CLINICAL SCIENCE OF NUTRITION

Original Article

DOI: 10.5152/ClinSciNutr.2023.23090

Is Immunonutrition Effective on Surgical Site Infection and Length of Hospital Stay in Pancreaticoduodenectomy Patients?

Pınar Taşar, Sadik Kılıçturgay

Department of General Surgery, Bursa Uludağ University, Faculty of Medicine, Bursa, Turkey

Cite this article as: Taşar P, Kılıçturgay S. Is immunonutrition effective on surgical site infection and length of hospital stay in pancreaticoduod enectomy patients? *Clin Sci Nutr.* 2023;5(2):63-69.

ABSTRACT

Objective: Studies emphasize the importance of nutritional support in pancreatic cancer patients with malnutrition and suggest that immunonutrition products reduce postoperative morbidity compared to standard products. In this study, we evaluated the effect of standard nutritional support and immunonutrition on surgical site infection and postoperative length of hospital stay in patients undergoing pancreaticoduodenectomy for malignancy.

Methods: Patients who underwent pancreaticoduodenectomy between 2018 and 2022 were divided into 3 groups: those who received no nutritional support, those who received standard nutritional support, and those who received immunonutrition. Patients' age, gender, body mass index, weight loss, Nutritional Risk Screening-2002 score, preoperative prealbumin and albumin values, whether they received nutritional support or not, the period of nutritional support use and whether standard nutritional support or immunonutrition was applied, postoperative surgical site infection development and length of hospital stay were evaluated.

Results: The study included 114 patients, 66 of whom were male. The mean age of the patients was 63.8 ± 10.45 years, the mean body mass index was 26.53 ± 5.29 kg/m^2, and the median Nutritional Risk Screening-2002 score was 4 (2-6). Weight loss was observed in 57% of the patients. Of the 65 patients with weight loss, 14 (21.5%) did not receive nutritional support. In total, 49 patients received immunonutrition. There were 31 patients in the no nutritional support group. When the groups were compared, the difference in the incidence of surgical site infection was significant (P=.030). However, there was no difference between the groups regarding length of hospital stay (P=.147). When the groups were compared among themselves, there was no difference in surgical site infection between the standard nutritional support or immunonutrition groups (P=.128). In those with weight loss, surgical site infection was highest in the no nutritional support group with 71.4%, while it was 23.3% and 23.8% in the immunonutrition and standard nutritional support groups, respectively (P=.004). Length of hospital stay was similar. In those without weight loss, there was no difference between the groups regarding surgical site infection and length of hospital stay (P=.057, P=.271, respectively).

Conclusion: In malnourished or at risk of malnutrition patients undergoing pancreaticoduodenectomy for periampullary site malignancy, nutritional support positively affects the development of surgical site infection, whereas specifically, immunonutrition does not reduce postoperative surgical site infection or length of hospital stay.

Keywords: Immunonutrition, morbidity, periampullary cancer

INTRODUCTION

Tumors of the periampullary region (PAT) localized within 2 cm of the major papilla, including the ampulla vateri, distal choledochal, pancreatic head-uncinate process, and duodenum, account for 0.5%-2% of all gastrointestinal cancers.[1] Pancreaticoduodenectomy (PD) is considered the most effective treatment in these patients. Although mortality after PD gradually decreases, morbidity is still around 50%. A significant portion of the morbidity is caused by surgical site infection (SSI).[2] Among the causes of SSI, malnutrition is an important factor.[3] Cancer patients are immunosuppressive and severe malnutrition may be encountered in 50%-80% of patients due to impaired oral intake, malabsorption, and the effects of the catabolic process.[4] In pancreatic cancer, impairment in both endocrine and exocrine function of the pancreas leads to alterations in food digestion and glucose hemostasis, resulting in increased caloric requirements and malabsorption, leading to weight loss in 80%

Preliminary data for this study were presented as a oral presentation at the Turkish Society of Clinical Enteral & Parenteral Nutrition Congress, March 2023.

