Impact of total parenteral nutrition versus exclusive enteral nutrition on postoperative adverse outcomes in patients with penetrating Crohn's disease undergoing surgical resection: A retrospective cohort study

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Abstract

Achieving optimal nutritional status in patients with penetrating Crohn's disease (CD) is crucial in preparing for surgical resection. However, there is a dearth of literature comparing the efficacy of total parenteral nutrition (TPN) versus exclusive enteral nutrition (EEN) in optimizing postoperative outcomes. Hence, we conducted a case-matched study to assess the impact of preoperative EEN versus TPN on the incidence of postoperative adverse outcomes, encompassing overall postoperative morbidity and stoma formation, among penetrating CD patients undergoing bowel surgery. From December 1, 2012 to December 1, 2021, a retrospective study was conducted at a tertiary center to enroll consecutive patients with penetrating CD who underwent surgical resection. Propensity score matching (PSM) was utilized to compare the incidence of postoperative adverse outcomes. Furthermore, univariate and multivariate logistic regression analyses were conducted to identify the risk factors associated with adverse outcomes. The study included 510 patients meeting the criteria. Among them, 101 patients in the TPN group showed significant improvements in laboratory indicators at the time of surgery compared to pre-optimization levels. After matching, TPN was increased occurrence of postoperative adverse outcomes (92.2% vs. 64.1%, p = 0.001) when compared to EEN group. In the multivariate analysis, TPN showed a significantly higher odds ratio for adverse outcomes than EEN (OR = 4.241; 95% CI 1.567-11.478; p = 0.004). The study revealed that penetrating CD patients who were able to fulfill their nutritional requirements through EEN exhibited superior nutritional and surgical outcomes in comparison to those who received TPN.

Keywords: Crohn’s disease; total parenteral nutrition; exclusive enteral nutrition; postoperative complications

INTRODUCTION

Crohn's disease (CD) is a chronic, transmural inflammatory disease that can affect any part of the gastrointestinal tract, from the mouth to the anus. Repeated episodes of active inflammation in the intestinal lumen can lead to serious complications, such as strictures and perforation of the intestinal wall[1]. Penetrating CD can present as phlegmons, abscesses, or fistulas[2]. The penetrating nature of the disease can lead to the malnutrition status and inflammatory response which are associated with postoperative morbidity[3; 4]. Thereafter, prehabilitation or preoperative optimization, which involves interventions such as antibiotics, percutaneous drainage, and nutrition support, plays a crucial role in the management of patients with CD who are undergoing surgical resection[2; 5]. Optimization of nutritional status is essential in the initial management of penetrating CD, as it prepares the patient for surgical resection if needed.

Exclusive enteral nutrition (EEN) can promote mucosal healing, correct nutritional imbalances, and minimize disease activity in patients with inflammatory bowel disease (IBD)[6; 7; 8]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend using enteral nutrition (EN) formulas or liquids over parenteral nutrition (PN) unless EN is completely contraindicated. PN should only be used as the sole intervention in cases where EN is impossible, especially in the surgical management of nutrition in IBD. Contraindications to EEN include intestinal obstruction or ileus, severe shock, intestinal ischemia, high output fistula, and severe intestinal hemorrhage[9]. Preoperative nutrition therapy is demonstrated to be effective in decreasing postoperative complications and the reduced rate of stoma creation[10]. Enteral nutrition before surgery is also found to be associated with the shorter length of resected bowel[11].

Despite the potential benefits of EEN, there is a lack of literature comparing the differences between total parenteral and exclusive enteral nutrition optimization on postoperative complications. Therefore, we conducted a case-matched study to assess the impact of preoperative EEN versus TPN on the incidence of complications in patients undergoing bowel surgery for penetrating CD, while considering potential variables that may influence

the development of postoperative complications. We hypothesize that patients with penetrating Crohn's disease receiving preoperative TPN have increased postoperative adverse outcomes compared to those receiving EEN.

METHOD

Patients and data collection

Between December 1, 2012, and December 1, 2021, we enrolled all consecutive patients with penetrating CD who underwent surgery at a tertiary inflammatory bowel disease (IBD) center. Penetrating CD was defined as CD imaging showing abdominal abscess, phlegmon, or intra- or extra-intestinal fistula[12]. The diagnosis of penetrating CD was established based on symptoms and conventional imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), or abdominal ultrasound (US). Patients with perianal fistulae/abscess without abdominal/pelvic abscess/fistulae were excluded from the study. Additionally, we excluded patients who underwent emergency surgery or received preoperative partial enteral nutrition plus parenteral nutrition.

We collected various data including demographics, disease location according to the Montreal Classification, smoking status, preoperative medications, history of previous CD bowel resection, preoperative laboratory test results, type of surgery, use of laparoscopic or open access, operative time, operative blood loss, creation of primary anastomosis or diversion stoma, and postoperative outcomes. Propensity score matching was employed to minimize potential selection bias and compare the effect of EEN versus TPN, considering all covariates that may influence the management of preoperative nutritional status. Matching was performed using a 1:3 "nearest neighbor" caliper = 0.02, case-control match without replacement, based on several factors, including upper gastrointestinal lesion, type of penetrating lesion, and type of surgery. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the [Ethics Committee of Jinling Hospital; No.2022DZKY-048-01].

