Effectiveness of preoperative nutritional supplementation on postoperative outcomes for patients undergoing pancreaticoduodenectomy for cancer

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Abstract

Objective:

The objective of this review was to synthesise the evidence regarding effectiveness of preoperative nutritional supplementation on postoperative outcomes for patients undergoing pancreaticoduodenectomy for cancer.

Introduction:

Pancreaticoduodenectomy surgery is complex, high-risk, and associated with significant postoperative morbidity. It remains the only curative option for patients with pancreatic cancer. Strategies to improve outcomes for patients are essential. Preoperative nutritional supplementation such as immunonutrition may enhance recovery from surgery and reduce complications.

Inclusion criteria:

This review considered randomised and quasi-randomised trials that recruited a minimum of one patient in intervention and control groups undergoing pancreaticoduodenectomy for cancer. Intervention groups could receive any form of nutritional supplementation for a minimum of 48 hours. Outcomes included infectious complications, anastomotic leak, pancreatic fistula, delayed gastric emptying, mortality, haemorrhage, and hospital length of stay.

Methods:

Electronic databases (MEDLINE, CINAHL, Scopus, Cochrane Library) and trial registers were searched for published and unpublished research. All articles from database inception to February 2021 in any language were included. One reviewer performed the literature search, screened texts for inclusion and extracted data. Two reviewers assessed methodological quality of the literature using the JBI critical appraisal tool. Statistical meta-analysis through synthesis and pooling of data for each intervention was completed where meaningful. Narrative findings are described where meta-analysis was not possible.

Results:

The search strategy generated 4688 studies for title and abstract screening. Seventeen trials were then included in this review, with six randomised controlled trials and two quasi-

experimental studies on immunonutrition found suitable for meta-analysis. Other nutritional interventions included synbiotics and standard oral dietary formulas, with findings explored narratively. Critical appraisal found the majority of studies to be of moderate quality. Preoperative immunonutrition for three to seven days led to a decreased risk of postoperative infectious complications by 58%, which reached statistical significance (RR 0.42; 95% CI 0.28, 0.63; P = <0.0001). Furthermore, a reduced risk of wound infections (RR 0.39; 95% CI 0.2, 0.75; P = 0.005) and intrabdominal abscesses (RR 0.51; 95% CI 0.29, 0.92; P = 0.02) was identified in pooled results. There was no significant risk reduction for pancreatic fistula rates (RR 0.91; CI 0.64, 1.20; P = 0.59). Pooled results comparing preoperative immunonutrition to control for other types of infections, anastomotic leak, delayed gastric emptying, haemorrhage and mortality demonstrated no difference between groups, although findings were limited by small patient numbers. Immunonutrition may reduce hospital LOS but pooling of data was not possible due to inconsistencies in reporting across studies. The certainty of evidence for overall infectious complications, wound infections, pancreatic fistula and mortality was determined as moderate, while delayed gastric emptying results had low certainty.

Conclusions:

This study found that short term immunonutrition supplementation before pancreaticoduodenectomy reduces postoperative infectious complications. We suggest that preoperative immunonutrition can be an option to implement in clinical practice before pancreaticoduodenectomy. Further robust clinical trials with longer follow up are needed to establish if this translates to improved adjuvant chemotherapy completion rates and longer survival.

Declaration

I, Jordyn Kate Dangen, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

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Chapter 1: Introduction

The first chapter describes the structure of the thesis, including contents of each chapter. The setting of the systematic review is introduced and background information about the topic presented. Next, the systematic review question is stated followed by the methodological basis around this thesis, including the systematic review process. Finally, definitions of key terms used throughout this thesis are listed.

1.1 Structure of the thesis

The thesis consists of four chapters. Chapter one provides background information on the topic, proposes the research question, and discusses the systematic review process with justification for this review. Chapter two describes the methodology that was designed and followed for this systematic review, while chapter three presents the results of the systematic review and meta-analysis. Finally, chapter four is a discussion and interpretation of results, while outlining the limitations of included studies and the review process, leading to conclusion of the thesis. Implications for clinical practice and future research avenues are proposed.

1.2 Context of the review

1.2.1 The pancreas

The pancreas is a retroperitoneal organ situated at the level of the transpyloric plane or lower border of the first lumbar vertebrae.[1] The gland is around fifteen centimetres and divided into the head, neck, body and tail of pancreas.[1] It contains a pancreatic duct which is a continuous tube from tail to head of pancreas and accessory pancreatic duct, both of which carry pancreatic juice and open into the duodenum of the small intestine (Fig 1).

The endocrine function of the pancreas is carried out by the islets of Langerhan which contain five types of secretory cells (Fig 1).[2] An important function is regulation of intermediary metabolism of carbohydrates, proteins and fats by insulin and glucagon which are released into the bloodstream. Insulin is anabolic and produced by the beta cells which comprise 70% of each islet, with secretion predominantly influenced by glucose and its metabolites.[2] Insulin plays a key role in keeping plasma glucose levels within a narrow range through facilitating storage of glucose as glycogen in the liver and muscles or converting glucose to triglycerides for storage in adipose tissue. The reciprocal glucagon is catabolic and produced by alpha cells which make up 20% of each islet, with secretion chiefly stimulated

by protein ingestion and inhibited by glucose.[2] When blood glucose levels are low, glucagon is released leading to breakdown of stored glycogen in the liver into glucose. Combined, insulin and glucagon allow glucose homeostasis.

Somatostatin plays a role in regulating hormonal secretions including insulin and glucagon, and is produced by delta cells of the islets, as well as in the gastrointestinal tract and hypothalamus cells.[2] Pancreatic polypeptide (PP) cells release PP following a meal which has an inhibitory effect on pancreatic exocrine secretion, gallbladder contraction and gut motility.[3] The PP also influences insulin sensitivity and therefore glucose homeostasis. Release may lead to decreased food ingestion and consequently act as a satiety mediator. Finally, Epsilon cells release ghrelin which can inhibit insulin, increase appetite, and facilitate growth hormone release.[2]

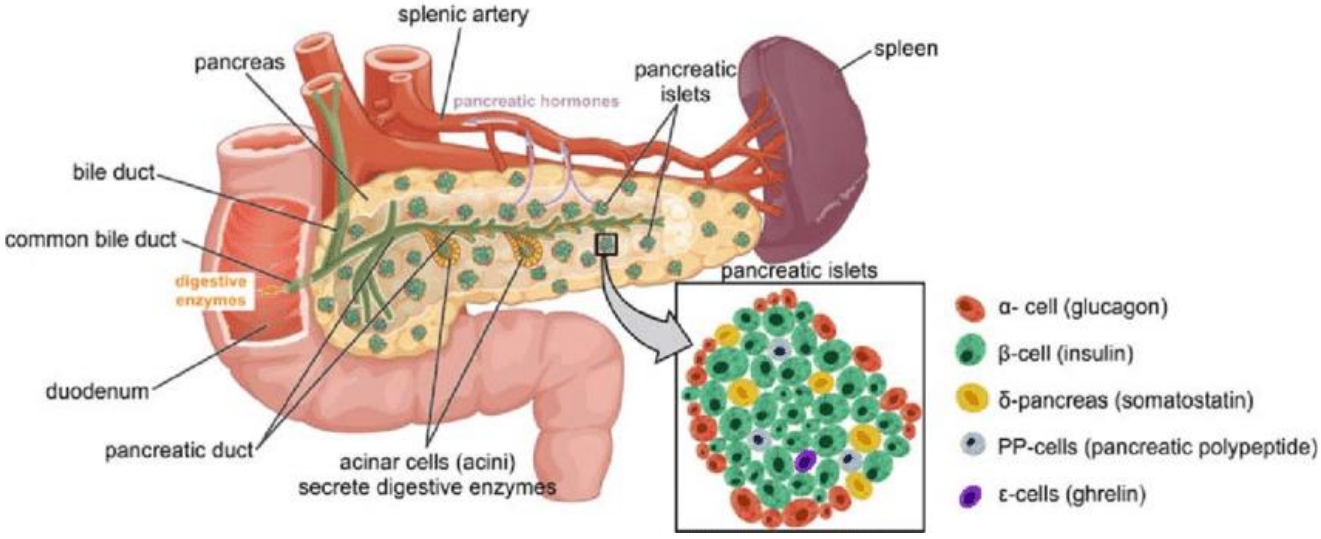

Figure 1: Anatomy of the pancreas including pancreatic ducts, acinar cells and islets of Langerhan. Image adopted from Mühlemann et al.[4]This image is licensed under the Creative Commons Attribution-ShareAlike 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by-sa/4.0/ or send a letter to Creative Commons, PO Box 1866, Mountain View, CA 94042, USA.

