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Preoperative Immunonutrition Modulates Inflammatory Cytokine Expression in Colorectal Cancer: Findings from a Pilot Randomized Clinical Trial

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ABSTRACT

Surgery is the cornerstone treatment for colorectal cancer, and preoperative nutritional support is commonly used to reduce perioperative complications. Immunonutrition, in particular, is suggested to enhance outcomes, but its direct effects on tumor-associated inflammation are not well established. In this pilot randomized trial, 26 patients undergoing colonoscopy at diagnosis provided baseline blood and tumor samples (sample A). Patients were assigned to either standard oral nutritional supplements (3× Nutricia Nutridrink Protein daily; group 1) or immune-enriched supplements (2× Nestle Impact Oral daily; group 2) for two weeks before surgery. Tumor tissue was subsequently collected at resection (sample B). We assessed perioperative changes in inflammatory mediators, including TNF-α, CXCL8, SDF1a, CXCL6, CXCL2, MPO, and CXCL1, as well as leukocyte infiltration.
TNF-α levels differed between groups after supplementation (immune: 31.63 ± 13.28 vs control: 21.54 ± 6.84; p = 0.049) and decreased in the control group from baseline (35.68 ± 24.41 to 21.54 ± 6.84; p = 0.038). CXCL8 expression also declined in the control group (2975.93 ± 1484.04 to 1584.85 ± 1659.84; p = 0.041). CXCL1 increased in the immune group but decreased in controls (2698.27 [1538.14–5124.70] vs 953.75 [457.85–1534.60]; p = 0.032). Both groups exhibited reduced superficial neutrophil infiltration, statistically significant only in the immune group. Surgical outcomes, including complications, length of stay, and readmission rates, were similar across groups. Short-term preoperative immunonutrition appears to alter tumor inflammatory signaling and immune cell infiltration in colorectal cancer, highlighting potential immunomodulatory effects independent of immediate surgical outcomes.

Keywords: Immunonutrition, Colorectal cancer, Tumor inflammation, Perioperative nutrition, Randomized trial

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Introduction

Surgical intervention remains the mainstay treatment for colorectal cancer. Preoperative oral nutritional supplementation (ONS) is widely employed to mitigate perioperative complications, particularly in patients with malnutrition, which is a major contributor to adverse postoperative outcomes across cancer types [1–4]. While conventional nutritional support is broadly accepted, immunonutrition—comprising nutrients that modulate immune function such as arginine, glutamine, omega-3 fatty acids, nucleotides, and zinc—has not been universally adopted. Evidence indicates that immunonutrition may reduce postoperative infectious complications compared with standard ONS [5, 6]; however, these findings pertain primarily to short-term clinical endpoints. The influence of immunonutrition on tumor biology remains largely unexplored. Experimental studies provide conflicting evidence: some suggest potential promotion of tumor progression [7, 8], whereas others indicate beneficial immunomodulatory effects [9]. No clinical trials have yet assessed the direct impact of immunonutrition on tumor tissue in vivo. Given its established perioperative benefits, investigating whether immunonutrition affects tumor inflammation and immune cell infiltration is critical. To address this gap, we conducted a

randomized controlled study to compare the effects of preoperative immunonutrition versus standard nutritional support on inflammatory cytokine expression and leukocyte infiltration in colorectal tumor tissue.

Materials and Methods

Study design

This was a single-center, randomized, controlled, non-inferiority trial with two parallel arms, conducted between November 2017 and November 2018 at a tertiary university hospital in Krakow, Poland. The study protocol received ethical approval and was registered on ClinicalTrials.gov (NCT04732442).

Participants

Patients aged 18 years or older with a confirmed diagnosis of colorectal adenocarcinoma were eligible. Exclusion criteria included: non-adenocarcinoma histology, urgent or emergency surgery, active infection, inflammatory or systemic immune disorders, prior neoadjuvant therapy, metastatic disease, T4 tumors on preoperative CT, and inability to adhere to at least 85% of the prescribed ONS regimen. After informed consent, participants were randomized to receive either immune-enriched ONS (group 1) or standard ONS (group 2) during the two weeks preceding elective surgery.