Total parenteral nutrition and exclusive enteral nutrition groups

Our exposure of interest was total parenteral nutrition, defined as patients who had received TPN for a minimum of 7 consecutive days before surgery and were subsequently included in the study[13; 14]. The decision to initiate TPN was based on the patient's characteristics and contraindication to enteral nutrition, as determined by the colorectal surgeon and nutritionist. Patients received a personalized total parenteral nutrition formula through either a central venous catheter or peripherally inserted central catheter. Macronutrient dosages were based on the patient's body weight, with 1.2-1.5 g/kg of amino acids, 2 mg/kg/min of 70% dextrose, and 250–500 mL of lipids. A specialist parenteral nutrition pharmacist made daily micronutrient and electrolyte adjustments tailored to the individual needs of the patient.

The comparator was enteral nutrition, defined as patients who received exclusive enteral nutrition for at least two weeks before surgery, with a normal diet excluded[9; 11; 15]. Preoperative EEN in penetrating CD is routinely administered via nasogastric or nasointestinal tube using an infusion pump. Nutritional requirements are calculated according to the guidelines of the parenteral and enteral nutrition team manual[16], with a target range of 25-35 kcal/kg/day and a maximum increase of 500 kcal/day in cases of malnutrition. One or more of the following products was prescribed for use: Enteral Nutritional Emulsion (TP)®, Enteral Nutritional Emulsion (TP-HE)®, [Fresenius Kabi, China]; Enteral Nutritional Suspension (TP-MCT)®, Enteral Nutritional Suspension(TPF)®, Peptisorb Liquid®, Nutrison®, [Nutricia, China]; ENSURE®, [Abbott Nutrition, China].

Outcome

Our primary outcome was the incidence of postoperative adverse outcomes, comprising overall postoperative morbidity and stoma formation. overall postoperative morbidity referred to any complications within 30 days after surgery. We categorized postoperative complications as superficial wound infection, ileus, anastomotic bleeding, abdominal bleeding, septicemia, pneumonia, urinary infection, catheter infection, reoperation, severe postoperative complications, intra-abdominal septic complications (IASCs), surgical site

infection (SSI), infectious complications, and overall morbidity. We defined ileus as the inability to tolerate oral food for more than five days in the absence of clinical and imaging evidence of mechanical obstruction[17]. Severe postoperative complications were those with a grade >2 according to the Clavien-Dindo classification[18]. IASCs were defined as peritonitis, abscess, or anastomotic leak. SSI encompassed intra-abdominal septic complications, wound infection, or wound dehiscence[19]. Infectious complications included all infectious complications such as SSI, septicemia, pneumonia, urinary infection, and catheter infection. We also collected the length of postoperative hospital stay and requirement for temporary stoma.

Statistical analysis

Categorical variables were compared using frequency counts and either the chi-square or Fisher's exact test, depending on appropriateness. Continuous variables were reported as means and standard deviations or medians and interquartile ranges, based on normality, and compared using ANOVA or Kruskal-Wallis tests, as appropriate. Paired t-tests and Wilcoxon signed-rank tests were utilized to compare laboratory indicators of total parenteral nutrition before and after treatment. All variables associated with a P value of less than 0.1 were subsequently included in a binary logistic regression model. Statistical significance was defined as a P-value of less than 0.05. We conducted statistical analyses using R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria), along with the MatchIt package, and analyzed data using IBM SPSS version 21. The total sample size was determined using G*Power version 3.1.9.7 for logistic regression analysis, with an odds ratio of 3.47, a significance level (α) set at 0.05, and a statistical power of 0.95. This calculation yielded a total sample size of 424 participants.

RESULTS

Patient characteristics

This study is a retrospective cohort study which enrolled 660 patients with penetrating CD who underwent surgery. Among them, 510 patients met the inclusion criteria, while the remaining patients were excluded for various reasons. Specifically, 22 patients lacked clinical data, 30 patients received partial enteral nutrition plus parenteral nutrition, and 98 patients underwent emergency surgery. Consequently, 409 cases in the enteral nutrition group and 101 cases in the parenteral nutrition group were subjected to PSM analysis **(Figure 1)**.

Table 1 displays the baseline characteristics of the 510 patients. Analysis of the data revealed significant differences in clinical characteristics and surgical procedures between the two groups. The EEN group had a significantly higher frequency of enterocutaneous fistula compared to the TPN group (P=0.001). In contrast, the TPN group had a significantly higher frequency of abscess and internal fistula presence compared to the EEN group (P=0.009 and P=0.043, respectively). Additionally, the EEN group had a significantly lower frequency of small bowel resection compared to the TPN group (P=0.02), whereas the frequency of ileocolectomy was significantly higher in the EEN group compared to the TPN group (P=0.002). It is worth noting that the differences in the frequency of upper gastrointestinal lesions, phlegmon, and segmental colectomy between the two groups did not reach statistical significance (P=0.088, P=0.087, P=0.093, respectively).

