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Immunonutrition in patients who underwent major abdominal surgery: A comprehensive systematic review and component network metanalysis using GRADE and CINeMA approaches

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ABSTRACT

Background: The benefits of immunonutrition in patients who underwent major abdominal surgery have been recently established, but the optimal combination of immunonutrients has remained unclear. The aim is to clarify this point.

Methods: A systematic search of randomized clinical trials about immunonutrition in major abdominal surgery was made. A frequentist random-effects component network meta-analysis was conducted, reporting the *P* score and odds ratio or mean difference with a 95% confidence interval. The best components and best plausible strategies were described. The critical endpoints were morbidity and mortality rates. The important endpoints were infectious complication rate and length of stay.

Results: The meta-analysis includes 87 studies and 8,375 patients. The best approach for morbidity rate, with a moderate grade of certainty, was the use of perioperative enteral/oral immunonutrition with arginine, glutamine, and polyunsaturated fatty acids (odds ratio 0.32; 0.10 to 0.98; *P* score of 0.93). The mortality rate was reduced by postoperative enteral immunonutrition with RNA, arginine, and polyunsaturated fatty acids (odds ratio 59; 0.29 to 1.22; *P* score 0.84) but with a low grade of certainty. No significant heterogeneity or incoherence is observed. The length of stay and infectious results are "at risk" for high heterogeneity or network meta-analysis incoherence. The component analysis confirmed that postoperative oral/enteral use of 2 or 3 components is crucial to reducing morbidity rate.

Conclusion: The oral/enteral immunonutrition in the postoperative period, with multiple immunonutrients, can reduce the morbidity rate in patients undergoing major abdominal surgery. The effect of immunonutrition on mortality, infectious disease, and length of stay is unclear.

Introduction

In recent years, immunonutrition (IM) has gained visibility as one of the basic principles of enhanced recovery after surgery.[1] The hypothesis is that some nutrients such as amino acids (glutamine or arginine), polyunsaturated fatty acids (Ω_3), and RNA, alone or in combination, could function as immunomodulators.[2-4] For this reason, IM has been studied to reduce morbidity in major abdominal surgery. A recent umbrella review[5] has demonstrated a positive impact of IM in reducing postoperative complications and the infection rate. However, the main problem of these meta-analyses was that the randomized controlled trials included different schedules (formula, way of administration, and timing). Thus, some doubts remain about the efficacy of IM.

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Moreover, the enhanced recovery after surgery guidelines did not recommend a defined formula or an optimal timing for IM.[6-9] Our study aims to define the best approach considering all components of IMs: the type and combination of IMs, the timing of the administration, and the way of administration (oral/enteral or parenteral). To overcome the problem of a multi-arm setting, a network meta-analysis (NMA) was performed. To clarify the role of each component, the component NMA (CNMA)[10] was used. Whereas NMA focuses on estimating intervention effects, CNMA disentangles the impact of each element, reconstructing the ideal combination for way of administration, timing, and types of IMs. The CINeMA[11] and GRADE[12] approaches were used to present the results in an accessible form.

Methods

The study protocol was registered in PROSPERO (CRD42022347558A). The systematic search was performed according to the Cochrane recommendations. The article was structured following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[13]

Eligibility criteria

The eligibility criteria were established according to the Population, Intervention, Control, Outcomes, and Studies (PICOS) approach[14]: the "population" was represented by patients who underwent major abdominal surgery, excluding cholecystectomy, abdominal hernia repair, or obesity surgery; the "intervention" arms were any type of oral, enteral, or parenteral IM; in the "control" group any perioperative approach without IM was considered; the studies were included only when reporting at least 1 of the critical endpoints; only randomized controlled trials were considered.

Information source, search, study selection, and data collection process

The research was based on a classical meta-analysis,[15] and the systematic review was updated starting on August 1, 2015. The last search was carried out on June 28, 2022. The systematic review was conducted through PubMed and Embase. The search string was appropriately translated using the SR accelerator and reported in supplementary electronic files (Supplementary Materials).[16]

Data items

For each study, we described the first author, year of publication, affiliation/country, type of surgical procedure design, type of abdominal surgery, type of patients (well or malnourished), and study quality. The relevance of outcomes was established by a panel of authors using the GRADE scale[17] (not important, important, critical). As the primary endpoints, we evaluated the postoperative morbidity and mortality, which were judged "critical." The secondary endpoints were the rate of postoperative infectious complications and the length of stay (LOS), considered "important." The following minimal important differences were set: for morbidity, mortality, and infectious complications, 10 per 1,000 persons more or fewer; for LOS, at least ± 2 days.[18] The studies were clustered based on the type of IMs, timing (preoperative, perioperative, or postoperative), and the way of administration (oral/enteral or parenteral).

Geometries of the network and risk of bias within the individual study

The network geometry was described using nodes and edges. The nodes correspond to the interventions, and the edges display the observed intervention comparisons. The thickness of edges indicates the frequency with which each comparison occurs in the network (number of studies). The risk of bias within the individual studies was measured using a revised tool for assessing the risk of bias in randomized trials (Rob2).[19] The risk of indirectness was not negligible when the study population, interventions, and outcomes measurement were not entirely representative of PICOS criteria. Indirectness could reduce the transitivity across the common nodes in NMA, making it challenging to obtain reliable network estimates. Each study was judged as "low-risk," "some concerns," or "major concerns." L.A. and F.S. performed Rob2 and indirectness evaluation.