The pancreas has an exocrine function where around 1.5 litres of bicarbonate rich, alkaline fluid is produced daily by the acinar and duct cells.[2] Hormones and neural activity trigger the release of inactive digestive enzyme precursors such as trypsinogen and active digestive enzymes such as lipase from the acinar cells, while the duct cells produce the bicarbonate rich alkaline fluid. Combined, this pancreatic juice passes along the pancreatic duct to reach the duodenum (Fig 1) where it neutralises the gastric juice passing by and contributes to digestion of carbohydrates, fat, and protein. Greater than 95% of pancreatic

malignant neoplasms arise from the exocrine portion of the pancreas, which includes tumours of the pancreatic ductal, acinar or stem cells.[5]

1.2.2 Pancreatic cancer

There are multiple different types of pancreatic cancer which are broadly divided into exocrine (see Table 1 for further breakdown) and endocrine pancreatic neoplasms. Around five per cent of pancreatic cancers are endocrine, known as pancreatic neuroendocrine neoplasms (NENs).[6] Approximately 25-50% of NENs are functional, meaning they can produce hormones such as insulin, gastrin and glucagon, leading to a variety of clinical syndromes.[6] Surgery is the only cure for NENs and is indicated to ameliorate hormone overproduction in functioning NENs, treat any mass effect caused by the tumour and prevent metastases or malignant transformation.[6]

"Pancreatic cancer" generally refers to exocrine ductal adenocarcinoma of the pancreas which makes up around 85% of pancreatic neoplasms (Table 1).[7] The lifetime risk of pancreatic cancer is around one per cent however, in Australia, pancreatic cancer is the fifth leading cause of cancer related death with over 3500 new cases diagnosed annually.[8] Furthermore, this also carries a significant economic burden with pancreatic cancer expenditure for 2015-16 estimated at $160 million in Australia.[9] Worldwide, the five-year survival rate of pancreatic cancer is six per cent.[7] A combination of factors contribute to the poor prognosis of pancreatic cancer including late onset of symptoms, limited ability to detect precursor lesions, poor chemosensitivity and the tendency for venous invasion leading to rapid progression of disease.[10]

Table 1: Malignant tumours arising from the exocrine pancreas[5]

Exocrine	**Proportion of exocrine tumours**
Ductal adenocarcinoma	85-90%
IPMN with invasive carcinoma	2-3%
MCN with invasive carcinoma	1%
Solid pseudopapillary neoplasm*	<1%
Acinar cell carcinoma	<1%
Pancreatoblastoma**	<1%
Serous cystadenocarcinoma***	<1%

IPMN: Intraductal papillary mucinous neoplasms; MCN: mucinous cystic neoplasms; *predominantly affect young women and are considered low-grade malignancies;**arise in stem cells;***composed of multiple small cysts with progression from cystadenoma to malignancy very rare.

Around 70% of pancreatic adenocarcinomas occur in the head of pancreas, 15% in the body and the remaining 15% in the tail.[7] Step-wise mutations occur to the pancreatic mucosa leading to adenocarcinoma, with several possible precursor lesions.[7] The first is pancreatic intraepithelial neoplasia (PanIN) which is a microscopic lesion of the small pancreatic ducts and is divided into low and high grade. It has been proposed that high grade lesions have a lifetime risk of 28-33% of transitioning to malignancy however, currently there is no reliable method of detecting and managing these precursor lesions.[11]

Around one per cent of the population will have a cystic lesion of the pancreas, which is usually detected incidentally [7]. Intraductal papillary mucinous neoplasm (IPMN) are cysts of thick mucinous fluid. They are the second possible precursor lesion and can develop in the main pancreatic duct or side-branches. These lesions are detectable by multidetector computed tomography (MDCT) or magnetic resonance cholangiopancreatography (MRCP) with features divided into "worrisome features" and "high-risk stigmata" which help guide surveillance, further investigation and decision for surgical resection.[12] Main duct IPMN are the highest risk with around 60% being malignant.[12]

The third precursor lesion is mucinous cystic neoplasm (MCN) which contains ovarian stroma and does not communicate with the pancreatic ducts. They almost exclusively affect women.[13] These lesions are detected by MDCT or MRCP also, with surgical resection recommended in all cases.[12]

Non-modifiable risk factors for pancreatic ductal adenocarcinoma include age with around 90 per cent of new diagnoses of pancreatic cancer in people aged over 55.[7] Furthermore, sex and ethnicity influence risk, likely from a combination of environmental and genetic factors with pancreatic cancer being 30% more common in males and African-American ethnicity increasing risk by 50-90% compared to Caucasian.[7, 14] Interestingly, blood group O has a lower risk than other blood groups, with pathogenetic mechanisms yet to be discovered. Up to 10% of pancreatic cancer are attributed to inherited germline mutations with BReast CAncer gene 2 (BRACA2) mutation being most common.[7] Familial cancer

syndromes and Partner And Localiser of BRCA2 mutations (PALB2) also have an association.

Smoking is considered the most significant modifiable risk factor, where risk is proportional to number of years and cigarettes smoked.[7] Current smokers are 74% more likely to get pancreatic cancer than those who never smoked.[7] Other modifiable risk factors include chronic pancreatitis due to the inflammatory process, which leads to a lifetime risk of five per cent.[7] People with diabetes are twice as likely to develop pancreatic cancer, and importantly, new onset diabetes can be a manifestation of pancreatic cancer.[7] Obesity and dietary factors such as consumption of red and processed meat may also increase risk.

The most common symptoms of pancreatic cancer are abdominal pain, jaundice and weight-loss.[15] However, many of the signs and symptoms of pancreatic cancer are non-specific, with close to 60% of patients with highly suggestive features found to have an alternate diagnosis.[16] Diagnosis of pancreatic cancer is based on imaging and sometimes cytology.[7] Suspicious lesions may be detected on abdominal ultrasonography, MRCP or abdominal computed tomography (CT), depending on the patient's presenting symptoms. CT should be performed once a lesion is detected for assessment of metastases.

Elevated serum carbohydrate antigen 19-9 (CA 19-9) has a sensitivity and specificity for pancreatic cancer from 70-92%, however low positive predictive value limits use for population screening.[7, 17] Furthermore, patients with a small cancer or the 10% with Lewis-negative phenotype will have normal levels.[7] Importantly, CA-19-9 does have value in prognostication and surveillance for patients with initially elevated levels.[7]

If no metastases are detected, and the patient is fit for surgery, a CT pancreatic protocol or triple phase CT is then performed to determine how locally advanced the cancer is and categorise into resectable, borderline resectable or unresectable.[7] Histologic confirmation is required for patients with nonresectable or metastatic disease before proceeding to chemotherapy, but is not always necessary for those proceeding to surgery.[18] Borderline resectable pancreatic cancer is where the tumour encases a short segment of the hepatic artery, without extension to the coeliac axis and vascular resection of this area with reconstruction is possible; less than 180 degree of the circumference of the superior mesenteric artery is abutted by tumour; or there is tumour involvement and/or blockage of a

short segment of the superior mesenteric vein, portal vein or their confluence.[19] These patients undergo neoadjuvant chemotherapy prior to surgery, with the aim of tumour regression to allow favourable resection.

When no lesion is detected on these imaging modalities, but suspicion remains, an Endoscopic ultrasound (EUS) with biopsies can aid diagnosis.[7] Endoscopic retrograde cholangiopancreatography (ERCP) also allows fine needle aspirate samples of lesions but is less sensitive for detecting malignancy than EUS.[7] ERCP can also be indicated where choledocholithiasis remains a differential or bile duct decompression is required.[7] Proceeding to surgery, followed by chemotherapy, can improve five-year survival rates to around 21%.[20]

1.2.3 Pancreatic cancer surgery

Surgery is the only potentially curative treatment for early pancreatic cancer however, unfortunately only around 20% of patients have surgically resectable disease at diagnosis.[7] Resection for head of pancreas cancers and periampullary lesions involves a pancreaticoduodenectomy (PD) (Whipple's procedure). Pancreaticoduodenectomy was first described in 1912 by Krauch and gained widespread recognition in 1935 after a series of operations were described by Dr. A. O. Whipple.[21] In PD the head of pancreas, portion of the stomach, duodenum, gallbladder and part of the bile duct are removed (Fig 2 and 3).[22] The pancreas, biliary system, stomach and small bowel are then reconstructed with three separate anastomoses using the small bowel jejunum to form a pancreaticojejunostomy, a hepaticojejunostomy and a gastrojejunostomy (Fig 4).

This extensive and complex operation is required due to shared blood flow in resected anatomy and to ensure favourable oncologic outcomes.[20] The ideal outcome is an R0 resection where there is no cancer in the surgical margin.[23] These patients will often still proceed to chemotherapy but have longer predicted survival than patients with an R1 resection where there is residual cancer at the surgical margin.[23]

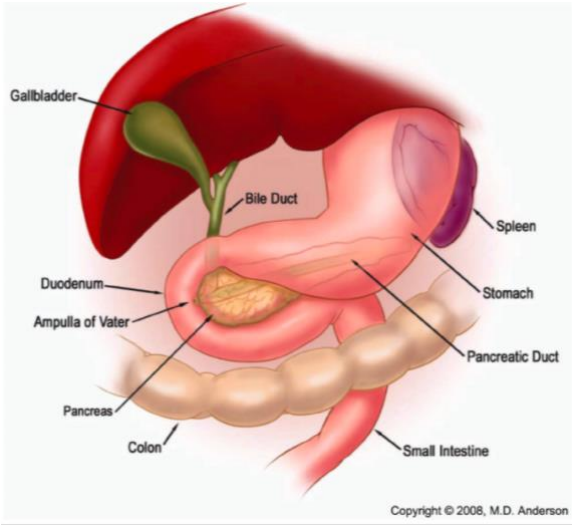

Figure 2. Anatomy of the pancreas, duodenum, bile duct and stomach. Image adopted from Pappas et al.[24] who reprinted from Evans D, ed. Questions and Answers Pancreatic Cancer. Houston TX: M.D. Anderson: 2008:1,6-7 with permission from M.D. Anderson.