TPN and EEN composition characteristics

Overall, the mean daily protein intake for patients receiving TPN was 100 grams (range 75-100), corresponding to an average protein intake of 2.1 grams per kilogram of body weight (range 1.8-2.4). The mean amount of dextrose administered per day was 150 grams (range 150-175), equivalent to a mean intake of 3.3 grams per kilogram of body weight (range 2.9-4.1). In terms of lipid administration, there was a mean of 50 grams (range 50-60), resulting in a mean intake of 1.17 grams per kilogram of body weight (range 1.02-1.32). On average, the TPN formula provided a mean of 1450 calories per day (range 1445-1612), corresponding

to a mean energy intake of 32.2 kilocalories per kilogram of body weight (range 29.1-37.8). Conversely, the EEN formula supplied a mean of 1500 calories per day (range 1500-2000), which equated to a mean of 33.3 kilocalories per kilogram of body weight (range 28.8-40.0). The mean daily protein intake for patients receiving EEN was 64 grams (range 60-80), representing a mean intake of 1.3 grams per kilogram of body weight (range 1.1-1.6). The average daily lipid intake for patients undergoing EEN was 34 grams (range 25.5-63.9). Enteral nutrition lipids encompass different varieties, including Long Chain Triglycerides (LCT), Medium Chain Triglycerides (MCT), and Omega-3 Fatty Acids. On the other hand, Parenteral nutrition lipids consist of various types, such as LCT, MCT, fish oil-based emulsions, and structured lipids.

Preoperative nutritional optimization

Table 2 presents the distribution of different contraindications to EEN in the TPN population. Obstructed bowel is the most prevalent condition, accounting for 39.6% of all cases, followed by internal fistula observed in 33.7% of cases and gut dysfunction present in 18.8% of cases. The remaining cases are divided between abscess and high output fistula, with a prevalence of 5.9% and 2.0%, respectively.

All 101 patients in the TPN group exhibited significant improvements in albumin and hemoglobin following TPN pre-optimization compared to baseline levels. The changes in parameters are shown in **Supplemental Figure 1**. Mean-while, the data presented in Table 1 revealed statistically significant differences between the TPN and EEN groups across multiple variables. Specifically, individuals in the EEN group exhibited significantly higher mean BMI values compared to those in the TPN group ($p = 0.001$). Furthermore, the EEN group showed significantly higher mean hemoglobin levels ($p = 0.001$) and mean albumin levels ($p = 0.001$) compared to the TPN group. Additionally, individuals in the EEN group displayed significantly lower mean C-reactive protein levels than those in the TPN group ($p = 0.001$). Moreover, the EEN group demonstrated a significantly lower CDAI mean score (182.8 ± 33.6) when compared to the TPN group (323.4 ± 33.8), with a p-value of 0.001. The EEN group also exhibited a significantly lower weight loss rate (36.2%) in contrast to the

TPN group (61.4%), with a p-value of 0.001. Furthermore, the pre-surgery weight was significantly higher in the EEN group (50 kg [IQR: 45-57]) as opposed to the TPN group (45 kg [IQR: 40-51]), with a p-value of 0.001.

Post-operative outcomes

Table 3 presents a comparison of post-operative outcomes between two groups of patients who underwent surgery: those who received enteral nutrition (EEN group) and those who received total parenteral nutrition (TPN group). The EEN group had a lower incidence of abdominal bleeding (0.5% vs. 3.0%, P=0.056) and catheter infection (0.5% vs. 6.9%, P=0.001) compared to the TPN group. However, there were no significant differences between the two groups in the incidence of ileus, superficial wound infection, intra-abdominal septic complications, surgical site infection, anastomotic bleeding, septicemia, pneumonia, urinary infection, infectious complications, severe postoperative complications, and overall postoperative morbidity. Additionally, there was no significant difference between the two groups in terms of the length of postoperative hospital stay. The median postoperative hospital stay was 9 days for the EEN group and 10 days for the TPN group (P=0.227).

Propensity score matching

Following a 1:3 PSM, 90 patients were included in the TPN group and 223 in the EEN group. The incidence of upper gastrointestinal lesions was comparable between the TPN and EEN groups (14.4% vs. 11.2%, respectively, P = 0.428), as well as the type of penetrating lesions and type of surgery, as shown in **Table 4**. Additionally, there were no significant differences in age, sex, disease duration, Montreal classification, smoking habits, surgical history, and preoperative medication between the two groups.

Preoperative prehabilitation outcomes after PMS

Table 4 displays the preoperative prehabilitation outcomes for two groups of patients who underwent PMS, comparing BMI, hemoglobin levels, albumin levels, and CRP levels. The results indicate that the EEN group had a higher median BMI, hemoglobin levels, and albumin levels, and a lower median CRP level compared to the TPN group. In addition, the P values for the differences between the two groups were all statistically significant (P<0.001).

Post-operative outcomes after PMS

After PMS, the study found that the laparoscopic approach was utilized more frequently in the EEN group compared to the TPN group (20.6% vs. 5.6%, p = 0.001). On the other hand, stomas were more commonly created in the TPN group (81.1%) than in the EEN group (37.2%, p = 0.001).

Regarding postoperative complications, there were no significant differences between the two groups in most aspects. However, the EEN group exhibited a lower overall postoperative morbidity rate than the TPN group (44.8% vs. 57.8%, p = 0.038). Additionally, a statistically significant difference was observed between the groups in terms of postoperative catheter infection, with the TPN group having a higher incidence of catheter infection than the EEN group (7.8% vs. 0.9%, p = 0.003). Although the TPN group had slightly higher rates of surgical site infection and infectious complications, these differences did not reach statistical significance (refer to **Table 5)**.

