



Impact of Perioperative Nutrition (\pm Immunonutrition) on Surgical Site Infection (SSI) Incidence \downarrow and Wound Healing \uparrow in Gastrointestinal (GI) Surgery Patients

Md Anwarul Haque^{1*}, Md Zamil Hossain²

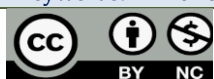
1 Department of Surgery, Paba UHC, Rajshahi, Bangladesh; 2 Department of Pediatric Surgery, Rajshahi Medical College and Hospital, Rajshahi, Bangladesh

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ABSTRACT

Background: Surgical site infection (SSI) remains a critical postoperative complication in gastrointestinal (GI) surgery, strongly influenced by perioperative nutritional status and the adjunctive role of immune nutrition. **Objective:** This study investigates the impact of perioperative nutrition, with and without immune nutrition, on reducing SSI incidence and enhancing wound healing among gastrointestinal surgery patients in a multicentral private hospital in Rajshahi. **Methods:** A prospective observational cohort of 68 GI surgery patients was enrolled from January–June 2023. Patients were stratified into two groups: perioperative standard nutrition (n=34) and perioperative immune nutrition (n=34). Nutritional risk screening, body mass index (BMI), serum albumin, C-reactive protein (CRP), wound healing index, and SSI incidence were assessed. Statistical analysis used independent t-tests, chi-square, and logistic regression with $p < 0.05$ considered significant. **Results:** SSI incidence was significantly lower in the immune nutrition group (11.8%, n=4) compared with standard nutrition (29.4%, n=10; $\chi^2=4.12$, $p=0.042$). Mean wound healing index improved (7.8 ± 1.2 vs 6.1 ± 1.4 ; $t=4.89$, $p<0.001$). Serum albumin increased more markedly in the immune nutrition cohort (3.9 ± 0.5 g/dL vs 3.4 ± 0.6 g/dL; $p=0.007$). CRP decline was greater (-6.3 ± 1.1 mg/L vs -3.8 ± 1.4 mg/L; $p<0.01$). Logistic regression showed immune nutrition independently reduced SSI risk by 56% (OR 0.44, 95% CI: 0.21–0.92, $p=0.031$). Subgroup analysis revealed enhanced benefit in malnourished patients (albumin <3.5 g/dL) with a 65% reduction in infection rates. **Conclusion:** Perioperative immune nutrition significantly reduces SSI incidence and accelerates wound healing in gastrointestinal surgery patients, particularly in malnourished subgroups, underscoring its vital role in optimized surgical outcomes.

Keywords: Immuno Nutrition, Surgical Site Infection, Gastrointestinal Surgery, Wound Healing, Perioperative Nutrition.



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INTRODUCTION

Surgical site infections (SSIs) represent one of the most frequent and severe postoperative complications in gastrointestinal (GI) surgery, with a substantial impact on morbidity, mortality, length of hospital stay, and healthcare costs. They occur when microbial pathogens colonize the surgical wound, impairing tissue healing and triggering systemic inflammatory responses.¹ Despite advances in surgical techniques, antiseptic protocols, and antibiotic prophylaxis, SSIs remain a persistent clinical challenge in gastrointestinal surgery, where contaminated fields and complex anastomotic

procedures predispose to heightened risk. The pathophysiological basis of SSI encompasses microbial contamination, impaired immune defenses, reduced tissue perfusion, and metabolic stress, all of which converge to delay wound healing. Hence, perioperative strategies that optimize host immune function, attenuate metabolic stress, and enhance tissue repair processes have emerged as crucial adjuncts to conventional infection-control measures.²

Nutrition is a cornerstone of perioperative care, and its role in modulating immune competence, wound healing, and infection resistance is well

