0.53 to 0.69, $P=0.80$, $I^2=0\%$).

Economic cost of TPN and EEN was analyzed in two studies, but these data were unable to be pooled. Specifically, Roth et al. [4] reported that costs of TPN were €614 higher per patient. Declercq et al. [18] revealed that EEN group saved €512 per patients compared with TPN group for parenteral nutritional bags, and saved another €2608 by reducing hospital stays by 4 days.

Publication bias and sensitivity analysis

The publication bias was not assessed due the fact that less than ten studies were included for any of primary outcomes. We performed sensitivity analysis for primary outcomes in which we included only the study by Roth et al. [4] with a low risk of bias, this showed that the results were stable (data not shown).

Discussion

The present meta-analysis focused on TPN versus EEN following cystectomy and indicated that TPN had a significant impact on minimizing overall postoperative complications, especially infectious complications. Nevertheless, no significant difference was found between TPN and EEN treatment groups after cystectomy in terms of the incidence of mortality, POI, LOS, and time to resumption of full diet.

According to the spectrum of previous meta-analyses that focused on TPN versus EEN for gastrointestinal surgery or critically ill patients, the benefit of EEN on reducing the incidence of infectious complications was universal. Mazaki and Ebisawa [8] showed that EEN was beneficial in the reduction of complications (relative risk (RR) 0.85; $P=0.04$) and infectious complications (RR 0.69; $P=0.001$) after gastrointestinal surgery compared with TPN, while no significant difference in mortality was observed. Peter et al. [7] reported that EEN was associated with a decrease in both infectious and non-infectious complications in hospitalized patients compared with TPN, but no effect on mortality was demonstrated with EEN. However, in terms of intra-abdominal infection, Zhao et al. [6] found no significant difference between patients treated with TPN and EEN after major abdominal surgery (OR 0.78; $P=0.228$).

Possible reasons for such adverse effects with TPN in terms of infections are multiple. Firstly, TPN increases the risk of bacteremia and catheter-related bloodstream infections [5, 20]. TPN may also cause dysfunction of B and T lymphocytes, macrophages, and neutrophils, and may also result in more proinflammatory cytokines production that are less supportive of the immune system [5]. Additionally, TPN may lead to intestinal mucosal atrophy and impaired function of the gastrointestinal barrier, which consequently increase the possibility of intestinal bacterial translocation [21, 22]. Finally, TPN is always associated with increased blood glucose level, which appears to have a negative impact on the immune system and increases the risk of infection [4, 23].

Postoperative ileus is the most common gastrointestinal complication after cystectomy, occurring in up to 26% of cystectomy patients [3]. Whether recovery of gastrointestinal function following cystectomy could be improved by postoperative TPN or EEN, however, has never been clearly shown. A meta-analysis by Zhao et al. [6] revealed that those patients treated with EEN had a shorter time