Adverse outcomes and their risk factors

Both univariate and multivariate analyses were conducted to assess potential factors associated with postoperative adverse outcomes after PSM. In the univariate analysis, several factors demonstrated significant associations with adverse outcomes. These factors included disease location (L3 vs. L1), BMI, hemoglobin level, albumin level, C-reactive protein level, operative blood loss, operative time, surgical approach, small bowel resection, and segmental colectomy.

In the multivariate logistic regression models, First, L3 disease location relative to L1 was found to be significantly associated with adverse outcomes (p = 0.033; OR = 2.466; 95% CI 1.074-5.661). Second, CRP level exhibited a significant association with adverse outcomes (p = 0.009; OR = 1.033; 95% CI 1.008-1.058). Moreover, independent risk factors of adverse outcomes included operative blood loss (p = 0.001; OR = 1.009; 95% CI 1.004-1.013) and operative time (p = 0.035; OR = 1.009; 95% CI 1.001-1.017). Lastly, the multivariate analysis indicated that patients receiving TPN had a significantly higher odds ratio of adverse outcomes compared to those receiving EEN (OR = 4.241; 95% CI 1.567-11.478; p = 0.004) (**Table 6)**.

DISCUSSION

The objective of this study was to compare surgical outcomes in two groups of patients with penetrating Crohn's disease (CD): 101 patients who received preoperative total parenteral nutrition (TPN) optimization and 409 patients who received preoperative exclusive enteral nutrition (EEN) optimization. The study found that patients who received TPN demonstrated significantly higher serum albumin and hemoglobin levels at the time of surgery compared to pre-optimization levels. After performing PSM, our data showed that preoperative pre-rehabilitation outcomes were better in the EEN group compared to the TPN group. Specifically, the EEN group had higher BMI, hemoglobin, and albumin levels, and lower CRP levels, which may indicate better nutritional status and less inflammation. Furthermore, the EEN group exhibited lower rates of postoperative stoma, catheter-related infections, and overall complications when compared to the TPN group.

Optimizing the nutritional status of patients is crucial in the initial management of penetrating Crohn's disease, as malnutrition is an independent risk factor for all postoperative complications after abdominal surgery[20; 21; 22]. According to the guidelines of the American Society for Parenteral and Enteral Nutrition, enteral nutrition is usually the preferred choice in clinical practice due to its lower incidence of infectious complications and cost-

effectiveness[23]. Total parenteral nutrition is reserved for patients who cannot tolerate the energy provided by enteral nutrition. However, there are limitations to the available research on this topic. In this retrospective study, we compared the outcomes of total parenteral and total enteral nutrition for penetrating Crohn's disease and evaluated their respective impacts on postoperative complications. Our study is the first to compare these two nutritional support methods for this patient population.

Our study revealed a significant increase in preoperative albumin and hemoglobin levels after TPN optimization compared to before optimization. Similarly, a recent study demonstrated that exclusive preoperative TPN can significantly enhance nutritional status and prompt clinical and laboratory remission in patients with severe active Crohn's disease[24]. However, the use of TPN as an alternative to preoperative nutrition has shown mixed benefits among surgical patients. Specifically, preoperative TPN administration has been linked to rapid improvement in nitrogen balance and lymphocyte function recovery[25]. Other studies have also reported noteworthy improvements in nutritional indicators after TPN treatment [26; 27]. Collectively, these findings suggest that preoperative TPN can lead to significant nutritional enhancement.

EEN has demonstrated therapeutic effects in Crohn's disease that extend beyond addressing malnutrition and improving nutritional status. The ability of EEN to induce remission and reduce gut inflammation holds potential implications for surgical outcomes in these patients. EEN acting as an induction therapy for Crohn's disease. Research has consistently shown that EEN leads to improvements in clinical symptoms and promotes mucosal healing in individuals with Crohn's disease[28]. This is achieved through the modulation of the inflammatory response by EEN, which involves decreasing pro-inflammatory cytokine production and increasing the release of anti-inflammatory mediators[29]. As a result, EEN effectively attenuates Crohn's disease activity. Moreover, EEN exerts an influence on the composition of the gut microbiota. This alteration in the microbial balance contributes to the reduction of inflammation and the promotion of mucosal healing[30]. It is worth noting that one notable advantage of EEN is its excellent tolerability and absence of the adverse effects commonly associated with corticosteroid therapy. Consequently, EEN is considered a favorable treatment option, particularly in children[31].