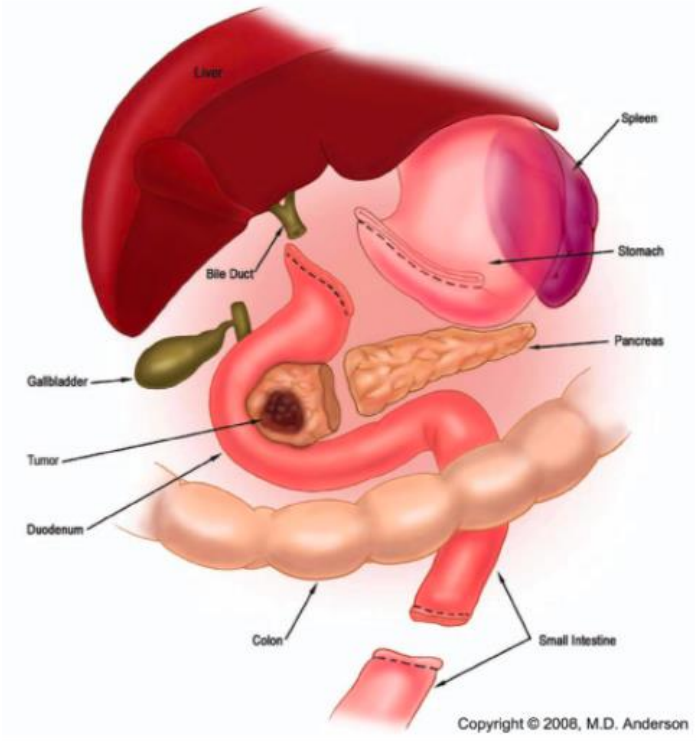

Figure 3: Head of pancreas, portion of the stomach, duodenum, gallbladder and part of the bile duct are removed.

Image adopted from Pappas et al.[24] who reprinted from Evans D, ed. Questions and Answers Pancreatic Cancer. Houston TX: M.D. Anderson: 2008:1,6-7 with permission from M.D. Anderson.

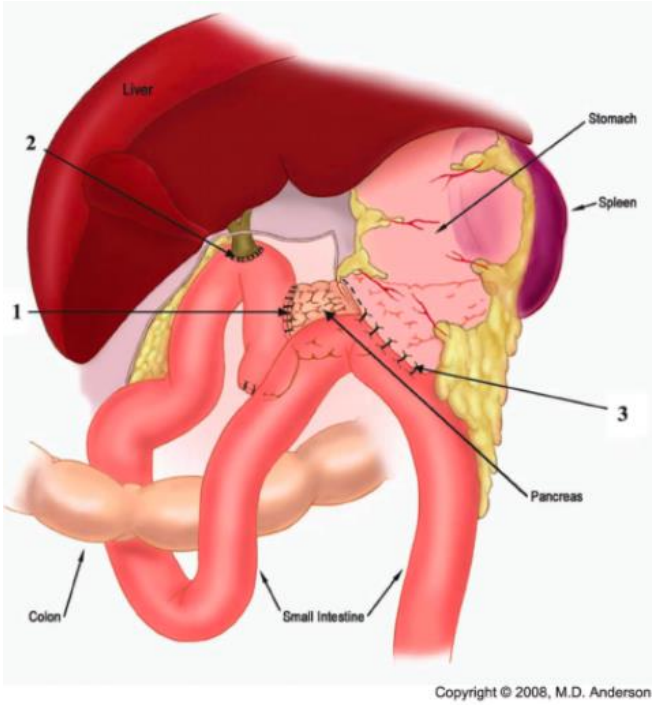

Figure 4: Reconstruction with three separate anastomoses using the small bowel jejunum/intestine to form a (1) pancreaticojejunostomy, a (2) hepaticojejunostomy and a (3) gastrojejunostomy.

Image adopted from Pappas et al.[24] who reprinted from Evans D, ed. Questions and Answers Pancreatic Cancer. Houston TX: M.D. Anderson: 2008:1,6-7 with permission from M.D. Anderson.

Over time, the thirty-day mortality after PD has improved from 30% to near one per cent in some centres.[25-27] This is likely a result of improvement in perioperative management such as the evolution of Enhanced Recovery After Surgery (ERAS) protocols; improved patient selection for resection due to routine high-quality cross sectional imaging with treatment discussion at multidisciplinary meetings among specialists involved in patient care; and concentration of cases to expert surgeons in high-volume centres.[28] Despite improvements in postoperative mortality, morbidity associated with PD remains high at approximately 45%.[26, 27] Infectious complications occur in one third of PD patients and include surgical site infections (SSI) such as intra-abdominal collections or wound infections, sepsis, pneumonia and urinary tract infections.[29] This can lead to increased hospital length of stay (LOS), further procedures and mortality.[29] Furthermore, delay or omission of chemotherapy can occur for patients after PD due to these infections, potentially affecting long-term survival.[29, 30]

Other potential complications more specific to PD include delayed gastric emptying (DGE) and pancreatic fistula.[27] Delayed gastric emptying is a common complication

affecting around 21% of PD patients.[27] It is defined as the inability to return to normal diet by the end of the first postoperative week and leads to prolonged hospital stay and potentially invasive alternate modalities to obtain sufficient nutrition for healing.[31] The pathogenesis of DGE remains unclear, but is likely multifactorial and related to devascularisation and denervation of the pylorus of the stomach, reduced gastrointestinal hormonal production and affected by extent of gastric resection.[32]

Pancreatic fistula involves leakage of pancreas derived fluid from raw pancreatic surface or failure of healing/sealing of the pancreaticojejunostomy anastomosis.[33] It occurs in up to a quarter of PD patients and can range from having no clinical impact to severe complications of sepsis and delayed haemorrhage.[33] Risk of postoperative pancreatic fistula can be related to patient factors that affect healing such as older age, history of smoking, poor nutritional status and history of chronic pancreatitis.[34] The pancreas being of soft texture with a small diameter pancreatic duct may also be factors as this indicates the exocrine function of the pancreas is preserved leading to more pancreatic juice production and possibly higher pressure withing the pancreaticojejuonostomy anastomotic communication.[34] Operative factors that may contribute include poor sealing or blood supply to the pancreaticojejunostomy anastomosis and injury to the pancreas which can trigger pancreatic autolysis.[34]

Anastomotic leak from the other joins is less common, but also a potentially significant complication that can increase mortality.[35, 36] Hepaticojejunostomy leaks occur in around two per cent of PD patients, while gastrojejunostomy/duodenojejunostomy leak incidence is less than one per cent.[35, 37] Higher grade leaks can require percutaneous drainage or reoperation, often taking several months to completely heal.[35] Again, patient factors that affect healing such as older age and poor nutritional status are thought to increase risk.[38] Bile leak risk from hepaticojejunostomy anastomosis is greater in difficult cases with small diameter common bile ducts (CBD) or very thick/inflamed CBD.[38] Other factors which affect healing include poor blood supply to the anastomosis, associated pancreatic fistula and poor surgical technique.[38]

Post-pancreatectomy haemorrhage occurs in around one to eight per cent of cases but can be the causal factor in up to half of deaths.[39] Causes include bleeding from sites of anastomosis or residual vessel stumps, pancreatic enzyme leakage leading to digestion of

blood vessels, intrabdominal infection involving blood vessels and pseudoaneurysms forming at the stump of the gastroduodenal artery.[39, 40]

A pylorus-preserving PD (PPPD) is a variation on traditional technique where the gastric antrum and pylorus are not resected and reconstruction involves a duodenojejunostomy.[24] It was hoped this would reduce the postoperative complication of DGE, however no significant differences in short and long-term outcomes compared to the traditional technique have been identified.[41] The majority of PD are performed as open surgeries, however there is increasing interest in PD performed laparoscopically and robotically in appropriate patients, with the hope they may reduce hospital LOS and complication rates. Equivalent radicality of resection has been demonstrated with these less invasive approaches, although operative time is significantly longer and potential advantages of shorter hospital LOS and reduced complication rates remains controversial.[42, 43 44]

Cancers of the body or tail of the pancreas require a distal pancreatectomy where the duodenum and bile duct are left intact, and the pancreas is divided usually to the left of the superior mesenteric vein/portal vein trunk.[45] Distal pancreatectomy often includes splenectomy given the cancer can invade into the splenic artery and vein or spread to the lymph nodes at the hilum of the spleen.[45] Cancers of the body or tail of pancreas have less proximity to the biliary system and therefore reduced tendency to cause clinical symptoms of jaundice, leading to later presentations.[45] Cancers of the body or tail of pancreas may invade neighbouring organs, leading to multi-visceral resections which may include portions of colon, kidney, liver, adrenal gland or stomach being removed in around 36% of cases.[45]

Standard distal pancreatectomy surgery tends to be shorter and less complex than PD with mortality rates less than one per cent and morbidity around 30%.[46] Complications include new onset insulin dependent diabetes, pancreatic fistula, intrabdominal abscess and haemorrhage.[46] Furthermore given the spleens role in protecting from encapsulated bacterial infections, distal pancreatectomy with splenectomy carries a rare risk of life-threatening infection and demonstrates higher postoperative infection rates compared to when the spleen is able to be preserved in surgeries for non-malignant or low grade tumours.[47] In contrast to PD, a standard distal pancreatectomy does not require extensive reconstruction with multiple anastomosis that have the potential to leak.

