1-1-2017

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HHS Public Access

Author manuscript

Dis Colon Rectum. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Dis Colon Rectum. 2017 January ; 60(1): 68–75. doi:10.1097/DCR.0000000000000740.

Preoperative Immunonutrition and Elective Colorectal Resection Outcomes

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Abstract

Background—Randomized, controlled trials demonstrate the efficacy of arginine-enriched nutritional supplements (immunonutrition) in reducing complications after surgery. The effectiveness of preoperative immunonutrition has not been evaluated in a community setting.

Objective—Determine whether immunonutrition prior to elective colorectal surgery improves outcomes in the community at large.

Design—Prospective cohort study with a propensity score matched comparative effectiveness evaluation.

Settings—Washington State hospitals in the Surgical Care Outcomes Assessment Program from 2012–2015.

Patients—Adults undergoing elective colorectal surgery.

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DISCLAIMERS: The Strong for Surgery initiative in Washington State was supported, in part by an educational grant to evaluate new methods in quality improvement provided to the University of Washington by Nestle Healthcare Nutrition. Nestle USA Inc, (Glendale, CA) produces an immunonutrition product. These funds were not used to evaluate any specific product or in the research related to the Strong for Surgery initiative.

PRESENTATION: This work was presented at a podium at the 2016 American Society of Colon and Rectal Surgeons Annual Meeting; April 30th – May 4th, 2016.

AUTHOR CONTRIBUTION:
Study design: Thornblade, Varghese, Flum
Statistical analysis: Thornblade, Shi, Flum
Manuscript: Thornblade, Varghese, Shi, Johnson, Bastawrous, Billingham, Thirlby, Fichera, Flum

CLASSIFICATIONS: outcomes research, colon and rectal surgery, general surgery

Interventions—Surgeons used a preoperative checklist that recommended patients take oral immunonutrition (237mL, three times daily) for five days prior to elective colorectal resection.

Main outcome measures—Serious adverse events (infection, anastomotic leak, reoperation, and death) and prolonged length of stay.

Results—3,375 patients (mean age 59.9±15.2 years, 56% female) underwent elective colorectal surgery. Patients receiving immunonutrition more commonly were in a higher American Society of Anesthesiologists class (III–V, 44% vs. 38%, p=0.01) or required an ostomy (18% vs. 14%, p=0.02). The rate of serious adverse events was 6.8% vs 8.3% (p=0.25) and prolonged length of stay was 13.8% vs 17.3% (p=0.04) in those who did and did not receive immunonutrition, respectively. After propensity score matching, covariates were similar among 960 patients. Although differences in serious adverse events were non-significant (RR 0.76, 95% CI:0.49–1.16), prolonged length of stay (RR=0.77, 95% CI:0.58–1.01 p=0.05) was lower in those receiving immunonutrition.

Limitations—Patient compliance with the intervention was not measured. Residual confounding including surgeon-level heterogeneity may influence estimates of the effect of immunonutrition.

Conclusions—Reductions in prolonged length of stay, likely related to fewer complications, support the use of immunonutrition in quality improvement initiatives related to elective colorectal surgery. This population-based study supports previous trials of immunonutrition, but shows a lower magnitude of benefit, perhaps related to compliance or a lower rate of adverse events, highlighting the value of community-based assessments of comparative effectiveness.

Keywords

immunonutrition; propensity scores; comparative effectiveness; outcomes

INTRODUCTION

Despite advances in technique and perioperative care, approximately 20–25% of people undergoing elective colon resections develop infectious, anastomotic, or wound complications.[1–3] Infections comprise the single most common cause of complications and are estimated to cost $10 billion annually.[4] Surgical complications are related to a patient's nutritional status and this effect may be exerted through several mechanisms. Preoperative malnutrition, due to poor oral intake, significantly increases the risk of adverse events after surgery and leads to increased length of stay.[5] Another mechanism by which nutrition plays a role in surgical complications involves arginine, an amino acid which is found in nitrate-rich foods. There is a known depletion of arginine related to the stress of surgery.[6,7] This acute arginine "deficiency" occurs due to inflammation and tissue injury and causes both altered nitric oxide synthesis and T-cell dysfunction. Both of these predispose patients to infection and impaired wound healing.[8–10] This acute deficiency of arginine is potentially modifiable by preoperative supplementation of arginine. A number of commercial products contain arginine. This group of products is known as immunonutrition and is marketed for the reduction of infection and in surgical and critical care populations.

Immunonutrition reduced the incidence of infections, surgical complications or length of stay in 39 studies randomizing more than 2600 patients,[11,12] and seven RCTs have compared the use of preoperative immunonutrition with controls undergoing gastrointestinal surgery. A meta-analysis of these trials showed a near halving of infectious complications (RR=0.51, 95% CI 0.35–0.73) in patients receiving immune enhancing nutrition preoperatively.[12] The mean length of stay was also shorter among patients who received immunonutrition in these studies (13.6 versus 15.3 days, $p<0.01$).