A systematic analysis by Braunschweig et al. compared enteral nutrition (EN) with parenteral nutrition (PN) and found that EN was associated with a lower risk of infection, but higher mortality rates. In malnourished populations, the risk of infection tends to be higher with conventional oral diets with intravenous dextrose than with PN[32]. Elke G et al. found that in critically ill patients, EN had no effect on overall mortality but decreased infectious complications and ICU length of stay[33]. Mazaki et al.'s meta-analysis confirmed that EN is more beneficial than PN in reducing any complication, any infectious complication, anastomotic leak, intraabdominal abscess, and duration of hospital stay in patients after gastrointestinal surgery[34]. Zhao et al.'s meta-analysis of 18 RCTs with 2540 gastrointestinal cancer patients showed that patients who received EN had a shorter time to flatus, shorter lengths of hospital stay, and a greater increase in albumin levels compared with TPN[35]. The superiority of EEN over TPN has been established. One key mechanism that contributes to the potential advantages of EEN compared to TPN is its impact on the gut microbiota. EEN induces favorable changes in the microbial community's composition, leading to a more diverse and beneficial microbiota[36]. This modulation of the gut microbiota is believed to be associated with a reduction in inflammation and improved healing of the intestinal lining. Conversely, TPN bypasses the digestive system entirely and does not interact with the gut microbiota. Furthermore, EEN has been shown to effectively regulate pro-inflammatory cytokine production in the gut, resulting in a decrease in these cytokines' levels while simultaneously promoting anti-inflammatory mediator release[37]. However, TPN does not exert a direct effect on the gut inflammatory response. Another factor to consider is the potential impact of EEN on the integrity of the gut barrier function. EEN has been observed to enhance the strength of the intestinal barrier, preventing harmful substances and bacteria from entering the bloodstream[38]. This preservation of gut barrier function plays a crucial role in reducing inflammation and facilitating the healing of the intestinal mucosa. In contrast, TPN does not have the same influence on gut barrier function. This may also account for the greater weight loss observed in the TPN group compared to the EEN group. TPN delivers nutrients directly into the bloodstream, while EEN involves consuming a liquid formula that provides all necessary nutrients through a feeding tube, facilitating normal physiological processes of digestion and absorption. Additionally, the inflammatory state of the patient may

influence weight loss differences. Our findings also indicate a significantly lower mean CDAI score in the EEN group compared to the TPN group. These variations in delivery method and nutrient absorption could contribute to divergent weight loss outcomes. The ESPEN 2021 practical guidelines state that PN should be administered as soon as possible if nutrition therapy is indicated and there is a contraindication for EN[39]. However, EN should always take precedence over PN. When EN is completely contraindicated, PN is the better option. Our data suggest that TPN can optimise patient nutrition in cases where total enteral nutrition is contraindicated. However, compared to EEN optimization, the TPN group showed more severe disease activity and malnutrition at the time of surgery, as well as higher postoperative stoma rates, catheter infection rates and overall complications.

Our study is limited by several factors. The retrospective nature of our study design exposes it to the influence of unmeasured confounding variables. However, we addressed this concern by employing a matching process that enhanced comparability between the two groups in terms of baseline characteristics. As a result, potential bias in the analysis was mitigated. High utilization of TPN is that it may reflect a population of patients who are more unwell compared to those receiving EEN. It should be noted that the EN group exhibited higher mean BMI, albumin, and hemoglobin levels, as well as lower CRP levels compared to the TPN group. These inherent baseline differences render the achievement of our primary objective, which is to directly compare outcomes between TPN and EN, challenging. The inclusion of patients receiving TPN, who typically have more severe diseases, can significantly impact our experimental design and results. This potential bias may lead to a focus on more complex and critical cases in our study cohort, potentially distorting overall outcomes and limiting the generalizability of our findings. Moreover, the heightened severity of illness among TPN patients could influence treatment responses, clinical endpoints, and overall study outcomes. Besides, we agree that relying solely on BMI, hemoglobin, albumin, and CRP lacks both comprehensiveness and specificity in diagnosing malnutrition or evaluating overall nutritional status. We acknowledge that the absence of more thorough assessments is indeed a limitation in our research, and a more comprehensive evaluation of nutritional status would have yielded valuable insights.

Optimizing the nutritional status of patients with penetrating Crohn's disease is a crucial step prior to surgical resection. According to the guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN), exclusive enteral nutrition (EEN) is the preferred mode of nutritional support for these patients due to its ability to promote intestinal mucosal healing, correct nutritional imbalances, and reduce disease activity[40]. However, limited literature is available regarding the comparison of total parenteral nutrition (TPN) and EEN optimization on postoperative complications. Some studies have suggested that EEN may be associated with a lower risk of postoperative complications compared to TPN[34; 41]. Nevertheless, further research is necessary to confirm these findings and determine the optimal mode of nutritional support for patients with penetrating Crohn's disease undergoing surgical resection. In this regard, our research highlights the importance of pre-operative TPN nutrition optimization for penetrating Crohn's disease patients with contraindications to EEN. Our study has demonstrated that patients who were able to meet their nutritional needs through EEN had better nutritional and surgical outcomes when compared to patients who received TPN. However, a prospective cohort study is required to validate these results.

