ORIGINAL ARTICLE

Value of immunonutrition in patients undergoing pancreatic resection: a trial sequential meta-analysis

Claudio Ricci[1,2], Francesco Serbassi[3], Laura Alberici[1], Carlo Ingaldi[1], Leonardo H. Eusebi[1,4], Emilio De Raffele[1], Loris Pironi[2,5], Anna S. Sasdelli[2,5], Cristina Mosconi[6], Valentina Vicennati[7,2] & Riccardo Casadei[1,2]

[1]Division of Pancreatic Surgery, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Via Albertoni 15, Italy, [2]Department of Internal Medicine and Surgery (DIMEC), Alma Mater Studiorum, University of Bologna, Italy, [3]Grad Student in Biology of the Health Faculty, Alma Mater Studiorum, University of Bologna, Italy, [4]Division of Gastroenterology, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Via Albertoni 15, Italy, [5]Clinical Nutrition and Metabolism Unit - Centre for Chronic Intestinal Failure, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Via Albertoni 15, Italy, [6]Division of Interventional Radiology, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Via Albertoni 15, Italy, and [7]Division of Endocrinology, IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Via Albertoni 15, Italy

Abstract

Background: The benefits of immunonutrition (IM) in patients who underwent pancreatic surgery are unclear.

Methods: A meta-analysis of randomized clinical trials (RCTs) comparing IM with standard nutrition (SN) in pancreatic surgery was carried out. A random-effects trial sequential meta-analysis was made, reporting Risk Ratio (RR), mean difference (MD), and required information size (RIS). If RIS was reached, false negative (type II error) and positive results (type I error) could be excluded. The endpoints were morbidity, mortality, infectious complication, postoperative pancreatic fistula (POPF) rates, and length of stay (LOS).

Results: The meta-analysis includes 6 RCTs and 477 patients. Morbidity (RR 0.77; 0.26 to 2.25), mortality (RR 0.90; 0.76 to 1.07), and POPF rates were similar. The RISs were 17,316, 7,417, and 464,006, suggesting a type II error. Infectious complications were lower in the IM group, with a RR of 0.54 (0.36–0.79; 95 CI). The LOS was shorter in IM (MD -0.3 days; –0.6 to –0.1). For both, the RISs were reached, excluding type I error.

Conclusion: The IM can reduce infectious complications and LOS The small differences in mortality, morbidity, and POPF make it impossible to exclude type II error due to large RISs.

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Correspondence

Claudio Ricci, Department of Internal Medicine and Surgery (DIMEC), Alma Mater Studiorum, University of Bologna, Italy Alma Mater Studiorum-Università di Bologna, Policlinico S.Orsola-Malpighi, Via Massarenti n.9, 40138, Bologna, Italy. E-mail: claudio.ricci6@unibo.it

Introduction

In the last twenty years, immunutrition (IM) has been extensively studied in patients who underwent major abdominal surgery. Several metanalyses of randomized controlled trials (RCTs) have demonstrated some benefits in the postoperative course,[1] and many different types of immuno-nutrients have been proposed, alone or in combination, such as L-glutamine, arginine, Ω_3-fatty acids, and RNA.[2–5] The rationale for IM is based on the effect of some nutrients on the immune system. Glutamine and arginine ameliorate the immune response improving lymphocyte proliferation and function, while Ω_3-fatty acids and RNA modulate cytokine production, reducing postoperative inflammation-related disorders.[6–8] For these reasons, IM has captured the interest of pancreatic surgeons, who are always looking for new strategies to mitigate the postoperative morbidity rate.[9] However, the enhanced recovery after surgery (ERAS) society suggested IM for patients scheduled for colonic resections[10] but not for those who underwent

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pancreatic resection.[11] Indeed, the results of three meta-analyses[12–14] of RCTs available in the literature are unclear. All of these demonstrated a reduction of infectious complications and length of stay (LOS) without significantly reducing overall morbidity and mortality rates. These data are conflicting and counterintuitive, making IM difficult to accept in clinical practice. However, these apparent contradictions could depend on type I or II errors. Type I error (alfa error) in statistics is a false positive conclusion. The significance level is usually set at $P < 0.05$ or 5%, which means that the results only have a 5% chance of occurring as "false," and it was not influenced by the sample size in a single study. However, when more studies are cumulated in chronological order, such as in a cumulative metanalysis, the type I error could be inflated, and obtaining a statistical significance could not be sufficient to exclude the false positive result. The trial sequential analysis uses the cumulative sample size to monitor this effect, establishing when the risk of false-positive results is absent. In other words, this analysis recognizes if the false positive results are present in the presence of a significant p-value.[15] Concerning type II error (beta error), similar to a single study, false negative results are observed when non-significant p-values are obtained, but the absence of difference depends on the small sample size available. It should be noted that when the required sample size (RIS) is reached, the IM could be definitively accepted or rejected, avoiding further expensive and time-consuming RCTs. On the contrary, in case of false (negative or positive) results, the RIS calculation permits to plan of new RCTs with an adequate number of patients if reasonable. The present study aims to clarify the presence of type I or II errors by performing an updated systematic review, including all RCTs available, comparing IM versus standard nutrition (SN) in patients who underwent pancreatic surgery. The trial sequential metanalysis methodology was applied to demonstrate or exclude type I or II.

Material and methods

The study protocol was registered in PROSPERO with the following code CRD42022353450. The systematic search was performed according to the Cochrane recommendations.[16] The manuscript was prepared according to the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[17]

Eligibility criteria

The eligibility criteria were established according to the "Population-Intervention-Control-Outcomes-Studies" (PICOS) approach[18]: the "Population" was represented by patients who had pancreatic surgery for malignancy; the "Intervention" arm was oral, enteral, or parenteral IM; in the "Control" group any peri-operative management without IM including placebo was considered; the studies were included only when reported the morbidity, or mortality, or infectious complications rate or length of stay; only RCTs were considered.

