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RESEARCH

Perioperative immunonutrition intervention on postoperative outcomes among gynaecological cancer patients under enhanced recovery after surgery setting

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Abstract

Purpose Enhanced Recovery After Surgery (ERAS) and immunonutrition (IMN) are established strategies for enhancing postoperative outcomes and modulating immune response. However, current research often overlooks the influence of patients' nutritional status and acceptability in the effectiveness of these combined therapies. The study was aimed at evaluating the effectiveness of perioperative IMN in gynaecological cancer (GC) patients.

Method This was an open-label randomised controlled trial. The primary outcomes were postoperative hospitalisation, nutritional status, and functional status.

Results A total of 110 participants were randomised into the perioperative IMN intervention (I-ERAS) or control (CO) group under an ERAS protocol. Mean age was 50.15 ± 13.07 years in I-ERAS and 49.27 ± 13.80 years in CO. Compared with CO, I-ERAS had a significantly shorter hospital stay (81.5 ± 40.9 h vs. 102.7 ± 58.7 h, $p < 0.05$) and faster gastrointestinal recovery, including earlier transition to a solid diet and return of bowel sounds. Importantly, none of the I-ERAS patients were readmitted within 30 days, compared with a 7.4% readmission rate in the CO group ($p < 0.05$). In addition, I-ERAS patients had improved wound healing ($p < 0.05$); better preservation of nutritional status ($p < 0.05$), a more favourable inflammatory profile ($p < 0.01$), and faster recovery of functional status ($p < 0.05$) and physical performance ($p < 0.01$).

Conclusion Perioperative IMN within an ERAS protocol for GC surgery is a valuable intervention that reduces hospitalisation, enhances wound healing, improves inflammatory profiles, and lowers readmissions, making it suitable for routine ERAS practice.

Trial registration NCT06039306, dated 14 September 2024

Protocol version POIMNERAS2023, version 2, September 2023

Keywords Perioperative · Immunonutrition · ERAS · Gynaecologic cancer

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Introduction

Surgical treatment remains a cornerstone in the treatment of gynaecologic cancer (GC), providing both curative potential and disease control [1]. However, surgery causes tremendous physiological stress, resulting in a systemic inflammatory response syndrome (SIRS) and a complex immunosuppressive catabolic state [2]. This response is characterised by increased proteolysis, muscle atrophy, and metabolic dysregulation, all of which slow recovery and increase the risk of postoperative complications [3]. To counter such adverse consequences, the Enhanced Recovery After Surgery (ERAS) protocol was established, which focuses on multimodal ways to improve perioperative care [4]. Nutritional optimisation is an important component of ERAS [5], particularly the incorporation of oral nutritional support (ONS) techniques that aim to maintain metabolic and immunological homeostasis [6]. Among these, immunonutrition (IMN) has received attention for its ability to modify the immune response, increase tissue repair, and improve surgical results [7].

Perioperative nutritional management is pivotal in maintaining muscle mass, metabolic stability, and overall patient resilience following surgery [5]. Nutritional interventions, including hydroxymethylbutyrate (HMB), have been shown to attenuate muscle degradation and promote anabolism, making them essential in surgical recovery pathways [8, 9]. IMN formulations, enriched with bioactive compounds such as omega-3 fatty acids, glutamine, arginine, nucleotides, and trace minerals (iron, zinc, copper, and selenium), have been extensively studied for their immunomodulatory properties [10]. These nutrients contribute to improving wound healing, attenuation of inflammatory cascades, and preservation of mucosal integrity. The ability of IMN to reduce systemic inflammation, enhance cellular immunity, and minimise oxidative stress may play a crucial role in mitigating surgical stress responses and reducing postoperative morbidity [11].

While a growing body of evidence supports the IMN in gastrointestinal and oncologic surgery, where trials have reported reduced infection rates, shorter hospital stays, and improved functional recovery [12], data in GC remains scarce. Importantly, systematic reviews indicate inconsistent findings related to the timing (pre-, post-, or perioperative) and duration of IMN supplementation, making its role in GC uncertain [12–14]. Although early trials indicate that preoperative IMN supplementation may be beneficial (e.g., dosing 3–5 days before surgery) [12], more research is needed to determine its specific value in GC surgery under ERAS protocols [14]. Moreover, there is lack of randomised controlled trials evidence from Southeast Asia, where variations in nutritional status, dietary practices, and cancer care delivery may influence intervention effectiveness. Addressing these knowledge gaps is imperative, as GC patients often present with pre-existing nutritional compromise that may further modulate treatment response and postoperative recovery. Evidence tailored to this population and region is essential to guide ERAS protocols and inform clinical practice with patient-specific needs to enhance clinical outcomes [13]. Therefore, this study was aimed at evaluating the effectiveness of an IMN intervention within the ERAS protocol among GC patients.

Methods and materials

Study design

This manuscript reports the findings of an open-label randomised controlled trial (RCT) evaluating the effectiveness of perioperative immunonutrition (IMN) within an Enhanced Recovery After Surgery (ERAS) framework among patients undergoing surgery for GC. The RCT forms part of a broader explanatory sequential mixed-methods research programme, in which a subsequent qualitative phase was conducted to explore patients' perceptions and experiences of the intervention [13]. The qualitative findings will be reported separately. The RCT was conducted at the *Institut Kanser Negara*, Malaysia, within the Surgical Gynaecologic Department, encompassing both a multidisciplinary clinic and a female surgical ward. The RCT study period spanned from 1st October 2024 to 31st March 2025.

Study population

A total of 110 eligible patients were enrolled. Inclusion criteria comprised ambulatory Malaysian women aged ≥ 18 years scheduled for elective open surgery for histologically confirmed GC. Exclusion criteria included allergy to soy or whey protein, chronic renal disease, ischaemic heart disease, diabetes mellitus, emergency or minimally invasive surgery, adherence to vegan or vegetarian diets, and concurrent participation in other interventional studies. Recruitment occurred from the time of clinic consultation until postoperative day (POD) 30.