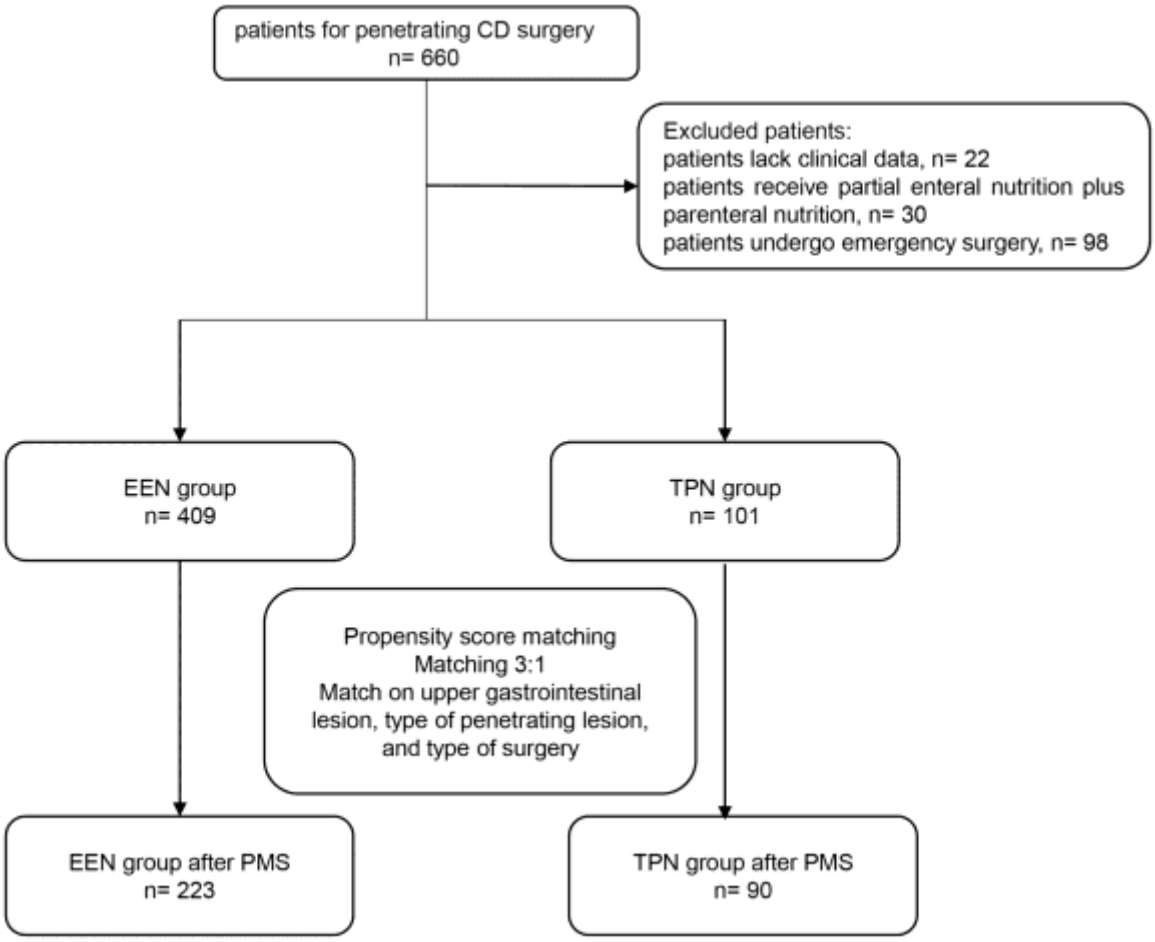

Figure 1: Flow chart of the study

Supplemental Figure 1: TPN group exhibited significant improvements in albumin and hemoglobin following TPN pre-optimization compared to baseline levels. (Wilcoxon matched-pairs signed rank test, P value <0.0001: Wilcoxon matched-pairs signed rank test, P value <0.0001)

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Author Contributions: Zhenya Sun, Lei Cao, and Yusheng Chen con-tributed equally to this work. Yi Li and Weiming Zhu conceived and designed the study, interpretation of data and revision of content. Zhenya Sun, Lei Cao, and Yusheng Chen were involved in the acquisition, interpretation of data and drafting of the manuscript; Tianrun Song and Zhen Guo was involved in the interpretation of data and revision of content. All authors read and approved the final manuscript.

Data availability: The database is available if properly requested and can be directly addressed to the corresponding author's email address.

Abbreviation：*CD* Crohn's disease, *TPN* total parenteral nutrition, *EEN* exclusive enteral nutrition, *PSM* propensity score matching, *IBD* inflammatory bowel disease, *ESPEN* European Society for Clinical Nutrition and Metabolism, *PN* parenteral nutrition, *CT* compute tomography, *MRI* magnetic resonance imaging, *US* ultrasound, *IASCs* intra-abdominal septic complications, *SSI* surgical site infection, *LCT* Long Chain Triglycerides, *MCT* Medium Chain Triglycerides, *IQR* Interquartile range, *BMI* body mass index, *CRP* C-reactive protein

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Table 1. Outcomes of preoperative-EEN group and preoperative-TPN group before PSM