Despite these encouraging findings, no study has examined the comparative effectiveness of immunonutrition use across varied clinical practices outside of a clinical trial. Ideally, an effectiveness assessment evaluates outcomes in a non-research center setting, including a variety of patients, disease states and clinicians from both academic and community hospitals, and without the restrictive criteria of a trial. Evidence of an intervention's effectiveness may strengthen the results from efficacy studies and addresses the question of generalizability to other populations and communities. The purpose of this study was to examine the effectiveness of immunonutrition after colorectal surgery as part of a state-wide public health intervention conducted across surgeons' practices at rural community hospitals, urban secondary and tertiary hospitals, and a single academic medical center in Washington State (WA).

MATERIALS AND METHODS

The Surgical Care and Outcomes Assessment Program (SCOAP) is a quality-improvement collaborative of over 50 hospitals in WA State that began in 2006. SCOAP hospitals include six critical access hospitals, numerous rural and urban secondary and tertiary medical centers, and a single quarternary referral center. Strong for Surgery (S4S) is a statewide public health campaign developed by investigators at the University of Washington's Surgical Outcomes Research Center (funded in part through the Agency for Healthcare Research and Quality, Grant Number R01HS020025) that focuses on implementation of evidence based practices to optimize patients' health before surgery. Initiated in 2012, S4S engages with surgeons by employing preoperative checklists that guide providers in promoting smoking cessation, assuring preoperative medication reconciliation, and nutritional optimization before surgery. For patients undergoing elective gastrointestinal surgery, S4S promotes the routine use of immunonutrition prior to surgery. Surgeons participate voluntarily in S4S. Beginning in 2011, in order to measure the effectiveness of preoperative immunonutrition, SCOAP began prospectively recording the use of immunonutrition at all of its member hospitals, many of which include surgeons who participate in S4S.

We conducted a prospective cohort study of all adult patients undergoing colorectal surgery in the SCOAP collaborative during the time period of interest. Patients were included in the study if they underwent surgery at one of the SCOAP hospitals between January 1, 2012, and June 30, 2015. In order to control for hospital-level factors we only included patients from hospitals that administered immunonutrition to at least 10 patients during the study period (n=7 hospitals). Patients were excluded from this study if they underwent an emergency surgery or if they had an urgent condition for which they would not qualify for

preoperative immunonutrition (bowel obstruction, colon ischemia, perforation, gastrointestinal bleeding, or volvulus). Patients younger than 18 were excluded. At all hospitals, trained abstractors examined charts to determine whether surgeons instructed the patient to take immunonutrition prior to surgery. Patients receiving immunonutrition were instructed to take the oral supplement (Impact, 237mL; Nestle USA Inc., Glendale, CA) by mouth three times daily for the five days prior to surgery. This regimen matched the prescribed course of immunonutrition in most clinical trials.

Abstractors reviewed the medical record for demographic, laboratory, operative, and other clinical details, including outcomes, during the 30-day period following surgery. The primary outcome was any serious adverse events (SAE) including infection [surgical site infection (SSI), abscess, urinary tract infection, and pneumonia], reoperation, anastomotic leak, and death. The secondary outcome was prolonged length of stay (PLOS) as defined by any length of stay greater than 1.5-times the median length of stay in the final cohort. SCOAP variable definitions are available online (http://www.scoap.org).

Patient characteristics are summarized by frequencies (categorical variables) and means with standard deviation (continuous variables). To evaluate for differences between patients who did and did not receive immunonutrition, we performed a univariate analysis with chi-squared tests or Fisher's exact tests (categorical variables) and 2-tailed unpaired Student's t-tests (continuous variables).

Because of significant differences between patients who were recommended to receive immunonutrition and those patients who did not, we performed a one-to-one propensity score matching of the two groups. Based upon a logistic regression model including all demographic and clinically relevant covariates including age, body mass index (BMI), American Society of Anesthesiology (ASA) class, indication, operation type, use of colostomy, and insurance type, we calculated a propensity score as the probability of receiving immunonutrition for each patient. There was a significant increase in use of immunonutrition over time from the beginning to the end of the study, so the regression model for calculating propensity scores also controlled for year in the study. Because of differences in surgeon and hospital practices, and the influence of other quality improvements such as Enhanced Recovery after Surgery (ERAS), there was concern that variation across hospitals may lead to bias and confounding in both the receipt of immunonutrition and outcomes. In order to account for these differences, patients receiving immunonutrition were only matched one-to-one with non-treated patients from their own hospital using a nearest-neighbor and no replacement method. After matching within each hospital, effects of immunonutrition on primary and secondary outcomes were assessed using an unadjusted generalized linear model with a binomial distribution and a log link.

All statistical analyses were performed using commercially available software (Stata, version 14; StataCorp, College Station, TX; R-software, version 3.1.3). All statistical tests were considered significant if $p \leq 0.05$. This study was exempted from institutional review board (IRB) review by agreement of the Washington State IRB and UW Human Subjects committee. All data used in this analysis were de-identified.