Summary measurements and methods of the analysis

The effect estimates were reported as odds ratios (ORs) or mean differences (MDs), with 95% CIs. Confidence intervals, including 1 for odds ratios or 0 for mean difference, imply a non–statistically significant relative effect for the compared interventions. The referent arm included a placebo and standard therapy. The results were also reported as a *P* score that represents the probability, without uncertainty, that each treatment would be the best based on the outcome analyzed.[20-22] The intervention was considered among the best if the *P* score was $\geq$0.66; when the *P* score was between 0.65 and 0.33, the intervention was deemed inferior to the best/better than the worst, and when the *P* score was low to 0.33, the intervention was considered among the worst. The main idea of CNMA lies in decomposing multicomponent interventions to estimate the effects of their components. The additive effects model first estimates the impact of each component. Then, the effect of each multicomponent intervention is estimated by summing the relative impact of the components comprising this intervention.[10] Results were tabulated according to the GRADE recommendation.[23] All analysis was made using the *netmeta* package for R version 4.0.1 (R Foundation for Statistical Computing) and STATA v.17 (StataCorp, LLC).

Inconsistency, risk of bias across the studies, and meta-regression analysis

The transitivity across the common node was evaluated by testing the global and local inconsistency (within the closed triangular or quadratic loops).[24] The inconsistency, also called incoherence, measured the unreliability of the networks, and it was reported as the ratio of odds ratio or difference of MD between direct and indirect evidence. The inconsistency was not significant when the *P* value was <.05. The heterogeneity was tested with tau^2 (τ^2).[25,26] Publication/reporting bias was investigated using Egger's tests.[27]

Assessment of the certainty of the evidence

Based on the GRADE approach,[28] 4 levels were considered: (1) high quality, which means that the actual effect lies close to that of the NMA estimates; (2) moderate quality, which means the actual effect is likely to be close to the NMA estimates, but there is a possibility that it is substantially different; (3) low quality, namely that the actual effect may be substantially different from the NMA estimates; (4) very low quality, which means the actual effect is likely to be substantially different from the NMA estimates. The

certainty of the evidence was established using CINeMA software[28] by evaluating 6 parameters: within-study bias (Risk of Bias 2), reporting bias, indirectness, imprecision, heterogeneity, and incoherence. When some or major concerns are present for 1 of the 6 parameters, the certainty of the evidence is downgraded.

Results

Studies selected

The systematic literature search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist statement is reported in Supplementary Figure S1. The references to the included studies are reported in Supplementary Table S1.

Study characteristics and risk of bias within studies

In Supplementary Table S2 and the Supplementary Materials, the characteristics of the studies ($n = 87$) are described. For the NMA approach, a total of 8,357 patients were clustered into the following arms: Arm A, including 2,844 (30.3%) patients who received placebo or standard therapy; Arm B, including 1,409 (15%) patients who received postoperative parenteral supplementation without IM; Arm C, including 994 (10.6%) patients who received preoperative oral/enteral IM with arginine, RNA, and Ω_3; Arm D, including 35 (0.4%) patients who received preoperative oral/enteral IM with arginine alone; Arm E, including 13 (0.1%) patients who received preoperative oral/enteral IM with arginine and Ω_3 fatty acids (OIM-Pre3); Arm F, including 11 (0.1%) patients who received postoperative oral/enteral IM with Ω_3 fatty acids alone; Arm G, including 291 (3.1%) patients who received postoperative oral/enteral IM with arginine, RNA, and Ω_3 (OIM-Post1); Arm H, including 535 (5.7%) patients who received postoperative enteral/oral IM with arginine, glutamine, and Ω_3; Arm I, including 8 (0.1%) patients who received postoperative enteral/oral IM with Ω_3 alone (OIM-Post3); Arm K, including 44 (0.5%) patients who received postoperative enteral/oral IM with glutamine-alanine; Arm L, including 474 (5.1%) patients who received postoperative parenteral IM with glutamine-glycine; Arm M, including 57 (0.6%) patients who received postoperative parenteral IM with arginine-based; Arm N, including 611 (6.5%) patients who received postoperative parenteral IM with Ω_3 alone; Arm O, including 51 (0.5%) patients who received postoperative parenteral IM with Ω_3 and glutamine; Arm P, including 722 (7.7%) patients who received perioperative oral/enteral IM with arginine, RNA, and Ω_3; Arm Q, including 46 (0.5%) patients who received perioperative oral/enteral immunonutrition with arginine, glutamine, and Ω_3 (OIM-Peri2); Arm V, including 212 (2.3%) patients who received perioperative oral/enteral immunonutrition with Ω_3 alone.

Network structures and geometries

The network geometry of the morbidity, mortality, and infectious complications are similar (Figure 1), whereas in the network of LOS, the arm OIM-Pre3 and OIM-Post3 are lacking.

Synthesis of results

Morbidity

Table I shows the results for the morbidity rate. The overall heterogeneity and inconsistency were absent ($\tau^2 = 0.043$; $I^2 = 13.2\%$; $P = .161$). Figure 2, *A* describes the ORs. The evidence certainty and risk of bias were exhaustively reported in Supplementary Table S3 and Supplementary Figure S2, *A*, respectively. Incoherence and heterogeneity were evaluable in Supplementary Figure S2, *B*. Publication bias was absent (Egger test, $P = .230$; Supplementary Figure S2, *C*). Four arms resulted among the best: OIM-Peri2, PIM-post3, OIM-Post1, and OIM-Peri.[1] All details are exhaustively described in the Supplementary Materials.

Mortality

Table II and Figure 2, *C* shows the results for the mortality rate. The overall inconsistency was not significant ($P = .862$). The local and global inconsistency cannot be evaluated due to the low number of events. The evidence certainty and risk bias are reported in Supplementary Table S4 and Supplementary Figure S3, *A*, respectively. Publication bias was absent (Egger's test, $P = .610$; Supplementary Figure S3, *B*). Only 1 intervention arm can be considered among the best: OIM-Post1 reduced the mortality rate of 8 cases per 1,000 patients fewer (OR 59; 0.29 to 1.22; *P* score 0.84). The certainty was moderate due to imprecision.