Sample size calculation

Sample size was calculated using the two-population means formula. Based on a previous study [5] indicating a mean change in handgrip strength of 0.7 (SD 0.4) in controls

versus −1.4 (SD 4.8) in the intervention group, 42 participants per arm were required to achieve 80% power at a two-sided α of 0.05. Allowing for a 20% attrition rate, the target enrolment was 53 per group.

Recruitment and baseline assessment

Before being enrolled, all individuals provided written informed permission. The confidentiality of patient data was protected at all times, with access limited to authorised research personnel. The RCT followed the Consolidated Standards of Reporting Trials (CONSORT) standards and had two parallel arms: an intervention group (I-ERAS) and a control group (CO). Eligible patients were identified during scheduled gynaecologic oncology consultations. Research staff screened patients against eligibility criteria, explained study procedures, and provided the patient information sheet and consent form. Participants could review these at home before consenting. Upon enrolment, baseline data were recorded, including demographic characteristics, comorbidities, American Society of Anaesthesiologists (ASA) score, and nutritional status via the Patient-Generated Subjective Global Assessment (PG-SGA). A trained dietitian conducted comprehensive assessments encompassing anthropometry, body composition, biochemical parameters, dietary intake, and functional status (handgrip strength, performance status).

Randomisation and allocation concealment

Participants were randomised in a 1:1 ratio to the intervention (I-ERAS) or control (CO) group using block randomisation with a block size of four. Allocation concealment was maintained with opaque, sealed envelopes. Analyses were conducted according to the intention-to-treat (ITT) principle.

Blinding

As an open-label trial, participants, investigators, and healthcare providers were aware of group allocation.

Perioperative exercise protocol

All participants were encouraged to undertake perioperative exercise comprising aerobic walking (20–30 min, three to five times weekly) and deep-breathing exercises to enhance cardiovascular and pulmonary function. Physiotherapy assessment occurred preoperatively and on POD 1–2. Early mobilisation, including sitting out of bed and ambulation, was encouraged from POD 1.

Intervention group (I-ERAS)

Participants received a dietitian-led nutrition assessment during their multidisciplinary clinic visit. Preoperatively, they consumed two daily servings (77 g) of an IMN oral nutritional supplement (ONS) (Valens Onthera+, PharmD Health Science, Malaysia) for 5 days. As part of carbohydrate loading, they consumed 300 ml of a clear protein–carbohydrate drink (100 g carbohydrate, 12 g protein) on the evening before surgery, and 150 ml of the same drink (50 g carbohydrate, 6 g protein) 3 hours before surgery. Patients fasted from solids food six hours before surgery. Postoperatively, they received two bottles (400 ml) of the clear protein–carbohydrate drink (134 g carbohydrate, 16 g protein) four hours after surgery. On achieving tolerance to $\geq$ 500 ml clear fluids, patients transitioned to a high-protein, high-calorie diet and continued two daily servings of IMN ONS for seven postoperative days. Compliance was monitored by counting returned supplement containers.

Control group (CO)

Participants in the control group received identical dietitian-led assessments and followed the same preoperative protein-carbohydrate-loading protocols. They maintained their habitual diet pre-admission. Postoperatively, they transitioned to a high-protein, high-calorie diet. If unable to consume $\geq$ 75% of ward meals, they were provided with two daily servings of a standard polymeric formula (protein to carbohydrate ratio was 1:2.8).

Data collection and outcome measures

The variables were pre-specified in protocol. Data were collected at baseline, POD 1, POD 3, and POD 14. Primary outcomes included changes in nutritional status (lean body mass, weight, phase angle), functional capacity (handgrip strength, Karnofsky Performance Status), and biochemical markers (albumin, CRP, IL-6, immunoglobulin A, G, and M, full blood count, C-reactive-Albumin Ratio, Neutrophile-Lymphocytes Ratio, Platelet-Lymphocytes Ratio). Secondary outcomes included clinical recovery parameters: length of postoperative hospitalisation, tolerance of clear fluids, time to solid diet, return of bowel function, ICU admission rate, postoperative nausea vomiting (PONV) incidence, wound healing (Southampton Wound Scoring System), and infection-related readmissions.

Clinical outcomes

Length of postoperative hospitalization was calculated from surgery completion to hospital discharge. Tolerance of clear fluids, resumption of a normal diet, and bowel function recovery (time to first flatus) were documented by ward

staff. Wound healing was assessed by a gynaecologic surgeon using the Southampton Wound Scoring System [15]. All outcomes were recorded in standardised data collection forms.

Anthropometry and body composition

Height was measured using a SECA® 769 stadiometer (0.1-cm precision). Body composition was assessed using a calibrated Fresenius Medical Care Body Composition Monitor. To ensure the accuracy of bioimpedance analysis (BIA) and minimise the confounding effects of perioperative fluid shifts, measurements were specifically timed to avoid the acute phase of surgical inflammation. Assessments were conducted at preoperatively (baseline) and 14 days postoperation, coinciding with the 'recovery phase' when patients have typically achieved haemodynamic stability and resolved any acute fluid retention.

Dietary intake

Dietary intake was assessed via 24-h recall by a credentialed dietitian using the Malaysian Atlas of Food Exchanges, food models, and standard household measures. Analysis was performed using Nutritionist Pro Dietary Software (version 2.4; San Bruno, CA, USA).

Functional status

Handgrip strength was measured with a Jamar hand dynamometer (Fred Sammons Inc., Illinois, USA), averaging three consecutive trials for each participant. Karnofsky Performance Status (KPS) scale (standardized tool to assess functional status) was used.

Biochemical analysis

Blood samples were collected and analysed for albumin, CRP, IL-6, complete blood count, and immunoglobulin A, G, and M.

