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Unveiling the intrinsic role of malnutrition in patients with Crohn's disease undergoing major surgery using *entropy balancing* weighting analysis

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Abstract

The negative role of malnutrition in patients with Crohn's disease is known; however, many coexisting disease-related factors could cause misinterpretation of the real culprit. This study aimed to describe the role of malnutrition using a novel methodology, *entropy balancing*. This was a retrospective analysis of consecutive patients undergoing elective major surgery for Crohn's disease, preoperatively screened following the European Society for Clinical Nutrition guidelines. Two-step *entropy balancing* was applied to the group of malnourished patients to obtain an equal cohort having a null or low risk of malnutrition. The first reweighting homogenised the cohorts for non-modifiable confounding factors. The second reweighting matched the two groups for modifiable nutritional factors, assuming successful treatment of malnutrition. The *entropy balancing* was evaluated using the *d*-value. Postoperative results are reported as mean difference or OR, with a 95 % CI. Of the 183 patients, 69 (37·7 %) were at moderate/high risk for malnutrition. The malnourished patients had lower BMI ($d = 1{\cdot}000$), Hb ($d = 0{\cdot}715$), serum albumin ($d = 0{\cdot}981$), a higher lymphocyte count ($d = 0{\cdot}124$), Charlson Comorbidity Index ($d = 0{\cdot}257$), American Society of Anaesthesiologists ($d = 0{\cdot}327$) and Harvey-Bradshaw scores ($d = 0{\cdot}696$). Protective loop ileostomy was more frequently performed ($d = 0{\cdot}648$) in the malnourished group. After the first reweighting, malnourished patients experienced a prolonged length of stay (mean difference = 1·9; 0·11, 3·71, days), higher overall complication rate (OR 4·42; 1·39, 13·97) and higher comprehensive complication index score (mean difference = 8·9; 2·2 15·7). After the second reweighting, the postoperative course of the two groups was comparable. *Entropy balancing* showed the independent role of preoperative malnutrition and the possible advantages obtainable from a pre-habilitation programme in Crohn's disease patients awaiting surgery.

Keywords: Malnutrition: Crohn's disease: Entropy balancing: Postoperative outcomes: Pre-habilitation

It is estimated that the prevalence of malnutrition in patients undergoing elective abdominal surgery reached 50 %[1]. This is particularly true for Crohn's disease (CD) patients who, in a recent prospective study, were reported to be malnourished in up to 38 % of cases[2]. Moreover, it has been demonstrated that the risk of malnutrition is associated with increased post-operative complications, mortality, longer hospital stays and higher costs[3]. On the other hand, preoperative improvement of the patient's nutritional status and early postoperative nutritional support significantly decrease these risks[4]. In CD patients, the risk of malnutrition is related to inflammatory activity, decreased oral intake or impaired digestive capacity or adsorption. Perioperative artificial nutrition could be useful for decreasing inflammatory activity and, therefore, for decreasing morbidity. To limit this, some approaches, including a temporary diverting stoma, have been proposed; however, this could lead to an additional risk of specific complications, such as elevated output and dehydration. Despite the international guidelines regarding nutritional management in CD patients, the recommendations on preoperative nutritional support are principally based on small-sample retrospective studies that have, for the most part, used total parenteral nutrition[5]. The role of malnutrition in patients with CD has previously been reported; however, the sole cause of the malnourishment might have been misinterpreted based on multiple confounding factors. The present study was designed to shed light on this conundrum, using a novel methodology called *entropy balancing (EB)*[6]. EB is a novel pre-processing technique for researchers to achieve covariate balance in observational studies using a binary treatment, which is more accurate than any propensity score matching system[6].

Abbreviations: ASA score, American Society of Anaesthesiologists score; CACI, age-adjusted Charlson Comorbidity Index; CCI, Comprehensive Complication Index; CD, Crohn's disease; EB, entropy balancing; ECOG-PS, Eastern Cooperative Oncology Group – performance status; LOS, length of stay; MD, mean difference; NRS, nutritional risk screening.

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Most commonly, researchers 'manually' iterate between propensity score modelling, matching and balance checking until they attain a satisfactory balancing solution. The hope is that propensity score matching would then stochastically balance the covariates; however, this requires finding the correct model specification and often on fairly large samples. As a consequence, low balance levels prevail in many studies, and the user experience can be tedious. Instead, EB involves a reweighting scheme that directly incorporates covariate balance into the weight function applied to the sample units in order to generate a better-performing matching system[6].

The goal of this study was to demonstrate exclusively the role of malnutrition on postoperative outcomes in patients with CD, using a novel, more accurate processing technique called entropy balancing. This method could determine the potential role of pre-habilitation programmes on reducing surgical morbidity in patients with CD and how much the risk associated with surgery could be mitigated by treating malnutrition.