Randomization procedure

Randomization was performed using a computer-generated even/odd allocation sequence following colonoscopy, which confirmed tumor location and allowed collection of baseline tissue and blood samples for histopathological and molecular analysis. The investigator responsible for randomization did not participate in perioperative care to maintain allocation concealment.

Study protocol

Eligible patients were informed about trial participation during the initial surgical consultation. Colonoscopy, performed several weeks prior to surgery, provided tumor tissue samples for histopathology (three samples) and molecular assays (three samples) alongside standard diagnostic biopsies to assess immune cell infiltration. Blood samples were simultaneously collected for biochemical analysis. All specimens were immediately frozen at −80 °C for later analysis. Baseline demographic and clinical data, including age, sex, body mass index (BMI), smoking history, preoperative immunosuppression, and comorbidities, were recorded. After adenocarcinoma diagnosis and clinical staging, patients were randomized into the study groups.

Nutritional intervention

Participants assigned to the control group received conventional preoperative nutrition in the form of three daily servings of Nutridrink Protein® (Nutricia, UK) over a two-week period before surgery. The intervention group was provided with immune-enhanced oral nutritional supplements, specifically two daily doses of Impact Oral® (Nestlé, Switzerland), for the same duration. Patients were instructed to avoid any additional dietary supplements or functional foods throughout the study period. All participants were managed according to the Enhanced Recovery After Surgery (ERAS) guidelines for colorectal procedures [2]. Elective tumor resections were performed laparoscopically following established surgical protocols [10]. On the day of surgery, blood samples were collected for biochemical analysis. Tumor specimens were promptly dissected in the operating room, and tissue samples were harvested for molecular and histological analysis. Adherence to the nutritional regimen and perioperative protocols was closely monitored; patients who failed to complete at least 85% of the prescribed intervention or recommendations were excluded from subsequent analyses.

Perioperative management

All participants underwent standardized perioperative care consistent with the colorectal ERAS protocol [2], as previously implemented in our center, including preoperative optimization, anesthesia, and postoperative recovery measures.

Cytokine profiling in tumor tissue

Tumor biopsies obtained during colonoscopy were immediately frozen at −80 °C for molecular assessment. Cytokines quantified included TNF-α, CXCL8, SDF1a, CXCL6, CXCL2, MPO, and CXCL1. Following surgical

resection, tumor tissue was processed in the same manner to ensure consistency. Serum cytokine levels were measured using Luminex MagPlex Microsphere assays (Merck, Burlington, MA, USA) on the Luminex MAGPIX System (Luminex Corp., Austin, TX, USA), with results normalized to total protein (pg/100 µg) according to the manufacturer's instructions and previous protocols [11].

Assessment of neutrophil infiltration

Tumor specimens from both colonoscopy and surgical resection were fixed in 10% buffered formalin and submitted for histopathological evaluation. Neutrophil infiltration was quantified separately in epithelial and stromal compartments at superficial and deeper layers (up to 100 µm beneath the epithelial surface) by counting neutrophils in ten high-power fields per section.

Study endpoints

Primary outcome

The principal outcome was the variation in tumor tissue cytokine expression following the preoperative nutritional intervention.

Secondary outcome

The secondary outcome was the change in neutrophil infiltration within tumor tissue after supplementation.

Sample size estimation

Based on prior data showing TNF-α concentrations of 38 ± 20 pg/100 µg in controls, a 60% anticipated increase in TNF-α expression guided the sample size calculation. To achieve 80% power at a 0.05 significance level, 24 patients were required. Considering potential dropouts, 14 patients per group were targeted.