RESULTS

A total of 3,375 patients (mean age 59.9±15.2 years, 56% female) underwent elective colon (79%) or rectal (21%) surgery at seven hospitals. A total of 642 patients (18.7%) were instructed by their surgeon to take immunonutrition prior to surgery. With each passing year in the study, patients were more likely to receive immunonutrition, 1.4% in 2012 versus 34.1% in 2015. Patients who received immunonutrition were less often female (52% vs. 57%, p=0.02), included more patients in the higher ASA classes (III–V, 44% vs. 38%, p=0.01), more commonly had diagnoses of cancer (60% vs. 50%, p<0.01) or inflammatory bowel disease (14% vs. 8%, p<0.01), and more commonly required an ostomy (18% vs. 14%, p=0.02) (Table 1). PLOS (1.5x the median LOS) in the final matched cohort was any stay greater than 8 days.

The unadjusted rate of SAE was 6.8% in the group receiving immunonutrition and 8.3% among those who did not receive treatment (p=0.25). PLOS was 13.8% in the immunonutrition group and 17.3% in the untreated group (p=0.04). PLOS was more common among patients with than without SAE (73.4% vs. 13.1%, p<0.001). Figure 1 shows the distribution of propensity scores between patients recommended to receive immunonutrition and patients who did not receive immunonutrition. 480 patients receving immunonutrition were matched to 480 non-treated patients at their own hospitals. After matching, there were no significant differences in demographic or operative characteristics between patients in the treated and non-treated groups (Table 2).

After matching, the rate of SAE was 7.1% in the group receiving immunonutrition and 9.4% in those who did not (RR=0.76, 95% CI: 0.49–1.16, p=0.19). The relative risk of prolonged length of stay was 23% lower among patients receiving immunonutrition (15.6%) compared with the untreated group (20.4%) (RR=0.77, 95% CI: 0.58–1.01, p=0.05).

DISCUSSION

This study examined the effectiveness of preoperative immunonutrition among patients undergoing elective colorectal surgery. There was a 23% reduction in PLOS associated with immunonutrition use. Although non-significant, we found a 24% reduction in SAE (infections, anastomotic leaks, reoperation, and death) among patients recommended to take immunonutrition that appeared to be related to the reduction in PLOS. Importantly, our estimate of reduced adverse events is similar in magnitude to that identified in a meta-analysis of randomized trials (33%).[12]

For decades, researchers have explored the role of nutrients, including arginine, in the treatment of patients with inflammation after physical injury, including surgery, with the goal of identifying a modifiable target to improve outcomes. Arginine has been proposed as one of those targets, in part because of the several implicated roles it plays in mitigating the harmful effects of inflammation. Arginine is a known substrate for immune cells, and arginine deficiency appears to lead to T-cell dysfunction in animal models.[6,8,10] Arginine is also a precursor for polyamines and hydroxyproline, compounds involved in wound healing. In the early 2000's arginine supplementation was found to reduce infectious complications

in patients undergoing elective surgery,[11] although the exact mechanism for this effect is still under debate. Compounding the challenge of evaluating arginine is that many of the commercial preparations that include arginine also include Omega-3 fatty acids, and these too may have an effect on surgical outcomes.[13]

Numerous RCTs have examined the efficacy of different immune enhancing diets in gastrointestinal surgery.[14,15] Drover *et al.*[4] reviewed 33 studies randomizing patients to perioperative use of immunonutrition around the time of elective surgery.[16–48] They reported a 39% reduction in infectious complications as well as significantly lower lengths of stay. Notably, 18 of the 21 trials on gastrointestinal (GI) surgery were in patients undergoing upper GI surgery. Among trials of lower GI surgery (n=2) there were no differences in length of stay, however complication rates were lower in treated patients. Seven trials included use of immunonutrition exclusively in the preoperative period, and aggregated results showed a 43% reduction in infectious complications but no difference in length of stay.[16,18,30,36,37,47,48] A recent Cochrane review includes a meta-analysis of six trials of preoperative immunonutrition and reports a 33% reduction in total complications among patients receiving immunonutrition in GI surgery.[12,16,18,30,36,37,48]

Recent meta-analyses have brought into question the efficacy of immunonutrition, in part because of differences in both timing of administration and comparison groups.[49,50] Hegazi *et al.*[49] reviewed trials of preoperative immunonutrition and found a reduction in infectious complications (OR=0.49, $p<0.01$) when compared to control patients receiving no supplementation. But when comparing preoperative immunonutrition to controls that did receive oral supplementation, the difference in infectious complications was not significant (OR=0.71, $p=0.44$).[16,18,30,36,37,47,51–58] Failure in this analysis to detect a difference in outcomes may have occurred because of a subdividing of the cohort by control type, resulting in smaller sample sizes.[59]