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

The systematic review was done through PubMed, Scopus, and Web of Science. The last search was carried out on August 20, 2022. The systematic review was conducted through PubMed, Scopus, and ISI Web of science. The search string for Pubmed was the following ("pancreatic cancer" [MESH] OR "pancreatic cancer" [tiab] OR "pancreaticoduodenectomy" [MESH] OR "pancreaticoduodenectomy" [tiab] OR "total pancreatectomy" [MESH] OR "total pancreatectomy" [tiab] OR "distal pancreatectomy" [MESH] OR "distal pancreatectomy" [tiab]) AND ("immunonutrition" [MESH] OR "immunonutrition" [tiab] OR "omega-3" [MESH] OR "omega-3" [tiab] OR "glutamine" [MESH] OR "glutamine" [tiab] OR "arginine" [MESH] OR "arginine" [tiab]). The term "RNA" was not used to obtain a manageable string because this term was frequently used as a keyword in basic science papers. At the same time, the lacking of RNA terms did not increase the risk of insufficient search."The string was adapted for Pubmed, Scopus, and Web of science using the SR accelerator.[19]

Data items and risk of bias in individual study

For each study, we described the first author, year of publication, affiliation/country, type of surgical procedures design (blinded or not), presence of sponsor, way of IM administration (oral, enteral, or parenteral), timing (peri-operative, postoperative or preoperative), and study quality. The importance of outcomes was evaluated by the authors using the GRADE approach[20] (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, POPF defined according to the new ISGPF definition[21] (when possible), and the LOS, which are considered "important." but not "critical". The outcomes were described as frequencies and percentages or means and standard deviations (SD). The mean and SD were calculated using a proper algorithm when the studies reported medians and interquartile or ranges.[22,23] The risk of bias within the individual studies was evaluated using the revised tool for assessing the risk of bias in randomized trials (Rob2).[24] Two authors (XX and XY) carried out independently the search, data collection, data extraction, and bias assessment. Any disagreement between the two assessors was solved by a discussion with the first author (XZ).

Summary measurements and synthesis of the results

The effect estimates were reported as risk ratios (RRs) or mean differences (MDs) along with 95% confidence intervals (95 CI). When confidence intervals did not include 1 for RR or 0 for MD, a statistically significant effect was present. RIS was calculated,

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considering the heterogeneity among the included studies. The type I error was set at 5% and type II at 20% (power 80%).[25] RIS was obtained using meta-analytical values of RRs or MDs. A Cartesian plane was used to represent the RIS graphically. Y-axis corresponds to the Z-score, and the conventional P-value of 0.05 equals |1.96|Z value. The relation between the Z-score and P-value is inverse: increasing Z-value, the P-value decrease. Thus, when the| Z-score| is higher than 1.96, the intervention effect could be considered significant for classical meta-analysis. The X-axis represents the number of randomized patients, called "accrued sample size." The Z-curve is built, adding each RCT. The Z-curve could cross three lines: the conventional boundaries (dotted red horizontal lines), monitoring boundaries (dotted black logarithmic lines), and futility boundaries (dotted black lines). The conventional boundaries correspond to the P = 0.05. False-positive results (type I error) are observed even if statistical significance is obtained (Z-curve crosses this limit) in the absence of adequate sample size (RIS). Namely, further RCTs are required to demonstrate the significance. On the contrary, the monitoring edge is the values of Z-scores at which type I error could be excluded. In other words, when Z-curve overcomes both conventional and monitoring lines, the significant results are credible, and no further randomization is required to demonstrate the significance. The false-negative effect (type II error) can be observed when the Z-curve does not overcome the conventional (P > 0.05), but RIS is not reached.[26,27] In other words, the two comparative arms seem to have a similar effect, but a type II error cannot be excluded. Conversely, any additional randomization could be useless when the Z line gets into the futility area. Fig. 1 is an example in which all four possibilities were represented. The Mantel-Haenszel random-effects model was used to calculate effect sizes.[28] Only for the LOS a post hoc analysis was planned. If the difference between the two arms is significant but not clinically relevant (<2 days), additional RIS was calculated. This additional RIS represents the sample size that should be reached to demonstrate a significant difference of two days in LOS between the two arms. All analysis was made using the *meta* package for R software and Trial Sequential Analysis software.

Risk of bias across studies and meta-regression analysis

The heterogeneity was tested using I^2 and Cochran's Q statistics.[29] The heterogeneity was also reported as diversity (D^2).[30] The publication bias was evaluated using the Begg and the Egger tests,[31] and a P-value <0.05 indicated a significant "small-study effect." When heterogeneity was present, the causes were investigated with a meta-regression analysis.[32]

Results

Studies selected

The PRISMA statement is reported in Supplementary Fig. 1. Six studies[33–38] were eligible for the analysis.