Statistical analysis

Data were presented as mean ± SD for normally distributed continuous variables or median (IQR) for non-normal data. Comparisons used Student's t-test, Mann–Whitney U, or Wilcoxon signed-rank tests as appropriate. Categorical variables were analyzed via chi-squared tests, with Yates' correction or Fisher's exact test when necessary. A two-sided p-value <0.05 was considered significant. Analyses were performed using Statistica 13.5 (TIBCO Software, Palo Alto, CA, USA).

Results and Discussion

Among 29 randomized patients, three (10%) were excluded due to insufficient compliance with the prescribed nutritional intervention (<85% of ONS doses). One additional patient was excluded after allocation due to rescheduling of surgery. The flow of participants through the study is depicted in **Figure 1**.

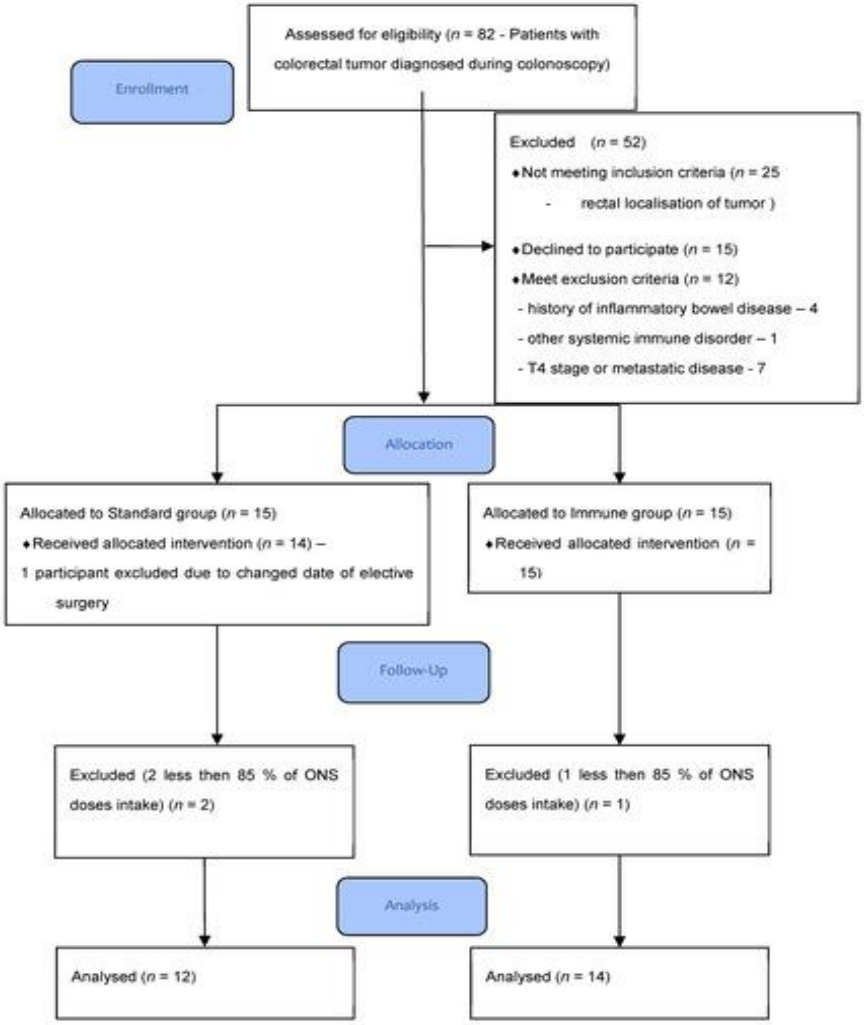

Figure 1. Patients flow-chart.

The demographic and baseline clinical characteristics of participants are presented in **Table 1**, with corresponding laboratory parameters detailed in **Table 2**. Although both total serum protein and albumin levels rose over the preoperative period, the increase was more pronounced in the immunonutrition group; however, these differences did not achieve statistical significance.