Rarely, a total pancreatectomy is required for pancreatic cancer, usually when a pancreatic head tumour extends into the body or tail of the pancreas.[48] Total pancreatectomies make up only two per cent of all pancreatic surgeries and lead to permanent exocrine insufficiency and diabetes which can significantly impact patient quality of life.[48] Although total pancreatectomy avoids a pancreaticojejunostomy anastomosis and risk of pancreatic fistula, mortality is higher than PD at 5.4% with similar rates of morbidity.[48] Given the key differences is surgical technique and postoperative complications for PD compared to distal pancreatectomy and total pancreatectomy, a decision was made to keep this systematic review specific to the more common PD to allow transferrable results.

1.2.4 Nutrition and pancreaticoduodenectomy surgery

Due to the high morbidity associated with PD, methods to improve outcomes for these patients requires thorough consideration. Poor preoperative nutrition is an established significant risk factor for postoperative complications in patients undergoing major abdominal surgery.[49] Studies of PD patients have found that preoperative malnutrition is significantly related to postoperative complications including pneumonia, pancreatic fistula, surgical site infection and hospital LOS;[50, 51] with suggestion that analysis of nutrition factors can predict complications in these patients.[50]

An association of malnutrition is cancer cachexia, defined as weight loss of at least 10% within six months resulting from tumour and proinflammatory cytokine activity triggering a catabolic state.[24] Cachexia is present in around 40.5% of pancreatic cancer patients preoperatively and is associated with a significant reduction in survival.[52] As well as disease state; chemotherapy and comorbidities of this predominantly older patient group mean malnutrition affects 50-80% of PD patients preoperatively.[51, 53] Surgery then leads to activation of the body's stress response and triggers an inflammatory cascade, where pancreatic surgery is considered one of the highest-risk surgeries leading to significant stress on the body.[53] The increased metabolic demands postoperatively requires sufficient nutritional reserve and substrate to facilitate effective healing and recovery.[53] Given the potential implications of nutrition on complication risk in PD patients, this review will explore the effectiveness of nutritional supplementation before PD on outcomes.

Routine evaluation of nutritional status prior to PD is recommended however, there are many nutritional markers and scoring systems utilised in the literature to predict

postoperative outcomes, with no consensus on preferred standard.[54] There is a wide range of both subjective and objective evaluations tools which have been validated in general surgery.[53, 55] Weight loss and body mass index (BMI) measurements are simple to use and therefore advised, although both are limited by not accounting for body weight composition or level of recent dietary intake.[55, 56]

Albumin is a serum protein with osmotic and transport functions that is made in the liver.[57] Circulating albumin carries many essential substrates including fatty acids and minerals, for delivery to the tissues.[58] Furthermore, albumin is considered the most important serum antioxidant.[58] Levels can decrease with acute illness or injury and reduce up to 50% per day with fasting.[57] Hypoalbuminaemia reflects the degree of stress on the body as a result of inflammation related to disease or trauma and often coincides with a negative nutrient balance.[58] In patients with upper gastrointestinal malignancies such as pancreatic cancer, hypoalbuminemia is associated with poor nutrition state and higher risk of operative complications.[55, 56, 59]

Another laboratory test that can reflect malnutrition is total lymphocyte count where malnutrition is found to lead to thymic atrophy and consequent drop in lymphocyte number, therefore impairing immune response.[60] Decreased lymphocyte count potentially correlates with infections complications such as pneumonia in PD patients and is an objective measure incorporated in several nutritional risk screening tools.[50] Furthermore, lymphocyte count is used in multiple nutritional intervention studies for cancer patients, particularly when studying immune-enhancing diets.[55]

The nutrition risk index (NRI) is a tool that has been used in prospective clinical trials, with validated sensitivity and specificity in general surgery.[55] The NRI combines weight loss and albumin in a formula (1.519 x albumin in g/L + 0.417 x current weight/usual weight) and was developed as part of a large randomised control trial (RCT).[61] Malnutrition defined using the NRI has been found to correlate with postoperative morbidity and mortality in surgical patients and specifically, surgical site infections after PD better than albumin or weight loss alone.[51, 62, 63]

Current guidelines have no consensus recommendations on preoperative nutritional screening and supplementation before PD due to lack of clinical trials, despite preoperative

malnutrition being consistently recognised as a risk factor for complications such as pancreatic fistula.[53, 55] The preoperative period has been identified as the window for nutrition supplementation in patients undergoing PD, given the high rates of malnutrition leading up to surgery.[64] There are many different nutritional supplements described in reviews of cancer literature including immunonutrition (IN), fish oil, antioxidants, green tea extract, protein supplementation and carbohydrate rich drinks.[55, 65, 66]

One form of nutritional optimisation with growing presence in the literature is IN or formulas with nutrients such as arginine, glutamine, fatty acids and nucleotides which improve the immune function and can be referred to as nutritional pharmacology.[67] Arginine is involved in multiple metabolic pathways and is important for tissue repair. Furthermore, it plays an important part in lymphocyte function, being an essential substrate for immune cells.[65] Glutamine's role in improving immunity includes increasing protein synthesis, preservation of structure and function of gut barrier, enhancing glucose metabolism and reducing oxidative stress.[65] Supplementation for 72 hours is required to ensure maximum effect, providing a feasible option for preoperative PD patients.[67]

Reviews of IN supplements indicate they may be beneficial at improving immune parameters and clinical outcomes such as hospital LOS and infection rates for malnourished patients undergoing major cancer surgery.[55, 67] Furthermore, The American Society of Parenteral and Enteral Nutrition has made a grade A recommendation for nutritional supplementation with immune enhancing formulas for malnourished patients undergoing major cancer operations.[55] The European Society also endorses immunonutrition in this setting, recognising the benefit in reducing morbidity and hospital LOS after major abdominal cancer surgery.[68]

Omega-three fatty acids, such as those found in fish oil supplements or as part of pharmaconutrition may help promote immune function and reduce inflammation in cancer patients.[55] Supplementation in cancer patients may help to stabilise weight or decrease the rate of weight loss.[55] The benefit before major cancer surgery remains unclear with an RCT of patients having oesophogastric surgery showing no difference in clinical outcomes when supplemented with omega 3 fatty acids for seven days prior to surgery compared to those on standard nutrition.[69] A meta-analysis of this form of supplementation prior to surgery for

gastrointestinal malignancy concluded benefit, however all outcome measures were laboratory tests as appose to clinically significant complications.[70]

1.3 Statement of the systematic review question

The systematic review question addressed the following: What is the effectiveness of preoperative nutritional supplementation, such as IN, on postoperative outcomes such as infection rates and pancreas specific complications for patients undergoing pancreaticoduodenectomy for cancer?

1.4 Researchers experience in the field

The researcher is a general surgery registrar physician who has been working at University Hospital Geelong, currently perusing a career of becoming a general surgeon. University Hospital Geelong is one of many specialised hospitals with a hepatobiliary surgical team, including co-supervisor Professor Abbas, that contribute to the approximate 335 pancreatic surgeries performed annually in Victoria.[71] As a junior physician the researcher was part of this team for multiple rotations where a large portion of the job was supporting postoperative PD patients, many with complications. Given the complexity of PD and impact complications have on patient quality of life, the author developed an interest in exploring novel strategies to improve patient outcomes after PD.

1.5 Methodological basis for the review

1.5.1 Methodology

Medical decision making is multifactorial and includes patient preferences and values, clinician factors and experience, and availability of resources.[72] The other key is using the best available scientific evidence through systematic identification and synthesis of research, a transition modern medicine has made from previously using expert consensus.[72] Good medical decision-making leads to safe, effective, and cost appropriate health care.[72]

Evidence contributing to clinical guidelines can be evaluated according to strength, relevance, quality and level.[72] Strong clinical effects demonstrated in an experimental study are more likely to be true and clinically relevant. Relevance refers to the transferability of findings to other settings, while quality relates to the methodology of the research and degree of effort to minimise bias and ensure reliable findings. Finally, level refers to the study design with a well-established hierarchy of evidence where a systematic review of RCTs is at the top

of the hierarchy. This thesis is based on research aimed at contributing to level I evidence by conducting a systematic review and meta-analysis.