There have been no prior studies that examine outcomes of immunonutrition outside of a clinical trial, where compliance may be a challenge, and where there is more heterogeneity in clinical practice and patient characteristics. We found that the recommendation to take immunonutrition before surgery was associated with a reduced rate of PLOS, and that PLOS was related to SAE. The relative risk reduction associated with immunonutrition was not statistically significant, but the direction of effect on SAE was similar (a lowering of 24%) to many prior RCTs. One explanation that may account for this was the relatively low rate of observed infectious complications in our study (7.1% vs. 9.4% in patients not receiving immunonutrition) compared to previously reported studies. The review by Drover *et al.* reported a 41% reduction in infectious complications among 28 trials reporting infections, but observed this effect with a much higher rate of adverse events (16.5% vs. 27.7%, $p<0.0001$).[4] Burden *et al.* also reported significant reductions in infectious complications (14.2% vs. 27%, $p<0.001$) but with a similarly high level of events.[12] Based upon a sample size estimation, a study designed to detect the risk reduction identified in our study (from 9% to 7%) would require enrollment of 2,987 patients per arm. This suggests that our study may be underpowered to detect significant reductions in serious complication rates. This difference in adverse event rates may be due to the predominance of high-risk and upper GI surgery in trials (esophagectomy, gastrectomy, and pancreaticoduodenectomy) compared

with the relatively lower-risk colorectal resections included in this study. Lower complication rates observed in this study also may be due to concurrent implementation of ERAS protocols over the same period. We did observe a difference in rates of immunonutrition use between earlier and later years in this study, and the regression model used to calculate propensity scores adjusted for year to account for this observation.

There are several limitations to this study. In particular, confounding by indication may have occurred, meaning that patients who received the intervention are different in both measured and unmeasured factors from those who did not receive it. Propensity score matching allows for a comparison of patient groups that are more balanced in measured factors, allowing them to look more like populations from a randomized trial which are balanced through the randomization process. Using this approach, patient, clinical and surgical factors were not significantly different between matched groups. The SCOAP database does not provide surgeon-specific data such as number of years in practice or fellowship training. However, by exclusively matching patients recommended to receive immunonutrition to non-treated patients from the same hospitals, we hoped to control for major differences in outcome that may be due to surgeon factors. Patients who received immunonutrition either paid for it themselves or were provided the supplement from the clinic or hospital free of charge. There is a possibility that patients with limited financial resources were unable to access immunonutrition. However, the rates of Medicaid insurance among those who did and did not receive immunonutrition was similar (15.7% vs 14.1%). It is unclear whether patients who were advised to take immunonutrition actually complied with the recommendation, and if so, took all of the supplements. Rather, SCOAP abstractors identify whether the patients were instructed by their surgeon to take the supplement by reviewing the medical record. This may represent a conservative bias (e.g., some patients who appear to have received the supplement did not in fact use it). This bias might be expected to minimize differences in outcomes between groups, and if accounted for, might even accentuate the observed differences. It is also possible that, during the early phases of this study, the low rate of immunonutrition use was because the recommendation for receipt of the supplement was not documented consistently. This is also a bias which might be expected to minimize the observed difference between treatment and non-treatment. Lastly, most patients who received immunonutrition were also part of the broader S4S initiative focused on improved glucose control, smoking cessation, and medicine reconciliation. While not controlling for these elements directly, after matching we found no significant differences in perioperative hyperglycemia (10.8% vs 9.4%), cigarette smoking (27.9% vs. 27.1%) or beta blocker continuation (95.9% vs. 93.1%) between the groups who did and did not receive immunonutrition.

In conclusion, the use of preoperative immunonutrition as part of the S4S public health campaign helped to improve surgical outcome and was associated with fewer patients requiring a PLOS (≥8 days). This study supports the adoption of immune enhancing nutrition before elective surgery as a way to reduce prolonged length hospitalizations and improve the quality of surgical care.

Acknowledgments

We would like to thank our hospital partners in Strong for Surgery. Also special thanks to Ms. Rebecca G. Symons, head analyst at SORCE, for help in data acquisition.

SOURCE OF SUPPORT:

Dr. Thornblade is supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Number T32DK070555. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ABBREVIAIONS AND ACRONYMS

ASA	American Society of Anesthesiologists
BMI	Body mass index
CERTAIN	Comparative Effectiveness Research Translation Network
ERAS	Enhanced Recovery after Surgery
GI	gastrointestinal
IRB	institutional review board
PLOS	prolonged length of stay
RCT	randomized controlled trial
SAE	serious adverse event
SCOAP	Surgical Care Outcomes Assessment Program
SSI	surgical site infection
S4S	Strong for Surgery
WA	Washington State

References

1. Cohen ME, Bilimoria KY, Ko CY, Hall BL. Development of an American College of Surgeons National Surgery Quality Improvement Program: Morbidity and Mortality Risk Calculator for Colorectal Surgery. J Am Coll Surg. 2009; 208:1009–1016. [PubMed: 19476884]
2. Kolfschoten NE, Marang-van de Mheen PJ, Wouters MWJM, et al. A combined measure of procedural volume and outcome to assess hospital quality of colorectal cancer surgery, a secondary analysis of clinical audit data. PLoS One. 2014; 9:e88737. [PubMed: 24558418]
3. Govaert JA, van Dijk WA, Fiocco M, et al. Nationwide outcomes measurement in colorectal cancer surgery: improving quality and reducing costs. J Am Coll Surg. 2016; 222:19–29.e2. [PubMed: 26721750]
4. Drover JW, Dhaliwal R, Weitzel L, Wischmeyer PL, Ochoa JB, Heyland DK. Perioperative use of arginine-supplemented diets: a systematic review of the evidence. J Am Coll Surg. 2011; 212:385–399. [PubMed: 21247782]
5. McClave SA, Kozar R, Martindale RG, et al. Summary Points and Consensus Recommendations from the North American Surgical Nutrition Summit. JPEN. 2013; 37:S99S–105S.