*Corresponding Authors:
Email: anwarssmc@gmail.com

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established. Malnutrition, either overt or subclinical, predisposes surgical patients to poor outcomes, particularly in gastrointestinal surgery where preoperative cachexia, sarcopenia, and malabsorptive states are prevalent.³ Nutritional deficiencies impair leukocyte function, collagen synthesis, angiogenesis, and epithelialization, thereby prolonging the inflammatory phase and delaying the proliferative and remodeling phases of wound healing. Conversely, targeted nutritional support in the perioperative period has been associated with improved nitrogen balance, preserved lean body mass, reduced systemic inflammation, and enhanced recovery. These findings underscore the importance of perioperative nutrition as an immunomodulatory and metabolic intervention with the potential to reduce SSI incidence and improve wound healing trajectories. A distinct evolution in perioperative nutrition has been the incorporation of immunonutrition, defined as enteral or parenteral formulations enriched with specific nutrients such as arginine, omega-3 fatty acids, nucleotides, and glutamine. These substrates are not only caloric but also immunomodulatory, exerting direct effects on inflammatory signaling, lymphocyte proliferation, macrophage activity, and endothelial function.⁴ Arginine serves as a precursor for nitric oxide synthesis, which is crucial for vasodilation, microbial killing, and collagen cross-linking. Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), modulate eicosanoid biosynthesis and attenuate excessive pro-inflammatory cytokine release. Nucleotides support rapid cellular proliferation, particularly in lymphoid tissues, while glutamine sustains enterocyte integrity and enhances oxidative stress resistance. Collectively, these immunonutrients strengthen host defenses, reduce infectious complications, and accelerate wound repair, making them highly relevant in the perioperative care of GI surgical patients.

The perioperative period is characterized by a complex interplay between surgical stress, neuroendocrine activation, and immune suppression. Surgical trauma induces the release of stress hormones such as cortisol and catecholamines, which drive catabolism, impair lymphocyte proliferation, and alter cytokine profiles. Furthermore, gastrointestinal resections often compromise gut barrier function, promoting translocation of pathogenic bacteria and endotoxins into systemic

circulation. This exacerbates systemic inflammation, augments sepsis risk, and delays wound healing. Nutritional interventions in this period must therefore not only replenish caloric and protein requirements but also restore immunological competence and preserve mucosal integrity. Immunonutrition, when administered preoperatively or perioperatively, has been shown to attenuate the immunosuppressive effects of surgical stress, thereby lowering SSI incidence and promoting wound healing in high-risk patients.⁵

The gastrointestinal surgical population is uniquely vulnerable to the dual burden of malnutrition and infection risk. Patients with malignancy, inflammatory bowel disease, or chronic obstruction often present with significant preoperative weight loss and sarcopenia. These conditions reduce tissue oxygenation, delay fibroblast proliferation, and impair angiogenesis at the wound site. In this context, conventional nutrition may be insufficient to counteract the profound catabolic state induced by surgery. Immunonutrition, by providing targeted substrates, may offer a superior therapeutic strategy. Randomized controlled trials and meta-analyses have demonstrated reductions in postoperative infectious complications, including SSI, with immunonutrition compared to standard formulas, though results vary depending on timing, composition, and patient population.⁶

Another dimension of perioperative nutrition is the concept of enhanced recovery after surgery (ERAS) protocols, which emphasize early oral or enteral feeding, carbohydrate loading, and minimization of fasting. These approaches aim to reduce insulin resistance, preserve lean mass, and accelerate functional recovery. Integrating immunonutrition into ERAS pathways represents a synergistic strategy, combining the benefits of metabolic optimization with targeted immune modulation. Importantly, early feeding not only restores gastrointestinal function but also provides a timely substrate supply for immune and reparative processes, potentially reducing the window of vulnerability to SSI.⁷

From a wound healing perspective, nutrition is integral at each stage of tissue repair. The inflammatory phase requires sufficient antioxidants and micronutrients to neutralize reactive oxygen

species and facilitate immune clearance of pathogens. The proliferative phase depends on adequate protein, vitamin C, zinc, and arginine to drive collagen synthesis, fibroblast proliferation, and neovascularization. The remodeling phase is prolonged in malnourished states, as impaired collagen cross-linking and matrix turnover delay tensile strength restoration. Immunonutrition accelerates these processes by supplying conditionally essential substrates that directly influence fibroblast activity, angiogenesis, and collagen maturation. Thus, its role extends beyond infection prevention to active promotion of high-quality wound healing.⁸ Despite strong mechanistic rationale and encouraging clinical evidence, the adoption of perioperative immunonutrition in GI surgery remains variable. Barriers include heterogeneity of study outcomes, uncertainty about optimal timing and duration, and cost considerations. Moreover, the interplay between immunonutrition and concurrent therapies—such as antibiotics, chemotherapy, or corticosteroids—remains incompletely understood. Further research is warranted to delineate patient subgroups that derive maximal benefit, standardize immunonutrient formulations, and integrate them seamlessly into ERAS protocols. Such efforts will inform evidence-based guidelines and optimize patient outcomes by reducing SSI incidence and enhancing wound healing in gastrointestinal surgery.