Methods

This was a retrospective cohort study of a prospectively maintained database. This dedicated database is designed to prospectively monitor clinical outcomes in our unit and identify potential associations with preoperative, intraoperative and postoperative factors. The study was conducted according to the guidelines laid down in the Declaration of Helsinki. The study was approved by the Institutional Review Board as part of an internal surgical auditing programme (Ravenna Surgical Quality Improvement Program – RaSQIP) with the following code: 214/2016/O/OssN. Written consent was obtained from patients for the use of their treatment-related data for research purposes upon initial consultation. All consecutive patients who underwent elective surgery for CD between January 2017 and October 2022 were included. Patients who underwent surgery without bowel resection (i.e. loop ileostomy for severe perianal disease and/or exploration under anaesthesia), as well as those with unavailable nutritional data, were excluded from the study. All patients were preoperatively screened for malnutrition with both the nutritional risk screening (NRS-2002), derived from the European Society for Clinical Nutrition guidelines[7], and the BMI (kg/m2). Other demographic data, routinely recorded for all patients, included serum levels of lymphocytes (10^9/L), Hb (g/dl), creatinine (mg/dl), albumin (g/L), age-adjusted Charlson Comorbidity Index (CACI)[8], Eastern Cooperative Oncology Group – Performance status (ECOG-PS) (which is also utilised in the authors' practice for non-cancer patients as a frailty tool)[9,10], American Society of Anaesthesiologists (ASA) score, smoking habit and Harvey-Bradshaw score[11] for CD activity. To reduce potential selection biases, the study included only patients with at least a 4-week wash-out from biological or steroidal therapy before surgery. For study purposes, the ASA score was dichotomised into 1–2 (mild systemic disease) *v.* 3–4 (severely ill). Other disease-specific factors included in the analysis were type and number of previous bowel surgeries, type of disease (fistulising *v.* stenosing), presence of an enterocutaneous fistula and need for preoperative nutritional support. The surgical factors were type of surgery (only ileal, only colonic, ileo-colonic), surgical approach (open *v.* laparoscopic), number of resections during the same procedure (single or multiple) and need for a diverting ileostomy. All patients were treated according to a comprehensive enhanced recovery pathway. The pathway included avoiding preoperative fasting, favouring opioid-sparing analgesia, prophylaxis of postoperative nausea and vomiting, early resumption of a normal diet and ambulation. The protocol included the early removal of the Foley catheter and the avoidance of both drain placement and the use of a nasogastric tube whenever possible.

The postoperative course was classified prospectively at the time of discharge, and postoperative complications were recorded and considered up to 90 d after discharge. They were classified according to the Clavien-Dindo Classification[12]. The Comprehensive Complication Index (CCI®)[13] scores were calculated from all the single postoperative complications using an online calculator (www.assessurgery.com/about_cci-calculator/). The length of stay (LOS) was defined as the time from the day of surgery to the day of discharge. Based on nutritional risk screening (NRS), the patients were divided into two groups: patients with a low or null risk of malnutrition ($NRS < 2$) and patients with moderate or severe risk ($NRS \geq 2$) in agreement with the previous literature[14]. The postoperative course was compared between the two groups regarding ileus and anastomotic leak rates, readmission, overall and major complications (Clavien-Dindo Classification ≥ 3a), CCI score and LOS before and after balancing.

Statistical analysis – entropy balancing methodology

The data were reported as percentages or means and SD. The two groups were compared for both the confounding factors and the nutrition-related parameters.

Hainmueller's entropy balance analysis[6] is used to achieve a balance between treatment and control groups in observational studies, aiming to mimic the conditions of a randomised controlled trial. This method adjusts the weights of the observations to ensure that the distributions of the covariates are as similar as possible between the groups, thereby reducing bias and making the groups comparable.