Statistical test

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA) on an ITT basis. Normality was assessed with the Shapiro–Wilk test. Continuous variables were summarised as mean ± standard deviation (SD) or median (interquartile range) as appropriate. Between-group comparisons were performed using independent samples *t*-tests or Mann–Whitney *U* tests. Within-group changes were analysed using paired *t*-tests or Wilcoxon signed-rank tests. Categorical variables were expressed as frequencies and percentages, with between-group comparisons assessed using chi-square or Fisher's exact tests. Repeated-measures outcomes were analysed using two-way repeated-measures ANOVA or linear mixed-effects models to evaluate the main effects of time, group, and their interaction. Effect sizes were calculated for key outcomes. A two-sided p-value < 0.05 was considered statistically significant.

Throughout the research, the intervention product had a high compliance rate, with 45 of 56 individuals (80.4%) successfully adhering to the regimen. To examine the effect of the intervention on the study outcomes, an Intention-to-Treat (ITT) analysis was undertaken in accordance with best practice. The ITT analysis thus provides a more conservative and pragmatic estimate of the intervention's genuine efficacy in a real-world clinical environment by keeping the benefits of randomisation and correcting for non-adherence.

Results

There were 110 participants who fulfilled the eligibility criteria and enrolled in this study (Fig. 1). The sociodemographic and baseline characteristics of participants are summarised in Tables 1 and 2. No significant differences were observed between groups at baseline. The majority of subjects were Malay (75.5%) and most were diagnosed with ovarian cancer (48.8%), stage I (47.3%), ECOG score 0 (68.2%), and ASA physical score II (66.4%). The mean age was 50.15 ± 13.07 years in the I-ERAS group and 49.27 ± 13.80 years in the CO group. Baseline PG-SGA scores were 7.9 ± 4.5 in I-ERAS and 7.8 ± 5.1 in CO. Mean weight loss over the preceding month was −5.7% ± 5.1% in I-ERAS and −5.1% ± 4.5% in CO. No statistically significant differences were observed between groups for any baseline variable. The I-ERAS group demonstrated significantly faster recovery than the CO group (Table 3). Length of postoperative hospitalization was shorter in I-ERAS (81.5 ± 40.9 h) compared with CO (102.7 ± 58.7 h, $p < 0.05$). The transition to a solid diet occurred earlier (21.0 ± 4.3 h vs. 24.5 ± 8.0 h, $p < 0.01$). I-ERAS patients also achieved faster bowel sound (10.2 ± 9.5 h vs. 17.6 ± 12.6 h, $p = 0.001$) and flatus (24.0 ± 9.1 h vs. 31.3 ± 15.6 h, $p < 0.01$) compared with CO (Table 3). Postoperative complications occurred less frequently in I-ERAS than in CO ($p < 0.05$), with a lower incidence of postoperative nausea and vomiting. The 30-day readmission rate was significantly lower in I-ERAS (0%) compared with CO (7.4%, $p < 0.05$) (Table 3). In the CO group, readmissions were primarily due to infection (75%) and wound debridement (25%). The I-ERAS group had a significantly better wound healing than the CO group ($p < 0.05$). The I-ERAS group exhibited significantly better preservation of nutritional status ($p < 0.01$) and demonstrated a more favourable biochemical profile in terms of acute-phase inflammatory markers ($p < 0.05$) compared with CO. Functional status recovery was also achieved