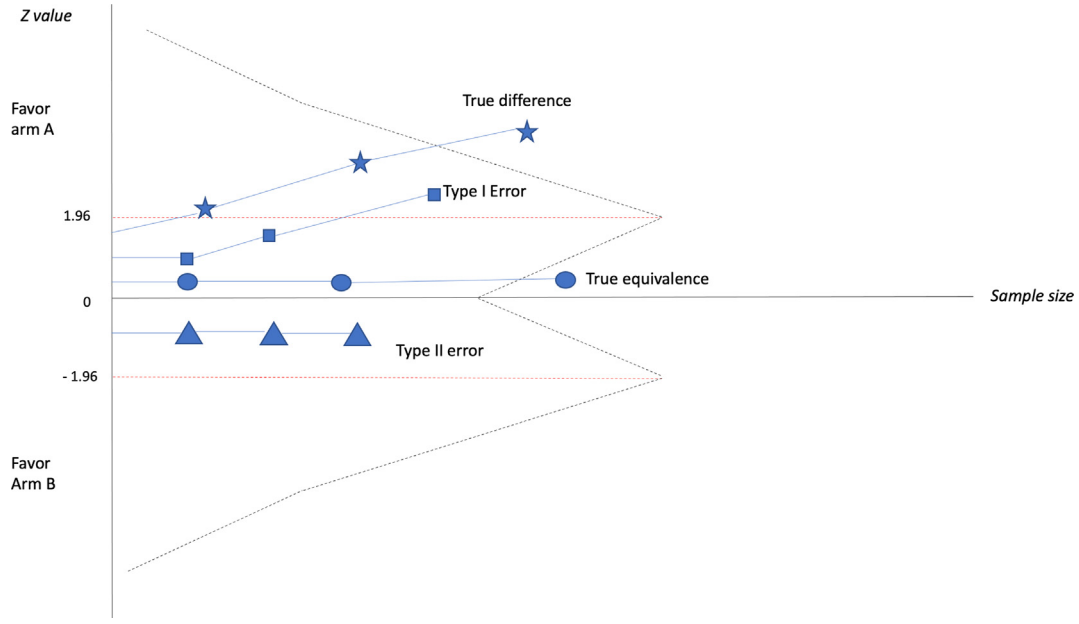

Figure 1 Example plot with the four different results in TSA. Legend: stars = studies included in metanalysis in which the difference between Arm A and B is not affected by type I error; squares = studies included in metanalysis in which the difference between Arm A and B is affected by type I error; circles = studies included in metanalysis in which the equivalence between Arm A and B is not affected by type II error; triangles = studies included in metanalysis in which the equivalence between Arm A and B is not affected by type II error

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Study characteristics and risk of bias within studies

Table 1 summarizes the characteristics of the studies. Three (50%) studies were conducted in western countries. All studies reported only pancreaticoduodenectomy (PD) except the paper of Gade et al.[37], which also included distal (DP) and total pancreatectomy (TP). Only two studies,[35,38] were double-blinded (33.3%). Four studies[33,35–37] were without a sponsor (66.6%). One study[35] used parenteral nutrition (16.6%). In four (66.6%) studies,[33–35,38] the IM was performed in the post-operative period. Three studies ((50%) presented some concerns, while the remaining have a low risk of bias. The accrued sample size was 477: 286 (60%) in the SN arm and 191 (40%) in IM.

Synthesis of results

Critical endpoints

Table 2 shows the results of a trial sequential meta-analysis. The risk of mortality (Fig. 2- panel A) was similar among the two groups, with a pooled RR of 0.77 (0.26–2.25, 95 CI). The RIS, at the current RR, was 17,136, suggesting that 16,659 patients should be further randomized before concluding that IM is not different from SN without occurring in type II error (Fig. 3- panel A). The risk of morbidity (Fig. 2- panel B) was similar among the two groups, with a pooled RR of 0.90 (0.76–1.07, 95 CI). The RIS, at the current RR, was 7,417, suggesting that 6940 patients should be further randomized before concluding that IM is not different from SN without occurring in type II error (Fig. 3- panel B).

Non-critical endpoints

Table 2 shows the results for the infectious complications, POPF and LOS. The risk of POPF (Fig. 2- panel C) was similar among the two groups, with a RR of 0.84 (0.54–1.30; 95 CI) and a RIS of 464,006 (Fig. 3- panel C). Additional 463,564 patients should be randomized before accepting or rejecting the equivalence hypothesis of the two approaches. Concerning infectious complications (Fig. 2- panel D), the risk is significantly low in the IM arm with a RR of 0.54 (0.36–0.79; 95 CI). The RIS was yet reached, and the Z-score line crossed both conventional and monitoring boundaries in favor of IM (Fig. 3- panel D).

Regarding the LOS, similar results were found (Fig. 4 - panel A). The MD was −0.3 days (−0.6 to −0.1; 95 CI). The RIS of 432 was near reached because the accrues sample size was 407 (Fig. 4 – panel B). The post hoc analysis demonstrated that a sample size of 680 was required to demonstrate a significant difference of 2 days between IM and SN (Fig. 4 - panel C).

Table 1 Characteristics of the eighty-seven included studies

First Author/year	IMs	Affilation/Country	Surgical procedures	Blinded	Sponsored	Way	Timing	Rob2
Di Carlo et al.[33] 1999	Arginine, Glutamine, and Ω_3	University of Milano, S. Raffaele Hospital (Italy)	PD	No	No	O/EN	Post.	Some Concerns
Gianotti et al.[34] 2000	Arginine, Glutamine, and Ω_3	University of Milano, S. Raffaele Hospital (Italy)	PD	No	Yes	O/EN	Post.	Some Concerns
Jo et al.[35] 2006	Glutamine alone	Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Gangnamgu, Seoul (South Korea)	PD	Double blinded	No	PN	Post.	Low Risk
Aida et al.[36] 2014	Arginine, RNA, and Ω_3	Department of General Surgery, Chiba University Graduate School of Medicine, Chiba (Japan)	PD	No	No	O/EN	Preop.	Low Risk
Gade et al.[37] 2016	Arginine, RNA, and Ω_3	Department of Surgical Gastroenterology, Rigshospitalet, Copenhagen (Denmark)	PD, TP, DP	No	No	O/EN	Preop.	Some Concerns
Ashida et al.[38] 2018	Arginine, RNA, and Ω_3	Division of Hepato-Biliary-Pancreatic Surgery, Shizuoka Cancer Center, Nagaizumi (Japan)	PD	Double blinded	Yes	O/EN	Post.	Low Risk

Legend: IMs = immuno-nutrients; O/EN = oral or enteral; PN = parenteral; PD = pancreaticoduodenectomy; TP = total pancreatectomy; DP = distal pancreatectomy.