The process of entropy balance works as follows: authors identified the covariates or confounding factors that need to be balanced between the treatment and control groups. These are characteristics that could influence the outcome of interest and should be equally distributed across the groups. Initial weights are assigned and calculated for all observations. In an unweighted analysis, all observations would ideally have equal weight. However, in real life, two groups are typically different for many covariates, bringing different weights. The first step is then to optimise weights via entropy balancing. The goal is to find a set of weights for the observations that minimises the difference in the covariate distributions between the treatment and control groups. The optimisation process involves an entropy function, which measures the divergence between the initial and adjusted weights. The function ensures that the adjusted weights are as close as possible to the initial weights, maintaining the original sample structure, which is why categorical variables did not differ after the weighting. On the contrary, continuous variables may vary slightly, as they inherently represent the weight of the covariate. Weights were computed and obtained using the calliper matching method in Stata, with the default calliper set to satisfy the balance constraints (mean and SD or variance) between the groups. Constraints are added to ensure that the weighted means of the covariates are equal across the groups. This means that after weighting, the average value of each covariate should be the same in both the treatment and control groups. The algorithm adjusts the weights to minimise the entropy function while satisfying the balancing constraints. Once the optimal weights are found, they are applied to the observations. The resulting weighted sample should have balanced covariates, meaning that the treatment and control groups are comparable with respect to the measured covariates. As noted by Heinmüller *et al.*[6], classical statistical analyses can be performed with weighted data. Although EB may violate the independence assumption, its impact on statistical analyses, such as regression, is minimised due to its rigorous balancing methodology. After each step, a logistic regression multivariate analysis and linear regression were carried out to evaluate the risk factors related to the postoperative results and to calculate the OR or mean difference (MD).The balanced sample allows for a more accurate estimation of the treatment effect, as it reduces the bias from confounding variables. In summary, entropy balance is a powerful tool for reducing bias in observational studies by creating weighted samples with balanced covariate distributions, thus facilitating more reliable causal inferences[6].

In an ideal world, to measure the exact role of malnutrition alone over its absence, we should know the impact of both conditions (good nutrition and malnutrition) on the surgical outcomes of every single patient, but this is obviously impossible since a patient can be only well or malnourished. A possible way to solve the problem is to identify the causal effect of preoperative malnutrition over its absence. The causal effect defines how the malnourished patients would fare if they were well-nourished. The results obtained are called counterfactual outcomes. The analysis was made in two steps: in the first one, only non-nutritional confounding factors were balanced to estimate the true effect of preoperative status on postoperative outcomes. In the second step, also the clinical and biochemical indicators of malnutrition were balanced.

Given that the association between malnutrition factors and postoperative complications (using regression tests) is already widely demonstrated in the literature, in this study, we wanted to make a different reasoning. The statistical method allowed us to simulate a hypothetical intervention on our patients. In the first step, the intervention was to make them similar in terms of general characteristics, leaving the differences regarding nutrition intact. In the second step, on the other hand, the model homogenised the nutritional values, leaving the basic characteristics of the patients unchanged. In other words, several confounding factors could magnify or mitigate the true impact of preoperative malnutrition on the postoperative course. The entropy balance method is designed to try to solve this problem. Differences between the groups were measured using standardised differences (*d*-value). In the context of EB, *d*-values are employed as a metric to ensure that the covariate means in the treatment and control groups are balanced after applying weights. EB transforms categorical variables into binary indicator variables and applies balancing techniques typically used for continuous variables. This allows for the balancing of categorical distributions across treatment and control groups by ensuring that the weighted means and variances of these binary indicators are aligned. Despite treating categorical variables in this transformed binary form, the goal remains to achieve balance in the original categorical distributions across groups. The *d*-value[15] essentially reports the differences between groups in units of SD. When two groups have no difference on a certain variable, their populations completely overlap. In statistics, the 'non-overlap' population refers to the portion of one group's population that remains different for such a variable, either at baseline or after an intervention. The *d*-value provides a standardised measure of effect size, with thresholds defined and benchmarked in the literature by Cohen *et al.*[15]. A *d*-value $\leq$ 0·2 indicates a percentage of the non-overlap population of $\leq$ 15 % (small between-group difference); a *d*-value > 0·2 and $\leq$ 0·5 (average difference) indicates a percentage of the non-overlap population from 15 to 33 %; a *d*-value from > 0·5 to 1·0 (large difference) indicates a percentage of the non-overlap population of > 33 %[16,17]. The *d*-values serve as a guide for assessing the balance of covariate distributions rather than as a strict measure of distribution shape.

The statistical analysis was carried out using STATA software (StataCorp 2017, StataCorp LP). Entropy balancing was carried out using the 'ebalance' module, for which a tutorial is linked in the references[18].