	EEN group (N = 409)	TPN group (N = 101)	P
Age, years [IQR]	33 [26-43]	34 [24.5-44.5]	0.974
Male (n/N, %)	282 (68.9)	69 (68.3)	0.902
Duration of CD, months [IQR]	36 [12-78]	48 [12-96]	0.165
Disease Location			
L1 (n/N, %)	177 (43.3)	44 (43.6)	
L2 (n/N, %)	22 (5.4)	10 (9.9)	
L3 (n/N, %)	210 (51.3)	47 (46.5)	0.222
Upper gastrointestinal tract involvement (n/N, %)	47 (11.5)	18 (17.8)	0.088
Anal disease (n/N, %)	157 (38.4)	44 (43.6)	0.34
CD-related surgical history (n/N, %)	172 (42.1)	34 (33.7)	0.124
Smoking habit (n/N, %)	37 (9.0)	7 (6.9)	0.498
Medical treatment < 3 months before surgery			
None (n/N, %)	337 (82.4)	88 (87.1)	
Immunomodulator (n/N, %)	44 (10.8)	10 (9.9)	
Biologics (n/N, %)	28 (6.8)	3 (3.0)	0.321
Phlegmon (n/N, %)	34 (8.3)	14 (13.9)	0.087
Enterocutaneous fistula (n/N, %)	200 (48.9)	23 (22.8)	0.001
Internal fistula (n/N, %)	185 (45.2)	57 (56.4)	0.043
Presence of abscess (n/N, %)	11 (2.7)	9 (8.9)	0.009
CDAI, mean (SD)	182.8±33.6	323.4±33.8	0.001
weight loss (n/N, %)	148 (36.2)	62 (61.4)	0.001
Weight pre-surgery, kg [IQR]	50 [45-57]	45 [40-51]	0.001
Weight post-surgery, kg [IQR]	53 [48-60]	51 [46.5-56]	0.072
BMI, kg/m^2 [IQR]	17.8 [16.3-19.6]	16.1 [14.4-17.7]	0.001
Hemoglobin, g/L [IQR]	120 [109-132]	104 [94-116.5]	0.001
Albumin, g/L [IQR]	38.7 [35.4-41.4]	35.0 [31.5-38.5]	0.001
CRP, mg/L [IQR]	3.2 [0.75-13.1]	24 [4.8-58.2]	0.001
Operative blood loss, mL [IQR]	100 [80-190]	150 [65-200]	0.478
Operative time, minutes [IQR]	148 [120-180]	140 [110-170]	0.148
Surgical approach			
Open (n/N, %)	322 (78.7)	93 (92.1)	
Laparoscopic approach (n/N, %)	87 (21.3)	8 (7.9)	0.002
Stoma (n/N, %)	143 (35)	82 (81.2)	0.001

Surgical type			
Small bowel resection (n/N, %)	85 (20.8)	32 (31.7)	0.02
Segmental colectomy (n/N, %)	22 (5.4)	10 (9.9)	0.093
Ileocolectomy (n/N, %)	302 (73.8)	59 (58.4)	0.002

Table 2. Indications of TPN

	N = 101
Gut dysfunctiona (n/N, %)	19 (18.8)
Obstructed bowel (n/N, %)	40 (39.6)
Interna fistula (n/N, %)	34 (33.7)
Abscess (n/N, %)	6 (5.9)
High output fistula (n/N, %)	2 (2.0)

Table 3. Comparison of post-operative outcomes of preoperative-EEN group and preoperative-TPN group before PSM

	EEN group (N = 409)	TPN group (N = 101)	P
Ileus (n/N, %)	114 (27.9)	34 (33.7)	0.251
Superficial wound infection (n/N, %)	95 (23.2)	26 (25.7)	0.595
Intra- abdominal septic complications (n/N, %)	16 (3.9)	5 (5.0)	0.849
Surgical site infection (n/N, %)	101 (24.7)	27 (26.7)	0.672
Anastomotic bleeding (n/N, %)	8 (2.0)	1 (1.0)	0.812
Abdominal bleeding (n/N, %)	2 (0.5)	3 (3.0)	0.056
Septicemia (n/N, %)	12 (2.9)	3 (3.0)	1.0
Pneumonia (n/N, %)	4 (1.0)	2 (2.0)	0.748
Urinary infection (n/N, %)	4 (1.0)	2 (2.0)	0.748
Catheter infection (n/N, %)	2 (0.5)	7 (6.9)	0.001
Infectious complications (n/N, %)	108 (26.4)	31 (30.7)	0.386
Reoperation (n/N, %)	8 (2.0)	6 (5.9)	0.064
Severe postoperative complications (Clavien–Dindo score >2) (n/N, %)	24 (5.9)	10 (9.9)	0.146
Overall postoperative morbidity (n/N, %)	193 (47.2)	56 (55.4)	0.137
Adverse events (n/N, %)	264 (64.5)	92 (90.1)	0.001
Postoperative hospital stay, days [IQR]	9 [7-13]	10 [7-14]	0.227