Corresponding author: Pınar Taşar, e-mail: pinartasar@gmail.com

Received: June 17, 2023 Accepted: July 17, 2023
Publication Date: July 31, 2023

of patients at diagnosis.[5] This has been demonstrated to decrease the immune response in surgical patients, increase postoperative complications, length of hospital stay (LoHS), and cost, and has a negative impact on quality of life.[6,7] Therefore, the nutritional status of patients and the presence or risk of malnutrition should be evaluated preoperatively and supported with patient-based nutrition protocols. For this purpose, immunonutrition (IN) products can be used in addition to standard nutritional support (SNS) products. Immunonutrition containing specific nutritional products can be administered enteral and parenteral. These products contain arginine, glutamine, dietary nucleotides, and omega-3 fatty acids. Therefore, both preoperative and postoperative IN is founded in European Society for Clinical Nutrition and Metabolism (ESPEN) 2017[8] and 2021[9] for patients undergoing upper gastrointestinal surgery. However, some recent studies have not shown that IN is more effective on postoperative infectious complications than SNS.[10-15] At the same time, while the Enhanced Recovery After Surgery (ERAS) guideline in 2012 found the use of IN for 5-7 days preoperatively in PD patients,[16] the revised guideline in 2019 showed that the use of IN did not affect complications when industry-sponsored studies were excluded.[17] Thus, ERAS does not find the use of IN in PD patients with a high level of evidence and a strong level of recommendation.[17]

This study evaluates the effect of IN or SNS on postoperative SSI and LoHS in patients undergoing PD for PAT.

Main Points

- Weight loss appears to be an effective factor on length of hospital stay (LoHS).
- In patients with malnutrition and/or malnutrition, nutritional support is effective on early postoperative outcomes such as surgical site infection (SSI) and LoHS.
- Although most of the studies have shown the effectiveness of the use of immunonutrition products on postoperative infections complications for cancer patients, conflicting results still remain.
- In our study, the superiority of specialized nutritional support products over standard products in terms of SSI and LoHS, especially in patients with malnutrition and at risk of malnutrition, could not be demonstrated.
- The retrospective nature of the study also enabled us to evaluate the results of nutritional approaches of different surgical teams, regardless of the type of nutritional support used (immunonutrition-standard nutritional support). This is weight loss, and it is also significant in terms of showing the effect of malnutrition on early postoperative outcomes in patients who are on a standard diet and who do not receive nutritional support.

METHODS

The data of patients who underwent PD for PAT in our clinic between 2018 and 2022 were retrospectively analyzed. Ethics committee date January 11, 2023, approval numbered 2023-1/45 of Bursa Uludag University, Faculty of Medicine was obtained. Patients with non-malignant pathologic diagnoses and patients with missing data were excluded from the study. Patients' age, gender, weight loss (>10% within 6 months), body mass index (BMI), Nutritional Risk Screening-2002 (NRS-2002) score (Table 1),[18] prealbumin and albumin values, preoperative biliary drainage (as a factor that increases infectious complications), preoperative and postoperative nutritional support (NS) and IN were analyzed from file data. Patients with NRS-2002 score ≥ 3 and >10% within weight loss were considered at nutritional risk. Patients were divided into 3 groups as "No NS (NNS)," "SNS," and "IN." The preoperative nutritional support (NS) decision was taken according to the personal preferences of 3 different surgeon teams who performed these surgeries. For this reason, it was observed that NS was not given to a group of patients who could need perioperative NS. immunonutritional support (IN), on the other hand, was given according to the physician's decision. In a small number of patients, although IN was started due to intolerance, taste problems (too much sugar), and more difficult control of diabetes, it could not be continued and standard nutritional support (SNS) was applied. Oral Impact Powder® (Nestle, Vevey, Switzerland)) (3 packets-711 mL/day-1023 kcal/day and 54 g/day of L-arginine-milk protein) and glutamine (Resource glutamine (Nestle, Vevey, Switzerland) 30 g/day) were used as IN products. These products were administered orally for 7 days preoperatively and enteral/orally for 7 days postoperatively. In the IN group, SNS products containing calorie 1.0 kcal/mL and 14 g protein were added to patients who could not meet the daily calorie requirement of 25-30 kcal/kg and 1-1.2 g/kg protein requirement. In the postoperative period, patients were started on a nasojejunal (NJ) tube with 10 mL/h at the 6th hour, and it was aimed to increase the dose to 50 mL/h on the third day. Oral intake was then started based on clinical findings. The group receiving standard NS provided similar caloric and protein support as the IN group. Surgical site infection and LoHS were evaluated in the postoperative period. Surgical site infection was classified as superficial, deep, and organ-cavity infection.[19]