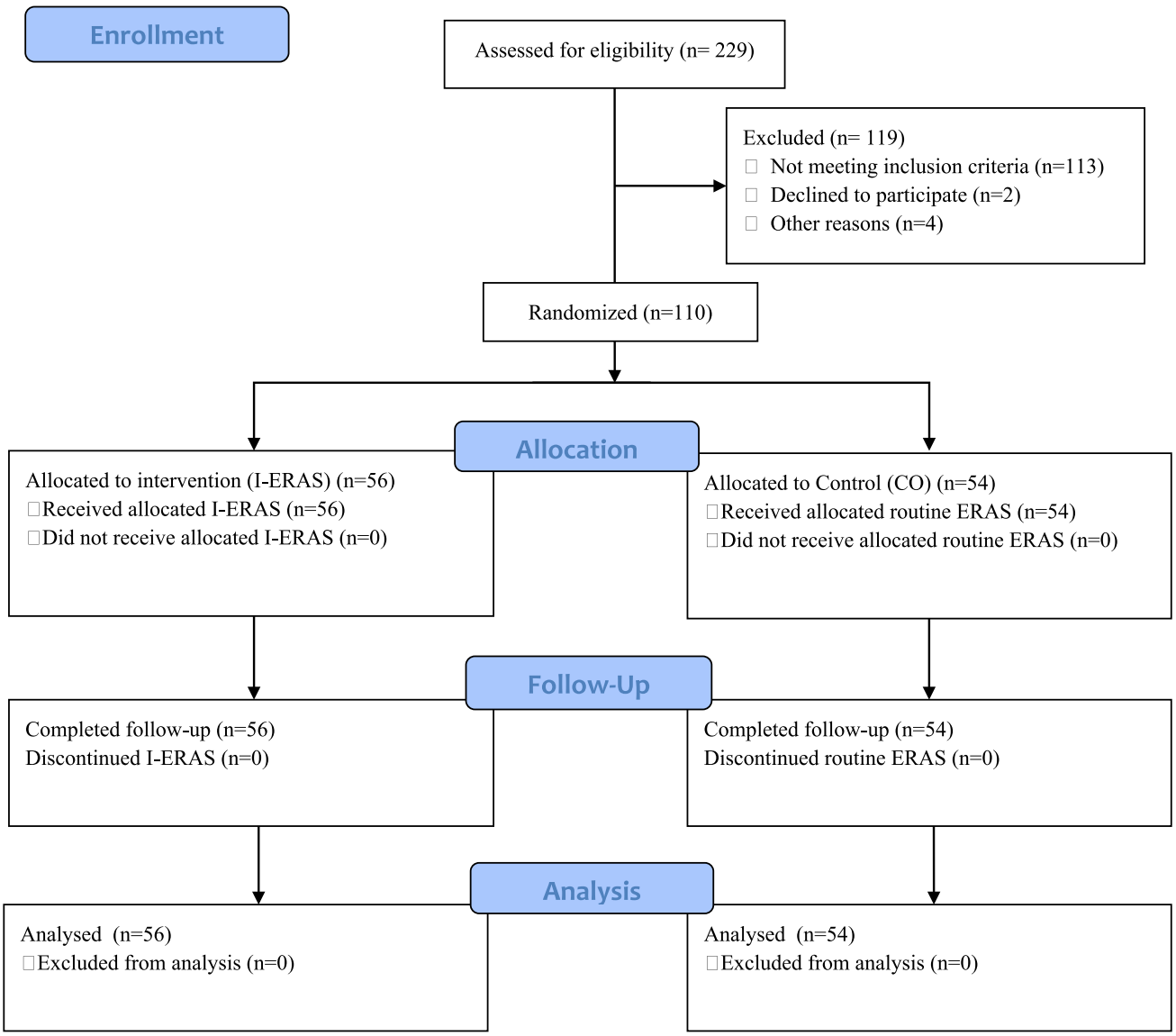

Fig. 1 Study flow diagram

significantly faster in I-ERAS ($p < 0.05$) and a better physical performance in I-ERAS ($p < 0.001$) (Table 4). The I-ERAS preserved significantly more weight, lean muscle mass, fat free mass and handgrip strength as well as the phase angle of the I-ERAS also improved significantly than CO (Table 5).

Discussion

This study presents the first evidence from Malaysia that including perioperative immunonutrition (IMN) into a multimodal Enhanced Recovery After Surgery (ERAS) pathway for gynaecological cancer (GC) surgery results in significant positive clinical, nutritional, and functional outcomes. The complete absence of 30-day readmissions in the intervention group is particularly notable, as unplanned readmissions are increasingly used as a quality-of-care metric and a driver of healthcare costs. The intervention showed less postoperative nutritional decline, preserved lean muscle mass, maintained handgrip strength and physical performance, and reduced acute-phase inflammatory response, while also improving wound healing, lowering postoperative nausea and vomiting (PONV), infection-related readmissions, and the need for postoperative intensive care unit (ICU) admission. These benefits were obtained without worsening postoperative complications, and they were accompanied by a statistically and clinically significant reduction in postoperative hospitalization, with the intervention group being discharged an average of 21.2 h (0.88 days) earlier than the controls. This is in agreement with international ERAS findings, which

Table 1 Sociodemographic and clinical characteristics of participants ($N = 110$)

	I-ERAS ($n = 56$)	CO ($n = 54$)	p-value
Age (years) (mean ± SD)	50.15 ± 13.07	49.27 ± 13.80	0.133
Ethnicity (*n*, %)			
Malay	42 (75.0)	41 (75.9)	
Chinese	7 (12.5)	6 (11.1)	
India	7 (12.5)	7 (13.0)	
Diagnosis (*n*, %)			0.240
Ovarian cancer	24 (42.9)	29 (54.7)	
Endometrial cancer	19 (33.9)	15 (27.8)	
Cervical cancer	5 (8.9)	4 (7.4)	
Uterine cancer	8 (14.3)	6 (11.1)	
Stage (*n*, %)			0.524
I	27 (48.2)	25 (46.3)	
II	13 (23.2)	14 (25.9)	
III	15 (26.8)	14 (25.9)	
IV	1 (1.8)	1 (1.8)	
Comorbidity (*n*, %)			0.311
Hypertension	10 (17.9)	14 (25.9)	
Hypertension and dyslipidaemia	18 (32.1)	11 (37.9)	
No underlying	28 (50.0)	29 (53.7)	
Family history of cancer (*n*, %)			0.587
Yes	20 (35.7)	22 (40.7)	
No	36 (64.3)	32 (59.3)	
ECOG score (*n*, %)			0.08
0	45 (80.4)	30 (55.6)	
1	9 (16.0)	21 (38.9)	
2	2 (3.6)	3 (5.6)	
ASA Physical Status score (*n*, %)			0.491
I	20 (35.7)	16 (29.6)	
II	36 (64.3)	37 (70.3)	

Independent t-test

ECOG Eastern Cooperative Oncology Group, *ASA* American Society of Anaesthesiologists

suggest that optimal perioperative nutrition can enhance sooner tolerance to oral intake, faster mobilisation, and gastrointestinal recovery. The qualitative component of this research programme, which explored patient experiences and intervention acceptability, will be reported separately and is therefore not discussed in detail here.

These effects are most likely mediated through minimising the catabolic stress response and providing early substrates for tissue repair [16]. IMN appeared to have a beneficial effect on perioperative immunometabolism and immune-inflammatory status [12], as evidenced by lower postoperative interleukin-6 (IL-6) concentrations, a lower C-reactive protein-to-albumin ratio (CAR), and a more favourable neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) compared with controls. These markers are well-established predictors of surgical stress, systemic inflammation, and prognosis in oncology patients, and their modulation suggests that targeted nutritional strategies can suppress excessive cytokine release, maintain lymphocyte-mediated immunity, and reduce acute-phase responses [17].