Results

The demographic characteristics of the two groups (Fig. 1) are reported in Table 1. Of the 183 patients surgically treated for CD, 69 patients (37·7 %) were found to be at moderate or high risk of malnutrition based on NRS, while 114 (63·3 %) were considered well-nourished/low risk. As expected, the two groups had *average* to *large* differences in BMI (*d* = 1·000), preoperative Hb (*d* = 0·715), creatinine (*d* = 0·553) and serum albumin (*d* = 0·981), while lymphocyte count (*d* = 0·124) showed *small* difference. The malnourished patients had a higher CACI score (*d* = 0·257), higher ECOG-PS and ASA scores (*d* = 0·689 and *d* = 0·327, respectively) and a higher H-B score (*d* = 0·696). They also required preoperative nutritional support more often (*d* = 0·766), and the rate of a diverting ileostomy was almost three times higher in this group (*d* = 0·648). The two groups showed *small* differences regarding smoking habit (*d* = 0·148), previous bowel surgery (*d* = 0·154), disease behaviour (*d* = 0·104) and rate of enterocutaneous fistulas (*d* = 0·162). On the contrary, the two groups were almost equivalent with respect to age (*d* = 0·026), type of surgery (*d* = 0·060), laparoscopic approach (*d* = 0·060) and the intraoperative need for multiple resections (*d* = 0·063).

Postoperative results (Table 2) *before balancing* showed similar rates for postoperative ileus, anastomotic leaks and Clavien-Dindo Classification $\geq$ 3a complications (*P* = 0·757,

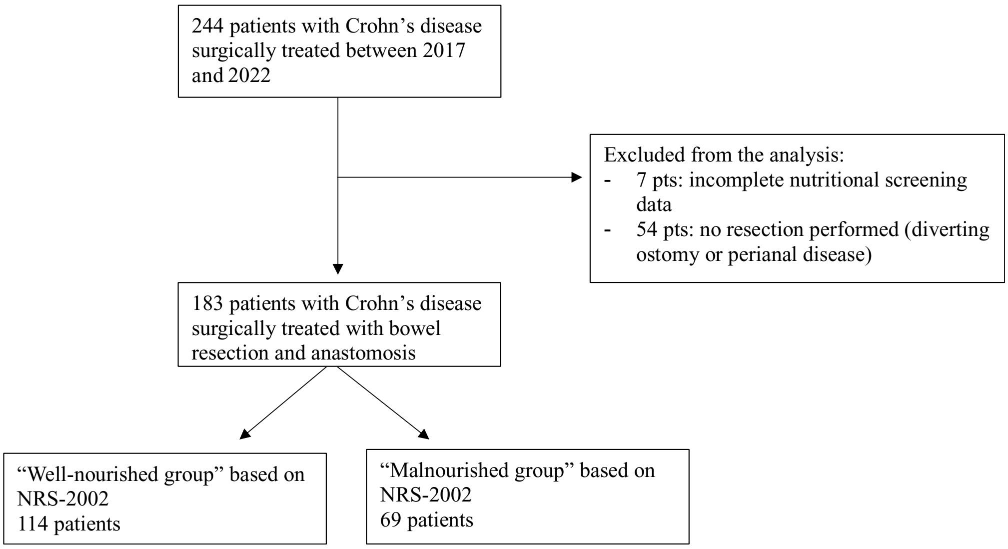

Fig. 1. Flow chart of the included patients.

$P = 0{\cdot}532$ and $P = 0{\cdot}670$, respectively). Malnourished patients experienced a 3-fold higher readmission rate (15·9 % *v.* 5·3 %; OR 3·41; 95 % CI 1·20, 9·70; $P = 0{\cdot}021$) and a prolonged LOS (6·5 *v.* 5 d; MD = 1·47; 95 % CI 0·33, 2·6; $P = 0{\cdot}012$). They also showed a higher rate of overall complications (59·4 % *v.* 35·1 %; OR 2·71; 95 % CI 1·46, 5·01; $P = 0{\cdot}002$) and a higher CCI score (13·1 *v.* 7·2; MD = 5·90; 95 % CI 2·29, 9·45; $P = 0{\cdot}001$).

After first reweighting (STEP 1)

As previously described, in the first reweighting, the two groups were equalised for all the confounding and non-modifiable factors. This created a 'virtual malnourished group' that was optimally balanced with the 'normal nutrition' group for all disease-specific and intraoperative characteristics ($d = 0$), thus enhancing the differences in the nutritional/modifiable parameters which remained the same as before balancing. The first balance included sex, age, CACI, ECOG-PS, ASA score, previous bowel surgery, type of disease (fistulising *v.* stenosing), Harvey-Bradshaw index, presence of enterocutaneous fistulas, preoperative nutritional support, type of surgery and surgical approach, number of resections and the need to create a diverting ileostomy. Postoperative results after the first reweighting are shown in Table 3. As in the baseline analysis, the malnourished patients experienced prolonged LOS (MD = 1·9; 95 % CI 0·11, 3·71; $P = 0{\cdot}038$), higher overall complication rate (OR 4·42; 95 % CI 1·39, 13·97; $P = 0{\cdot}012$) and a higher CCI score (MD = 8·9; 95 % CI 2·2, 15·7; $P = 0{\cdot}010$). Moreover, they showed a trend towards a higher anastomotic leak rate (OR 6·69; 95 % CI 0·98, 46·4; $P = 0{\cdot}052$), even if it was not statistically significant.