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Table 2 Meta-analysis of all outcomes

Outcomes of interest	No. of studies	Event rate (%) or mean (SD)		RR or SMD (95% CI)	P-value	RIS	Δ	C-Q, I^2 (%), D (%)	P-value for reporting bias ^	
		IM arm	SN arm						Egger	Begg
Mortality	6	4/191 (2.1)	9/286 (3.1)	0.77 (0.26–2.25)	0.630	17,136	–16,659	0.186; 0; 0	0.806	0.624
Morbidity	6	66/191 (34.6)	87/286 (30.4)	0.90 (0.76–1.07)	0.216	7417	–6940	0.253; 0; 0	0.760	0.573
POPF	5	27/172 (15.7)	39/270 (14.4)	0.84 (0.54–1.30)	0.930	464,006	463,564	0.770;0;0	0.624	0.547
Infectious complication	4	22/140 (15.7)	62/242 (25.6)	0.54 (0.36–0.79)	0.001	352	+30	0.780; 0; 0	0.536	1.000
LOS	4	17.9 ± 6.7	15.7 ± 6.8	–0.3 (–0.6 to –0.1)	0.001	432	–25	<0.001; 30;25	0.724	0.497

Legend: SN= Standard nutrition; IM= Immunonutrition; SD=Standard Deviation; RR= Risk Ratio; SMD = mean difference; RIS = required information size; C-Q= P-value of Cochran's test; I^2= Higgins test; D^2 = Diversity; ^ = A reporting bias non-negligible is considered for P values < 0.10; POPF= Clinical Relevant Postoperative Pancreatic Fistula; LOS = length of stay; - = not applicable.The null hypothesis (H0) supposed that IM and SB have similar results. The alternative hypothesis (H1) supposed SN and IM have different results; Power = This data is the probability of rejecting a false null hypothesis (H0); the pre-specified target value is 0.80; Alpha = It is the probability of rejecting a true null hypothesis; the pre-specified target value is 0.05.

Heterogeneity, meta-regression analysis, and publication bias

No significant heterogeneity was observed for mortality, morbidity, POPF, and infectious complications. The LOS presented a significant heterogeneity (30%; P < 0.001). Meta-regression showed that MD is small in double-blinded studies (coefficient 0.536 ± 0.283; P = 0.04). The other covariates did not influence the magnitude of MD. No publication bias was observed (Supplementary Fig. 2 panel A–E).

Discussion

The present study demonstrated that IM could benefit patients who underwent pancreatic surgery. This result is robust and not affected by type I or II errors because a novel statistical and pragmatic approach was used. Indeed, the TSA approach avoids overestimating or underestimating the intervention's effect. The previous meta-analyses[12–14] concluded that IM did not reduce the mortality and morbidity rates but only the infectious complications rate. However, these results seemed counterintuitive and senseless because if infectious diseases are reduced, a certain proportion, at least, of overall morbidity and mortality should decrease. The TSA approach clarifies these findings. Also, in the present study, mortality rates are similar in both arms.

However, the TSA showed that it is impossible to exclude a false-negative result given that the futility boundary was not reached. Indeed, 16,659 patients should be further randomized to definitively exclude a positive IM effect. Similar results can be observed considering the morbidity rate and POPF. The IM seems not to guarantee a reduction of the overall complication rate, but at least 6940 patients should be randomized to exclude a false-negative result. The RIS required for POPF is the largest (more than 400,000 patients), suggesting that the demonstration of IM superiority, equivalence, or inferiority is impossible to obtain using an RCT. Only the infectious complications are two times inferior in the IM group, and this data is conclusive because the type I error can be excluded.

It should be noted that these data, although similar to previous meta-analyses, are congruent and easy to interpret. First, it stands to reason that only a small part of complications could be avoided with IM use.[32] Most complications after pancreatic resection could be classified as "infectious" because they could cause sepsis and local or diffuse peritonitis (e.g. anastomotic leakages).[39] However, these complications depend on several reasons, including patients' preoperative comorbidity or technical aspects. In other words, it seems illogical to expect a reduction of anastomotic leakage using IM. Indeed, the RIS to demonstrate or reject an effect on overall morbidity is high and reasonably difficult to reach in the next years. This finding does not mean that a positive effect of IM on morbidity is absent in an absolute way but that this effect, if present, is so small to require a giant number of patients to be statistically demonstrated. This concept is very well demonstrated by POPF results. Even if POPF is an infectious complication by definition,[20] it is well known that it could depend on types of anastomosis, characteristics of the pancreatic remnant, or the patient. It is illogical for any pancreatic surgeon to hypothesize that the IM could reduce POPF occurrence. Indeed, TSA showed that the sample size required to demonstrate or reject a significant effect of IM on the POPF rate is very large. In other words, the difference produced by IM on POPF occurrence could be too small that a giant number of patients should be exposed to the treatment to obtain a significant and detectable effect. Similar considerations could be made about mortality. A small positive effect of IM on mortality could exist, but it is very hard to demonstrate. Mortality after pancreatic resection is a multifactorial event that depends on complications occurrence, pre-existent comorbidity, and the ability of the surgical team to manage the adverse events and guarantee the rescue of patients.[33] Probably, pneumonia, urinary, and incision infection rates can be reduced directly by IM,