Infectious complications

Supplementary Table S5 and Figure 2, *D* show the infectious complication results after surgery. The overall heterogeneity and inconsistency were significant ($\tau^2 = 0.199$; $I^2 = 37.9\%$; $P = .001$). The evidence certainty and risk bias are reported in Supplementary Table S6 and Figure S4, *A*, respectively. Incoherence and heterogeneity are evaluable in Supplementary Figure S4, *B*. Publication bias was absent (Egger's test, $P = .620$; Supplementary Figure S4, *C*). Five arms resulted among the best; the details are reported in the Supplementary Materials.

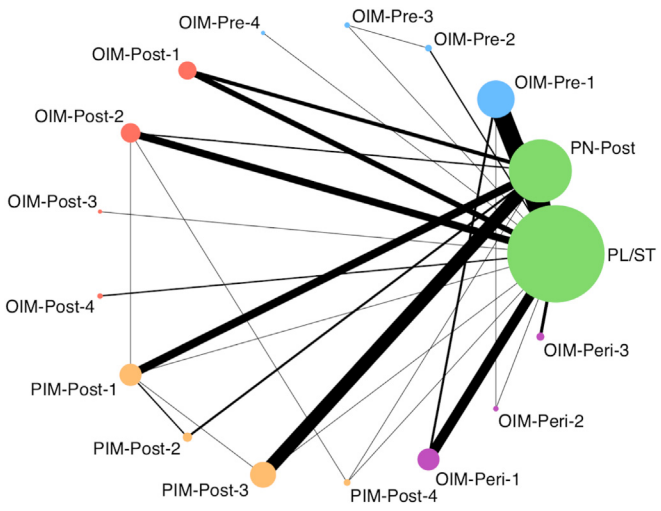

Figure 1. Network geometries. *PL-ST*, Placebo or conventional postoperative nutrition without supplement or immunonutrition; *PN-Post*, Postoperative parenteral supplementation without immunonutrition; *OIM-Pre1*, Preoperative oral immunonutrition with arginine, RNA, and Ω_3; *OIM-Pre2*, Preoperative oral immunonutrition with arginine alone; *OIM-Pre3*, Preoperative oral immunonutrition with arginine and Ω_3; *OIM-Pre4*, Preoperative enteral immunonutrition with Ω_3 alone; *OIM-Post1*, Postoperative enteral immunonutrition with arginine, RNA, and Ω_3; *OIM-Post2*, Postoperative enteral immunonutrition with arginine, glutamine, and Ω_3; *OIM-Post3*, Postoperative enteral immunonutrition with Ω_3 alone; *OIM-Post4*, Postoperative enteral immunonutrition with glutamine-alanine; *PIM-Post1*, Postoperative parenteral immunonutrition with glutamine-glycine; *PIM-Post2*, Postoperative parenteral immunonutrition arginine-based; *PIM-Post3*, Postoperative parenteral immunonutrition with Ω_3; *PIM-Post4*, Postoperative parenteral immunonutrition with Ω_3 and glutamine; *OIM-Peri1*, Perioperative oral immunonutrition with arginine, RNA, and Ω_3; *OIM-Peri2*, Preoperative oral immunonutrition with arginine, glutamine, and Ω_3; *OIM-Peri3*, Preoperative oral immunonutrition with Ω_3.