6. Zhu X, Herrera G, Ochoa JB. Immunosuppression and Infection after major surgery: a nutritional deficiency. Crit Care Clin. 2010; 26:491–500. [PubMed: 20643302]
7. Morris SM. Arginases and arginine deficiency syndromes. Curr Opin Clin Nutr Metab Care. 2012; 51:64–70.
8. Evoy D, Lieberman MD, Fahey TJ, Daly JM. Immunonutrition: the role of arginine. Nutrition. 1998; 14:611–617. [PubMed: 9684265]
9. Ochoa JB, Makarenkova V. T Lymphocytes. Crit Care Med. 2005; 33:S510–S513. [PubMed: 16340436]
10. Zhu X, Pribis JP, Rodriguez PC, et al. The central role of arginine catabolism in T-cell dysfunction and increased susceptibility to infection after physical injury. Ann Surg. 2014; 259:171–178. [PubMed: 23470573]
11. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA. 2001; 286:944–953. [PubMed: 11509059]
12. Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database of Systematic Reviews. 2012; (11) Art. No.: CD008879. doi: 10.1002/14651858.CD008879.pub2
13. Sorensen LS, Rasmussen HH, Aardestrup IV, et al. Rapid incorporation of omega-3 fatty acids into colonic tissue after oral supplementation in patients with colorectal cancer: a randomized, placebo-controlled intervention trial. J Parenter Enteral Nutr. 2014; 38:617–624.
14. Wodja TR, Mohammed O, Evans DC. Perioperative nutrition support for surgical patients: aspects and commentary. Curr Surg Rep. 2015; 3:27.
15. Cerantola Y, Hubner M, Grass N, Demartines N, Schafer M. Immunonutrition in gastrointestinal surgery. Br J Surg. 2011; 98:37–48. [PubMed: 20931620]
16. Braga M, Gianotti L, Nespoli L, et al. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg. 2002; 137:174–180. [PubMed: 11822956]
17. Braga M, Gianotti L, Radaelli G, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg. 1999; 134:428–433. [PubMed: 10199318]
18. Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. Surgery. 2002; 132:805–814. [PubMed: 12464864]
19. Braga M, Vignali A, Gianotti L, et al. Immune and nutritional effects of early enteral nutrition after major abdominal operations. Eur J Surg. 1996; 162:105–112. [PubMed: 8639722]
20. Casas-Rodera P, Gómez-Candela C, Benítez S, et al. Immunoenhanced enteral nutrition formulas in head and neck cancer surgery: a prospective, randomized clinical trial. Nutr Hosp. 2008; 23:105–110. [PubMed: 18449445]
21. Celik JB, Gezginç K, Ozçelik K, Celik C. The role of immunonutrition in gynecologic oncologic surgery. Eur J Gynaecol Oncol. 2009; 30:418–421. [PubMed: 19761135]
22. Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. Surgery. 1992; 112:56–67. [PubMed: 1377838]
23. Daly JM, Reynolds J, Sigal RK, et al. Effect of dietary protein and amino acids on immune function. Crit Care Med. 1990; 18:S86–93. [PubMed: 2105184]
24. Daly JM, Weintraub FN, Shou J, et al. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg. 1995; 221:327–338. [PubMed: 7726669]
25. de Luis DA, Aller R, Izaola O, et al. Postsurgery enteral nutrition in head and neck cancer patients. Eur J Clin Nutr. 2002; 56:1126–1129. [PubMed: 12428179]
26. de Luis DA, Izaola O, Cuellar L, et al. Randomized clinical trial with an enteral arginine-enhanced formula in early postsurgical head and neck cancer patients. Eur J Clin Nutr. 2004; 58:1505–1508. [PubMed: 15138461]
27. de Luis DA, Izaola O, Cuellar L, et al. Clinical and biochemical outcomes after a randomized trial with a high dose of enteral arginine formula in postsurgical head and neck cancer patients. Eur J Clin Nutr. 2007; 61:200–204. [PubMed: 16929239]