Statistical Analysis

Whether the numerical data fit the normal distribution was tested by the Shapiro–Wilk test. Numerical variables fitting the normal distribution were given as mean ± standard deviation, and those not fitting the normal distribution

Table 1. NRS 2002 (Nutritional Risk Score)[18]

Deterioration in Nutritional Status			Severity of Disease	
Score			Score	
Normal Nutrition	0 (None)		Normal Nutrient Requirement	0 (None)
>5% weight loss in 3 months or food intake in the last week is below 50%-75% of normal requirements	1 (mild)	+	Hip fracture, especially in chronic patients with acute complications: liver cirrhosis, COPD, chronic hemodialysis, diabetes, cancer	1 (mild)
Weight loss > 5% within 2 months or BMI 18.5-20.5 + general condition disorder or food intake in the last week is 25%-50% of normal requirements	2 (moderate)		Major abdominal surgery, stroke, severe pneumonia, hematologic malignancy	2 (moderate)
Weight loss > 5% within 1 month (>15% in 3 months) or BMI <18.5 + general impairment or last week's food intake was 0%-25% of normal needs	3 (severe)		Head trauma, bone marrow transplantation, intensive care unit patients (APACHE > 10)	3 (severe)

Patient age ≥ 70 years + 1 point.
Point ≥ 3: Nutritional risk exists, and a nutrition plan is initiated.
Point < 3: An NRS 2002 assessment should be performed once a week. If a major surgical intervention is planned, a nutritional plan should be implemented as a precaution against possible risks.

were given as median (minimum–maximum) values. In the comparison of numerical variables between 2 independent groups, the independent sample *t*-test was used for the comparison of independent groups if the data were normally distributed, 1-way analysis of variance was used for the comparison of more than 2 independent groups, Mann–Whitney *U* test was used for the comparison of 2 independent groups if the data were not normally distributed, and Kruskal–Wallis test was used for the comparison of more than 2 Independent groups. Categorical variables were expressed as n and percentages. Fisher's exact chi-square and Fisher–Freeman–Halton tests were used to compare categorical variables between groups. The Spearman correlation coefficient was used to analyze the relationships between variables. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences Statistics 23.0 package program.

RESULTS

The study included 114 patients, 66 of whom were male. The mean age of the patients was 63.8 ± 10.45 years. The mean BMI was 26.53 ± 5.29 kg/m^2, and 57% of the patients had weight loss. The median NRS-2002 score was 4 (2-6). The median prealbumin was 0.19 g/L (0.07-0.32), and the median albumin was 38.0 (23.0-48.0) g/L. Postoperative LoHS was 12 (6-75) days. Of the 65 patients with weight loss (>10%), 14 (21.5%) did not receive NS. There were a total of 31 patients who did not receive NS. In total, 49 patients received IN. While 48 of these patients received both preoperative and postoperative IN, 1 patient received only postoperative IN because blood glucose regulation could not be achieved in the preoperative period. Of a total of 34 patients who received SNS, only one-fourth (8 patients) received both preoperatively and postoperatively, whereas 26 patients received SNS only postoperatively. Weight loss was present in 21 (61.8%) of the patients who received SNS. Biliary drainage was performed in 20 patients (64.5%) in the NNS group, 21 patients (42.9%) in the IN group, and 16 patients (47.1%) in the SNS group. The distribution of all these parameters in the groups was similar and showed no statistically significant difference (Table 2).