Analysis of tumor tissue cytokines before and after supplementation is summarized in **Table 3**. Following the intervention, TNF-α levels were higher in the immunonutrition group compared with controls (31.63 ± 13.28 vs. 21.54 ± 6.84 pg/100 µg, p = 0.049). In the control group, TNF-α decreased significantly relative to baseline values (35.68 ± 24.41 pre-intervention vs. 21.54 ± 6.84 post-intervention, p = 0.038). CXCL8 expression also declined in the control group after supplementation (2975.93 ± 1484.04 vs. 1584.85 ± 1659.84 pg/100 µg, p = 0.041). Conversely, CXCL1 concentrations increased in the immunonutrition group (2698.27 [1538.14–5124.70] pg/100 µg) while declining in the control group (953.75 [457.85–1534.60] pg/100 µg, p = 0.032).

Histopathological evaluation of neutrophil infiltration is reported in **Table 4**. At baseline, there were no significant differences between groups in either superficial or deeper tissue layers. After the intervention, both groups exhibited a reduction in superficial neutrophil infiltration, reaching statistical significance only in the immunonutrition group. Deep-layer neutrophil counts decreased in both groups, but these changes were not statistically significant.

Postoperative outcomes were comparable between groups. The incidence of complications was similar (immune group: 4/14, 28.5%; control group: 3/12, 25%; p = 0.91). Median length of hospital stay did not differ (immune: 5 days [range 4–15]; control: 5 days [range 4–9]; p = 0.84). No mortality was reported, and only one patient in the control group required readmission.

Table 1. Demographic analysis of patient groups.

Parameter	Group 1 IMMUNE	Group 2 CONTROL	p-Value
Number of patients, n	14	12	-
Females, n (%)	7 (50.0%)	7 (58.3%)	0.6708
Males, n (%)	7 (50.0%)	5 (41.7%)	
Mean age, years ± SD	69.9 ± 10.9	68.4 ± 7.62	0.6908
Body mass index (BMI), kg/m^2 ± SD	29.2 ± 5.5	27.8 ± 3.9	0.2565
ASA 1, n (%)	1 (7.1%)	1 (8.3%)	0.8402
ASA 2, n (%)	8 (57.1%)	8 (66.7%)	
ASA 3, n (%)	5 (35.7%)	3 (25.0%)	
Any comorbidity, n (%)	12 (85.7%)	8 (66.7%)	0.2504
Cardiovascular, n (%)	5 (35.7%)	3 (25.0%)	0.5551
Hypertension, n (%)	10 (71.4%)	7 (36.1%)	0.4849
Diabetes, n (%)	2(14.2%)	3 (25.0%)	0.4895
Renal disease, n (%)	1 (7.1%)	1 (8.3%)	0.7587
Other comorbidity, n (%)	2 (14.2%)	1 (8.3%)	0.9095
Smoking, n (%)	3 (21.4%)	2 (16.7%)	0.6357
AJCC Stage I, n (%)	3 (21.4%)	2 (16.7%)	0.4241
AJCC Stage II, n (%)	4 (28.6%)	6 (50.0%)	0,004
AJCC Stage III, n (%)	6 (42.9%)	2 (16.7%)	-0,03
AJCC Stage IV, n (%)	1 (7.1%)	2 (16.7%)	0,004
NRS 2000 median, (IQR)	2 (1–3)	2 (1–3)	-0,037 0.7970
Tumor location			
Cecum, n (%)	3 (21.4%)	2 (16.7%)	0.7865
Ascending colon, n (%)	1 (7.1%)	3 (5.5%)	-0,051
Transvers colon n (%)	2 (14.2%)	1 (36.1%)	-0,054
Descending colon n (%)	1 (7.1%)	1 (11.1%)	0,006
Sigmoid colon, n (%)	7 (50.0%)	5 (41.7%)	-0,038
Grading			
G1	3 (21.4%)	1(8.3%)	0.6533
G2	10(71.5%)	11(91.7%)	
G3	1 (7.1%)	-	

SD—Standard Deviation, ASA score—American Society of Anesthesiologists score, AJCC—American Joint Committee on Cancer, NRS—Nutrition Risk Screening, IQR—Interquartile range, G1-G3—Grading score 1–3.