Although no statistically significant between-group differences were observed in postoperative immunoglobulin A, G, and M levels, a numerically smaller postoperative decline was noted in the intervention group. This tendency shows that IMN may have a protective effect on humoral immunity, potentially reducing immune suppression associated with postoperative stress [18]. IgA preservation promotes mucosal barrier defence [19], but maintained IgG and IgM levels may increase pathogen clearance and lower infection susceptibility [20]. These findings are consistent with the idea that IMN promotes both innate and adaptive immunity during the perioperative period [10, 13]. Given that perioperative immunological competence is critical for controlling infection risk, wound healing, and general recovery, even little immunoglobulin levels preservation could result in

Table 2 Baseline nutrition status, functional status, and biochemical profile ($N=110$)

	I-ERAS ($n=56$)	CO ($n=54$)	p-value
Anthropometry			
Height (m) (mean ± SD)	1.56 ± 0.07	1.56 ± 0.07	0.702
Weight past 1 month (kg) (mean ± SD)	69.8 ± 17.3	68.6 ± 18.0	0.723
Weight past 6 months (kg) (mean ± SD)	69.1 ± 17.0	67.8 ± 18.1	0.702
Percentage weight loss past 1 month (%) (mean ± SD)	5.7 ± 5.1	5.1 ± 4.5	0.690
Percentage weight loss past 6 months (%) (mean ± SD)	4.8 ± 4.6	4.0 ± 3.4	0.438
Weight (kg)	66.0 ± 17.5	65.2 ± 18.3	0.811
Body composition			
Lean muscle mass (kg) (mean ± SD)	24.1 ± 4.9	26.6 ± 6.5	0.520
Fat mass (kg) (mean ± SD)	30.6 ± 12.6	28.3 ± 13.7	0.375
Percentage fat (%) (mean ± SD)	44.6 ± 8.1	41.3 ± 10.1	0.057
Fat-free mass (kg) (mean ± SD)	35.3 ± 6.6	36.8 ± 7.5	0.274
Resistance (Ω) (mean ± SD)	718.5 ± 111.01	697.5 ± 139.2	0.409
Phase angle (mean ± SD)	4.7 ± 0.7	4.7 ± 0.8	0.824
Nutrition assessment			
SGA score (mean ± SD)	8.2 ± 4.0	7.9 ± 4.8	0.779
SGA Category (n, %)			0.641
A	19 (34.0)	23 (42.6)	
B	36 (64.3)	30 (55.6)	
C	1 (1.7)	1 (1.8)	
PG-SGA score (mean ± SD)	7.9 ± 4.5	7.8 ± 5.1	0.918
PG-SGA category (n, %)			0.554
0–1	12 (21.4)	14 (25.9)	
2–3	2 (3.6)	3 (5.5)	
4–8	18 (32.1)	11 (20.4)	
More than 9	24 (42.9)	26 (48.2)	
Nutrition intake			
Daily energy intake (kcal/day) (mean ± SD)	1120 ± 213	1151 ± 314	0.500
Daily protein intake (g/day) (mean ± SD)	43.5 ± 11.2	42.5 ± 12.8	0.671
Functional status			
Handgrip strength (kg) (mean ± SD)	18.8 ± 5.2	17.6 ± 6.4	0.297
KPS (n, %)			0.552
Normal activities and work	46 (82.1)	43 (79.6)	
Requires varying levels of assistance	10 (17.9)	11 (20.4)	
Biochemical profile			
Albumin (mean ± SD)	42.0 ± 5.5	40.8 ± 4.7	0.235
C-reactive protein (mean ± SD)	5.0 ± 6.6	6.3 ± 5.4	0.242
Red blood cells (mean ± SD)	4.7 ± 0.5	5.1 ± 0.6	0.632
Haemoglobin (mean ± SD)	11.8 ± 1.7	11.7 ± 1.9	0.756
Lymphocytes (mean ± SD)	2.12 ± 0.64	1.95 ± 0.59	0.149
Neutrophil (mean ± SD)	5.28 ± 2.24	5.45 ± 2.66	0.726
Monocytes (mean ± SD)	0.59 ± 0.28	0.59 ± 0.27	0.971
Platelets (mean ± SD)	369 ± 103	360 ± 129	0.648
Interleukin-6 (mean ± SD)	5.03 ± 4.19	6.46 ± 4.23	0.077
Immunoglobulin A (mean ± SD)	2.98 ± 1.17	2.84 ± 1.03	0.514
Immunoglobulin G (mean ± SD)	14.73 ± 3.86	14.35 ± 3.37	0.582
Immunoglobulin M (mean ± SD)	1.22 ± 0.48	1.20 ± 0.57	0.838
CAR (mean ± SD)	0.12 ± 0.08	0.17 ± 0.06	0.184
NLR (mean ± SD)	2.65 ± 1.22	3.08 ± 2.03	0.166
PLR (mean ± SD)	188.4 ± 73.6	206.9 ± 63.7	0.312

Independent t-test

SGA Subjective Global Assessment, *PG-SGA* Patient-Generated Subjective Global Assessment, *KPS* Karnofsky Performance Status, *CAR* C-reactive to albumin ratio, *NLR* neutrophile to lymphocyte ratio, *PLR* platelet to lymphocyte ratio

Table 3 Postoperative clinical outcomes ($N=110$)