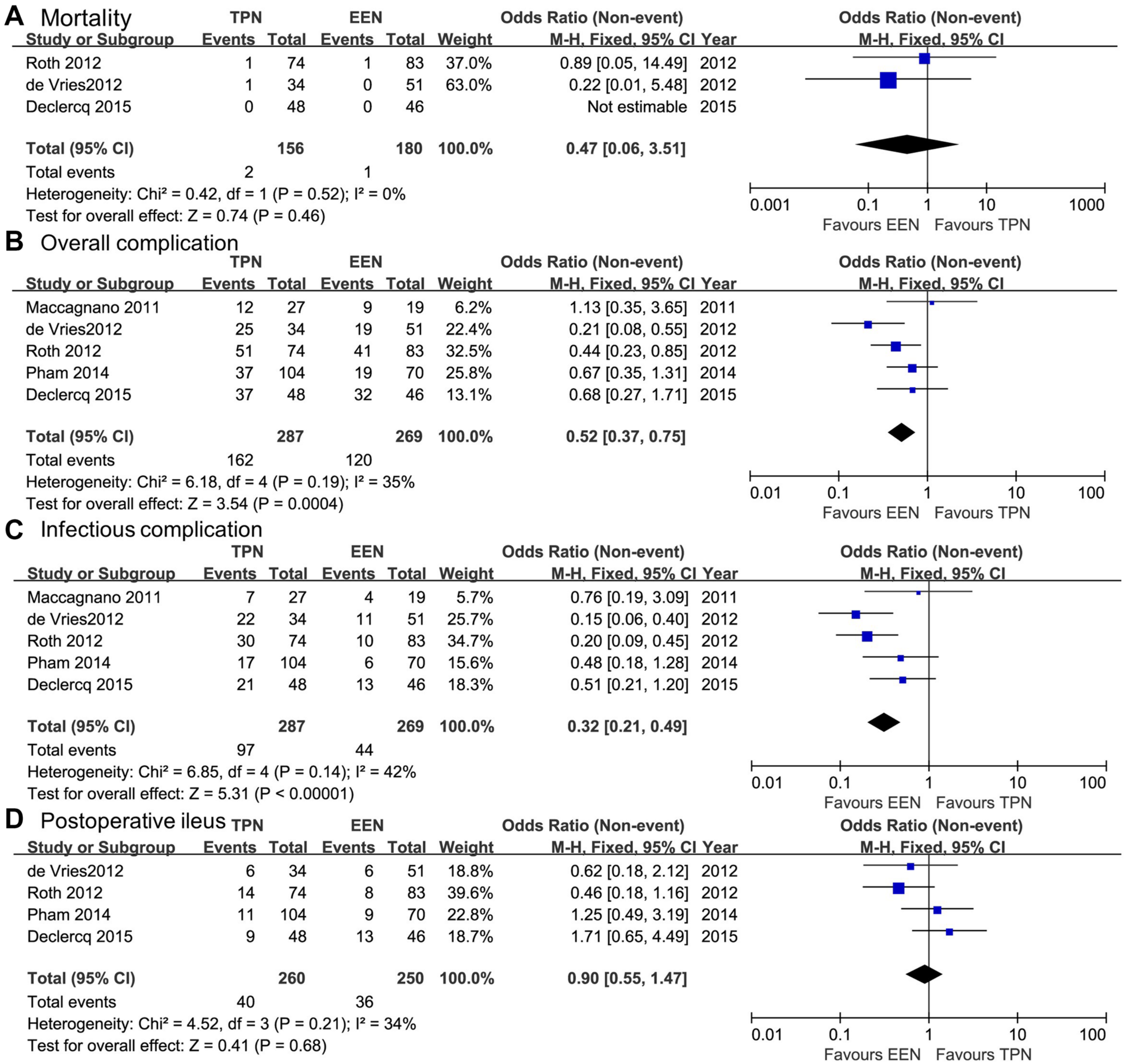

Fig. 2 Meta-analysis of primary outcomes. **a** Mortality rate; **b** incidence of overall complication; **c** incidence of infectious complication; **d** postoperative ileus

to flatus after major abdominal surgery for gastrointestinal cancer compared with the TPN group (pooled difference mean = − 1.27; $P < 0.001$). The present meta-analysis suggested that there was no significant benefit of EEN on reducing the incidence of POI and shortening the time necessary for resumption of full diet after cystectomy compared with TPN. In fact, both EEN and TPN played an important role in the recovery of gastrointestinal function. It was suggested that delivering nutrition via the enteral route was an important factor to maintain gastrointestinal motility, as enteral nutrients could stimulate the secretion of motility-regulating gastrointestinal hormones [22].

TPN was also used to prevent hypoproteinemia caused by the extensive wound area of cystectomy because hypoproteinemia might lead to edema of the bowel wall which would aggravate the postoperative ileus [4]. Although no significant difference was found in terms of time to recovery of bowel function after cystectomy during perioperative period, Vidal et al. [3] suggested that, compared with EEN, patients with postoperative TPN had worse gastrointestinal