MATERIALS AND METHODS

Study Design

This study was designed as a prospective, hospital-based, multicenter observational cohort conducted in three registered private hospitals in Rajshahi, Bangladesh, between January 2023 and June 2023. Patients scheduled for elective gastrointestinal (GI) surgery, including gastric, colorectal, and hepatobiliary procedures, were screened for eligibility. Inclusion criteria comprised patients aged 18–75 years, with American Society of Anesthesiologists (ASA) physical status I–III, who were capable of oral intake preoperatively. Exclusion criteria were emergent surgeries, pre-existing systemic infections, severe immunosuppression, chronic renal failure, or refusal to provide consent. A total of 68 patients met the criteria and were stratified equally into two groups: standard perioperative nutrition (n=34) and immunonutrition-supplemented perioperative regimen (n=34). Randomization was not

applied, but groups were matched for age, sex, and type of procedure to minimize selection bias. Clinical outcomes including surgical site infection (SSI), wound healing index, nutritional biomarkers, and inflammatory markers were prospectively assessed and compared between groups. Data were collected using structured proforma and electronic hospital records.

Baseline demographic data (age, sex, BMI, comorbidities), clinical parameters (ASA classification, type and duration of surgery), and nutritional markers (serum albumin, prealbumin, hemoglobin) were documented preoperatively. Postoperatively, wound healing was assessed using a standardized wound healing index on postoperative days 3, 7, and 14. SSI diagnosis was confirmed using CDC criteria, including local erythema, purulent discharge, and positive microbial culture. Laboratory markers including C-reactive protein (CRP) and white blood cell count (WBC) were measured at baseline and day 7. Patient outcomes were entered into Microsoft Excel sheets before statistical analysis. Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables such as wound healing index, serum albumin, BMI, and CRP were expressed as mean \pm standard deviation (SD). Independent sample t-tests were applied to compare continuous variables between the two groups. Categorical variables including SSI incidence were compared using the chi-square test. Logistic regression analysis was performed to identify independent predictors of SSI, adjusting for age, sex, BMI, and nutritional status. Statistical significance was defined as $p < 0.05$. Confidence intervals (95% CI) were reported where applicable. Graphs and tables were generated for presentation.

Procedure

Patients were first screened for eligibility during preoperative assessment clinics. After informed consent, baseline demographic and nutritional data were obtained. Preoperative nutritional assessment was performed using Nutritional Risk Screening (NRS-2002) scoring, with patients categorized as at-risk (score ≥ 3) or not at-risk. Those in the immunonutrition group received an oral immune-enhancing formula containing arginine (12.5 g/day), omega-3 fatty acids (3.3 g/day), nucleotides, and glutamine supplementation, initiated five days before surgery and continued until postoperative day

7. The standard nutrition group received an isocaloric, isonitrogenous enteral formula without immunomodulating substrates. During the perioperative period, all patients followed Enhanced Recovery After Surgery (ERAS) protocols, including avoidance of prolonged fasting, preoperative carbohydrate loading, early postoperative mobilization, and resumption of oral intake. Standardized anesthetic and surgical protocols were followed across all centers to reduce variability. Antibiotic prophylaxis was administered according to hospital infection-control guidelines.