	I-ERAS ($n=56$)	CO ($n=54$)	p-value
Postoperative hospitalisation (mean ± SD)	81.5 ± 40.9	102.7 ± 58.7	[a] 0.03*
Operation type (*n*, %)			[a] 0.929
TAHBSO	50 (89.3)	47 (87.0)	
Radial hysterectomy	6 (10.7)	7 (13.0)	
Operation period (mean ± SD)	189.4 ± 66.8	193.3 ± 74.8	[a] 0.768
ICU after surgery (*n*, %)			[a] 0.019*
Yes	6 (10.7)	9 (16.7)	
No	50 (89.3)	45(83.3)	
Blood loss (mean ± SD)	662.5 ± 267.2	775.2 ± 259.4	[a] 0.164
Period bowel sound (mean ± SD)	10.2 ± 9.5	17.6 ± 12.6	[a] 0.001**
Period clear fluid initiation (mean ± SD)	5.4 ± 0.7	5.6 ± 1.0	[a] 0.363
Period diet initiation (mean ± SD)	21.0 ± 4.3	24.5 ± 8.0	[a] 0.006**
Period flatus (mean ± SD)	24.0 ± 9.1	31.3 ± 15.6	[a] 0.004**
Period mobilisation (mean ± SD)	23.1 ± 3.2	24.9 ± 7.4	[a] 0.114
Bowel adhesion (*n*, %)			[b] 0.518
Yes	5 (9.1)	7 (13.0)	
No	50 (90.9)	47 (87.0)	
Omentectomy (*n*, %)			[b] 0.417
Yes	31 (55.4)	34 (63.0)	
No	25 (44.6)	20 (37.0)	
Appendectomy (*n*, %)			[b] 0.224
Yes	11 (19.6)	16 (29.6)	
No	45 (80.4)	38 (70.4)	
Residue tumour (*n*, %)			[b] 0.730
Yes	8 (14.3)	9 (16.7)	
No	48 (85.7)	45 (83.3)	
Pelvic lymph node dissection (*n*, %)			[b] 0.617
Yes	48 (85.7)	48 (88.9)	
No	8 (14.3)	6 (11.1)	
Postoperative nausea vomiting (*n*, %)			[b] 0.019*
Yes	8 (14.3)	18 (33.3)	
No	48 (85.7)	36 (66.7)	
Postoperative ileus (*n*, %)			[b] 0.537
Yes	1 (1.8)	2 (3.7)	
No	55 (98.2)	52 (96.3)	
Wound debridement (*n*, %)			[b] 0.306
Yes	0 (0)	1 (1.9)	
No	56 (100)	53 (98.1)	
Postoperative infection (*n*, %)			[b] 0.306
Yes	0 (0)	1 (1.9)	
No	56 (100)	53 (98.1)	
Readmission 30 days postdischarge (*n*, %)			[b] 0.038*
Yes	0 (0)	4 (7.4)	
No	56 (100)	47 (92.6)	
Reason readmission (*n*, %)			
Infection	0 (0)	3 (75.0)	
Wound debridement	0 (0)	1 (25.0)	
Southampton wound scoring system (*n*, %)			[c] 0.015*
0	40 (71.4)	25 (46.3)	
I a	13 (23.2)	11 (20.4)	
I b	1 (1.8)	6 (11.1)	

Table 3 (continued)

	I-ERAS ($n=56$)	CO ($n=54$)	p-value
I c	1 (1.8)	2 (3.7)	
II a	1 (1.8)	1 (1.9)	
II b	0 (0)	7 (13.0)	
III a	0 (0)	2 (3.7)	

TAHBSO total abdominal hysterectomy with bilateral salpingo-oophorectomy

*$p<0.05$; **$p<0.001$

[a]Independent *t*-test

[b]Chi-square test

[c]Fisher Exact test

significant therapeutic advantages [3, 21]. These findings are consistent with previous evidence indicating that specific immunonutrient supplementation can improve immune resilience, particularly in the context of major surgery [10], and highlight the importance of adequately powered trials to confirm whether the observed immunological preservation leads to tangible improvements in postoperative outcomes [13].

Clinically, IMN was linked to improved wound healing, fewer wound breakdowns, decreased PONV, and a lower rate of infection-related readmissions. A lower proportion of ICU admissions was observed in the intervention group demonstrates IMN's ability to stabilise postoperative physiology, minimise the severity of problems, and prevent care escalation [7]. The bioactive ingredients in the formula—arginine, omega-3 fatty acids, and nucleotides—provide biologically reasonable reasons for these results [21]. Arginine stimulates collagen synthesis, angiogenesis, and fibroblast proliferation; omega-3 fatty acids regulate inflammation by altering eicosanoid production and cytokine balance; and nucleotides promote lymphocyte proliferation and protein synthesis, which are necessary for tissue regeneration and immune competence [10]. The lower PONV rate may also represent enhanced gut mucosal function and decreased systemic inflammation, allowing for earlier oral intake, a fundamental ERAS goal [5, 22].

Equally crucial is the preservation of lean muscle mass, body weight, and cellular integrity, as indicated by higher phase angle values in the intervention group. Maintaining muscle mass and function is crucial in oncologic surgery because perioperative stress and underlying illness cause protein catabolism [23]. Adequate protein-energy provision, when paired with immune-modulating nutrients, may reduce proteolysis, maintain nitrogen balance, and sustain mitochondrial function [24, 25]. Higher phase angle readings imply higher cell membrane integrity and hydration condition, which have been linked to increased recovery and survival in surgical oncology [23]. The immediate postoperative period (typically 48–72 h) is characterised by significant 'third-spacing' and aggressive intravenous fluid resuscitation, which can artificially lower resistance (R) and inflate lean mass estimates. By performing assessments preoperatively and postoperative Day 14, we captured measurements during 'stable hydration windows'. By day 14, the systemic inflammatory response has typically subsided, and patients have entered the 'recovery phase', where fluid homeostasis is restored. This timing ensures that our reported Phase Angle (PhA) and functional markers, such as handgrip strength, reflect true nutritional status rather than transient perioperative fluid shifts [26].

Strength, limitations, and direction of future research

This study's strengths include a comprehensive assessment of clinical, nutritional, inflammatory, and functional endpoints; the use of objective, validated measures such as the Southampton Wound Scoring System, phase angle, and handgrip dynamometry; and delivery within a standardised ERAS framework to reduce perioperative care variability. The combination of inflammatory biomarkers and functional outcomes provides a comprehensive knowledge of recovery, connecting the mechanistic and clinical domains. Throughout the research, no systemic adverse effects were reported. Participants tolerated the investigational product well, with no reports of gastrointestinal (GI) discomfort, supplement-related side effects, or other adverse reactions. These findings imply that the supplement has a favourable safety profile at the studied dosage.