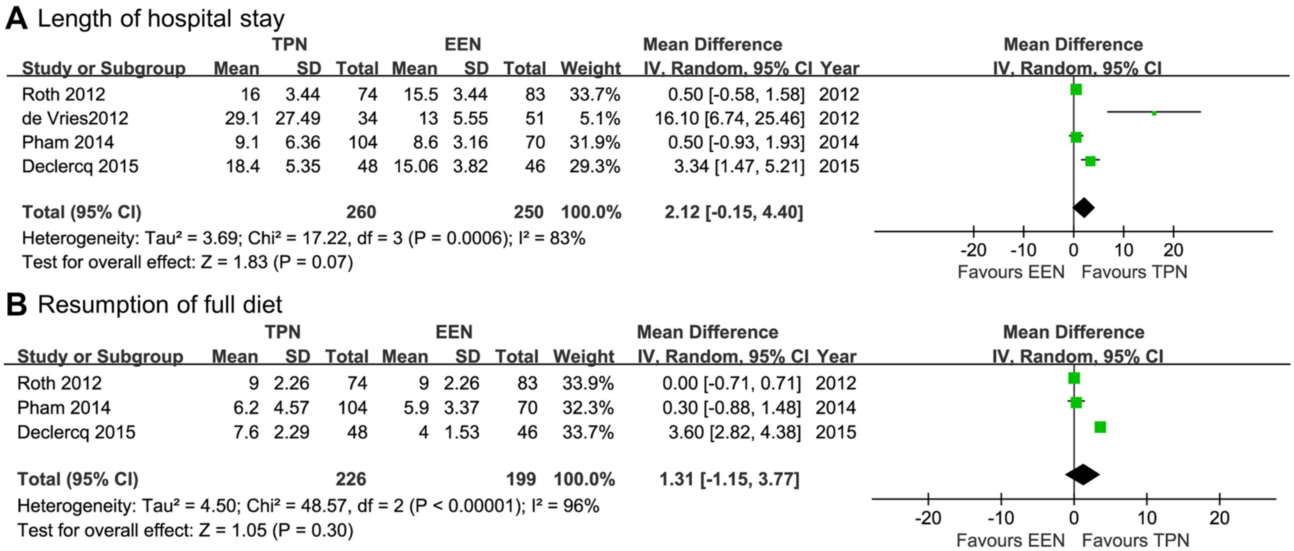

Fig. 3 Meta-analysis of secondary outcomes; **a** length of hospital stay; **b** time needed to resume a full diet

function 3 months and 12 months after cystectomy, with side effects such as abdominal pain, burping/belching, and diarrhea. Future studies should focus on the long-term outcome of gastrointestinal function between TPN and EEN.

The meta-analysis by Zhao et al. [6] revealed that those patients who received EEN had shorter LOS than those who received TPN after major abdominal surgery (pooled difference in mean = − 1.74; $P < 0.001$). In recent years, enhanced recovery after surgery programs (ERAS) has been introduced to improve recovery and reduce LOS after cystectomy, and postoperative feeding strategies, which are usually comprised of EEN, are an important part of EARS [24]. The present meta-analysis, however, indicated that EEN alone did not shorten LOS compared with TPN. This result should again be examined with caution because of the significant heterogeneity of this estimate. Although LOS reflects the rehabilitation after cystectomy, the criteria for discharge may differ in different countries and are based on the health care system [24]. Currently, there is no demonstrable benefit of TPN or EEN on mortality, and studies with long-term follow-up are also sparse. Vidal et al. [3] investigated the impact of TPN and EEN on long-term outcomes after cystectomy with a median follow-up of 50 months and found TPN did not impair long-term oncological outcomes.

Several limitations of the present meta-analysis should be considered. First, only two RCTs and three retrospective studies were included in this analysis. So the sample size was relatively small which might increase the risk of bias. Secondly, significant heterogeneities existed among included studies, specifically the protocols and nutrient composition of TPN and EEN, the definitions of infectious complications and POI were varied across studies. Finally, subgroup analysis of the effect of TPN and EEN on different nutritional statuses was not possible due to lack of data. So, future studies to evaluate the impact of TPN and EEN on malnourished patients are needed. Finally, the data of long-term influence of TPN and EEN on the gastrointestinal function are lacking, which also warrants future studies.

Despite the limitations of this analysis, our results are critical in light of the increasing use of EARS after cystectomy worldwide. Because TPN could increase the economic cost and infectious complications after cystectomy, compared with EEN, and no benefit to TPN was shown, it therefore seems reasonable to limit the use of TPN after cystectomy to patients who are well nourished and have normal gastrointestinal function. Whether preoperative and postoperative TPN achieves better outcomes than EEN for malnourished patients after cystectomy remains to be evaluated in future studies.

In conclusion, we found a significant benefit as part of EEN administration in reducing infectious complications compared with TPN after cystectomy. Despite the expectation that EEN would be superior to TPN in restoring gastrointestinal function, EEN did not reduce the incidence of POI, the time needed to resume a full diet or LOS. These findings support the use of EEN after cystectomy due to its considerable economic and clinical benefits.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest.

Ethical approval This study was a meta-analysis based on the existing published data, and therefore did not require the approval of an institutional review board.

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