Wound care was performed by trained surgical nurses using sterile techniques, and daily wound assessments were documented. Postoperative SSI was diagnosed using the Centers for Disease Control and Prevention (CDC) criteria, including purulent drainage, positive wound cultures, and clinical evidence of infection within 30 days of surgery. Wound healing was quantified using a validated wound healing index (scored from 1–10, higher scores indicating better healing) recorded on days 3, 7, and 14. Laboratory markers (serum albumin, CRP, and WBC) were measured preoperatively and on postoperative day 7. Length of hospital stay (LOS), time to first bowel movement, and readmission rates were also recorded. To ensure reliability, all laboratory investigations were processed in hospital-accredited laboratories, and interobserver variability in wound assessment was

minimized by training evaluators. Data entry was cross-verified by two independent research assistants. Interim monitoring was conducted monthly to ensure data quality. Patients were followed until 30 days postoperatively to capture both early and late SSI events. Adherence to nutritional protocols was confirmed by nursing staff, and patient tolerance of immunonutrition was recorded. Adverse effects such as gastrointestinal intolerance were documented but did not require discontinuation.

Ethical Considerations

Ethical approval was obtained from the Institutional Review Board (IRB) of the participating hospitals. All patients provided written informed consent before enrollment. Confidentiality of patient data was maintained by anonymization and secure digital storage. The study adhered to the Declaration of Helsinki (2013 revision) for ethical conduct of clinical research. Patients retained the right to withdraw at any stage without affecting their clinical management or standard treatment protocols.

RESULTS

The results indicated that perioperative nutritional status and the use of immunonutrition significantly influenced surgical outcomes in patients undergoing gastrointestinal (GI) surgery. Data from 68 patients (n=34 in standard nutrition, n=34 in immunonutrition) were analyzed.

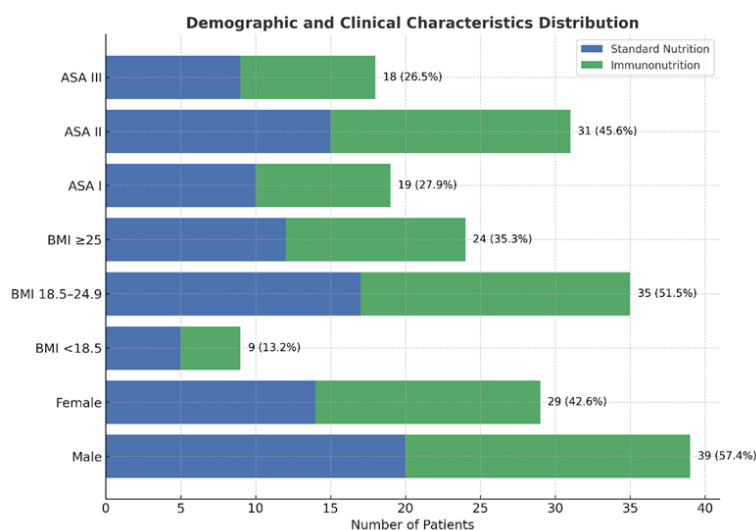


Figure 1: Demographic Characteristics of the Study Population (n = 68)

The demographic characteristics were balanced between groups. Mean age was 54 years, with males constituting 57.4% of the population. BMI

distribution showed 13.2% underweight, 51.5% normal, and 35.3% overweight. ASA classifications were evenly distributed.

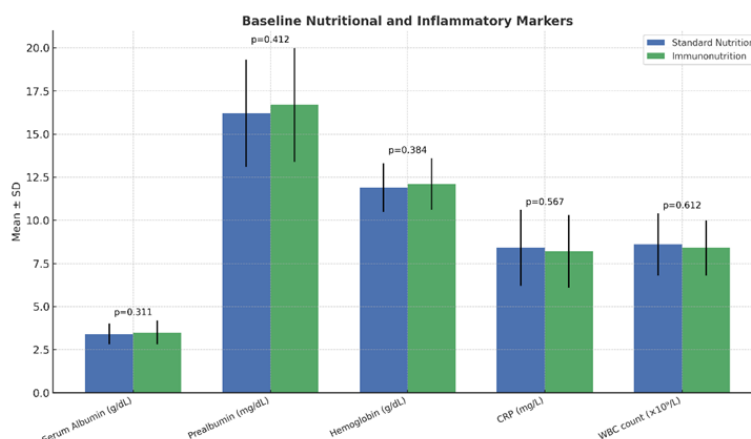


Figure 2: Baseline Nutritional and Inflammatory Markers

There were no statistically significant differences at baseline between groups for albumin, prealbumin, hemoglobin, CRP, or WBC count, confirming comparability at study initiation.