A significant strength of this study is the timing of BIA measurements. It is acknowledged that intravenous hydration drastically influences BIA results in the immediate postoperative period. However, our measurements were taken either preoperatively or after day 14. By day 14, the 'third-spacing' and capillary leak typical of the early postsurgical period (usually peaking at 48–72 h) have typically resolved, and patients have entered the diuretic phase to restore fluid homeostasis. Consequently, the Phase

Table 4 Postoperative nutrition and functional and biochemical profile outcomes ($N=110$)

	I-ERAS ($n=56$)	CO ($n=54$)	t-value/F-value	p-value
Weight (kg) (mean ± SD)	64.0 ± 16.8	61.2 ± 17.2	0.863	[a] 0.039*
Body composition				
Lean muscle mass (kg) (mean ± SD)	24.2 ± 5.9	22.9 ± 5.8	−1.132	[a] 0.046*
Fat mass (kg) (mean ± SD)	29.1 ± 12.5	26.8 ± 12.1	0.945	[a] 0.347
Percentage fat (%) (mean ± SD)	43.9 ± 9.9	42.3 ± 8.9	0.898	[a] 0.371
Fat-free mass (kg) (mean ± SD)	34.6 ± 7.1	33.7 ± 7.0	0.624	[a] 0.534
Resistance (Ω) (mean ± SD)	748.3 ± 121.9	733.1 ± 144.3	−0.583	[a] 0.561
Phase angle (mean ± SD)	4.7 ± 0.8	4.5 ± 0.7	1.353	[a] 0.179
Nutrition intake				
Daily energy intake (kcal/day) (mean ± SD)			12.91	[b] < 0.001***
Pre-operative clinic	1120 ± 213	1151 ± 314		
POD 1	990 ± 188	799 ± 246		
POD 3	1281 ± 248	880 ± 280		
POD 14	1552 ± 259	1258 ± 272		
Daily protein intake (g/day) (mean ± SD)			50.45	[b] < 0.001***
Pre-operative clinic	43.5 ± 11.2	42.5 ± 12.8		
POD 1	32.1 ± 9.2	25.4 ± 10.2		
POD 3	68.7 ± 17.4	32.4 ± 11.9		
POD 14	81.4 ± 19.6	52.9 ± 15.1		
Functional status				
Handgrip strength (kg) (mean ± SD)	19.5 ± 5.6	16.7 ± 6.1	2.791	[a] 0.015*
KPS (n, %)				< 0.001***
Normal activities and work	51 (91.1)	30 (55.6)		
Requires varying levels of assistance	5 (8.9)	24 (44.4)		
Albumin (mean ± SD)			4.176	[b] 0.043*
Pre-operative clinic	42.0 ± 5.5	40.8 ± 4.7		
POD 1	33.0 ± 3.9	31.3 ± 4.8		
POD 3	32.4 ± 3.6	30.8 ± 4.3		
POD 14	37.9 ± 3.0	37.2 ± 4.6		
C-reactive protein (mean ± SD)			4.969	[b] 0.007**
Pre-operative clinic	5.0 ± 6.6	6.3 ± 5.4		
POD 1	53.4 ± 38.2	69.3 ± 45.7		
POD 3	43.8 ± 35.3	79.0 ± 36.1		
POD 14	5.0 ± 1.6	24.6 ± 13.8		
Haemoglobin (mean ± SD)			0.863	[b] 0.002**
Pre-operative clinic	11.8 ± 1.7	11.7 ± 1.9		
POD 1	11.4 ± 1.4	11.3 ± 1.5		
POD 3	10.9 ± 1.2	10.8 ± 1.2		
POD 14	11.7 ± 1.0	11.4 ± 1.2		
Neutrophils (mean ± SD)			9.183	[b] 0.003**
Pre-operative clinic	5.28 ± 2.24	5.45 ± 2.66		
POD 1	10.37 ± 2.54	11.55 ± 4.08		
POD 3	7.67 ± 2.32	10.07 ± 4.55		
POD 14	5.35 ± 1.28	8.85 ± 3.78		
Lymphocytes (mean ± SD)			5.433	[b] 0.022*
Pre-operative clinic	2.12 ± 0.64	1.95 ± 0.59		
POD 1	1.47 ± 0.47	1.19 ± 0.45		
POD 3	1.79 ± 0.59	1.57 ± 0.68		
POD 14	1.86 ± 0.52	1.77 ± 0.59		
Platelets (mean ± SD)			0.117	[b] 0.733

Table 4 (continued)