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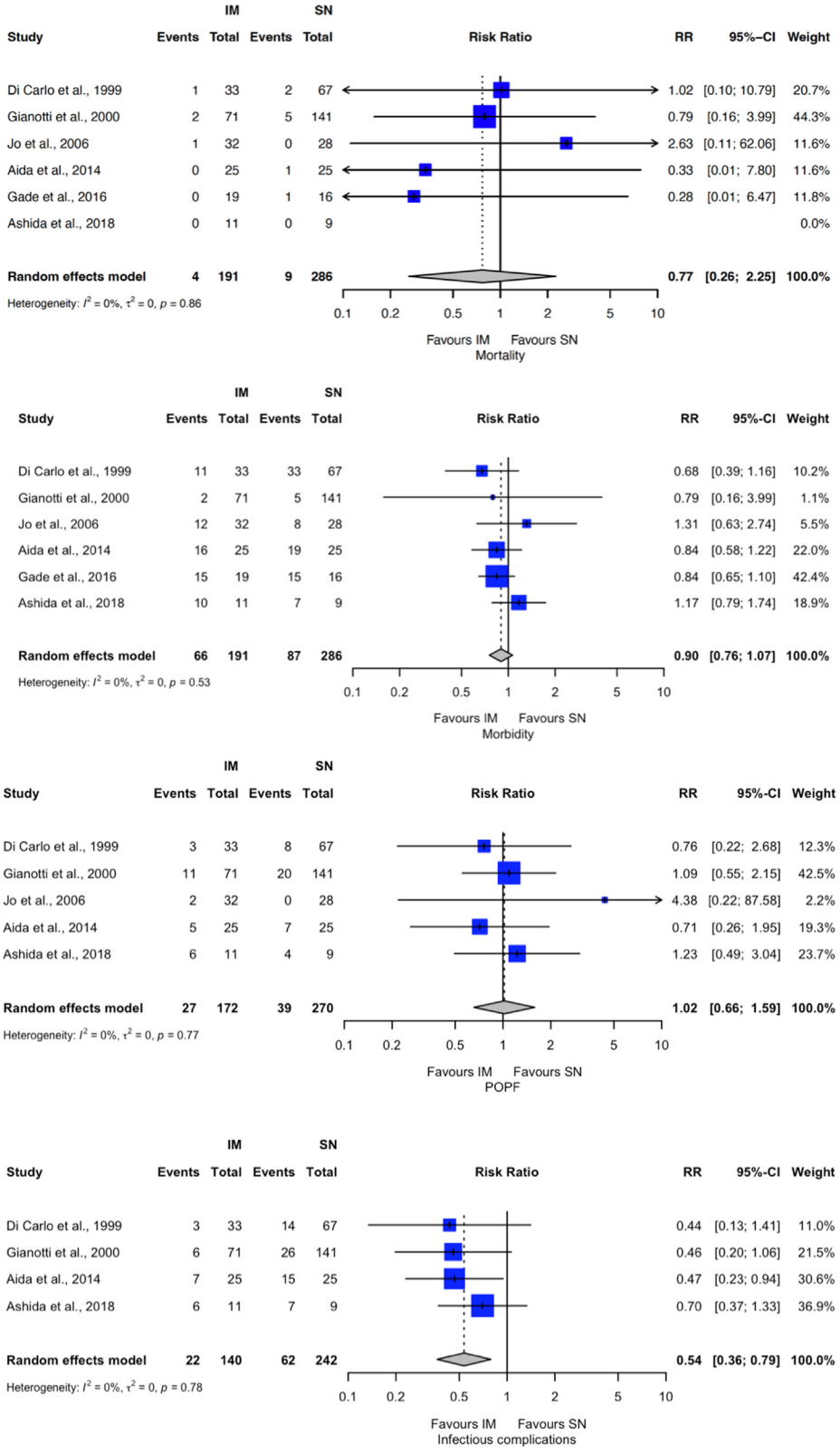

Figure 2 Forests plot (panel A = mortality; panel B = morbidity; panel C = postoperative pancreatic fistula; panel D = infectious disease). Legend: IM = . Immunonutrition; SN = standard nutrition; RR= Risk Ratio

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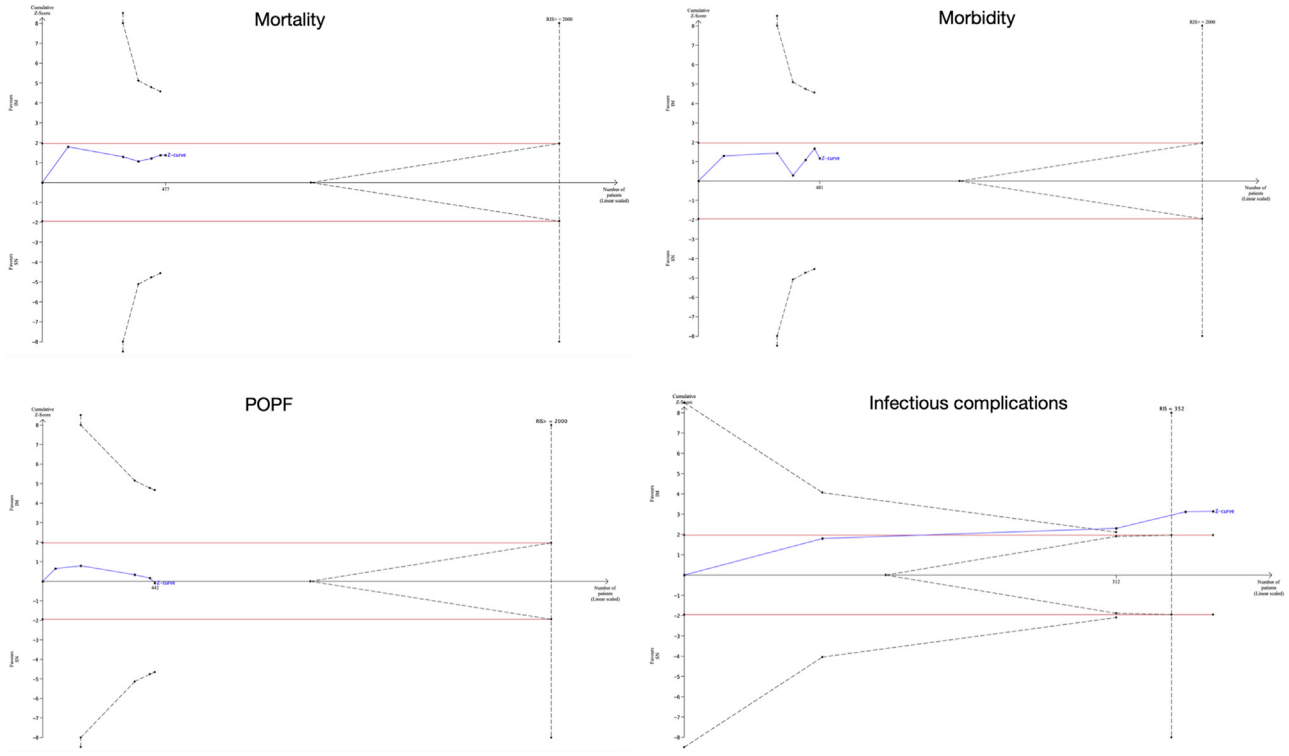