Table I
NMA for morbidity rate

Total studies: 87 RCT Total participants: 8,357 Inconsistency (τ^2): 0.043 ($P = .404$) Heterogeneity (I^2): 13.2% ($P = .056$) Overall total test for I^2 and τ^2: $P = .161$	OR[§] (95% CrI)	Anticipated absolute effect[*] (95% CrI)			Certainty of the evidence[‡]	*P* score
		With placebo/ standard therapy[†]	With intervention	Difference (Minimal important difference = 10)		
Placebo/standard therapy (A)	1.00 Reference comparator	No estimable	No estimable	No estimable	Reference comparator	.41
Postoperative parenteral nutrition (B) Mixed evidence (Direct evidence from 9 studies)	1.19 (0.89 to 1.59)	345 per 1,000	411 per 1,000	66 per 1,000 more (from 38 fewer to 204 more)	⊕◯◯◯ Very low Due to: -Within-study bias -Incoherence -Imprecision	.28
Preoperative oral IM with RNA, arginine, and Ω_3 (C) Mixed evidence (Direct evidence from 22 studies)	0.75 (0.62 to 0.91)	345 per 1,000	259 per 1,000	86 per 1,000 fewer (from 131 fewer to 31 fewer)	⊕◯◯◯ Very low Due to: -Within-study bias -Heterogeneity -Imprecision	.64
Preoperative oral IM with arginine alone (D) Mixed evidence (Direct evidence from 1 study)	0.84 (0.29 to 2.38)	345 per 1,000	290 per 1,000	55 per 1,000 fewer (from 244 fewer to 476 more)	⊕⊕◯◯ Low -Within-study bias -Imprecision	.55
Preoperative oral IM with arginine and Ω_3 (E) No direct evidence	2.16 (0.45 to 10.40)	345 per 1000	745 per 1,000	400 per 1,000 more (from 190 fewer to 3,243 more)	⊕◯◯◯ Very low Due to: -Within-study bias -Incoherence -Imprecision	.19
Preoperative oral IM with Ω_3 alone (F) Mixed evidence (Direct evidence from 1 study)	2.86 (0.21 to 37.99)	345 per 1,000	987 per 1,000	642 per 1,000 more (from 273 fewer to 12,761 more)	⊕⊕◯◯ Low - Imprecision - Incoherence	.21
Postoperative enteral IM with RNA, arginine, and Ω_3 (G) Mixed evidence (Direct evidence from 6 studies)	0.54 (0.34 to 0.87)	345 per 1,000	186 per 1,000	107 per 1,000 fewer (from 117 fewer to 300 fewer)	⊕⊕⊕◯ Moderate -Within-study bias	.83
Postoperative enteral IM with arginine, glutamine, and Ω_3 (H) Mixed evidence (Direct evidence from 10 studies)	0.77 (0.59 to 1.00)	345 per 1,000	266 per 1,000	79 per 1,000 fewer (from 141 fewer to 0)	⊕⊕◯◯ Low -Imprecision -Indirectness	.62
Postoperative enteral IM with Ω_3 alone (I) Mixed evidence (Direct evidence from 1 study)	2.33 (0.32 to 16.18)	345 per 1,000	804 per 1,000	459 per 1,000 more (from 235 fewer to 5,237 more)	⊕⊕◯◯ Low - Imprecision -Incoherence	.21
Postoperative enteral IM with glutamine-alanine (K) Mixed evidence (Direct evidence from 2 studies)	1.85 (0.34 to 2.13)	345 per 1,000	293 per 1,000	52 per 1,000 fewer (from 117 fewer to 390 fewer)	⊕◯◯◯ Very low -Within-study bias - Imprecision -Incoherence	.54
Postoperative parenteral IM with glutamine-glycine (L) Mixed evidence (Direct evidence from 2 studies)	1.11 (0.74 to 1.66)	345 per 1,000	383 per 1,000	38 per 1,000 more (from 38 fewer to 228 more)	⊕⊕◯◯ Low -Within-study bias -imprecision	.35
Postoperative parenteral IM with arginine (M) No direct evidence	1.07 (0.46 to 2.49)	345 per 1,000	369 per 1,000	24 per 1,000 more (from 186 fewer to 859 more)	⊕◯◯◯ Very low -Within-study bias -Imprecision -Incoherence	.40
Postoperative parenteral IM with Ω_3 alone (N) Mixed evidence (Direct evidence from 1 study)	0.55 (0.36 to 0.82)	345 per 1,000	190 per 1,000	155 per 1,000 fewer (from 221 fewer to 62 fewer)	⊕⊕⊕◯ Moderate -Within-study bias	.84
Postoperative parenteral IM with glutamine and Ω_3 (O) Mixed evidence (Direct evidence from 1 study)	0.95 (0.48 to 1.86)	345 per 1,000	328 per 1,000	17 per 1000 fewer (from 179 fewer to 297 more)	⊕⊕◯◯ Low -Indirectness - Imprecision	.47
Perioperative enteral IM with RNA, arginine, and Ω_3 (P) Mixed evidence (Direct evidence from 12 studies)	0.61 (0.47 to 0.78)	345 per 1,000	210 per 1,000	135 per 1,000 fewer (from 162 fewer to 76 fewer)	⊕⊕⊕◯ Moderate -Within-study bias	.79

(*continued on next page*)

Table I (*continued*)

Total studies: 87 RCT Total participants: 8,357 Inconsistency (τ^2): 0.043 ($P = .404$) Heterogeneity (I^2): 13.2% ($P = .056$) Overall total test for I^2 and τ^2: $P = .161$	OR[§] (95% CrI)	Anticipated absolute effect[*] (95% CrI)			Certainty of the evidence[‡]	*P* score
		With placebo/ standard therapy[†]	With intervention	Difference (Minimal important difference = 10)		
Perioperative enteral IM with, arginine, glutamine, and Ω_3 (Q) Mixed evidence (Direct evidence from 1 study)	0.32 (0.10 to 0.98)	345 per 1,000	107 per 1,000	235 per 1,000 fewer (from 314 fewer to 10 more)	⊕⊕⊕◯ Moderate -Imprecision	.93
Perioperative enteral IM with Ω_3 (I) Mixed evidence (Direct evidence from 4 studies)	1.32 (0.82 to 1.99)	345 per 1,000	455 per 1,000	110 per 1,000 more (from 59 fewer to 373 more)	⊕⊕◯◯ Low -Imprecision -Incoherence	.24

CrI, credible interval; *IM*, immunonutrition; *NMA*, network meta-analysis; *OR*, odds ratio; *RCT*, randomized controlled trial.

[*] Anticipated absolute effect compares 2 risks by calculating the difference between the risk of the intervention group with the risk of the control group; the *P* value represents the probability, without uncertainty, that the approach would be the best.

[†] The baseline morbidity rate was assumed to be those of placebo/standard group.

[‡] Certainty in evidence according to GRADE working group: (1) High quality: The true effect lies close to that of the estimate of the effect; (2) Moderate quality: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (3) Low quality: The true effect may be substantially different from the estimate of the effect; (4) Very low quality: The true effect is likely to be substantially different from the estimate of effect.

[§] NMA estimates are reported as odds ratio.

LOS

Supplementary Table S7 and Figure 2, *D* show the results of the LOS. The overall heterogeneity and inconsistency were significant ($\tau^2 = 5.396$; $I^2 = 84\%$; $P < .001$). The evidence certainty and risk bias are reported in Supplementary Table S8 and Supplementary Figure S5, *A*. Incoherence and heterogeneity are evaluable in Supplementary Figure S5, *B*. Publication bias was absent (Egger's test, $P = .850$; Supplementary Figure S5, *B*). Five arms resulted among the best (Figure 2; the details are reported in the Supplementary Materials.