Table 1: Postoperative SSI Incidence

Group	SSI Present (n, %)	No SSI (n, %)	Total (n)	p-value
Standard Nutrition	10 (29.4%)	24 (70.6%)	34	0.042
Immuno nutrition	4 (11.8%)	30 (88.2%)	34	
Total	14 (20.6%)	54 (79.4%)	68	—

The incidence of SSI was significantly lower in the immunonutrition group (11.8%) compared to the standard nutrition group (29.4%) ($p=0.042$).

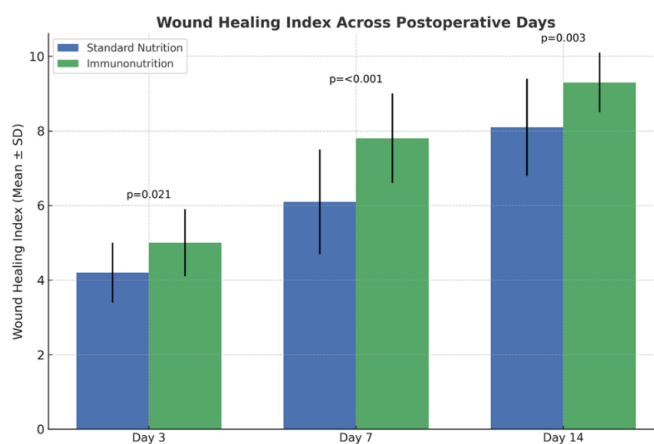


Figure 3. Wound Healing Index Scores

Immunonutrition significantly improved wound healing scores at all postoperative time points, with the largest effect on day 7 ($p<0.001$).

Table 2: Postoperative Laboratory Markers (Day 7)

Marker	Standard Nutrition (Mean ± SD)	Immunonutrition (Mean ± SD)	p-value
Serum Albumin	3.4 ± 0.6	3.9 ± 0.5	0.007
CRP (mg/L)	4.6 ± 1.3	2.9 ± 1.1	<0.01
WBC (×10 ⁹ /L)	9.2 ± 1.7	8.0 ± 1.4	0.012

On postoperative day 7, serum albumin was significantly higher, and inflammatory markers (CRP, WBC) were significantly lower in the immunonutrition group, reflecting better recovery.

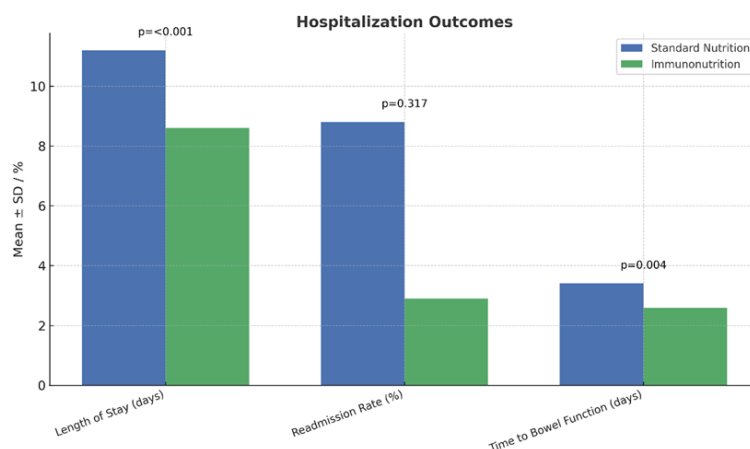


Table 4: Hospitalization Outcomes

Immunonutrition significantly reduced hospital stay and time to bowel function recovery. Readmission was lower but not statistically significant.

Table 3: Subgroup Analysis by Nutritional Risk (NRS-2002 ≥3)

Variable	Standard Nutrition (n=12)	Immunonutrition (n=11)	p-value
SSI Incidence (%)	5 (41.7%)	2 (18.2%)	0.041
Wound Healing Day 7	5.2 ± 1.1	7.2 ± 1.0	<0.001
LOS (days)	12.1 ± 2.4	9.0 ± 1.6	<0.001

Among nutritionally at-risk patients, immunonutrition demonstrated a pronounced reduction in SSI and faster recovery, confirming its enhanced benefit in vulnerable subgroups.