Table 2. Blood parameters.

Parameter	Group 1 IMMUNE	Group 2 CONTROL	p-Value
Number of patients, n	14	12	-
Median WBC before intervention, 10^3/mL (IQR)	6.60 (5.33–8.31)	8.11 (6.16–9.28)	0.1983
Median WBC after intervention, 10^3/mL (IQR)	6.49 (5.59–8.96)	7.34 (6.06–8.15)	0.9350
p-value	0.2945	0.5751	
Median neutrophil before intervention, 10^3/mL (IQR)	4.25 (5.40–2.15)	4.90 (3.20–5.80)	0.1063
Median neutrophil after intervention, 10^3/mL (IQR)	3.80 (2.82–5.50)	4.72 (2.94–5.20)	0.7281
p-value	0.9165	0.9528	
Median lymphocytes before intervention, 10^3/mL (IQR)	1.74 (1.57–2.47)	1.80 (1.53–2.46)	0.9128
Median lymphocytes after intervention, 10^3/mL (IQR)	1.83 (1.50–2.60)	1.86 (1.56–2.44)	0.8167
p-value	0.4421	0.9528	

Median plasma protein before intervention, g/L (IQR)	65.4 (59.0–72.0)	68.0 (68.8–73.4)	0.4250
Median plasma protein after intervention, g/L (IQR)	69.5 (64.0–72.0)	67.5 (59.5–70.0)	0.3913
p-value	0.7221	0.4990	
Median plasma albumin before intervention, g/L (IQR)	38.6 (35.9–42.0)	42.0 (38.1–50,2)	0.9212
Median plasma albumin after intervention, g/L (IQR)	40.0 (35.0–44.7)	39.9 (35.6–43.0)	0.2390
p-value	0.8588	0.2626	

WBC—White Blood Cells.

Table 3. Comparison of differences of selected cytokines in tumor tissue concentration before and after intervention.

	Group 1—IMMUNE		**p-Value**	**Group 2—CONTROL**		**p-Value**	**p-Value of Comparison of Changes in Parameters**
TNF-α (pg/100 ug total protein) mean ± SD	27.79 ± 14.01	31.63 ± 13.28	0.551	35.68 ± 24.41	21.54 ± 6.84	0.038	0.049
CXCL8 (pg/100 ug total protein) mean ± SD	2608.87 ± 1715.15	2676.41 ± 1530.15	0.910	2975.93 ± 1484.04	1584.85 ± 1659.84	0.041	0.095
SDF-1a (pg/100 ug total protein) median (IQR)	399.94 (319.78–469.63)	469.63 (395.47–565.72)	0.477	421.01 (384.89–501.80)	358.68 (333.02–371.16)	0.823	0.205
CXCL6 (pg/100 ug total protein) median (IQR)	247.73 (109.53–467.97)	241.76 (155.02–372.85)	0.309	238.11 (103.41–371.02)	133.14 (92.60–197.79)	0.671	0.640
CXCL2 (pg/100 ug total protein) mean ± SD	625.63 ± 793.10	879.19 ± 1008.23	0.438	631.87 ± 570.80	301.03 ± 287.39	0.407	0.261
MPO (pg/100 ug total protein) mean ± SD	54,176.82 ± 36,077.57	63,096.97 ± 38,509.00	0.473	51,313.49 ± 21,340.86	51,114.38 ± 30,976.68	0.935	0.655
CXCL1 (pg/100 ug total protein) median (IQR)	1902.86 (1170.34–3517.76)	2698.27 (1538.14–5124.70)	0.821	2144.59 (808.68–5933.12)	953.75 (457.85–1534.60)	0.403	0.032

TNF-α—tumor necrosis factor, CXCL8—interleukin 8 or chemokine (C-X-C motif) ligand, SDF-1a—stromal cell-derived factor 1 also known as CXCL-12, CXCL6—chemokine (C-X-C motif) ligand 6, CXCL2—chemokine (C-X-C motif) ligand 2, MPO—myeloperoxidase, CXCL1—chemokine (C-X-C motif) ligand 1.