Levels of evidence are as follows:[72]

- I: systematic review of randomised controlled trials
- II: evidence from a minimum of one properly designed randomised controlled trial
- III-1: Well-designed quasi-randomised controlled trial
- III-2: Non-randomised designs such as cohort studies using comparator and control groups, case-control studies or interrupted time series with a control group.
- III-3: Non-randomised studies using a historical control, two or more single arm studies, or interrupted time series without a control group.
- IV: Case series studies

The evolution of systematic reviews dates back to 1971 when Archibald Cochrane notably published "Effectiveness and Efficiency" which highlighted the lack of evidence being used in healthcare and prompted the movement towards evidence based medicine.[73] The term meta-analysis first emerged in 1978 when Dr Gene Glass coined the term and published a synthesis of 80 studies on the relationship between academic achievement and class room size.[74] In 1993 the Cochrane Collaboration was launched with the aim of providing up to date systematic reviews of RCTs of healthcare interventions to facilitate informed decision making in medical practice.[73] Since then, systematic reviews have gained momentum with around 10,000 published annually and recognition they are top of the research hierarchy as the most reliable source of evidence. Systematic reviews are used to inform clinical guidelines, with the proviso they require appraisal and cannot be assumed as high quality.[75]

The systematic review process developed by the Cochrane Collaboration has evolved and been refined since establishment, with focus on ensuring transparency and reproducibility. First, a research question is developed which aims to explore the extensive amount of primary research on a topic through the systematic review process, leading to a synthesised summary on the topic. Next the systematic review planning process is commenced, in the form of a protocol. The published protocol pre-specifies all methodological steps to minimise bias. The protocol will include specific details on

participant inclusion and exclusion criteria, followed by details on the intervention and comparator. Primary and secondary outcome measures are clearly defined and justification for levels of evidence to be included in the review are specified.

When conducting the review, the pre-formulated search strategy is executed to ensure all available evidence on the topic is found. This is reported in the review in a way that allows reproducibility. Next, the study selection process is conducted based on the inclusion criteria. Included studies are then required to undergo critical appraisal by two independent reviewers using a standardised assessment tool to allow comment on methodological quality of each included study. The protocol will specify the level of study quality required to be included in analysis and the results of critical appraisal are made available in the final report. Data is then extracted from included studies and synthesised where possible using meta-analysis software, allowing formation of results which can be used in the clinical setting.

The JBI (formally known as the Joanna Briggs Institute) is an international research organisation based at the University of Adelaide and has been instrumental in the advancement of systematic review methodology.[76] Founded by Professor Alan Pearson in 1996, the aim of JBI is to contribute to healthcare improvement globally through the systematic review process followed by transfer and implementation into clinical practice.[76] Tools have been developed by JBI including a reviewer's manual, JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) and critical appraisal instruments based on study design to provide structure and guidance through the systematic review process.[77] These tools were used throughout this systematic review process to facilitate a reproducible and transferrable process.

There are multiple types of systematic reviews and JBI offers guidelines for undertaking quantitative and qualitative studies including reviews of effectiveness; text and opinion; prevalence and incidence; economic evidence; aetiology and risk; mixed methods; diagnostic test accuracy; umbrella reviews; scoping reviews and measurement properties.[77] Choosing the type of systematic review is dependent on the review question. Given the question of the systematic review presented in this thesis aimed to determine the effect of an intervention (preoperative nutritional supplementation), a quantitative systematic review of effectiveness was determined to be appropriate. This type of review is designed to determine the magnitude to which the intervention of interest achieves the desired effect and can

determine effect size and direction. The JBI guidelines for systematic reviews of effectiveness details that the evidence about effects of interventions may be from experimental studies, quasi-experimental studies or observational studies. [77]

In this systematic review, inclusion was specific to experimental and quasi-experimental studies which involve participants receiving an intervention (preoperative nutritional supplementation) or acting as a control where they received either a control solution or a normal diet with no supplementation. Outcomes of interest such as postoperative complications were then measured for both groups after surgery. Randomised controlled trials are considered the reference standard and require three conditions including manipulation of intervention of interest, control conditions and an authentic randomisation process for participants such as using a table of random numbers.[77] Randomised controlled trials can also have variation in design including parallel design, cross-over design and cluster design; all of which were considered for inclusion in this review with justification provided on how cluster designs would be accounted for in analysis.

Findings from one RCT cannot be considered absolute or able to provide recommendations for clinical practice as the results from one RCT may contradict another, and quality of the studies may vary.[77] Critical appraisal is undertaken of each RCT identified to determine quality and strength of findings based on methodological factors of randomisation; allocation concealment; similarity of groups at baseline; blinding of participant, those delivering the intervention and outcome assessors; identical treatment and outcome measurement of intervention and control groups other than intervention of interest; appropriate statistical analysis including intention to treat; reliable outcome measurement; and appropriate study design.[77]

Non-RCT study design risks the introduction of bias. Pseudo-RCTs are where group allocation does not involve an authentic randomisation process and may be through methods such as alternate odd and even days, while quasi-experimental studies still involve manipulation of intervention and control conditions, but no randomisation process is used. Observational studies are where there is no manipulation of the intervention of interest or control and researchers observe the intervention of interest and outcomes. Analytical observational study types include cohort, case-control and analytical cross-sectional studies; while descriptive observational study types include case reports and case series. These were

excluded in this review given the number of experimental studies identified was likely to be sufficient to inform the review question.

The process of pooling and synthesising two or more homogenous studies, provides more transferable and generalisable results. Meta-analysis of data of multiple studies can be performed where studies are sufficiently homogenous or similar enough clinically and methodologically.[77] The benefits of meta-analysis, where appropriate, are that it allows improved statistical power to detect effect of treatment and can provide an estimate of summary average effect.[77] Furthermore, subgroup analysis can be performed to determine if certain factors are associated with a beneficial effect and any association between study-specific variables and the size or direction of treatment effect can be explored.

Results from meta-analysis can be visually represented with a forest plot which aids interpretation for the reader.[77] Forest plots include effect sizes, direction, and confidence intervals for each included study and for the summation of the studies. Statistical heterogeneity is represented on the forest plot with Chi^2, I^2 or Tau^2 values.[77] I^2 was selected in this review, which can be interpreted as the percentage of the difference in effect estimates that is due to between-studies variability, where at one end of the spectrum, zero per cent is favourable and represents statistically homogenous studies and 100% is substantial heterogeneity. For results that are unable to be included in meta-analysis, findings can be presented narratively. Given the specificity of design for this study, where the intervention of interest was narrowed to preoperative timing of nutritional supplementation for PD patients, it was probable that some of the results would be able to be pooled in meta-analysis. Studies with broader participant cohorts which include patients undergoing PD and patients undergoing other surgeries were also included to facilitate capturing all available experimental evidence, with the proviso that specific data would need to be obtained on PD patients, otherwise results would be presented narratively.

The JBI grades of recommendation also detail two grades that can be applied to health management strategies.[77, 78] A ‘strong’ or grade A recommendation is where the benefits of the strategy outweigh the risks; adequate quality evidence is available to support the strategy; impact on resources is negligible or beneficial; and patient factors and experience have been considered. The alternative is a ‘weak’ or grade B recommendation where it may be unclear if the benefits of the strategy outweigh the risks; the evidence supporting the strategy may be

of low quality; impact on resources is minimal, negligible, or beneficial; and patient factors and experience may or may not have been accounted for. When determining the grade, feasibility; appropriateness; meaningfulness; and effectiveness (FAME scale) of the health management strategy are explored through answering questions such as, "What is the cost effectiveness of the practice?" (under the feasibility section).[78] Following interpretation of the results from this review, a grade of recommendation will be presented and justified under implications for clinical practice.

1.5.2 Why this review is needed

The rationale for focusing on preoperative nutritional supplementation was to provide clinicians with evidence regarding nutritional interventions that can be instituted at clinic appointments, where surgery preparation begins, to facilitate best outcomes for patients. From the patient perspective, these interventions may be motivating and empowering during the anxious wait for major surgery.[79]

In 2001 the ERAS Society was formed with a focus on improving perioperative care for surgical patients through review and implementation of evidence-based practice and formation of guidelines based on type of surgery.[80] This facilitated change in clinical practice, with ERAS protocols being a notable presence in many hospitals. A key evolution of the ERAS guidelines for PD was the additional recommendation of prehabilitation in the updated 2019 edition.[81, 82] The concept of prehabilitation includes a trimodal approach of nutritional therapy, physical exercise and psychology before surgery and is gaining increasing momentum in the literature due to reduction in postoperative complications and hospital LOS.[82] The nutritional therapy component is variable throughout the literature and this review will further inform specifics around nutritional supplementation.

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted to establish if preoperative nutritional supplementation for patients undergoing PD for cancer has been explored. Two recently published systematic reviews have explored the potential benefit of nutritional supplementation for patients having surgery for cancer, finding a reduction in complications.[67, 83] A further meta-analysis of 81 RCTs on IN in major abdominal surgery concluded reduced overall complications, infectious complications and shortened hospital length of stay (LOS) although this effect was lost when

excluding trials at high and unclear risk of bias.[84] An earlier study summarised the findings of five systematic reviews and meta analyses for IN supplementation in surgical patients, concluding the benefit of lower morbidity and shorter hospital LOS.[85] In all studies, outcomes were not specific to PD combined with the preoperative period despite subgroup analysis.