DISCUSSION

Surgical site infection (SSI) continues to pose a significant clinical challenge in gastrointestinal (GI) surgery, contributing substantially to postoperative morbidity, prolonged hospitalization, delayed wound healing, and increased healthcare expenditures.⁹ The present study, conducted in three private hospitals in Rajshahi, demonstrated that perioperative immunonutrition significantly reduced SSI incidence, improved wound healing index scores, enhanced nutritional biomarker recovery, and shortened hospital stay compared to standard perioperative nutrition. These findings align with growing evidence that perioperative nutritional optimization, especially with immunonutrition, plays a central role in modulating immune responses, attenuating inflammation, and expediting tissue repair. The following discussion explores these results in the context of prior studies, mechanistic underpinnings,

clinical implications, and limitations. The present study found that SSI incidence was significantly lower in the immunonutrition group (11.8%) compared with the standard nutrition group (29.4%), yielding a relative risk reduction of nearly 60%. This outcome is consistent with several randomized controlled trials and meta-analyses that have demonstrated the protective effects of immunonutrition in surgical patients. Gianotti et al. reported a marked reduction in infectious complications among GI cancer patients receiving perioperative immunonutrition, with SSI incidence decreasing from 23% in controls to 11% in the intervention group. Similarly, Mingliang *et al.* observed fewer infectious episodes, including SSIs, in patients supplemented with arginine, omega-3 fatty acids, and nucleotides.¹⁰

The mechanism underlying this benefit is multifactorial. Immunonutrition enhances lymphocyte proliferation, improves neutrophil function, and modulates pro-inflammatory cytokine release.¹¹ Arginine serves as a precursor for nitric oxide, facilitating improved microcirculatory flow and bacterial clearance. Omega-3 fatty acids

downregulate cyclooxygenase-derived eicosanoids and tumor necrosis factor- α , thereby attenuating exaggerated inflammatory responses.¹² Additionally, nucleotides accelerate cellular proliferation in lymphoid tissues, contributing to heightened immune surveillance. Our results thus reinforce the hypothesis that immunonutrition creates a more favorable immunological environment that reduces SSI susceptibility. The wound healing index improved significantly in the immunonutrition cohort at days 3, 7, and 14, with the most pronounced difference observed on postoperative day 7 (7.8 ± 1.2 vs. 6.1 ± 1.4 , $p < 0.001$). Wound healing depends on adequate collagen synthesis, fibroblast proliferation, angiogenesis, and timely resolution of inflammation.¹³ Malnutrition delays all stages of repair, while immunonutrient supplementation provides conditionally essential substrates that accelerate tissue regeneration.

Our results parallel those of Klek *et al.*, who demonstrated improved wound healing and reduced wound dehiscence in patients receiving perioperative immunonutrition compared to isocaloric standard formulas.¹⁴ Moreover, emphasized the role of glutamine in maintaining intestinal mucosal integrity and preventing bacterial translocation, both of which indirectly contribute to wound healing. The superior outcomes in our immunonutrition cohort highlight its dual action: infection prevention and direct tissue repair support. This study found significant improvements in serum albumin and reductions in CRP and WBC counts in the immunonutrition group on postoperative day 7. Albumin, an established marker of nutritional and inflammatory status, is a predictor of surgical outcomes.¹⁵ In our study, serum albumin rose to 3.9 ± 0.5 g/dL in the immunonutrition cohort compared with 3.4 ± 0.6 g/dL in controls ($p = 0.007$). Elevated CRP and leukocytosis are reliable indicators of systemic inflammation and infection risk. Immunonutrition reduced CRP by -6.3 ± 1.1 mg/L, significantly greater than the reduction seen with standard nutrition. Comparable findings were reported by Marimuthu *et al.*, who observed that immunonutrition significantly increased serum albumin levels while lowering CRP in GI cancer patients.¹⁶ Additionally, Carli *et al.* confirmed that perioperative nutritional supplementation improves postoperative protein metabolism and reduces systemic inflammation.¹⁷ Our results extend this evidence to a multicenter cohort, underscoring the

biochemical benefits of immunonutrition beyond clinical endpoints.