Component NMA

Component NMA analysis is reported in Table III. None of each component alone significantly affects morbidity, mortality, infectious complications, or LOS. The best plausible combination included 2 or 3 IMs, the oral or enteral way, and frequently the postoperative administration. The CNMA suggested that no effect can be observed on the mortality rate, whereas IM could positively influence morbidity, infectious complications, and LOS.

Discussion

This study tries to provide some information about the best formula and timing for IM in patients who underwent major abdominal surgery. It should be noted that the problem of the multi-arm setting was overcome using the NMA approach. The certainty of the evidence was tested using CINeMA[11] and GRADE[12] methods, and the results were presented in an accessible form for readers using OR and MD. All approaches were compared with placebo or standard perioperative management without IM. Finally, the CNMA was used to estimate all possible plausible combinations of the components. Morbidity and mortality were considered critical outcomes, and a reduction of 10 events per 1,000 persons was considered clinically relevant.

Concerning morbidity, NMA provided some interesting information. These results are credible because they are unaffected by significant heterogeneity, incoherence, or publication bias and have a moderate probability of reflecting the clinical practice reality. The best approach (*P* score = .93) to reduce the morbidity rate seems to be the perioperative oral/enteral IM using a combination of arginine, glutamine, and Ω_3. This approach is near to an ideal approach, producing the most significant reduction in complication rate. Similar results, but with low magnitude, could be obtained using a combination of arginine, RNA, and Ω_3 fatty acids in the postoperative or perioperative period. Component NMA confirmed that: (1) the oral/enteral administration seems to be essential, independently from the formula used; (2) a formula containing 2 or more immunonutrients seems to maximize the effect of IM; (3) the postoperative timing is one of the essential crucial components of efficacious IM; (4) no single component alone can have a significant impact on morbidity.

Interestingly, all observations are in agreement with the physiopathologic IM assumptions. The different types of immunonutrients have synergic effects on the immune system, which is very useful in the postoperative period. Indeed, L-glutamine[29] and arginine[30] facilitate the immune response, improving lymphocyte proliferation and function.

On the other hand, Ω_3 fatty acids[30] and RNA[31] modulate the inflammatory response, reducing cytokine/chemokine gene expression and having beneficial effects on inflammation-related disorders. In the postoperative period, if a normal immune function is required to avoid infectious complications after surgery, an excessive inflammatory response could be harmful. For the same reasons, a high efficacy could be observed when IM was administrated in the postoperative period more than in the preoperative one alone.

However, preoperative supplementation could implement the results of postoperative IM because arginine and glutamine fall within the category of "conditionally essential amino acids." These amino acids are de novo synthesizable, but the demand increases in some gastrointestinal diseases or after surgery. Thus, in these situations, oral intake becomes the main source. Curiously, NMA suggested that postoperative PN with Ω3 fatty acid supplementation guarantees good results with moderate certainty, and this datum was not surprising. Indeed, it stands to reason that patients undergoing gastrointestinal surgery are unable to start early with oral/enteral feeding, requiring postoperative PN for the type of surgery or the presence of complications.[31,32] Thus, parenteral supplementation with endovenous Ω3 could reduce the morbidity rate in these patients, softening the postoperative inflammatory response.

Considering the mortality, the NMA analysis suffers from the events shortfall: the mortality rate was <1% in all arms. Moreover, when setting the minimal differences to 10 events per 1,000 persons, capturing a significant effect on mortality by IM is tough. On the other hand, when setting the minimally important differences inferior to 10, the analysis could produce results with a more