Figure 3 TSA plots (panel A = mortality; panel B = morbidity; panel C = postoperative pancreatic fistula; panel D = infectious disease). Legend: Y-axis = Z-score; |1.96|of z-score is equal to P value = 0.05; x-axis = number of randomized patients; blue square = randomized controlled studies; blue line = Z-curve; dotted red horizontal lines = conventional boundaries, namely lines at which P value is equal to 0.05 but at risk of type I error; dotted black logarithmic lines = monitoring boundaries namely lines at which the risk of type I error is avoided; the conic area between dotted black line = futility area in which further randomized studies are useless; IM = . Immunonutrition; SN = standard nutrition; RR= Risk Ratio

ameliorating the immune response. However, these complications represent a minoritarian part of incidence and importance, minimizing the impact on overall morbidity. In other words, any future RCT to demonstrate a reduction of overall morbidity rate is doomed to fail and will not help to create better meta-analytical knowledge. However, I should remember that the benefits of IM also depend on its ability to modulate the immune response and relieve postoperative inflammation-related disorders.[3–5] Thus, it was more logical to expect a reduction in the severity of complications than the incidence. This observation could explain the LOS results: it makes sense to register a significant reduction of LOS if the severity of the complication is reduced. However, the magnitude of the IM effect is very small and clinically irrelevant (one-third of the day), even if statistically significant and without type I error. Moreover, the magnitude of LOS reduction could be further inferior in the well-designed study (double-blinded). Nonetheless, the sample size required to demonstrate a clinically relevant effect is not so far and reasonable. Thus, LOS could be used to design further and more useful RCT.

The present study has some limitations. First, the paper analyzed covered a long period during which there were some changes in patients' surgical or clinical management. Another limitation was the lacking of a standardized definition of outcomes: i) infectious complications are defined differently in all included studies; ii) the definition of POPF changed during the study period, and the re-classification could be a source of bias; iii) none of the studies used the Clavien-Dindo classification or CCI[40] which could permit to capture the severity of the complication. Thirdly, several types of formulas and timing of IM were used, increasing the source of bias.

Finally, some limits could be ascribed to methodology. TSA has been mainly built on the principle of statistical significance and does not differentiate between clinically relevant and non-relevant effects. In other words, even if a false positive result could be excluded, the significant effect could remain not clinically relevant (e.g., 0.3 days in the length of stay). Moreover, TSA remains a retrospective, and it thus has the risk of data-driven hypotheses. Further, the TSA is a complex statistical approach unfamiliar to clinicians, so the Cochrane Scientific Committee Expert Panel did not routinely recommend using the TSA.

In conclusion, the present study clarifies some aspects of IM use in pancreatic resection. First, IM could benefit patients who underwent pancreatic resection, reducing infectious

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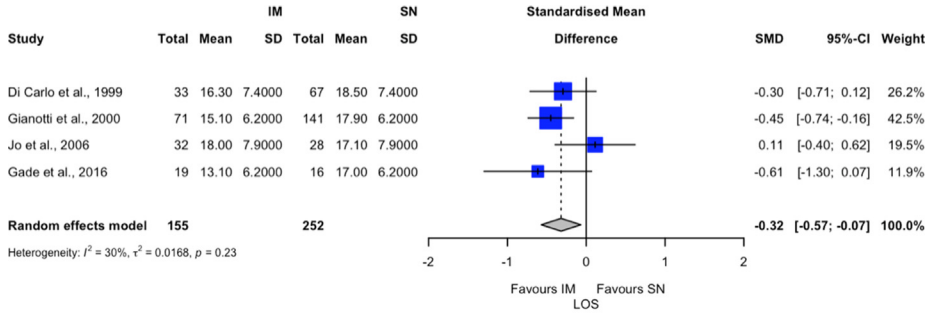