Table 4. Histopatological outcomes.

Parameter	**Group 1 IMMUNE**	**Group 2 CONTROL**	**p-Value**
Number of patients, n	14	12	-
Median superficial neutrophil infiltration prior to intervention, n/HPF (IQR)	47 (31.5–82)	61 (35–88)	0.5022
Median superficial neutrophil infiltration post-intervention, n/HPF (IQR)	39 (31–57)	59 (50–86)	0.0033
p-value	0.2651	0.1709	-
Median deep neutrophil infiltration prior to intervention, n/HPF (IQR)	51 (27.5–93.5)	54 (28–87)	0.9341
Median deep neutrophil infiltration post-intervention, n/HPF (IQR)	36 (27–50)	37 (31–50)	0.7775
p-value	0.0865	0.6071	-
Median change in total (superficial + deep) neutrophil infiltration between pre- and post-intervention, n/HPF (IQR)	−21 (−80.5–68.5)	−5 (−45–64)	0.5458

HPF—high-power field.

This study demonstrates that preoperative immunonutrition in patients with colorectal cancer exerts measurable effects not only systemically, as previously reported [5], but also within tumor tissue itself. To our knowledge,

this represents the first prospective randomized clinical trial to evaluate the direct impact of immune-enhanced nutrition on tumor biology. While prior studies have assessed immunonutrition in relation to perioperative outcomes [6, 12], none have explored its influence at the tissue level.

Both standard nutritional support and immune-enriched ONS improved the preoperative nutritional status of participants. Following the intervention, no patient exhibited clinical or laboratory signs of malnutrition, and all had a BMI above 21.5 kg/m². Only nine participants scored 3 or 4 on the NRS 2002 scale, with five of them aged over 70 years (receiving +1 point per the scale). Although total serum protein and albumin levels increased more in the immunonutrition group, these differences did not reach statistical significance. This likely reflects the relatively well-nourished status of most patients; as expected, nutritional improvements are more pronounced in malnourished individuals [13, 14]. These findings align with prior research demonstrating the benefits of both standard and immune-enriched nutritional interventions on preoperative patient status in colorectal surgery [15, 16].

No statistically significant differences were observed between groups in postoperative outcomes, including morbidity, length of hospital stay, readmissions, or mortality; however, the study was not designed to detect differences in these endpoints.

Given the critical role of chemokines in directing immune cell migration and orchestrating antitumor responses [17–19], we focused on key chemokines associated primarily with neutrophil recruitment as a proxy for overall immune activation in the tumor microenvironment. While lymphocytes, including NK and Th1 cells, are central to cancer immune surveillance, their regulation is highly complex due to the converging and diverging effects of multiple cytokines [20–22]. In this context, evaluating neutrophil-targeted chemokines provides insight into the broader immune-modulatory effects of preoperative nutrition.

Our results suggest that immunonutrition tended to increase the levels of all analyzed chemokines (except CXCL3) and MPO, although these trends did not reach statistical significance, likely due to the limited sample size. Conversely, the control group exhibited a downward trend, with TNF-α and CXCL8 decreasing significantly. Importantly, TNF-α and CXCL1 levels differed significantly between the groups post-intervention. TNF-α plays a pivotal role in immune regulation, inflammation, and apoptosis, and may inhibit tumor progression [23–25]. CXCL1, produced by multiple immune and epithelial cell types and inducible via IL1, TNF-α, or IL17 signaling through NF-κB or C/EBPβ pathways, has dual roles: it recruits immune cells but may also promote tumor angiogenesis and growth [26–31]. Similarly, CXCL8 is central to neutrophil recruitment and activation [32] and can act as an autocrine growth factor in colorectal cancer [33]. In our study, CXCL8 did not increase in the immune group, suggesting that immunonutrition did not enhance its potential pro-tumorigenic effects.