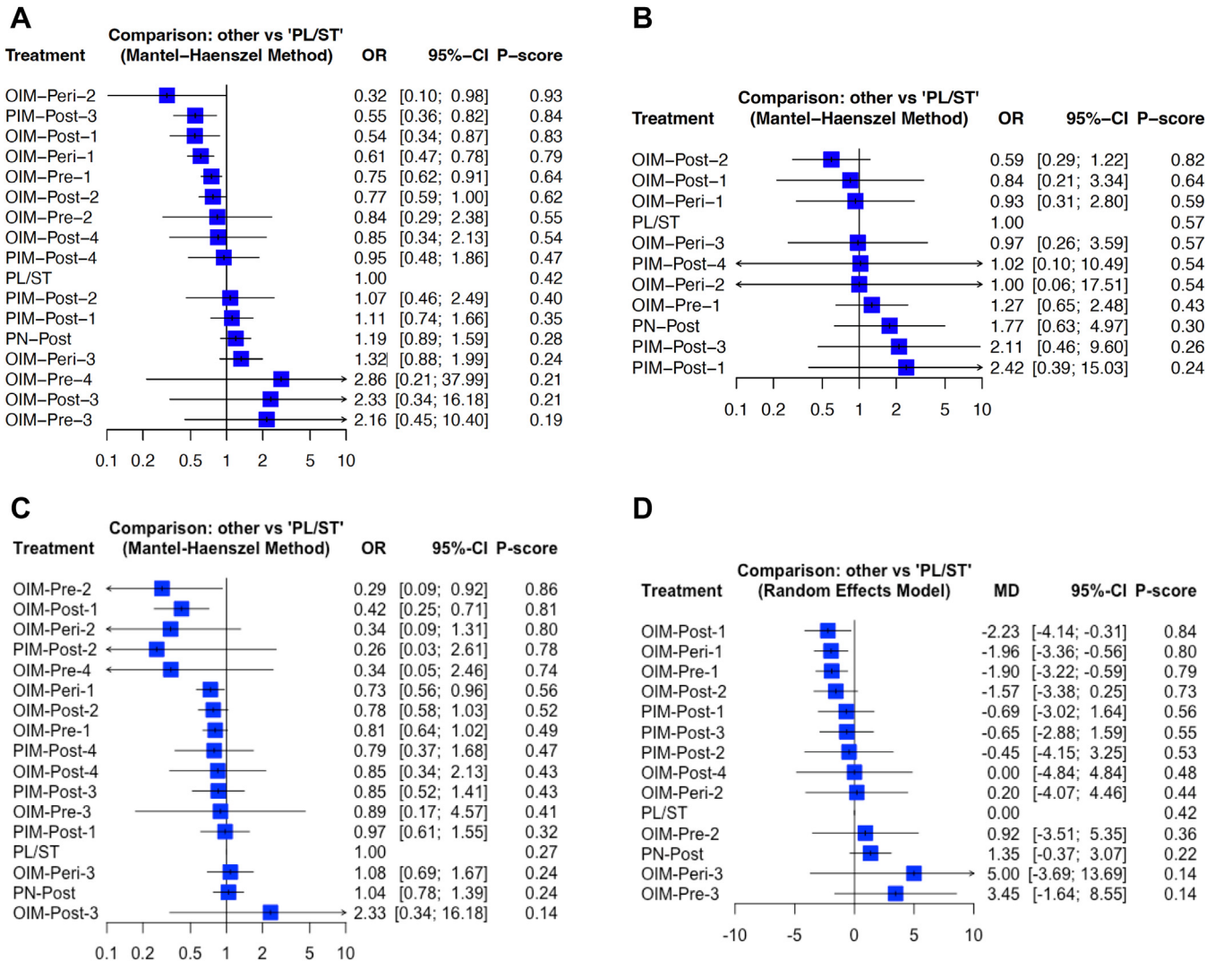

Figure 2. (A) Forest plot with network evidence of morbidity rate. (B) Forest plot with network evidence of mortality rate. (C) Forest plot with network evidence of infectious complications. (D) Forest plot with network evidence of the length of stay. The arms were sorted by *P* score. PL-ST, Placebo or conventional postoperative nutrition without supplement or immunonutrition; *PN-Post*, Postoperative parenteral supplementation without immunonutrition; *OIM-Pre1*, Preoperative oral immunonutrition with arginine, RNA, and Ω_3; *OIM-Pre2*, Preoperative oral immunonutrition with arginine alone; *OIM-Pre3*, Preoperative oral immunonutrition with arginine and Ω_3; *OIM-Pre4*, Preoperative enteral immunonutrition with Ω_3 alone; *OIM-Post1*, Postoperative enteral immunonutrition with arginine, RNA, and Ω_3; *OIM-Post2*, Postoperative enteral immunonutrition with arginine, glutamine, and Ω_3; *OIM-Post3*, Postoperative enteral immunonutrition with Ω_3 alone; *OIM-Post4*, Postoperative enteral immunonutrition with glutamine-alanine; *PIM-Post1*, Postoperative parenteral immunonutrition with glutamine-glycine; *PIM-Post2*, Postoperative parenteral immunonutrition arginine-based; *PIM-Post3*, Postoperative parenteral immunonutrition with Ω_3; *PIM-Post4*, Postoperative parenteral immunonutrition with Ω_3 and glutamine; *OIM-Peri1*, Perioperative oral immunonutrition with arginine, RNA, and Ω_3; *OIM-Peri2*, Preoperative oral immunonutrition with arginine, glutamine, and Ω_3; *OIM-Peri3*, Preoperative oral immunonutrition with Ω_3; *OR*, odds ratio; *MD*, mean difference.

"significant" but low clinical relevance, such as in the previous meta-analysis.[5] Nonetheless, despite the limits due to the rarity of this event, a specific effect of IM could be demonstrated: (1) postoperative supplementation with formulas containing arginine, glutamine, and Ω_3 is once again among the best; (2) postoperative or perioperative enteral IM with RNA, arginine, and Ω_3 is superior to the standard/placebo approach; (3) CNMA did not find an ideal combination. Considering the "noncritical" endpoints, some observations could be made: (1) the definition of infectious complications was significantly different among the studies; (2) broad-spectrum antibiotics availability has changed over the last 30 years; (3) the severity and frequency of hospital-acquired infections have changed due to the diffusion of bacteria such as methicillin-resistant *Staphylococcus aureus* or carbapenemase-producing *Klebsiella pneumoniae*. This extreme variability made the NMA and CNMA results weak and uncertain because they were burdened by a high grade of uncertainty (heterogeneity, within-study bias, and incoherence). Incoherence represents a significant problem for NMA reliability because the basic framework of NMA is lacking.

Regarding the LOS, a positive effect of IM can observed when a formula with multiple immunonutrients is used, and CNMA confirms this result. However, in this network, all intervention arms among the best were affected by within-study bias and heterogeneity, and the probability that the reality was close to the NMA and CNMA results is low. Moreover, it should be noted that global inconsistency was present even if incoherence is lacking in comparing the intervention arms versus the placebo/standard therapy one. In other words, by comparing "head to head" the different intervention arms, it is possible to observe conflicting results according to direct or indirect evidence. Thus, the results of LOS should be interpreted with prudence, which does not surprise us. Indeed, it is well known that LOS is a weak efficacy parameter