After second reweighting (STEP 2)

In the second reweighting, the two groups were equalised only for nutritional or preoperatively modifiable parameters, such as smoking habit, BMI, lymphocyte count, Hb, serum albumin and creatinine ($d = 0$). The other confounding factors were left as the baseline in order to simulate a nutritional intervention, which was effective in bringing the patient to an optimal nutritional level, while disease characteristics and intraoperative strategies were not modified. This statistical technique enables the researcher to highlight the role of nutritional optimisation. Postoperative results after the second reweighting are summarised in Table 3. The postoperative course of the normal nutrition group and the 'virtual, malnourished' patients balanced for nutritional parameters showed no differences.

Discussion and conclusions

The present study focused attention on some crucial aspects of nutritional status, which are highlighted in patients with CD by the use of *entropy balance*. Using innovative mathematical statistical systems was not a mere academic exercise in this case as it could help clinicians to prioritise preoperative interventions in order to mitigate substantial risk factors, such as malnutrition. First of all, as previously reported in the literature[19], the preliminary analysis in this study showed that malnourished patients had a higher risk of readmission and a higher complications rate (including a higher CCI index) as well as a longer LOS. These results should be treated with great caution as they reflected the huge differences between the two groups. Malnourished patients are more fragile at baseline (worse ASA and ECOG scores) have more comorbidities and a less favourable disease history (forming fistulas). They more frequently had surgery in the past and had a higher Harvey-Bradshaw index. These differences could increase surgical and postoperative risks independently or by association, making the evaluation of their individual burden challenging. The *EB* analysis, as previously reported in the literature[20], allowed a more focused evaluation of the individual risk factors by weighting and thus equalising each factor between two very diverse groups.

Patient characteristics in the two groups were then divided into unmodifiable (e.g. type of disease, Harvey-Bradshaw index, CACI, ECOG, ASA, etc.) and potentially modifiable with a

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Table 1. Characteristics of the patients at baseline and after entropy balancing (Numbers and percentages; mean values and standard deviations)

	Baseline					STEP 1*			STEP 2**		
Parameters	Well-nourished (*n* 114)		Malnourished (*n* 69)		D value	Virtual malnourished balanced for confounding factors		D value	Virtual malnourished balanced for nutritional status		*D* value
	n	%	*n*	%		*n*	%		*n*	%	
Sex											
Male	64	56·1	31	44·9	0·284	31	44·9	0	31	44	0·284
Female	50	43·9	38	55·1		38	55·1		38	55·1	
	Mean	SD	Mean	SD		Mean	SD		Mean	SD	
Age, years	49·5	14·4	49·9	16·7	0·026	49·5	15·1	0	49·5	13	0·026
BMI (kg/m^2)	24·8	3·6	20·1	2·9	1	20·1	2·9	1	24·8	3·1	0
Lymphocytes	1·8	0·75	1·7	0·95	0·124	1·7	0·95	0·124	1·8	0·8	0
Hb	13·2	1·6	12	1·8	0·715	12	1·8	0·715	13·1	1·7	0
Creatinine	0·86	0·23	0·84	0·51	0·553	0·84	0·51	0·553	0·86	0·30	0
Serum Albumin	41·1	4·1	36·2	6·2	0·981	36·2	6·2	0·981	40·9	3·7	0
CACI	1·28	1·73	1·77	2·16	0·257	1·31	1·88	0	1·77	2·16	0·257
	n	%	*n*	%		*n*	%		*n*	%	
ECOG-PS											
0	97	85·1	41	59·4	0·689	41	59·4	0	41	59·4	0·689
1	15	13·2	18	26·1		18	26·1		18	26·1	
2	2	1·8	10	14·5		10	14·5		10	14·5	
ASA score											
I	3	2·6	3	4·3	0·327	3	4·3	0	3	4·3	0·327
II	95	83·3	45	65·2		45	65·2		45	65·2	
III	16	14	21	30·4		21	30·4		21	30·4	
Active smoker											
No	81	71·1	45	65·2	0·148	45	65·2	0·148	45	65·2	0
Yes	33	28·9	24	34·8		24	34·8		24	34·8	
Previous bowel surgery											
No	69·	60·5	40	58	0·154	40	58	0	40	58	0·154
1 or laparoscopic	25	21·9	10	14·5		10	14·5		10	14·5	
> 1 or laparotomic	20	17·5	19	27·5		19	27·5		19	27·5	
Type of disease											
Fistulising	38	33·3	26	37·7	0·104	26	37·7	0	26	37·7	0·104
Stenosing	76	66·7	43	62·3		43	62·3		43	62·3	
H-B score											
< 4	60	52·6	23	33·3	0·696	23	33·3	0	23	33·3	0·696
05 Aug	44	38·6	18	26·1		18	26·1		18	26·1	
≥ 9	10	8·8	28	40·6		28	40·6		28	40·6	
Enterocutaneous fistula											
No	109	95·6	65	94·2	0·162	65	94·2	0	65	94·2	
Yes	5	4·4	4	5·8		4	5·8		4	5·8	0·162
Preoperative nutritional support											
No	55	48·2	13	18·8	0·766	13	18·8	0	13	18·8	0·766
Yes	59	51·8	56	81·2		56	81·2		56	81·2	
Type of surgery											
Jejunal only	5	4·4	3·	4·3	0·067	3	4·3	0	3	4·3	0·067
Colonic only	11	9·6	9	13		9	13		9	13	