28. Farreras N, Artigas V, Cardona D, et al. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. Clin Nutr. 2005; 24:55–65. [PubMed: 15681102]
29. Finco C, Magnanini P, Sarzo G, et al. Prospective randomized study on perioperative enteral immunonutrition in laparoscopic colorectal surgery. Surg Endosc. 2007; 21:1175–1179. [PubMed: 17356942]
30. Gianotti L, Braga M, Nespoli L, et al. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology. 2002; 122:1763–1770. [PubMed: 12055582]
31. Giger U, Büchler M, Farhadi J, et al. Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. Ann Surg Oncol. 2007; 14:2798–2806. [PubMed: 17632760]
32. Jiang ZM, Gu ZY, Chen FL, et al. The role of immune enhanced enteral nutrition on plasma amino acid, gut permeability and clinical outcome (a randomized, double blind, controlled, multi-center clinical trial with 120 cases). Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2001; 23:515–518. [PubMed: 12905875]
33. Klek S, Kulig J, Sierzega M, et al. Standard and immunomodulating enteral nutrition in patients after extended gastrointestinal surgery–a prospective, randomized, controlled clinical trial. Clin Nutr. 2008; 27:504–512. [PubMed: 18571296]
34. Klek S, Kulig J, Sierzega M, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. Ann Surg. 2008; 248:212–220. [PubMed: 18650630]
35. Lobo DN, Williams RN, Welch NT, et al. Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: a prospective, randomized, controlled, double-blind study. Clin Nutr. 2006; 25:716–726. [PubMed: 16777271]
36. McCarter MD, Gentilini OD, Gomez ME, Daly JM. Preoperative oral supplement with immunonutrients in cancer patients. J Parenter Enteral Nutr. 1998; 22:206–211.
37. Okamoto Y, Okano K, Izuishi K, et al. Attenuation of the systemic inflammatory response and infectious complications after gastrectomy with preoperative oral arginine and omega-3 fatty acids supplemented immunonutrition. World J Surg. 2009; 33:1815–1821. [PubMed: 19629583]
38. Riso S, Aluffi P, Brugnani M, et al. Postoperative enteral immunonutrition in head and neck cancer patients. Clin Nutr. 2000; 19:407–412. [PubMed: 11104591]
39. Sakurai Y, Masui T, Yoshida I, et al. Randomized clinical trial of the effects of perioperative use of immune-enhancing enteral formula on metabolic and immunological status in patients undergoing esophagectomy. World J Surg. 2007; 31:2150–2159. [PubMed: 17653789]
40. Schilling J, Vranjes N, Fierz W, et al. Clinical outcome and immunology of postoperative arginine, omega-3 fatty acids, and nucleotide-enriched enteral feeding: a randomized prospective comparison with standard enteral and low calorie/low fat i.v. solutions. Nutrition. 1996; 12:423–429. [PubMed: 8875537]
41. Senkal M, Mumme A, Eickhoff U, et al. Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. Crit Care Med. 1997; 25:1489–1496. [PubMed: 9295822]
42. Senkal M, Zumtobel V, Bauer KH, et al. Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. Arch Surg. 1999; 134:1309–1316. [PubMed: 10593328]
43. Snyderman CH, Kachman K, Molseed L, et al. Reduced postoperative infections with an immune-enhancing nutritional supplement. Laryngoscope. 1999; 109:915–921. [PubMed: 10369282]
44. Tepaske R, te Velthuis H, Oudemans-van Straaten HM, et al. Glycine does not add to the beneficial effects of perioperative oral immune-enhancing nutrition supplements in high-risk cardiac surgery patients. J Parenter Enteral Nutr. 2007; 31:173–180.
45. Tepaske R, Velthuis H, Oudemans-van Straaten HM, et al. Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial. Lancet. 2001; 358:696–701. [PubMed: 11551575]