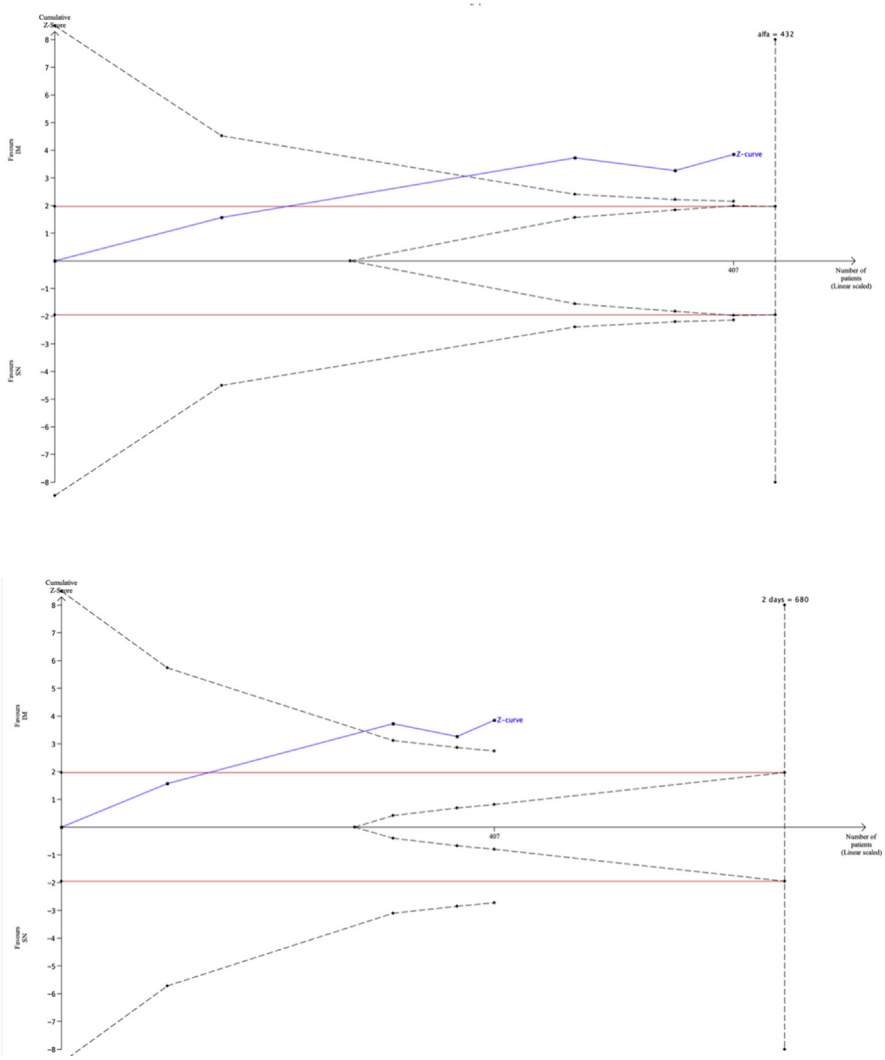

Figure 4 Plots for the length of stay (Panel A-forest plot; Panel B and C-TSA plots). Legend: Y-axis = Z-score; |1.96|of z-score is equal to P value = 0.05; x-axis = number of randomized patients; blue square = randomized controlled studies; blue line = Z-curve; dotted red horizontal lines = conventional boundaries, namely lines at which P value is equal to 0.05 but at risk of type I error; dotted black logarithmic lines = monitoring boundaries namely lines at which the risk of type I error is avoided; the conic area between dotted black line = futility area in which further randomized studies are useless; IM = . Immunonutrition; SN = standard nutrition; RR= Risk Ratio

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complications rate. However, IM remained a small part of the whole. Several medical and surgical strategies are available to mitigate complications after pancreatic resection, and IM is only one of them. Second, even if IM has no impact on overall morbidity, mortality, and POPF rate, there is a lack of conclusive evidence due to inadequate sample size, and, as the RIS values are too large, it is unrealistic to achieve an answer with future RCTs. In other words, if a beneficial effect on these outcomes exists, the statistical demonstration is expensive, time-consuming, and unrealistic. Third, future RCTs should be planned considering different outcomes, such as the severity of morbidity and failure to rescue patient rates.[41] LOS could be considered an outcome for future RCTs, but only within double-blinded studies.

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Conflicts of interest

All authors declared no conflict of interest.

References

1. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S *et al*. (2017) ESPEN guidelines: clinical nutrition in surgery. *Clin Nutr* 36: 623–650. https://doi.org/10.1016/j.clnu.2017.02.013.
2. Newsholme P. (2001) Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? *J Nutr* 131:2515S–2524S. https://doi.org/10.1093/jn/131.9.2515S.
3. Gutiérrez S, Svahn SL, Johansson ME. (2019) Effects of omega-3 fatty acids on immune cells. *Int J Mol Sci* 20:5028. https://doi.org/10.3390/ijms20205028, 11.
4. Grimble GK, Westwood OM. (2001) Nucleotides as immunomodulators in clinical nutrition. *Curr Opin Clin Nutr Metab Care* 4:57–64. https://doi.org/10.1097/00075197-200101000-00011.
5. Martin JM, Stapleton RD. (2010) Omega-3 fatty acids in critical illness. *Nutr Rev* 68:531–541. https://doi.org/10.1111/j.1753-4887.2010.00313.x.
6. Scott MJ, Baldini G, Fearon KC, Feldheiser A, Feldman LS, Gan TJ *et al*. (2015) Enhanced Recovery after Surgery (ERAS) for gastrointestinal surgery, part 1: pathophysiological considerations. *Acta Anaesthesiol Scand* 59:1212–1231. https://doi.org/10.1111/aas.12601.
7. Efron D, Barbul A. (2000) Role of arginine in immunonutrition. *J Gastroenterol* 35:20–23.
8. Soares AD, Costa KA, Wanner SP, Santos RG, Fernandes SO, Martins FS *et al*. (2014) Dietary glutamine prevents the loss of intestinal barrier function and attenuates the increase in core body temperature induced by acute heat exposure. *Br J Nutr* 112:1601–1610. https://doi.org/10.1017/S0007114514002608.
9. Smits FJ, Henry AC, Besselink MG, Busch OR, van Eijck CH, Arntz M *et al*., Dutch Pancreatic Cancer Group. (2022) Algorithm-based care versus usual care for the early recognition and management of complications after pancreatic resection in The Netherlands: an open-label, nationwide, stepped-wedge cluster-randomised trial. *Lancet* 399: 1867–1875. https://doi.org/10.1016/S0140-6736(22)00182-9.
10. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N *et al*. (2019 Mar) Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018. *World J Surg* 43:659–695. https://doi.org/10.1007/s00268-018-4844-y.
11. Melloul E, Lassen K, Roulin D, Grass F, Perinel J, Adham M *et al*. (2020) Guidelines for perioperative care for pancreatoduodenectomy: enhanced recovery after surgery (ERAS) recommendations 2019. *World J Surg* 44:2056–2084. https://doi.org/10.1007/s00268-020-05462-w.
12. Takagi K, Umeda Y, Yoshida R, Yagi T, Fujiwara T. (2020 Aug) Systematic review on immunonutrition in partial pancreatoduodenectomy. *Langenbeck's Arch Surg* 405:585–593. https://doi.org/10.1007/s00423-020-01916-w.
13. Yang FA, Chen YC, Tiong C. (2020 Sep 12) Immunonutrition in patients with pancreatic cancer undergoing surgical intervention: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 12: 2798. https://doi.org/10.3390/nu12092798.
14. Guan H, Chen S, Huang Q. (2019) Effects of enteral immunonutrition in patients undergoing pancreaticoduodenectomy: a meta-analysis of randomized controlled trials. *Ann Nutr Metab* 74:53–61. https://doi.org/10.1159/000495468.
15. Hu M, Cappelleri JC, Lan KK. (2007) Applying the law of iterated logarithm to control type I error in cumulative meta-analysis of binary outcomes. *Clin Trials* 4:329–340.
16. Moseley AM, Elkins MR, Herbert RD, Maher CG, Sherrington C. (2009) Cochrane reviews used more rigorous methods than non-Cochrane reviews: survey of systematic reviews in physiotherapy. *J Clin Epidemiol* 62:1021–1030.
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP *et al*. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 339:b2700. https://doi.org/10.1136/bmj.b2700.
18. Eriksen MB, Frandsen TF. (2018) The impact of patient, intervention, comparison, outcome (PICO) as a search strategy tool on literature search quality: a systematic review. *J Med Libr Assoc* 106:420–421.
19. Clark J, Glasziou P, Del Mar C, Bannach-Brown A, Stehlik P, Scott AM. (2020) A full systematic review was completed in 2 weeks using automation tools: a case study. *J Clin Epidemiol*, (28):81–90. https://doi.org/10.1016/j.jclinepi.2020.01.008, 2020.
20. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P *et al*. (2008) GRADEWorking Group., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336:924–926. https://doi.org/10.1136/bmj.39489.470347.
21. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M *et al*. (2017) The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. *Surgery* 161:584–591. https://doi.org/10.1016/j.surg.2016.11.014.
22. Hozo SP, Djulbegovic B, Hozo I. (2005) Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 5:135.
23. Wan X, Wang W, Liu J, Tong T. (2014) Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 14:982–989. https://doi.org/10.1186/1471-2288-14-135.