The study showed SSI developed in 32.5% (37 patients) (Table 3). Of these patients, 54.05% (20 patients) developed organ cavity infection, 32.4% (12 patients) developed deep SSI, and only 5 (13.51%) developed superficial SSI. The difference between the groups regarding SSI development was significant (P=.030). The incidence of SSIs in the group that did not receive NNS (48.4%) was significantly higher than in the SNS group (17.6%) (P=.008). In contrast, the rate of SSI in the IN group (32.7%) was similar to both the NNS group and the SNS group (P=.159, P=.128, respectively). When the types of SSI were evaluated, superficial SSI developed in 1 patient, deep SSI in 9 patients, and organ-cavity infection in 5 patients in the NNS group. Among the patients who received NS, 2 patients in the SNS group developed superficial SSI, 1 deep SSI, and 3 organ cavity infections,

Table 2. Comparison of the Preoperative Characteristics of the Cases				
	NNS (n=31)	**SNS (n=34)**	**IN (n=49)**	***P***
Age (years)*	65 (31-79)	65.5 (43-81)	65 (39-82)	.866
>10% Weight loss**	14 (45.2)	21 (61.8)	30 (61.2)	.295
BMI*	26.6 (20.7-35.5)	24.7 (19.2-45.8)	25.8 (16.9-43.9)	.625
NRS-2002*	3 (2-5)	4 (2-6)	4 (2-6)	.245
Albumin (g/L)#	38.45 ± 6.57	35.76 ± 5.06	36.41 ± 5.18	.131
Prealbumin (g/L)	0.18 (0.10-0.32)	0.15 (0.07-0.29)	0.19 (0.07-0.27)	.179
Presence of biliary drainage**	20 (64.5)	16 (47.1)	21 (42.9)	.155

BMI, body mass index; IN, immunonutritional support; NNS, no nutritional support; SNS, standard nutritional support.
*Median (minimum-maximum).
**n (%).
#Mean ± SD.

while 2 patients in the IN group developed superficial SSI, 2 patients developed deep SSI, and 12 patients developed organ cavity infections. It was statistically significant that 9 (75%) of the 12 patients with deep SSI were in the NNS group (*P*=.014), while it was not statistically significant that 12 (60%) of the 20 patients with organ cavity infections were in the IN group (*P*=.070).

Of the 17 patients who developed superficial or deep SSI, 10 (58.8%) were in the group not receiving NS. The difference was statistically significant compared to 7 patients in the standard or IN group (*P*=.037).

When the groups were compared among themselves, there was no difference between the SNS or the IN group regarding SSI (*P*=.128). When the patients with weight loss were analyzed, SSI was observed in the NNS group with a rate of 71.4%, while SSI was observed in the IN and SNS groups with rates of 23.3% and 23.8%, respectively (*P*=.004). In patients with weight loss, there was no difference in SSI infection between those who received IN and those who received SNS (*P*=1.000), while SSI was significantly lower in both the IN and SNS groups compared to the NNS group (*P*=.002, *P*=.005, respectively). Surgical site infection developed in 30.6% of those without weight loss. There was no difference between the groups in terms of SSI in those without weight loss (*P*=.057)

There was no difference between the groups when the LoHS was evaluated (*P*=.147)(Table 3). The median LoHS was 12 (6-41) days in patients with weight loss. Patients with weight loss and SNS had the longest LoHS with 19.5 (7-40) days, but it was not significant (*P*=.072). When the groups were compared pairwise, it was observed that those who did not receive NS had longer LoHS than the SNS and IN groups, and this difference was statistically