Two further systematic reviews were identified specific to patients undergoing PD and receiving nutritional supplementation.[66, 86] The research conducted by Guan et al[66] is not specific to the preoperative timing and included only one RCT looking specifically at preoperative supplementation. The other three studies included in the review investigated either postoperative or perioperative supplementation. Furthermore, this study was specific to IN and did not include other forms of supplementation. Takagi et al[86] also reviewed RCTs of IN for patients undergoing PD but did not investigate timing of supplementation. They found IN improved overall and infectious complications but had no impact on mortality or complications specific to PD. Recent experimental studies have been published specifically examining preoperative nutritional supplementation for patients undergoing PD and found either no difference or improved outcomes, further highlighting the need for a systematic review in the area.[87, 88]

During the preparation for this systematic review a preliminary search was conducted to establish potential available primary studies on the topic. A limited number of RCTs was identified, leading to a decision to also include quasi-randomised trials. JBI encourages exploring all available evidence on a topic, including grey literature as it importantly contributes to a background understanding of the topic and helps inform directions for future research. This was balanced with the goal of ensuring a review with strength and clinical application.

1.6 Key concepts and definitions of terms

Cachexia: weight loss of at least 10% within six months resulting from tumour and proinflammatory cytokine activity triggering a catabolic state.[24]

Cancer: a disease state where abnormal cells uncontrollably divide and can invade nearby tissues.[89]

Delayed gastric emptying (DGE): Complication of pancreaticoduodenectomy surgery defined as the inability to return to normal diet by the end of the first postoperative week.[31]

Duodenojejunostomy: the surgical creation of a communication or join between the stomach and duodenum (part of small bowel).[41]

ERAS: Enhanced Recovery After Surgery

Gastrojejunostomy: the surgical creation of a communication or join between the stomach and jejunum (part of small bowel).[90]

Hepaticojejunostomy: the surgical creation of a communication or join between the hepatic duct and the jejunum (part of small bowel).[35]

Hypoalbuminaemia: Albumin is a serum protein with osmotic and transport functions that is made in the liver.[13] Hypoalbuminaemia reflects the degree of stress on the body as a result of inflammation related to disease or trauma and often coincides with a negative nutrient balance.[58]

Immunonutrition: formulas containing specific nutrients such as arginine, glutamine, fatty acids and nucleotideds, with potential to modulate the activity of the immune system.[67]

Malnutrition: “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease”.[91]

Nutrition risk index (NRI): marker of nutrition calculated using the formula 1.519 x albumin in g/ L + 0.417 x current weight/usual weight).[63]

Pancreatic fistula: complication of pancreaticoduodenctomy surgery defined as leakage of pancreas derived fluid from raw pancreatic surface or failure of healing/sealing of the reconstruction where the pancreas is joined to small bowel.[33]

Pancreaticoduodenectomy (PD): surgical procedure predominantly done for pancreatic cancers where the head of pancreas, portion of stomach, duodenum and part of the bile duct are removed. The pancreas, biliary system, stomach and small bowel are then reconstructed with three separate joins.[22]

Pylorus-preserving pancreaticoduodenectomy (PPPD): a variation of the pancreaticoduodenectomy surgical procedure where the portion of stomach is not resected.[24] Developed with the aim of reducing the complication of delayed gastric emptying.

Chapter 2: The systematic review protocol

2.1 Introduction

This chapter describes the systematic review protocol. First, a detailed description of inclusion criteria and outcome measures with definitions. Next the search strategy is explained, listing databases used and sources of grey literature. The critical appraisal process and tools utilised is then presented. Data extraction and meta-analysis steps are detailed with method used for assessing certainty of findings also provided. This systematic review protocol was designed in accordance with the JBI methodology for systematic reviews of effectiveness[77] and in accordance with an a priori protocol that was registered in PROSPERO (CCRD42020215307) and published in JBI Evidence Synthesis.[92]

2.2 Review objectives

The overall objective of this review was to identify the best available evidence on the effectiveness of preoperative nutritional supplementation such as IN, for a minimum of 48 hours, on generalised surgical outcomes such as infection rates; and outcomes specific to PD such as pancreatic fistula and DGE, for patients undergoing PD for head of pancreas and peirampullary cancer lesions.

2.3 Inclusion criteria

2.3.1 Participants

This review considered studies with a minimum of one patient in both arms (intervention and comparator), undergoing PD or PPPD for cancer. All patients from 18 to 80 years of age were included. Studies with broader participant cohorts, such as all gastrointestinal (GIT) cancer surgery, were also included if there was a minimum of one participant undergoing PD in both intervention and comparator groups with PD population data reported separately, or if not, study authors were then contacted for this data.

Exclusion criteria for this review included participants with widespread metastatic disease as these patients are much less likely to undergo or benefit from PD.[88] Further exclusion included undergoing PD for a non-malignant reason, immunosuppressive or immunologic diseases, receiving other IN therapies and inflammatory bowel diseases as these factors could possibly confound any potential benefit of nutritional intervention such as IN.[88]

Patients with preoperative infection, gastrointestinal obstruction and poorly controlled diabetes were also excluded as these would confound measured outcomes.[88] Pregnant patients were excluded due to the unique physiology and treatment considerations of this patient group.[88]

2.3.2 Intervention

This review considered studies that evaluated preoperative nutritional supplementation of any form such as IN, protein supplementation, or carbohydrate-rich drinks to gain an understanding of all potential supplementation strategies being trialled in this group with an acknowledgement that some interventions are likely to have too few studies to facilitate meta-analysis. Studies examining nutrition delivery modes of oral intake, nasojejunal feeding and jejunostomy feeding were included, if the chosen modality was applied to both intervention and comparator group. Parenteral nutrition delivery mode was excluded as this is not recommended preoperatively and carries specific risks associated with the intravenous line that could confound outcomes such as infections.[93] Studies or patient groups/arms were also excluded if the postoperative nutrition differed between groups in order to isolate the effectiveness of preoperative nutritional supplementation alone. Studies with interventions of less that 48 hours preoperatively were excluded to ensure sufficient duration of effectiveness. Finally, studies with multimodal interventions such as combining nutritional supplements with exercise or as part of ERAS protocols were excluded to allow conclusions to be drawn about nutritional intervention alone.

2.3.3 Comparator

This review considered as a comparator the usual preoperative diet at the centre/hospital where the study was conducted or standard diet or control solutions. Furthermore, different forms of nutritional supplementation were planned to be compared to each other and control, however this was not possible given limited study numbers of nutritional interventions other than IN.

2.3.4 Outcomes

This review considered studies with a minimum of one pre-specified outcome. Primary outcome measures were infectious complications, mortality, hospital length of stay (LOS), delayed gastric emptying (DGE), pancreatic fistula, weight loss and serum albumin levels. Secondary outcome measures included anastomotic leak, haemorrhage, body mass

index (BMI), lymphocyte count and nutrition risk index (NRI) score (see table 2 for further information and definitions). Where specific outcomes were not reported, authors were contacted to establish if raw data was available.

Table 2: Outcome measures and their definition

Outcome measure	**Definition**
Infections complications	
Wound infection	Pus or surrounding cellulitis where wound opening is required
Intra-abdominal abscess	Evident by a collection treated by drainage with a positive bacterial culture or antibiotics
Sepsis	Presence of typical clinical signs associated with positive bacterial blood culture
Pneumonia	Fever combined with chest x-ray changes
Hospital LOS	Based on day of operation equated to day zero. Mortalities up to postoperative day (POD 90) were included
Delayed gastric emptying	Defined according to the International Study Group of Pancreatic Surgery (ISGPS) as the inability to return to normal diet by the end of the first postoperative week.[31]
Pancreatic fistula	Defined according to ISGPC as leakage of pancreas derived fluid from raw pancreatic surface or failure of healing/sealing of the pancreaticojejunostomy anastomosis.[33]
Gastrojejunostomy anastomotic leak	Leakage confirmed during relaparotomy or radiological presence of peri-anastomotic air, fluid or extravasation of contrast.[37]
Hepaticojejunostomy anastomotic leak	Leakage confirmed during relaparotomy, bile rich drainage, or bilious abdominal drainage confirmed by imaging with a contrast study through an abdominal drain or cholangiogram.[36]
Post PD haemorrhage	Defined according to ISGPS by three factors of onset (less than versus greater than 24 hours), location (intraluminal or extraluminal) and severity (mild or severe). These factors and clinical impact categorise haemorrhage as either grade A, B or C, where C is the most severe and all categories were included in this review.[40]
Body weight and BMI	Data was extracted from six weeks prior to operation, prior to nutritional interventions, day before surgery POD 7 and POD 30.