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Table 1. (*Continued*)

	Baseline					STEP 1*			STEP 2**		
	Parameters	Well-nourished (*n* 114)		Malnourished (*n* 69)		D value	Virtual malnourished balanced for confounding factors		*D* value	Virtual malnourished balanced for nutritional status	*D* value
	n	%	*n*	%		*n*	%		*n*	%	
Mixed	98	86	57	82·6		57	82·6		57	82·6	
Approach											
Laparoscopic	104	91·2	61	88·4	0·06	61	88·4	0	61	88·4	0·06
Open	5	4·4	5	7·2		5	7·2		5	7·2	
Converted	5	4·4	3	4·3		3	4·3		3	4·3	
N. of resection											
Single	94	82·5	58	84·1	0·063	58	84·1	0	58	84·1	0·063
Multiple	20	17·5	11	15·9		11	15·9		11	15·9	
Protective ileostomy											
No	105	92·1	54	78·3	0·648	54	78·3	0	54	78·3	0·648
Yes	9	7·9	15	21·7		15	21·7		15	21·7	

CACI, age-adjusted Charlson Comorbidity Index; ECOG-PS, Eastern Cooperative Oncology Group – performance status; ASA, American Society of Anaesthesiologists; H-B score, Harvey-Bradshaw score for Crohn's disease activity. A *d*-value ≤ 0·2 indicates a percentage of the non-overlap population of ≤ 15 % (small between-group difference); a *d*-value > 0·2 to ≤ 0·5 (average difference) indicates a percentage of the non-overlap population of between 15 and 33 %; a *d*-value > 0·5 to 1·0 (large difference) indicated a percentage of the non-overlap population of > 33 %.

*STEP 1: To reweight the malnourished patient group for all the preoperative, intraoperative and disease-specific confounding factors. The first step corrects the clinical and operative parameters, which are not directly related to malnutrition or which are unmodifiable (i.e. number of surgeries, fistulising disease).

**STEP 2: To reweight malnourished patients for all those parameters directly related to malnutrition, thus potentially modifiable.

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Table 2. Postoperative outcomes of the two groups at baseline (Numbers and percentages; odds ratios or mean difference and 95 % confidence intervals)

	Well-nourished		Malnourished				
Postoperative result	*n*	%	*n*	%	OR or MD	95 % CI	*P*
Ileus							
No	104	91·2	62	89·9	1·17	0·42, 3·24	0·757
Yes	10	8·8	7	10·1			
Anastomotic leak							
No	111	97·4	66	95·7	1·68	0·33, 8·57	0·532
Yes	3·	2·6 %	3	4·3			
Readmission							
No	108	94·7	58	84·1	3·41	1·20, 9·70	0·021
Yes	6	5·3	11	15·9			
LOS (days)							
Mean	5		6·5		1·47	0·33, 2·6	0·012
SD	3·8		3·8				
Any complication							
No	74	64·9	28	40·6	2·71	1·46, 5·01	0·002
Yes	40	35·1	41	59·4			
CDC ≥ 3a							
No	109	95·6	65	94·2	1·34	0·35, 5·17	0·670
Yes	5	4·4	4·	5·8			
CCI (%)							
Mean	7·2		13·1		5·90	2·29 9·45	
SD	11·2		13·3				0·001

MD, mean difference; LOS, length of stay; CDC, Clavien-Dindo Classification score; CCI, Comprehensive Complication Index.