Table 3. Surgical Site Infection and Length of Hospitalization in the Groups					
	Total	**NNS (n=31)**	**SNS (n=34)**	**IN (n=49)**	***P***
SSI**	37	15 (48.4%)	6 (17.6%)	16 (32.7%)	***.030***
Superficial SSI	5	1 (20.1%)	2 (40.0%)	2 (40.0%)	*.288*
Deep SSI	12	9 (75.0%)	1 (8.3%)	2 (16.7%)	***.014***
Organ cavity infection	20	5 (25.0%)	3 (15.0%)	12 (60.0%)	*.070*
LoHS (days)*		15 (6-40)	9 (6-41)	12 (6-75)	*.147*
>10% without weight loss	11 (6-75)	10.5 (6-30)	8 (6-40)	14 (6-75)	.271
>10% weight loss	12 (6-41)	19.5 (7-40)	11.5 (6-41)	11.5 (6-37)	.072

*Median (minimum-maximum).
**n (%).
Statistical significance in the comparison of the three groups.

significant ($P=.028$, $P=.045$, respectively). On the other hand, no difference was found between SNS and IN ($P=.372$). In those without weight loss, the median LoHS was 11 (6-75) days, and there was no difference in LoHS between the groups ($P=.271$).

In the correlation analysis, no correlation was found between albumin ($P=.320$), prealbumin ($P=.268$), and NRS ($P=.245$) and postoperative LoHS, while a significant negative correlation was observed between albumin and NRS ($r=-0.312$, $P<.001$).

DISCUSSION

The prognostic importance of weight loss in major surgery has been recognized since the 1930s.[20] Weight loss (due to anorexia, malabsorption, and increased caloric requirements) has been reported in more than 80% of pancreatic cancer patients at diagnosis, and more than two-thirds of these patients LoHS more than 10% of their initial body weight. Although body mass index (BMI) is an important indicator in determining malnutrition, it can be misleading in obese individuals. Therefore, obese patients may be more malnourished than those with low body mass index. In addition to the patient's weight loss and BMI, sarcopenia and sarcopenic obesity should also be considered. These patients have an NRS-2002 score of ≥3 and require further nutritional assessment.[21,22] In our study, although mean BMI and albumin values were within normal limits, 57% of the patients had weight loss. The NRS-2002 score was also high in proportion to weight loss.

In particular, malnourished patients and patients at risk of malnutrition are associated with a higher rate of postoperative complications and longer lengths of hospitalization than well-nourished patients.[23] Therefore, the 2017 ESPEN guidelines found oral/supplement, enteral, or parenteral feeding regimens aiming to achieve standard nutritional status before a major operation such as hepatopancreatobiliary surgery.[24] However, preoperative NS in pancreatic surgery has not been proven to reduce complication rates or accelerate recovery. Level A evidence (prospective randomized controlled trials showing the benefits of meaningful clinical outcomes are few and mostly dated, and none of the different screening methods for malnutrition have been shown to have any prognostic significance for patients undergoing pancreatic surgery.[25] On the other hand, although preoperative NS in patients with moderate to severe malnutrition is recommended by the 2017 ESPEN guideline, none of the 35 controlled studies that make up the database date after 2004. Therefore, preoperative NS is a controversial issue. The use of a nasogastric tube, NJ tube, or needle-catheter jejunostomy recommended by ESPEN guidelines for the postoperative period is not recommended by ERAS guidelines. Early initiation of oral feeding, available in the ERAS program, also varies between cases. Therefore, both ESPEN and ERAS recommendations can be combined to provide an additional benefit to the patient, and the use of artificial NS may be useful in patients at high risk of postoperative complications.[17,24,26] To optimize patient outcomes, it is generally accepted to delay surgery and initiate aggressive NS in patients with albumin < 2.5 mg/dL or weight loss > 10% or BMI:18.5 kg/m^2 and to give preoperative NS to patients with albumin < 3 mg/dL or weight loss between 5% and 10%.[27]