46. van Bokhorst-De Van Der Schueren MA, Quak JJ, von Blomberg-van der Flier BM, et al. Effect of perioperative nutrition, with and without arginine supplementation, on nutritional status, immune function, postoperative morbidity, and survival in severely malnourished head and neck cancer patients. Am J Clin Nutr. 2001; 73:323–332. [PubMed: 11157331]
47. Wachtler P, Axel Hilger R, König W, et al. Influence of a pre-operative enteral supplement on functional activities of peripheral leukocytes from patients with major surgery. Clin Nutr. 1995; 14:275–282. [PubMed: 16843943]
48. Xu J, Zhong Y, Jing D, Wu Z. Preoperative enteral immunonutrition improves postoperative outcome in patients with gastrointestinal cancer. World J Surg. 2006; 30:1284–1289. [PubMed: 16830214]
49. Hegazi RA, Hustead DS, Evans DC. Preoperative standard oral nutrition supplements vs immunonutrition: results of a systematic review. J Am Coll Surg. 2014; 219:1078–1087. [PubMed: 25260681]
50. Klek S, Szybinski P, Szczepanek K. Perioperative immunonutrition in surgical cancer patients: a summary of a decade of research. World J Surg. 2014; 38:802–812.
51. Aida T, Furukawa K, Suzuki D, et al. Preoperative immunonutrition decreases postoperative complications by modulating prostaglandin E2 production and T-cell differentiation in patients undergoing pancreatoduodenectomy. Surgery. 2014; 155:124–133. [PubMed: 24589090]
52. Barker LA, Gray C, Wilson L, et al. Preoperative immunonutrition and its effect on postoperative outcomes in well-nourished and malnourished gastrointestinal surgery patients: a randomised controlled trial. Eur J Clin Nutr. 2013; 67:802–807. [PubMed: 23801093]
53. Fujitani K, Tsujinaka T, Fujita J, et al. Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer. Br J Surg. 2012; 99:621–629. [PubMed: 22367794]
54. Giger-Pabst U, Lange J, Maurer C, et al. Short-term preoperative supplementation of an immunoenriched diet does not improve clinical outcome in well-nourished patients undergoing abdominal cancer surgery. Nutrition. 2013; 29:724–729. [PubMed: 23352174]
55. Gunerhan Y, Koksal N, Sahin UY, et al. Effect of preoperative immunonutrition and other nutrition models on cellular immune parameters. World J Gastroenterol. 2009; 15:467–472. [PubMed: 19152452]
56. Horie H, Okada M, Kojima M, Nagai H. Favorable effects of preoperative enteral immunonutrition on a surgical site infection in patients with colorectal cancer without malnutrition. Surg Today. 2006; 36:1063–1068. [PubMed: 17123134]
57. Hübner M, Cerantola Y, Grass F, et al. Preoperative immunonutrition in patients at nutritional risk: results of a double-blinded randomized clinical trial. Eur J Clin Nutr. 2012; 66:850–855. [PubMed: 22617278]
58. Mikagi K, Kawahara R, Kinoshita H, Aoyagi S. Effect of preoperative immunonutrition in patients undergoing hepatectomy; a randomized controlled trial. Kurume Med J. 2011; 58:1–8. [PubMed: 22027191]
59. Drover, JW. Immunonutrition: the evidence for its use in elective surgery. https://www.nestlenutrition-institute.org/resources/library/Free/conference-proceeding/eras-congress/Documents/11086-PRPLUS-ERAS%20Proceeding%20HR%20Professional%20Print-101215%20Final.PDF. Published May 10, 2015. Accessed March 30th, 2016

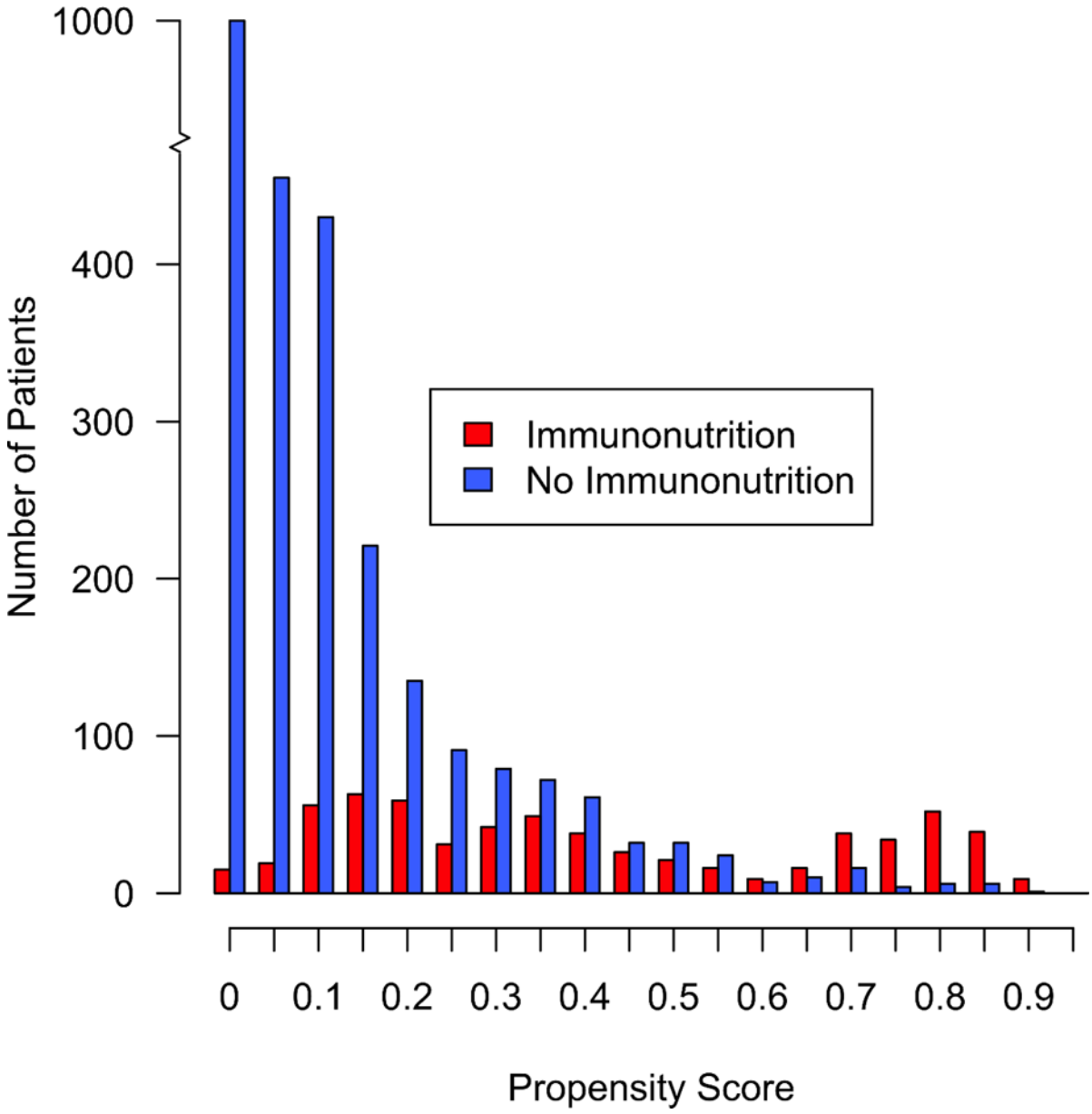

Figure 1.