	I-ERAS ($n=56$)	CO ($n=54$)	t-value/F-value	p-value
Pre-operative clinic	369 ± 103	360 ± 129		
POD 1	297.3 ± 75.6	294.4 ± 84.1		
POD 3	295.4 ± 58.2	289.5 ± 90.2		
POD 14	332.1 ± 85.3	332.9 ± 78.6		
Interleukin-6 (mean ± SD)			4.143	[b] 0.044*
Pre-operative clinic	5.03 ± 4.19	6.46 ± 4.23		
POD 1	29.9 ± 22.9	49.2 ± 22.7		
POD 3	15.3 ± 11.4	54.2 ± 18.1		
POD 14	5.1 ± 2.0	12.9 ± 16.8		
Immunoglobulin A (mean ± SD)			0.327	[b] 0.569
Pre-operative clinic	2.98 ± 1.17	2.84 ± 1.03		
POD 1	2.34 ± 0.78	2.24 ± 0.81		
POD 3	2.38 ± 0.69	2.31 ± 0.88		
POD 14	3.15 ± 1.22	3.05 ± 1.14		
Immunoglobulin G (mean ± SD)			0.343	[b] 0.559
Pre-operative clinic	14.73 ± 3.86	14.35 ± 3.37		
POD 1	10.75 ± 2.63	10.70 ± 4.29		
POD 3	10.66 ± 2.74	10.24 ± 2.62		
POD 14	14.04 ± 3.54	13.61 ± 3.28		
Immunoglobulin M (mean ± SD)			0.973	[b] 0.326
Pre-operative clinic	1.22 ± 0.48	1.20 ± 0.57		
POD 1	0.92 ± 0.35	0.89 ± 0.43		
POD 3	0.93 ± 0.29	0.86 ± 0.43		
POD 14	1.45 ± 0.62	1.24 ± 0.51		
CAR (mean ± SD)			12.445	[b] 0.001**
Pre-operative clinic	0.12 ± 0.08	0.17 ± 0.06		
POD 1	1.72 ± 1.47	2.39 ± 1.80		
POD 3	1.41 ± 1.29	2.71 ± 1.74		
POD 14	0.14 ± 0.10	0.75 ± 0.38		
NLR (mean ± SD)			5.37	[b] 0.005**
Pre-operative clinic	2.65 ± 1.22	3.08 ± 2.03		
POD 1	7.88 ± 3.50	11.52 ± 6.67		
POD 3	4.75 ± 2.27	7.20 ± 3.57		
POD 14	3.03 ± 1.00	4.58 ± 3.80		
PLR (mean ± SD)			5.755	[b] 0.018*
Pre-operative clinic	188.4 ± 73.6	206.9 ± 63.7		
POD 1	225.8 ± 111.3	206.9 ± 113.7		
POD 3	181.9 ± 69.1	214.2 ± 105.7		
POD 14	189.2 ± 65.1	1.98.5 ± 72.3		

POD postoperative day, *KPS* Karnofsky Performance Status, *CAR* C-reactive to albumin ratio, *NLR* neutrophile to lymphocyte ratio, *PLR* platelet to lymphocyte ratio

*$p<0.05$; **$p<0.01$; ***$p<0.001$

[a]Independent t-test

[b]Repeated-measures ANOVA test

[c]Chi-square test

Angle (PhA) and body composition data reported here represent stable physiological states rather than transient fluid fluctuations.

Limitations include the single-centre design, which may limit generalisability. Mechanistic biomarkers such as comprehensive cytokine profile, immune cell function assays,

Table 5 Postoperative changes of body composition and functional outcomes ($N=110$)

	I-ERAS ($n=56$)	CO ($n=54$)	p-value
Weight (median (min, max))	−1.80 (−6.8, 5.3)	−2.75 (−15.3, 4.0)	0.011*
Percentage of fat (median (min, max))	−0.22 (−8.1, 7.7)	−0.45 (−11.8, 2.5)	0.016*
Fat-free mass (median (min, max))	−0.91 (−8.3, 9.6)	−1.95 (−23.5, 2.2)	0.006**
Fat mass (median (min, max))	−0.80 (−7.9, 3.6)	−0.95 (−27.6, 14.5)	0.986
Lean muscle mass (median (min, max))	−0.63 (−6.7, 4.1)	−1.50 (−28.7, 6.0)	0.041*
Phase angle (median (min, max))	0.10 (−0.7, 1.6)	−0.18 (−1.8, 1.1)	0.036*
Handgrip strength (median (min, max))	0.15 (−6.1, 8.8)	−1.30 (−7.4, 7.8)	0.007**

Mann–Whitney U test

*$p<0.05$; **$p<0.01$

and protein turnover assessments were excluded, which limited physiological understanding. Follow-up was limited to the early postoperative period, so long-term consequences on nutritional status, treatment tolerance, and mortality are unknown. In open-label trials, where participants and researchers are aware of the treatment assignment, the internal validity is threatened by several biases. To mitigate these issues, researchers used a blinded outcome assessment by an independent third party, prioritised objective, quantifiable endpoints (biochemical profile, body composition, length of hospitalization) while applying standardised assessment tools for clinical outcomes.

Compliance with IMN was 80.4%, with the main challenges being an aversion to the fish-derived flavour of omega-3 fatty acids, a widely recognised problem in oncology patients with impaired taste perception. Partial adherence may have reduced the quantity of benefit and contributed to the absence of significant improvements in immunoglobulin levels. Nonetheless, even with 81% compliance, significant improvements in inflammatory regulation, wound healing, nutritional preservation, and functional performance were noted, as well as shorter hospitalization. It is possible that full adherence exacerbated these effects, resulting in demonstrable improvements in humoral immunity. Future research should look into measures for improving palatability and adherence, such as flavour masking, different formulations, and gradual preoperative introduction. The finding of higher-risk patients with diabetes, cardiovascular disease, or renal impairment remains to be established in the future.

Conclusion

Perioperative IMN in an ERAS protocol for GC surgery was linked to a shorter postoperative hospitalisation, improved inflammatory and immunological profiles, improved wound healing, better nutritional and functional preservation, less PONV, and fewer infection-related readmissions. These advantages, achieved despite moderate compliance, highlight the intervention's robustness and clinical relevance. Given the probable biological pathways, agreement with current international data, and potential impact on both short- and long-term outcomes, perioperative IMN should be seriously considered for inclusion in routine ERAS practice. Larger multicentre trials with extended follow-up and optimised adherence measures are required to confirm and extend these findings.

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Data availability The data may be made available on request of the corresponding author.

Code availability Not applicable.

Declarations

Ethics approval Ethic approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, under the identity number NMRR ID 23-01663-0NI (IIR). The

study protocol was registered at clinicaltrials.gov under the identifier NCT06039306. It was carried out in compliance with the Declaration of Helsinki and Good Clinical Practice recommendations.

Consent to participate All participants provided informed consent to participate in this research.

Consent for publication All participants consented to their non-identifiable data being used for publication.

Competing interests The authors declare no competing interests.

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