Proinflammatory cytokine levels are also high in PAT, especially in pancreatic cancer patients.[28] In light of all this theoretical information, it is thought that using specific agents such as IN products that both modulate the immune system and have trophic effects on the intestinal mucosa may have positive effects in the postoperative period. The ESPEN guidelines also recommend using IN (glutamine and arginine, ω-3 fatty acids, and nucleotides) in major abdominal surgery to prevent infectious complications.[24] Conflicting results have been reported in the literature. Some studies have reported no difference between IN and standard oral supplements regarding postoperative complications.[11,29] A meta-analysis published in 2014 provides similar data.[30] In a recent meta-analysis, the use of IN was not shown to affect overall postoperative complications, non-infectious complications, and mortality after PD, but it was reported to reduce infectious complications and shorten the LoHS.[31-33] The main problem is that most studies on this issue are severely biased, and these benefits are LoHS when industry-sponsored studies are excluded.[25] In addition, factors such as the malnutrition status of patients and differences between diagnoses may affect homogenization and cause heterogeneity of groups, leading to conflicting results in the data obtained from studies. The ERAS guidelines for pancreatic surgery recommend artificial NS only in patients with severe malnutrition and do not recommend using IN in any patient.[17]

In our study, SSI was most common in the group with weight loss and NNS, and there was no difference between whether the selected NS was SNS or IN support. No effect of NS or IN support could be demonstrated in patients without weight loss. However, borderline significant results were obtained between the groups in patients with weight loss regarding LoHS; the longest hospitalization period was seen in the patient group without NS. In short, the lack of NS in patients with weight loss can be considered an important risk factor for LoHS and SSI.

Considering the effect of factors such as biliary drainage and BMI on SSI, the similar distribution of these

parameters in all groups equalizes the negative effect of these parameters on SSI in all groups in our study.

In our study, the highest rate of SSI was observed in the NNS group, and while there was a significant difference between the NNS and SNS groups, there was no difference between the IN and NNS groups in terms of SSI. This may be explained by the fact that three-quarters of SSI in the IN group were organ cavity infections. After PD, organ cavity infection usually develops due to postoperative pancreatic fistula. In the IN group, 75% (9 cases) of the patients with organ cavity infection had Grade B pancreatic fistula, and 8.3% (1 case) had chylous leakage, leading to intra-abdominal collection in 83.3% of the cases. This rate was 100% in patients receiving SNS and 80% in the NNS group. Pancreatic fistula is associated with pancreatic fistula score, including parameters such as pancreatic nature, duct diameter, and preoperative blood transfusion. Therefore, we think that organ cavity infection in this group may be due to reasons other than nutritional status and supportive treatment. The effect of NS on the pancreatic fistula has not been demonstrated in the literature.[11,33,34] When organ cavity infection is excluded, incisional SSI is significantly more common in the NNS group than in the SNS and IN groups. This difference is due to the much higher incidence of deep SSI, especially in the NNS group. Incisional SSI was found to be 32.3% in 31 patients in the NNS group and 8.4% in 83 patients on NS. However, no difference was found between the types of NS.

The limitations of our study are that it is retrospective, the number of patients is limited, and some of the comorbid pathologies that may be effective on SSI are not included in the parameters of the study.

In conclusion, weight loss is a significant symptomatology for patients at risk of malnutrition. Providing NS in malnourished and malnourished patients at risk of malnutrition reduces postoperative infectious complications, whereas NS in well-nourished patients and customized NS were not effective on SSI and LoHS.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of University of Bursa Uludag (Date: January 11, 2023, number: 2023-1/45).

Informed Consent: Written informed consent was obtained from each patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Design – P.T.; Supervision – S.K.; Materials – S.K.; Data Collection and/or Processing – P.T.; Analysis and/or Interpretation – S.K; Literature Search – S.K., P.T.; Writing Manuscript – S.K., P.T.; Critical Review – S.K.