Distribution of propensity scores between patients recommended to receive immunonutrition and patients who did not receive immunonutrition. Higher scores represent a higher propensity for receipt of immunonutrition.

Table 1

Patient characteristics and outcomes for entire study cohort.

No. (%) of patients	No Immunonutrition (n=2743)	Immunonutrition (n=632)	P-value
Age, mean (SD), year	60.2 (15.1)	58.9 (15.4)	0.06
Female	1554 (57%)	326 (52%)	0.02
BMI	27.9 (6.4)	28.0 (6.9)	0.9
Race			0.59
Non-white	305 (11%)	75 (12%)	
White	2312 (84%)	523 (83%)	
Unknown	126 (5%)	34 (5%)	
Year			<0.01
2012	997 (36%)	15 (2%)	
2013	761 (28%)	207 (33%)	
2014	685 (25%)	255 (40%)	
2015	300 (11%)	155 (25%)	
ASA Class			0.01
I–II	1710 (62%)	357 (56%)	
III–V	1033 (38%)	275 (44%)	
Prior pelvic or colon surgery[1]	1264 (46%)	283 (45%)	0.58
Indication			<0.01
Cancer	1383 (50%)	379 (60%)	
Diverticulitis	496 (18%)	101 (16%)	
Inflammatory bowel disease	226 (8%)	87 (14%)	
Other indication[2]	638 (23%)	65 (10%)	
Surgical type			0.19
Colon resection	2189 (80%)	489 (77%)	
Rectal resection	554 (20%)	143 (23%)	
Ostomy Created	396 (14%)	116 (18%)	0.02
Insurance status			0.25
Private insurance	1395 (51%)	338 (53%)	
Non-private insurance	1348 (49%)	294 (47%)	
Serious Adverse events	227 (8%)	43 (7%)	0.25
Length of Stay, mean (SD), day	5.7 (4.9)	5.5 (4.8)	0.28
Prolonged Length of Stay (≥8 days)	475 (17%)	87 (14%)	0.04

[1] Prior pelvic or colon surgery includes hysterectomy, cholecystectomy, appendectomy and small bowel and colon resections in the pelvic area.

[2] Other indications include arterial malformation, iatrogenic injury, rectal prolapse, stricture, or gynecologic malignancy

Table 2

Patient characteristics and outcomes after propensity score matching.

No. (%) of patients	No Immunonutrition (n=480)	Immunonutrition (n=480)	P-value
Age, mean (SD), year	57.9 (15.7)	58.4 (15.5)	0.66
Female	248 (52%)	239 (50%)	0.61
BMI, mean (SD)	28.1 (6.5)	27.7 (6.8)	0.31
Race			0.2
Non-white	48 (10%)	60 (12%)	
White	419 (87%)	395 (82%)	
Unknown	13 (3%)	25 (5%)	
Year			0.88
2012	15 (3%)	15 (3%)	
2013	152 (32%)	161 (34%)	
2014	182 (38%)	183 (38%)	
2015	131 (27%)	121 (25%)	
ASA Class			0.07
I–II	255 (53%)	284 (59%)	
III–V	225 (47%)	196 (41%)	
Prior pelvic or colon surgery[1]	201 (42%)	201 (42%)	0.99
Indication			0.86
Cancer	282 (59%)	282 (59%)	
Diverticulitis	64 (13%)	72 (15%)	
Inflammatory bowel disease	72 (15%)	69 (14%)	
Other indication[2]	62 (13%)	57 (12%)	
Surgical type			0.65
Colon Resection	359 (75%)	366 (76%)	
Rectal Resection	121 (25%)	114 (24%)	
Ostomy Created	91 (19%)	91 (19%)	0.99
Insurance type			0.99
Private insurance	249 (52%)	248 (52%)	
Non-private insurance	231 (48%)	232 (48%)	
Serious adverse events	45 (9%)	34 (7%)	0.24
Length of Stay, mean (SD), day	5.8 (4.5)	5.9 (4.9)	0.92
Prolonged length of stay (≥8 days)	98 (20%)	75 (16%)	0.05

[1] Prior pelvic or colon surgery includes hysterectomy, cholecystectomy, appendectomy and small bowel and colon resections in the pelvic area.

[2] Other indications include arterial malformation, iatrogenic injury, rectal prolapse, stricture, or gynecologic malignancy