Table 3. Postoperative outcomes of the two groups after step 1 and step 2 of entropy balancing (Odds ratios or mean difference and 95 % confidence intervals)

	After first weighting – balanced for confounding factors			After second weighting – balanced for nutritional status		
	Normal *v.* virtual balanced malnourished			Normal *v.* virtual balanced malnourished		
Postoperative result	OR or MD	95 % CI	*P*	OR or MD	95 % CI	*P*
Ileus						0·793
No	1 (referent)		0·372	1 (referent)		
Yes	1·82	0·48, 6·88		1·34	0·15, 12·3	
Anastomotic leak						
No	1 (referent)		0·052	1 (referent)		0·163
Yes	6·69	0·98, 46·4		0·19	0·02, 1·97	
Readmission						
No	1 (referent)		0·259	1 (referent)		0·131
Yes	2·24	0·55, 9·21		3·81	0·62, 30·2	
LOS (days)	1·9	0·11, 3·71	0·038	–0·74	–2·2, 0·79	0·321
Any complication						
No	1 (referent)		0·012	1 (referent)		0·685
Yes	4·42	1·39, 13·97		1·42	0·25, 8·09	
CDC ≥ 3a						
No	1 (referent)		0·121	1 (referent)		0·221
Yes	0·93	0·73, 1·16		4·41	0·41, 46·7	
CCI (%)	8·9	2·2, 15·7	0·010	3·98	–8·7, 16·7	0·536

MD, mean difference; LOS, length of stay; CDC, Clavien-Dindo Classification score; CCI, Comprehensive Complication Index.

preoperative intervention (e.g. smoking habit, BMI, albumin, etc.). The first reweighting was carried out to correct the unmodifiable confounding factors in order to evaluate the true role of nutritional status alone. Once the two groups were equalised for those characteristics, the negative impact of malnutrition on the postoperative course was confirmed and highlighted, being an independent risk factor for complications and prolonged LOS. Interestingly, this first step also balanced the malnourished cohort for 'diverting ileostomy creation' by reducing its rate. By doing so, the EB allows to show a trend towards a higher anastomotic leak rate in patients with malnutrition alone, even if this was not statistically significant.

The second step confirmed the burden of malnutrition in an even more spectacular way. *Entropy balancing* step 2 aimed at creating a virtual cohort of malnourished patients in which a hypothetical optimal preoperative nutritional intervention would correct all the nutrition-related characteristics between the two original groups. Interestingly, some non-marginal advantages could have been obtained by correcting the preoperative nutritional status. All the postoperative outcome differences between the two groups disappeared in this step, underscoring what would have happened if the malnutrition had been successfully treated.

This additional evidence reinforced the concept that a multimodal pre-habilitation, also associating the cessation of smoking and initiatives to prevent sarcopenia, could not be only a viable pathway but a necessary pathway in order to improve patients' outcomes. While it is very well known that systemic inflammation or the inability of tolerating oral food could be reasons for failing to optimise patients, the results of this study should incentivise researchers to identify nutritional treatment, which could be more effective, even in these specific scenarios.

In order to treat malnutrition and reduce inflammation, many authors have already reported their results regarding the role of pre-habilitation before ileocolic resection in CD patients. The main impact on outcomes was obtained by nutritional correction, with a reduction in both anastomotic complications and the re-operation rate[21,22].

The current study has some obvious limitations: first, the sample size and the retrospective nature of a population that was selected from a prospectively maintained database, and second, the few intrinsic limitations related to the *EB* methodology. The main weakness of this system is the assumption that preoperative conditions, such as malnutrition, could be completely remedied, generating a virtual group that becomes equivalent to the real study population.

On the one hand, this points out the need for intensive pre-habilitation programmes in order to mitigate the role of poor nutritional status. On the other hand, this is difficult to achieve in real life.

Although this system is purely a statistical tool, it enables clinicians to simulate a randomised control study and establish a foundational basis before deciding to invest in a nutritional pre-habilitation clinical trial.

While many studies have focused on BMI, albumin and other laboratory findings in order to describe the fitness level and the success of nutritional treatments many lack data about sarcopenia and myosteatosis[23]. Unfortunately, the present study made no exception for the latter as these parameters were not recorded in this series. Future research should use *EB* to evaluate the role of sarcopenia and myosteatosis as they have been defined to be key players in inflammatory bowel disease patients[24].

In conclusion, despite its limitations, the present study highlighted the role of malnutrition on surgical outcomes for CD patients from a different and innovative point of view. The present results, together with other experiences, could be the foundation for paving the way for future studies on preoperative nutritional treatment in patients undergoing major surgery.

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Data described in the manuscript, code book and analytic code will be made available upon reasonable request to the corresponding author.