Acknowledgments: We would like to thank for statistical evaluation Dr. Deniz Sigirli for their contributions.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: There was no financial support or sponsorship provided for this study.

REFERENCES

1. Baghmar S, Agrawal N, Kumar G, et al. Prognostic factors and the role of adjuvant treatment in periampullary carcinoma: a single-centre experience of 95 patients. *J Gastrointest Cancer*. 2019;50(3):361-369. [CrossRef]
2. Suragul W, Rungsakulkij N, Vassanasiri W, et al. Predictors of surgical site infection after pancreaticoduodenectomy. *BMC Gastroenterol*. 2020;20(1):201. [CrossRef]
3. La Torre M, Ziparo V, Nigri G, Cavallini M, Balducci G, Ramacciato G. Malnutrition and pancreatic surgery: prevalence and outcomes. *J Surg Oncol*. 2013;107(7):702-708. [CrossRef]
4. Nicolini A, Ferrari P, Masoni MC, et al. Malnutrition, anorexia and cachexia in cancer patients: a mini-review on pathogenesis and treatment. *Biomed Pharmacother*. 2013;67(8):807-817. [CrossRef]
5. Bye A, Jordhøy MS, Skjegstad G, Ledsaak O, Iversen PO, Hjermstad MJ. Symptoms in advanced pancreatic cancer are of importance for energy intake. *Support Care Cancer*. 2013;21(1):219-227. [CrossRef]
6. Pinho NB, Martucci RB, Rodrigues VD, et al. Malnutrition associated with nutrition impact symptoms and localization of the disease: results of a multicentric research on oncological nutrition. *Clin Nutr*. 2018;38:1274-1279.
7. Kakavas S, Karayiannis D, Bouloubasi Z, et al. Global leadership initiative on malnutrition criteria predict pulmonary complications and 90-day mortality after major abdominal surgery in cancer patients. *Nutrients*. 2020;12(12): 12(12):3726. [CrossRef]
8. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr*. 2017;36(1):11-48. [CrossRef]
9. Muscaritoli M, Arends J, Bachmann P, et al. ESPEN practical guideline: clinical Nutrition in cancer. *Clin Nutr*. 2021;40(5):2898-2913. [CrossRef]
10. Ida S, Hiki N, Cho H, et al. Randomized clinical trial comparing standard diet with perioperative oral immunonutrition in total gastrectomy for gastric cancer. *Br J Surg*. 2017;104(4):377-383. [CrossRef]
11. Gade J, Levring T, Hillingsø J, Hansen CP, Andersen JR. 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*. 2016;68(2):225-233. [CrossRef]
12. Fu H, Li B, Liang Z. Effect of enteral immunonutrition compared with enteral nutrition on surgical wound infection, immune and inflammatory factors, serum proteins, and cellular immunity in subjects with gastric cancer undergoing a