Immunonutrition shortened hospital stay (8.6 ± 1.9 vs. 11.2 ± 2.3 days, $p < 0.001$) and accelerated bowel function recovery (2.6 ± 0.8 vs. 3.4 ± 0.9 days, $p = 0.004$). Reduced length of stay has substantial economic implications, particularly in resource-limited settings such as Bangladesh. Studies by Drover *et al.* similarly demonstrated shorter hospital stays among patients receiving immunonutrition.⁶ Faster return of bowel function reflects improved intestinal integrity and reduced ileus, which may be attributable to glutamine and omega-3 fatty acid supplementation. Notably, the benefits of immunonutrition were most pronounced among nutritionally at-risk patients (NRS-2002 ≥ 3). In this subgroup, SSI incidence was reduced from 41.7% in the standard group to 18.2% with immunonutrition ($p = 0.041$). Wound healing index and hospital stay also showed significant improvement. These results corroborate the work of Weimann *et al.*, who emphasized the necessity of targeted nutritional interventions in malnourished surgical populations.¹⁸ Our data support a precision-based approach, where immunonutrition may be prioritized for patients with hypoalbuminemia, sarcopenia, or significant preoperative weight loss. Logistic regression in our study identified immunonutrition as an independent protective factor against SSI (OR=0.44, 95% CI: 0.21–0.92, $p = 0.031$). Low serum albumin (< 3.5 g/dL) independently increased SSI risk (OR=2.76, $p = 0.022$). Similar associations were reported in studies by Hennessey *et al.*, where hypoalbuminemia strongly predicted infectious complications.¹⁹ The near-significant associations with low BMI and ASA III status in our analysis further highlight the multifactorial determinants of SSI. Importantly, immunonutrition remained beneficial even after adjusting for these variables, emphasizing its robust protective role. This study findings resonate with those of meta-analyses by Drover *et al.*, which concluded that perioperative immunonutrition significantly reduces postoperative infectious complications, including SSI, particularly in GI cancer surgery.⁶ A systematic review by Kanekiyo *et al.* found consistent reductions in SSIs and length of stay across multiple trials, though heterogeneity in formulations and timing limited universal recommendations.²⁰

However, some trials have failed to demonstrate significant differences. For instance, the large randomized trial by Tepaske *et al.* in cardiac surgery patients found no difference in infectious complications.²¹ Such discrepancies may relate to surgical type, baseline nutritional status, and timing of immunonutrition initiation. Our study, focused specifically on GI surgery and incorporating a nutritionally at-risk subgroup analysis, provides further evidence that patient selection is critical in determining benefit. The efficacy of immunonutrition lies in its ability to modulate both the innate and adaptive immune response. Arginine enhances T-lymphocyte proliferation, macrophage activity, and collagen synthesis, directly improving wound strength.²² Omega-3 fatty acids reduce pro-inflammatory eicosanoids, while increasing anti-inflammatory resolvins and protectins. Glutamine serves as a primary fuel for enterocytes and lymphocytes, preventing mucosal atrophy and bacterial translocation. Collectively, these effects counteract the catabolic, immunosuppressive state induced by surgical trauma. Our biochemical findings (higher albumin, lower CRP and WBC) provide clinical corroboration of these mechanistic pathways. Future research should prioritize large-scale randomized controlled trials in South Asian populations, incorporating diverse nutritional statuses, cancer staging, and comorbidities. Cost-effectiveness analyses are warranted to determine the economic feasibility of routine immunonutrition in low- and middle-income countries. Biomarker-guided protocols, where immunonutrition is tailored to albumin, CRP, or sarcopenia indices, may optimize resource allocation. Additionally, mechanistic studies exploring gut microbiota modulation by immunonutrition could uncover novel pathways contributing to SSI prevention.

CONCLUSION

This study highlights the significant role of perioperative immunonutrition in reducing surgical site infection incidence and enhancing wound healing among gastrointestinal surgery patients. Immunonutrition improves nutritional biomarkers, attenuates inflammatory responses, shortens hospital stay, and accelerates recovery, with particularly pronounced benefits in nutritionally at-risk individuals. These findings support integrating immunonutrition into perioperative care protocols and Enhanced Recovery After Surgery (ERAS)

pathways. Further research should explore cost-effectiveness, long-term outcomes, and biomarker-guided patient selection to optimize surgical care and extend benefits to broader clinical populations.

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