Table II
NMA for mortality rate

Total studies: 87 RCT Total participants: 8,357 Inconsistency (τ^2): NC Heterogeneity (I^2): NC Overall total test for I^2 and τ^2: P = .862	OR[§] (95% CrI)	Anticipated absolute effect[*] (95% CrI)			Certainty of the evidence[‡]	*P* score
		With placebo/ standard therapy[†]	With intervention	Difference (Minimal important difference = 10)		
Placebo/standard therapy (A)	1.00 Reference comparator	No estimable	No estimable	No estimable	Reference Comparator	.57
Postoperative parenteral nutrition (B) Mixed evidence (Direct evidence from 9 studies)	1.77 (0.63 to 4.97)	19 per 1,000	34 per 1,000	15 per 1,000 more (from 7 fewer to 75 more)	⊕⊕◯◯ Low Due to: -Within-study bias -Imprecision	.30
Preoperative oral IM with RNA, arginine, and Ω_3 (C) Mixed evidence (Direct evidence from 22 studies)	1.27 (0.65 to 2.48)	19 per 1,000	24 per 1,000	5 per 1,000 more (from 7 fewer to 28 fewer)	⊕⊕◯◯ Low Due to: -Within-study bias -Imprecision	.43
Preoperative oral IM with arginine alone (D) Mixed evidence (Direct evidence from 1 study) Zero cells in both arms	NC	19 per 1,000	NC	NC	NC	NC
Preoperative oral IM with arginine and Ω_3 (E) No direct evidence	NC	19 per 1,000	NC	NC	NC	NC
Preoperative oral IM with Ω_3 alone (F) Mixed evidence (Direct evidence from 1 study) Zero cells in both arms	NC	19 per 1,000	NC	NC	NC	NC
Postoperative enteral IM with RNA, arginine, and Ω_3 (G) Mixed evidence (Direct evidence from 6 studies)	0.84 (0.21 to 3.34)	19 per 1,000	16 per 1,000	3 per 1,000 fewer (from 15 fewer to 44 more)	⊕⊕◯◯ Low Due to: -Within-study bias -Imprecision	.64
Postoperative enteral IM with arginine, glutamine, and Ω_3 (H) Mixed evidence (Direct evidence from 10 studies)	0.59 (0.29 to 1.22)	19 per 1,000	11 per 1,000	8 per 1,000 fewer (from 14 fewer to 4 more)	⊕⊕⊕◯ Moderate Due to: -Imprecision	.82
Postoperative enteral IM with Ω_3 alone (I) Mixed evidence (Direct evidence from 1 study) Zero cells in both arms	NC	19 per 1,000	NC	NC	NC	NC
Postoperative enteral IM with glutamine-alanine (K) Mixed evidence (Direct evidence from 2 studies) Zero cells in both arms	NC	19 per 1000	NC	NC	NC	NC
Postoperative parenteral IM with glutamine-glycine (L) Mixed evidence (Direct evidence from 1 study)	2.42 (0.39 to 15.03)	19 per 1,000	46 per 1,000	27 per 1,000 more (from 12 fewer to 267 more)	⊕⊕◯◯ Low Due to: -Within-study bias -Imprecision	.24
Postoperative parenteral IM with arginine (M) No direct evidence	NC	19 per 1,000	NC	NC	NC	NC
Postoperative parenteral IM with Ω_3 alone (N) Mixed evidence (Direct evidence from 1 study)	2.11 (0.46 to 9.60)	19 per 1,000	40 per 1,000	21 per 1,000 fewer (from 10 fewer to 163 fewer)	⊕⊕◯◯ Low -Within-study bias -Imprecision	.26
Postoperative parenteral IM with glutamine and Ω_3 (O) Mixed evidence (Direct evidence from 1 study)	1.02 (0.10 to 10.49)	19 per 1,000	19 per 1,000	0 per 1,000 fewer (from 17 fewer to 180 more)	⊕⊕◯◯ Low -Indirectness -Imprecision	.54
Perioperative enteral IM with RNA, arginine, and Ω_3 (P) Mixed evidence (Direct evidence from 12 studies)	0.93 (0.31 to 2.80)	19 per 1,000	18 per 1,000	1 per 1,000 fewer (from 13 fewer to 34 more)	⊕⊕◯◯ Low -Within-study bias -Imprecision	.64
	1.00 (0.06 to 17.51)	19 per 1,000	19 per 1,000			.54

(*continued on next page*)

Table II (*continued*)

Total studies: 87 RCT Total participants: 8,357 Inconsistency (τ^2): NC Heterogeneity (I^2): NC Overall total test for I^2 and τ^2: P = .862	OR[§] (95% CrI)	Anticipated absolute effect[*] (95% CrI)			Certainty of the evidence[‡]	*P* score
		With placebo/ standard therapy[†]	With intervention	Difference (Minimal important difference = 10)		
Perioperative enteral IM with arginine, glutamine, and Ω_3 (Q) Mixed evidence (Direct evidence from 1 study)				0 per 1,000 fewer (from 18 fewer to 314 more)	⊕⊕◯◯ Low -Within-study bias -Imprecision	
Perioperative enteral IM with Ω_3 (R) Mixed evidence (Direct evidence from 4 studies)	0.97 (0.26 to 3.59)	19 per 1,000	18 per 1,000	1 per 1,000 more (from 14 fewer to 49 more)	⊕⊕⊕◯ Moderate Due to: -Imprecision	.57

CrI, credible interval; *IM*, immunonutrition; *NC*, not computable; *NMA*, network meta-analysis; *OR*, odds ratio; *RCT*, randomized controlled trial.

[*] Anticipated absolute effect compares 2 risks by calculating the difference between the risk of the intervention group with the risk of the control group; the *P* score represents the probability, without uncertainty, that the approach would be the best.

[†] The baseline mortality rate was assumed to be those of placebo/standard group.

[‡] Certainty in evidence according to GRADE working group: (1) High quality: The true effect lies close to that of the estimate of the effect; (2) Moderate quality: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (3) Low quality: The true effect may be substantially different from the estimate of the effect; (4) Very low quality: The true effect is likely to be substantially different from the estimate of effect.