total gastrectomy: a meta-analysis. *Int Wound J*. 2022;19(7):1625-1636. [CrossRef]
13. Mabvuure NT, Roman A, Khan OA. Enteral immunonutrition versus standard enteral nutrition for patients undergoing oesophagogastric resection for cancer. *Int J Surg*. 2013;11(2):122-127. [CrossRef]
14. Tumas J, Jasiūnas E, Strupas K, Šileikis A. Effects of immunonutrition on comprehensive complication index in patients undergoing pancreatoduodenectomy. *Medicina (Kaunas)*. 2020;56(2):56(2):52. [CrossRef]
15. Song GM, Tian X, Liang H, et al. Role of enteral immunonutrition in patients undergoing surgery for gastric cancer: a systematic review and meta-analysis of randomized controlled trials. *Med (Baltim)*. 2015;94(31):e1311. [CrossRef]
16. Lassen K, Coolsen MM, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery after Surgery (ERAS®) Society recommendations. *Clin Nutr*. 2012;31(6):817-830. [CrossRef]
17. Melloul E, Lassen K, Roulin D, et al. Guidelines for perioperative care for pancreatoduodenectomy: Eenhanced Recovery After Surgery (ERAS) recommendations 2019. *World J Surg*. 2020;44(7):2056-2084.
18. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. *Clin Nutr*. 2003;22(3):321-336. [CrossRef]
19. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) hospital infection control practices advisory committee. *Am J Infect Control*. 1999;27(2):97-132; quiz 133. [CrossRef]
20. Studley HO. Percentage of weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer. *JAMA*. 1936;106(6):458-460. [CrossRef]
21. Olson SH, Xu Y, Herzog K, et al. Weight loss, diabetes, fatigue, and depression preceding pancreatic cancer. *Pancreas*. 2016;45(7):986-991. [CrossRef]
22. Gilliland TM, Villafane-Ferriol N, Shah KP, et al. Nutritional and metabolic derangements in pancreatic cancer and pancreatic resection. *Nutrients*. 2017;9(3):243. [CrossRef]
23. Kim E, Lee DH, Jang JY. Effects of preoperative malnutrition on postoperative surgical outcomes and quality of life of elderly patients with periampullary neoplasms: a single-center prospective cohort study. *Gut Liver*. 2019;13(6):690-697. [CrossRef]
24. Weimann A, Braga M, Carli F, et al [ESPEN guideline]. ESPEN guideline: clinical nutrition in surgery. *Clin Nutr*. 2017;36(3):623-650. [CrossRef]
25. Probst P, Haller S, Bruckner T, et al. Prospective trial to evaluate the prognostic value of different nutritional assessment scores in pancreatic surgery (NURIMAS Pancreas). *Br J Surg*. 2017;104(8):1053-1062. [CrossRef]
26. Bozzetti F, Mariani L. Perioperative nutritional support of patients undergoing pancreatic surgery in the age of ERAS. *Nutrition*. 2014;30(11-12):1267-1271. [CrossRef]
27. Gianotti L, Besselink MG, Sandini M, et al. Nutritional support and therapy in pancreatic surgery: a position paper of the International Study Group on Pancreatic Surgery (ISGPS). *Surgery*. 2018;164(5):1035-1048. [CrossRef]
28. Poch B, Lotspeich E, Ramadani M, Gansauge S, Beger HG, Gansauge F. Systemic immune dysfunction in pancreatic cancer patients. *Langenbecks Arch Surg*. 2007;392(3):353-358. [CrossRef]
29. Ashida R, Okamura Y, Wakabayashi-Nakao K, Mizuno T, Aoki S, Uesaka K. 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*. 2019;36(4):348-356. [CrossRef]
30. Hegazi RA, Hustead DS, Evans DC. Preoperative standard oral nutrition supplements vs immunonutrition: results of a systematic review and meta-analysis. *J Am Coll Surg*. 2014;219(5):1078-1087. [CrossRef]
31. Guan H, Chen S, Huang Q. Effects of enteral immunonutrition in patients undergoing pancreaticoduodenectomy: a meta-analysis of randomized controlled trials. *Ann Nutr Metab*. 2019;74(1):53-61. [CrossRef]
32. Gianotti L, Braga M, Gentilini O, Balzano G, Zerbi A, Di Carlo V. Artificial nutrition after pancreaticoduodenectomy. *Pancreas*. 2000;21(4):344-351. [CrossRef]
33. Silvestri S, Franchello A, Deiro G, et al. Preoperative oral immunonutrition versus standard preoperative oral diet in well nourished patients undergoing pancreaticoduodenect omy. *Int J Surg*. 2016;31:93-99. [CrossRef]
34. Shirakawa H, Kinoshita T, Gotohda N, Takahashi S, Nakagohri T, Konishi M. Compliance with and effects of preoperative immunonutrition in patients undergoing pancreatic oduodenectomy. *J Hepatobiliary Pancreat Sci*. 2012;19(3):249-258. [CrossRef]