Outcome measure	Definition
Serum albumin and lymphocyte levels	Extracted prior to nutritional intervention, day before surgery, POD 1 and POD 7.
Nutrition risk index	scores where the formula (1.519 x albumin in g/L + 0.417 x current weight/usual weight) was used will be extracted, or calculated from raw data, where possible, for before and after nutritional intervention.[63]

2.3.5 Types of studies

This review considered for inclusion quantitative studies including experimental and quasi-experimental studies. Parallel group and cluster RCTs, nonequivalent control group posttest only studies, nonequivalent control group pretest-posttest studies and control time-series studies were considered for inclusion, regardless of the number of RCTs identified. This was to allow for the possibility of limited availability of RCTs in combination with ensuring thorough exploration of available experimental studies to facilitate understanding of the topic area. This combination of types of studies was also chosen to ensure future primary research suggestions are well informed.

2.4 Review methods

2.4.1 Search strategy

The search strategy used in this review aimed to identify both published and unpublished studies. A three-step approach was undertaken. First, an initial limited search of MEDLINE (via PubMed) was undertaken to identify articles on the topic. The text words contained in titles and abstracts of relevant articles, and index terms were used to develop a full search strategy for MEDLINE on the 7th of May 2020. Second, the search strategy was adapted for each included information source and a search of all included databases was undertaken on the 11th of February 2021. The full search strategies are provided in Appendix I. Thirdly, the reference lists of all systematic reviews of a similar topic found in the search, and studies meeting inclusion criteria was screened for additional articles.

2.4.2 Information sources

Information sources included electronic databases, trial registers and direct contact with authors. Databases were searched form inception to the 11th of February 2021. Studies published in any language were included. The databases that were searched included

MEDLINE (via PubMed), CINAHL (via EBSCO), Scopus (via Elsevier) and the Cochrane Library. Sources of grey literature included Cochrane Controlled Register of Trials (CENTRAL), World Health Organisation International Clinical Trials Registry Platform and Australian Cancer Trials.

2.4.3 Study selection

Following the search, all identified citations were collated and exported to EndNote X9.3.2 (Clarivate Analytics, PA, USA) and duplicates were removed. Next, the author screened the titles and abstracts against inclusion criteria or when no abstract was available, the full text was screened. Next, full texts of potentially relevant studies were retrieved, with citation details imported into JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia). Full texts were then explored in detail against inclusion and exclusion criteria by the author, with all uncertainties discussed with a second reviewer. Full text studies that did not meet the inclusion criteria were excluded, with reasons provided in Appendix II.

2.4.4 Assessment of methodological quality/critical appraisal

Eligible studies were critically appraised by two independent reviewers using standardised critical appraisal instruments from JBI.[77] Discrepancies that arose between the reviewers were resolved through discussion. All studies underwent data extraction and synthesis where possible, regardless of methodological quality scores. As this systematic review was part of the Master of Clinical Science for the author, a second reviewer was only used for the critical appraisal component. Outcome of the critical appraisal is discussed in the results section.

2.4.5 Data extraction

Data was extracted from included studies by the author using the standardised JBI extraction tool in JBI SUMARI.[77] Extracted data from each study included specific details about participant characteristic, specific details about the intervention used, outcomes measured and results. Missing or additional data was requested of the study author, where required.

2.4.6 Data synthesis

Characteristics of included studies is presented narratively and in table format in the results and appendix. Randomised controlled trials and quasi-experimental studies evaluating preoperative immunonutrition compared with control were able to be pooled in statistical meta-analysis using RevMan V5.4.1 (Copenhagen, The Nordic Cochrane Centre, Cochrane). A statistician was consulted to assist with the meta-analysis component of this review.

The choice of model and method for meta-analysis was based on guidance by Tufanaru et al,[94] which outlines an inclusive approach of all RCTs and quasi-experimental studies regardless of their risk of bias. A random effects model was used when five or more studies were included in meta-analysis of an outcome and a fixed effect model when less than five.[94] Where statistical pooling was not possible due to clinical or methodological heterogeneity, findings are presented in narrative form including tables. All outcomes that allowed meta-analysis were dichotomous and risk ratios are reported with 95% confidence intervals. Where possible, analysis is based on intention to treat.

Clinical and methodological heterogeneity is assessed by descriptively comparing trial and participant characteristics between the studies. The I^2 statistic was used to quantify heterogeneity with values greater than 50% considered to have substantial heterogeneity.

Subgroup analysis was performed to compare overall infectious complications for well-nourished patients receiving IN compared to control where well-nourished was defined as presence of one or more of the following: less than 10% weight loss within six months, BMI >18.5, serum albumin >30g/L or NRI score >83.5. Given low statistical heterogeneity was identified across the meta-analysis, sensitivity analysis was not performed.

2.4.7 Assessing certainty in the findings

Grading the certainty of evidence was performed by the author using the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation).[95] A Summary of Findings (SoF) was created using GRADEpro GDT (McMaster University, ON, Canada). The SoF presents information on absolute risks for treatment and control and risk ratios for dichotomous outcomes. The reported outcomes are overall infectious complications, wound infections, DGE, pancreatic fistula and mortality.

Furthermore the SoF presents a ranking of the quality of the evidence for each outcome based on risk of bias, indirectness, inconsistency, imprecision and risk of publication bias. Risk of bias may be impacted by factors such as lack of concealed allocation, lack of blinding, not adhering to intention to treat principles or failing to account for loss to follow up.[95] Grading indirectness is based on degree of confidence the results are from direct evidence for the prespecified population, intervention and outcome measures; while inconsistency involves analysing the degree of heterogeneity across included studies.[95]

Imprecision is determined through factors such as whether the boundaries of the confidence interval are on the same side of the forest plot and if the optimal information size is met.[95] Finally, risk of publication bias is determined by analysing if effect estimates could have been influenced by factors such as publishing positive findings early or if studies with negative findings were published.[95] From analysis of each of these factors which reflect the quality of the body of evidence, the outcome measure if given one of four grades; high: there is confidence that the true effect lies close to the effect estimate; Moderate: the true effect is likely to be close to the effect estimate but it is possible they are substantially different; Low: where there is limited confidence in the effect estimate and it may be substantially different from the true effect; very low: where there is very little confidence in the effect estimate and it is likely to be substantially different from the true effect.[95]

Chapter 3: Results

3.1 Introduction

This chapter first describes the results of the search strategy undertaken, followed by the outcome of assessing each included studies methodological quality. Further characteristics of included studies is then presented including geographical location; year of publication; along with study participants, interventions and outcome measures. Next, the review findings from the meta-analysis are detailed, with narrative description of study results that were unable to be pooled in meta-analysis. Finally, the summary of findings table is presented and described.

3.2 Study identification and inclusion

The database study search identified 5794 records, and after duplicates were removed, 4688 studies were screened by title and abstract (see Appendix I). Search of trial registers generated 4872 records, all of which were screened by title and abstract (see Appendix I). A further nine studies were identified through citation searching from the reference lists of identified studies. There were 47 studies identified for full text retrieval, with 38 being from the database search, nine from citation search and zero from the trial register search. Thirty of these were excluded, leaving 17 studies for inclusion in the review (Fig 5). The reason for exclusion of full-texts retrieved is presented in Figure 5 and Appendix II. The final 17 articles were eligible for data extraction. [87, 88, 96-109]