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24. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I *et al*. (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 28:366. https://doi.org/10.1136/bmj.l4898. l4898.

25. Kang H. (2021) Trial sequential analysis: novel approach for meta-analysis. *Anesthesiol Pain Med* 16:138–150.

26. Wetterslev J, Thorlund K, Brok J, Gluud C. (2009) Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol* 9:86. https://doi.org/10.1186/1471-2288-9-86, 30.

27. Wetterslev J, Jakobsen JC, Gluud C. (2017) Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 17:39. https://doi.org/10.1186/s12874-017-0315-7, 6.

28. Claire R, Gluud C, Berlin I, Coleman T, Leonardi-Bee J. (2020) Using Trial Sequential Analysis for estimating the sample sizes of further trials: example using smoking cessation intervention. *BMC Med Res Methodol* 20:284. https://doi.org/10.1186/s12874-020-01169-7.

29. Mantel N, Haenszel W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22:719–748.

30. Higgins JP, Thompson. SG. (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* 21:1539–1558.

31. Egger M, Davey Smith G, Schneider M *et al*. (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629–634. https://doi.org/10.1136/bmj.315.7109.629.

32. Higgins JP, Thompson SG. (2004) Controlling the risk from spurious findings from meta-regression. *Stat Med* 23:1663–1682. https://doi.org/10.1002/sim.1752.

33. Di Carlo V, Gianotti L, Balzano G, Zerbi A, Braga M. (1999) Complications of pancreatic surgery and the role of perioperative nutrition. *Dig Surg* 16:320–326. https://doi.org/10.1159/000018742.

34. Gianotti L, Braga M, Gentilini O, Balzano G, Zerbi A, Di Carlo V. (2000) Artificial nutrition after pancreaticoduodenectomy. *Pancreas* 21: 344–351. https://doi.org/10.1097/00006676-200011000-00004.

35. Jo S, Choi SH, Heo JS, Kim EM, Min MS, Choi DW *et al*. (2006) Missing effect of glutamine supplementation on the surgical outcome after pancreaticoduodenectomy for periampullary tumors: a prospective, randomized, double-blind, controlled clinical trial. *World J Surg* 30: 1974–1984. https://doi.org/10.1007/s00268-005-0678-5.

36. Aida T, Furukawa K, Suzuki D, Shimizu H, Yoshidome H, Ohtsuka M *et al*. (2014) Preoperative immunonutrition decreases postoperative complications by modulating prostaglandin E2 production and T-cell differentiation in patients undergoing pancreatoduodenectomy. *Surgery* 155:124–133. https://doi.org/10.1016/j.surg.2013.05.040.

37. Gade J, Levring T, Hillingsø J, Hansen CP, Andersen JR. (2016) The effect of preoperative oral immunonutrition on complications and length of hospital stay after elective surgery for pancreatic cancer–A randomized controlled trial. *Nutr Cancer* 68:225–233. https://doi.org/10.1080/01635581.2016.1142586.

38. Ashida R, Okamura Y, Wakabayashi-Nakao K, Mizuno T, Aoki S, Uesaka K. (2019) The impact of preoperative enteral nutrition enriched with eicosapentaenoic acid on postoperative hypercytokinemia after pancreatoduodenectomy: the results of a double-blinded randomized controlled trial. *Dig Surg* 36:348–356. https://doi.org/10.1159/000490110.

39. Simon R. (2021) Complications after pancreaticoduodenectomy. *Surg Clin* 101:865–874. https://doi.org/10.1016/j.suc.2021.06.011.

40. Ricci C, Ingaldi C, Grego DG, Alberici L, De Raffele E, Pagano N *et al*. (2021) The use of comprehensive complication Index® in pancreatic surgery: a comparison with the Clavien-Dindo system in a high volume center. *HPB* 23:618–624. https://doi.org/10.1016/j.hpb.2020.09.002.

41. Gleeson EM, Pitt HA, Mackay TM, Wellner UF, Williamsson C, Busch OR *et al*. (2021) Global audits on pancreatic surgery group (GAPASURG). Failure to rescue after pancreatoduodenectomy: a transatlantic analysis. *Ann Surg* 274:459–466. https://doi.org/10.1097/SLA.0000000000005000, 1.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.03.014.

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