Table 4. Outcomes of preoperative-EEN group and preoperative-TPN group after PSM

	EEN group (N = 223)	TPN group (N = 90)	P
Age, years [IQR]	34 [28-44]	34 [24.7-44.2]	0.35
Male (n/N, %)	150 (67.3)	62 (68.9)	0.781
Duration of CD, months [IQR]	36[12-84]	48[12-96]	0.522
Disease Location			
L1 (n/N, %)	108 (48.4)	36 (40.0)	
L2 (n/N, %)	12 (5.4)	9 (10.0)	
L3 (n/N, %)	103 (46.2)	45 (50.0)	0.199
Upper gastrointestinal tract involvement (n/N, %)	25 (11.2)	13 (14.4)	0.428
Anal disease (n/N, %)	85 (38.1)	39 (43.3)	0.393
CD-related surgical history (n/N, %)	83 (37.2)	32 (35.6)	0.782
Smoking habit (n/N, %)	19 (8.5)	6 (6.7)	0.584
Medical treatment < 3 months before surgery			
None (n/N, %)	186 (83.4)	78 (86.7)	
Immunomodulator (n/N, %)	24 (10.8)	9 (10.0)	
Biologics (n/N, %)	13 (5.8)	3 (3.3)	0.358
Phlegmon (n/N, %)	29 (13.0)	12 (13.3)	0.938
Enterocutaneous fistula (n/N, %)	67 (30.0)	23 (25.6)	0.427
Internal fistula (n/N, %)	132 (59.2)	50 (55.6)	0.555
Presence of abscess (n/N, %)	7 (3.1)	5 (5.6)	0.495
BMI, kg/m^2 [IQR]	17.9 [16.5-19.8]	16.2 [14.6-17.7]	0.001
Hemoglobin, g/L [IQR]	121 [109-132]	104 [94-114.2]	0.001
Albumin, g/L [IQR]	38.4 [35.4-41.7]	35.0 [31.4-38.4]	0.001
CRP, mg/L [IQR]	2.8 [0.6-11.7]	24.6 [5.8-62.4]	0.001
Operative blood loss, mL [IQR]	150 [100-200]	150 [50-200]	0.852
Operative time, minutes [IQR]	148 [120-180]	140 [110-174.2]	0.483
Surgical approach			
Open (n/N, %)	177 (79.4)	85 (94.4)	
Laparoscopic approach (n/N, %)	46 (20.6)	5 (5.6)	0.001
Stoma (n/N, %)	83 (37.2)	73 (81.1)	0.001
Surgical type			
Small bowel resection (n/N, %)	70 (31.4)	24 (26.7)	0.409
Segmental colectomy (n/N, %)	12 (5.4)	9 (10.0)	0.139
Ileocolectomy (n/N, %)	141 (63.2)	57 (63.3)	0.986

Table 5. Comparison of post-operative outcomes of preoperative-EEN group and preoperative-TPN group after PSM

	EEN group (N = 223)	TPN group (N = 90)	P
Ileus (n/N, %)	60 (26.9)	33 （36.7）	0.087
Superficial wound infection (n/N, %)	44 (19.7)	24 (26.7)	0.178
Intra- abdominal septic complications (n/N, %)	9 (4.0)	4 (4.4)	1.0
Surgical site infection (n/N, %)	47 (21.2)	25 (27.8)	0.202
Anastomotic bleeding (n/N, %)	4 (1.8)	1 (1.1)	1.0
Abdominal bleeding (n/N, %)	1 (0.4）	2 (2.2)	0.2
Septicemia (n/N, %)	7 (3.1)	3 (3.3)	1.0
Pneumonia (n/N, %)	3 (1.3)	2 (2.2)	0.951
Urinary infection (n/N, %)	3 (1.3)	1 (1.1)	1.0
Catheter infection (n/N, %)	2 (0.9)	7 (7.8)	0.003
Infectious complications (n/N, %)	54 (24.2)	29 (32.2)	0.146
Reoperation (n/N, %)	4 (1.8)	4 (4.4)	0.342
Severe postoperative complications (Clavien–Dindo score >2) (n/N, %)	14 (6.3)	7 (7.8)	0.631
Overall postoperative morbidity (n/N, %)	100 (44.8)	52 (57.8)	0.038
Adverse events (n/N, %)	143 (64.1)	83 (92.2)	0.001
Postoperative hospital stay, days [IQR]	9 [7-12]	10.5 [7-15]	0.112

Table 6. Univariate and multivariate analysis of risk factors for adverse outcomes after PSM

	Univariate	Multivariate
	p	OR (95%, CI), p
Age, years	0.203	
Male	0.7	
Duration of CD, months	0.532	
Disease Location		
L2 vs L1	0.998	
L3 vs L1	0.001	2.466 (1.074-5.661), 0.033
Upper gastrointestinal tract involvement	0.056	0.42 (0.172-1.025), 0.057
Anal disease	0.444	
CD-related surgical history	0.903	
Smoking habit	0.47	
Medical treatment < 3 months before surgery		
None	0.305	
Immunomodulator		
Biologics		
Phlegmon	0.125	
Enterocutaneous fistula	0.124	
Internal fistula	0.593	
Presence of abscess	1	
TPN vs EEN	0.001	4.241 (1.567-11.478), 0.004
BMI, kg/m^2	0.034	0.947 (0.846-1.06), 0.347
Hemoglobin, g/L	0.001	0.995 (0.974-1.017), 0.666
Albumin, g/L	0.001	0.985 (0.921-1.055), 0.673
CRP, mg/L	0.001	1.033 (1.008-1.058), 0.009
Operative blood loss, mL	0.001	1.009 (1.004-1.013), 0.001
Operative time, minutes	0.007	1.009 (1.001-1.017), 0.035
Surgical approach		
Laparoscopic approach vs Open	0.031	0.513 (0.221-1.192), 0.121
Small bowel resection	0.01	1.292 (0.549-3.037), 0.557
Segmental colectomy	0.007	
Ileocolectomy	0.355	