We also observed a modest increase in MPO levels in the immune group, consistent with neutrophil activation, although this change was not statistically significant. MPO, predominantly expressed in neutrophils, catalyzes the production of antimicrobial agents such as hypochlorous acid [34]. This finding implies that immunonutrition primarily stimulates neutrophil-related immune activity rather than directly affecting tumor cells.

Due to the small sample size and short-term follow-up, the clinical relevance of these immunological changes remains unclear. Likewise, histopathological analyses revealed only limited differences in neutrophil infiltration, making it difficult to draw conclusions regarding the functional impact on tumor progression.

It also remains uncertain which components of immunonutrition mediate these effects. Arginine is a likely candidate, serving as a substrate for inducible nitric oxide synthase (iNOS) and modulating both innate and adaptive immune responses [9]. However, iNOS exhibits a dual role in cancer, either promoting or inhibiting tumor growth depending on tumor type, cellular context, and microenvironment [9]. Clinical evidence supports arginine supplementation in improving postoperative outcomes and survival in head and neck cancer [35], and colorectal cancer may similarly benefit due to high expression of argininosuccinate synthase (ASS1) [36]. Nonetheless, further mechanistic and clinical studies are required to clarify these observations and confirm their relevance in colorectal malignancies.

Omega-3 fatty acids and nucleotides

The role of omega-3 polyunsaturated fatty acids in modulating inflammation and cytokine production remains incompletely understood. Their impact within immunonutrition is likely linked to alterations in eicosanoid profiles [37]. By modifying the ratio of omega-3 to omega-6 fatty acids in cell membranes, these nutrients influence the spectrum of prostaglandins and leukotrienes, which generally exert a lower pro-inflammatory effect compared with omega-6-derived mediators [38]. Such shifts in eicosanoid balance could potentially affect the activation of

lymphocytes and macrophages, thereby altering cytokine secretion and influencing neutrophil infiltration in tumor tissue. However, these mechanisms have not yet been thoroughly examined in clinical trials, and further investigation is warranted to validate these hypotheses.
Regarding nucleotides, current literature does not indicate a direct role in cytokine regulation. Their presumed contribution in immunonutrition is primarily related to compensating for relative shortages during periods of heightened immune cell activity. In our study, this component did not appear to exert a detectable effect.

Implications for clinical practice
Clinical evidence supports the beneficial effects of immunonutrition in patients with head and neck [39], gastric [40], and colorectal cancers [6]. Based on these data, it is plausible that similar benefits could extend to other solid tumors requiring major surgical intervention. Nevertheless, the impact of immunonutrition on tumor biology remains largely unexplored, emphasizing the need for further mechanistic and clinical studies.

Limitations
Several limitations should be acknowledged. First, discrepancies were observed between the TNF-α values in this study and those assumed during the sample size calculation. Post-hoc analysis indicated that, despite statistically significant differences, the power to detect changes in TNF-α was only 49%. Second, because the intervention used a single complex immunonutrition formula, it is not possible to identify which specific component contributed most to the observed effects. Third, the study population was limited to patients with colorectal cancer, limiting generalizability to other tumor types. Additionally, this study assessed changes only at the molecular and microscopic level, without demonstrating clinically meaningful effects on tumor progression or patient outcomes. Finally, being a single-center study, these findings require validation in larger, multicenter cohorts.

Conclusion

Preoperative immunonutrition may modulate the inflammatory milieu within colorectal tumor tissue compared with standard nutritional support. Specifically, differences in cytokine expression and neutrophil infiltration were observed following immune-enhanced supplementation. Further research is needed to elucidate the underlying mechanisms and to determine the clinical significance of these molecular and histological changes in relation to oncologic outcomes and perioperative care in colorectal cancer.

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