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References

1. Sungurtekin H, Sungurtekin U, Balci C, *et al.* (2004) The influence of nutritional status on complications after major intraabdominal surgery. *J Am Coll Nutr* **23**, 227–232.
2. Sun Z, Kong XJ, Jing X, *et al.* (2015) Nutritional risk screening 2002 as a predictor of postoperative outcomes in patients undergoing abdominal surgery: a systematic review and meta-analysis of prospective cohort studies. *PLoS One* **10**, e0132857. eCollection 2015.
3. Correia MI & Waitzberg DL (2003) The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr* **22**, 235–239.
4. Jie B, Jiang ZM, Nolan MT *et al.* (2012) Impact of preoperative nutritional support on clinical outcome in abdominal surgical patients at nutritional risk. *Nutrition* **28**, 1022–1027.
5. Jacobson S (2012) Early postoperative complications in patients with Crohn's disease given and not given preoperative total parenteral nutrition. *Scand J Gastroenterol* **47**, 170–177.
6. Hainmueller J (2012) Entropy balancing for causal effects: a multivariate reweighting method to produce balanced samples in observational studies. *Political Analysis* **20**, 25.e4.
7. Kondrup J, Allison SP, Elia M, *et al.* (2003) Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN). ESPEN Guidelines for Nutrition Screening 2002. *Clin Nutr* **22**, 415–421.
8. Chang CM, Yin WY, Wei CK, *et al.* (2016) Age-adjusted Charlson comorbidity index score as a risk measure of perioperative mortality before cancer surgery. *PLoS One* **11**, e0148076.
9. Ethun CG, Bilen MA, Jani AB, *et al.* (2017) Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J Clin* **67**, 362–377; Ther Adv Gastroenterol 2021; vol. 14: 1–12.
10. Kochar B, Orkaby AR, Ananthakrishnan AN *et al.* (2021) Frailty in inflammatory bowel diseases: an emerging concept. *Therap Adv Gastroenterol* **14**, 17562848211025474. eCollection 2021.
11. Hanzel J, Bossuyt P, Pittet V *et al.* (2022) Development of a core outcome set for real-world data in inflammatory bowel disease: a European Crohn's and Colitis Organisation (ECCO) position

paper. *J Crohns Colitis* **jjac136**. (Epublication ahead of print version 03 October 2022).
12. Dindo D, Demartines N & Clavien PA (2004) A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* **240**, 205–213.
13. Slankamenac K, Graf R, Barkun J, *et al.* (2013) The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg* **258**, 1–7.
14. Huisman MG, Veronese G, Audisio RA, *et al.* (2016) Poor nutritional status is associated with other geriatric domain impairments and adverse postoperative outcomes in onco-geriatric surgical patients – a multicentre cohort study. *Eur J Surg Oncol* **42**, 1009–1017.
15. Cohen J (1988) *Statistical Power Analysis for the Behavioral Sciences*. New York, NY: Routledge Academic.
16. Cook BG, Cook L & Therrien WJ (2018) Group-difference effect sizes: gauging the practical importance of findings from group-experimental research. *Learn Disabil Res Pract* **32**, 56.e63.
17. Watson SK & Elliot M (2016) Entropy balancing: a maximum-entropy reweighting scheme to adjust for coverage error. *Qual Quantity* **50**, 1781e97.
18. Stanford Ebalance: a Stata Packing for Entropy Balancing. Stanford University. JSS2013.pdf https://www.stanford.edu (2013). *Journal of Statistical Software* **54** (7), 1–18.
19. Kassin MT, Owen RM, Perez SD, *et al.* (2012) Risk factors for 30-day hospital readmission among general surgery patients. *J Am Coll Surg* **215**, 322–330.
20. Ricci C, Serbassi F, Ingaldi C, *et al.* (2022) Effect of malnutrition on postoperative results after pancreatic resection: an entropy balancing analysis. *Clin Nutr* **41**, 1781–1786.
21. Yamamoto T, Nakahigashi M, Shimoyama T, *et al.* (2020) Does preoperative enteral nutrition reduce the incidence of surgical complications in patients with Crohn's disease? A case-matched study. *Colorectal Dis* **22**, 554–561.
22. Ferrandis C, Souche R, Bardol T, *et al.* (2022) Personalized pre-habilitation reduces anastomotic complications compared to up front surgery before ileocolic resection in high-risk patients with Crohn's disease: a single center retrospective study. *Int J Surg* **105**, 106815.
23. Santarpia L, Alfonsi L, Castiglione F, *et al.* (2019) Nutritional rehabilitation in patients with malnutrition due to Crohn's disease. *Nutrients* **11**, 2947.
24. Nishikawa H, Nakamura S, Miyazaki T, *et al.* (2021) Inflammatory bowel disease and Sarcopenia: its mechanism and clinical importance. *J Clin Med* **10**, 4214.