[§] NMA estimates are reported as odds ratio.

because it is easily influenced by nonclinical factors such as the health care system, the home situation of patients, and the availability of day-hospital service to minor sequela treatment.

The present study has some limitations. First, the included studies covered a long period. Another limitation was the lack of a standardized definition of outcomes that were not corrigible with rigorous data extraction. These biases can be limited by using all statistical instruments to capture the heterogeneity, inconsistency, and publication bias. The GRADE and CINeMA approaches were used to downgrade the evidence when the data were at risk for within-study bias, publication bias, indirectness, imprecision, heterogeneity, and incoherence. Considering the studies' heterogeneity and the long publication period, none of the evidence obtained can be considered of high quality with the GRADE system.

In conclusion, in the present study, oral/enteral IM seems useful in reducing morbidity in patients who underwent major abdominal surgery. The ideal formula does not exist, but the simultaneous use of more types of immunonutrients is crucial to obtaining clinically relevant results. Regarding timing, postoperative administration is fundamental to guarantee the reduction of the morbidity rate, even if perioperative use seems to be the best strategy. More than preoperative use is required to obtain the best results. The quality of data did not support a significant effect in reducing mortality, infectious diseases, or LOS. The results of the present study could be useful in designing further high-quality and well-designed randomized studies.

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Table III
Estimates of incremental odds ratios or mean differences of each component when added to placebo or usual care

Component	Mortality[*] iOR (95 CI); *P* value	Morbidity[*] iOR (95 CI); *P* value	Infectious complications[*] iOR (95 CI); *P* value	LOS[†] MD (95 CI); *P* value
Arginine	1.96 (0.18 to 20.42); .570	0.66 (0.34 to 1.28); .214	0.29 (0.11 to 0.81); .019	−1.08 (−3.76 to 1.59); .428
Glutamine	0.77 (0.23 to 2.58); .674	1.24 (0.80 to 1.90); .325	1.01 (0.54 to 1.87); .965	−0.08 (−2.23 to 2.07); .943
Glutamine/alanine	0.89 (0.01 to 498.13); .972	0.98 (0.34 to 2.79); .969	1.06 (0.30 to 3.63); .928	-
Glutamine/glycine	1.30 (0.23 to 7.40); .765	1.01 (0.59 to 1.74); .954	1.02 (0.47 to 2.19); .958	−1.69 (−3.98 to 0.60); .148
RNA	0.45 (0.03 to 6.23); .552	1.04 (0.50 to 2.19); .908	2.04 (0.71 to 5.89); .184	−0.71 (−3.82 to 2.41); .657
Ω_3	1.01 (0.19 to 5.45); .983	0.69 (0.43 to 1.10); .119	0.98 (0.52 to 1.83); .946	−1.13 (−3.27 to 0.99); .295
Parenteral way	1.39 (0.57 to 3.33); .468	1.08 (0.79 to 1.48); .605	1.01 (0.69 to 1.44); .983	0.99 (−0.63 to 2.63); .232
Pre	1.25 (0.38 to 4.11); .718	1.61 (0.99 to 2.44); .061	1.39 (0.80 to 2.40); .246	1.34 (−0.73 to 3.40); .205
Post	0.45 (0.03 to 6.23); .553	0.87 (0.62 to 1.20); .390	0.82 (0.53 to 1.27); .327	0.19 (−1.84 to 1.46); .819
Best oral/enteral plausible combinations				
With 2 IMs				
Post + arginine + Ω_3	-	0.38 (0.18 to 0.82); .013	-	-
Post + arginine + RNA	-	0.54 (0.30 to 0.96); .013	-	-
Post + glu + Ω_3	-	0.61 (0.41 to 0.91); .001	-	-
With 3 IMs				
Post + arginine + glutamine + Ω_3	-	0.41 (0.19 to 0.85); .016	-	−3.11 (−4.76 to −1.47); .002
Post + arginine + glutamine + RNA	-	0.55 (0.30 to 0.99); .049	-	-
Post + arginine + RNA + Ω_3	-	0.37 (0.25 to 0.55); < .001	−3.11 (−4.77 to −1.47); < .001	-
Pre + arginine + RNA + Ω_3	-	0.61 (0.41 to 0.89); .011	−1.59 (−2.80 to −0.37); .010	−1.58 (−2.80 to −0.37); .011
Pre+ post +arginine + RNA + Ω_3	-	0.51 (0.33 to 0.79); .028	−1.78 (−3.11 to −0.45); .009	−1.78 (−3.11 to −0.45); .009

iOR, incremental odds ratio; *IM*, immunonutrition; *iMD*, incremental mean difference; *LOS*, length of postoperative stay; Ω_3, omega 3 fatty acids; *pre*, preoperative oral or enteral administration; *post*, postoperative oral or enteral administration; *RNA*, ribonucleic acid; *CI*, confidence interval.

[*] For binary outcomes, component network meta-analysis assumed that the effect of component (A) increased the impact of baseline component (x) and the final effect (iOR) depends on the following formula A + x / x. The baseline component was always the placebo or standard therapy. For example, the first-row iORs represent the results observed adding to placebo or standard therapy the oral/enteral arginine.

[†] For continuous outcomes, the iMD of the component was estimated following this formula (A + x) − (x), in which A represents the effect of component and x the baseline impact of component.

Conflict of interest/Disclosure

The authors have no conflicts of interests or disclosures to report.

Supplementary materials

Supplementary materials associated with this article can be found in the online version, at https://doi.org/10.1016/j.surg.2023.08.005.

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