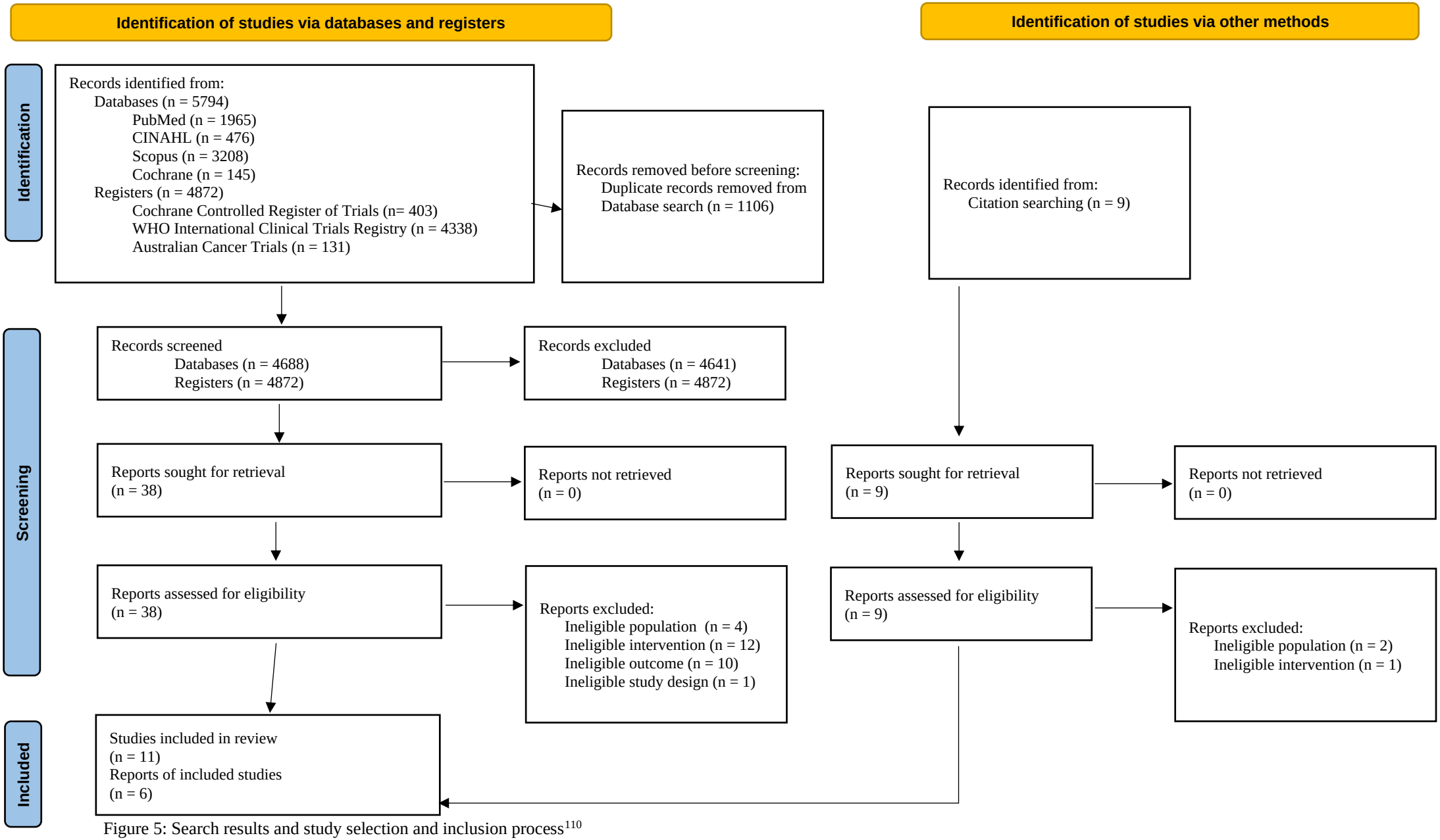

Figure 5: Search results and study selection and inclusion process[110]

3.3 Methodological quality

All 17 of the included studies were conducted using an experimental design, with 15 being RCTs and two studies being quasi experimental design. All RCTs except one[106] scored over 50% in total for methodological quality, although no studies adequately described all the details required. The key area of weakness across the studies was blinding with only three studies clearly describing blinding of participants and those delivering the nutritional intervention,[88, 105, 111] while two studies blinded only outcome assessors.[99, 104] Discussion between the reviewers arose regarding blinding of participant and those delivering the treatment given lack of explicit statements in some studies regarding blinding. The reviewers concluded that if there was no use of a placebo or control solution then it would be obvious to participants and those delivering the intervention they were not in the intervention group and lack of blinding could therefore be assumed.

The RCTs were of variable quality regarding descriptions of the randomisation process, potentially allowing some bias (see Table 3, with studies in bold included in meta-analysis). Eight studies were unclear regarding the randomisation procedure used such as computer-generated list of random numbers.[87, 88, 98, 102, 105-107, 111] For example, the study by Aida et al[98] stated randomisation was through 'numbered, sealed envelopes', but it was unclear the procedure used to generate the numbers. Concealed allocation through use of sealed envelopes was described in eight RCTs,[98, 100-102, 105, 109, 111, 112] the rest being unclear.

Baseline characteristics were similar between groups across the studies except one study with a gender imbalance between groups.[109] One study was classified as unclear following discussion between authors, as the intervention group had more patients with benign pancreatic tumours (n 8/19) compared to the control group (n 3/16) although this did not reach statistical significance ($p = 0.167$).[112] This could have biased results given cancer patients are proposed to benefit more from nutritional supplementation, given the catabolic state.[113] Experimental groups were treated similar other than the intervention of interest with clear description of the surgical process and technique. However, the studies by Gade et al[112] and Ashida et al[88] were unclear given there was no description of the postoperative care patients received. Both studies clearly described a focus on preoperative intervention and therefore an assumption could be made that postoperative care was the same for both groups, however this is a source of potential bias. MacFie et al[106] was also categorised as unclear for question seven, given patients were rerandomised postoperatively.

Follow up was generally complete across the RCTs with CONSORT statements presented and explanations for loss to follow up. The study by Tumas et al[101] did not present data for all patients on several outcomes with no explanation of reasoning. Participants were mostly analysed in the groups they were randomised except for one study where participant numbers differed in results without explanation.[101] Outcomes were measured in the same way for intervention and control groups across all studies. Differences in scoring arose between reviewers regarding if outcome measures were measured in a reliable way in two studies.[101, 111] Through discussion, the two reviewers concluded that if definitions of all outcome measures were not presented, the article would be scored as unclear for this question. One study scored no for this question for including pancreatic fistula as an infectious complication potentially affecting results,[88] while all other studies analysed it separate from infectious complications. Analysis was overall appropriate and using intention to treat. One study used a different study design where participants were randomised to a nutritional intervention preoperatively and then rerandomised to a nutritional intervention again postoperatively.[106]

Table 3: Critical appraisal results of eligible Randomised Controlled Trials

Citation	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Total (%)**
Aida et al. 2014[98]	U	Y	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	69
Ashida et al. 2019[88]	U	U	Y	Y	Y	U	U	Y	Y	Y	N	Y	Y	62
Barker et al. 2013[109]	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	62
Braga et al. 2002[99]	Y	U	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	77
Gade et al. 2016[112]	Y	Y	U	N	N	N	U	Y	Y	Y	Y	Y	Y	62
Gianotti et al. 2002[104]	Y	U	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	77
Giger et al. 2007[100]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	85

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total (%)
Giger-Pabst et al. 2013[111]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	85
Hübner et al. 2012[105]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	92
MacFie et al. 2000[106]	U	U	Y	N	N	N	U	Y	U	Y	Y	Y	N	38
Nakamura et al. 2005[107]	U	U	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	62
Suzuki et al. 2010[102]	U	Y	Y	N	U	U	Y	U	Y	Y	Y	Y	Y	62
Tumas et al 2020[87]	U	U	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	62
Tumas et al. 2020[101]	Y	Y	Y	U	U	U	Y	N	N	Y	U	Y	Y	54
Yokoyama et al. 2016[103]	Y	U	Y	N	N	N	Y	U	U	Y	Y	Y	Y	54
%	47	53	87	20	20	33	80	80	80	100	80	100	93	

Studies in **bold** are included in meta-analysis. Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for randomised controlled trials: Q1 = Was true randomisation used for assignment of participants to treatment groups? Q2 = Was allocation to treatment groups concealed? Q3 = Were treatment groups similar at baseline? Q4 = Were participants blind to treatment assignment? Q5 = Were those delivering treatment blind to treatment assignment? Q6 = Were outcome assessors blind to treatment assignment? Q7 = Were treatment groups treated identically other than the intervention of interest? Q8 = Was follow-up complete, and if not, were strategies to address incomplete follow-up utilised? Q9 = Were participants analysed in the groups to which they were randomised? Q10 = Were outcomes measured in the same way for treatment groups? Q11 = Were outcomes measured in a reliable way? Q12 = Was appropriate statistical analysis used? Q13 = Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?

The two quasi-experimental studies both scored an overall total of 78% for methodological quality (see Table 4, with studies in bold included in meta-analysis). A key area of weakness was question six related to loss to follow up which could lead to over-estimation of effect. Shirikawa et al[96] analysed data for 18 of the 25 enrolled patients with

reasons for drop out described and Silvestri et al[97] analysed 48 of 54 patients enrolled in the treatment group with no clear description of reasons for drop out. Neither study included outcomes that were specifically before and after the nutritional intervention, although the reviewers concluded the clinical postoperative outcomes presented were arguably the most important.

Table 4: Critical appraisal results of eligible quasi-experimental studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total (%)
Shirakawa et al. 2012.[96]	Y	Y	Y	Y	U	N	Y	Y	Y	78
Silvestri et al. 2016.[97]	Y	Y	Y	Y	U	N	Y	Y	Y	78
%	100	100	100	100	0	0	100	100	100	

Studies in **bold** included in meta-analysis. Y = Yes, N = No, U = Unclear; JBI critical appraisal checklist for quasi-experimental studies: Q1 = Is it clear in the study what is the 'cause' and what is the 'effect' (i.e., there is no confusion about which variable comes first)? Q2 = Were the participants included in any comparisons similar? Q3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q4 = Was there a control group? Q5 = Were there multiple measurements of the outcome both pre and post the intervention/exposure? Q6 = Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed? Q7 = Were the outcomes of participants included in any comparisons measured in the same way? Q8 = Were outcomes measured in a reliable way? Q9 = Was appropriate statistical analysis used?

3.4 Characteristics of included studies

Characteristics of included studies are presented in Appendix III and described in further detail below.

3.4.1 Geographical location

Six included studies were conducted in Japan,[88, 96, 98, 102, 103, 107] nine in Europe,[87, 97, 99-101, 104-106, 111, 112,] and one in Australia[109] (see Fig 6 for geographical distribution of included studies). Geographical location of included studies is likely to influence patients' preoperative diet and nutrition. One component of IN is fatty acids where there is considerable worldwide variation in daily intake with typical diets in Japan and Denmark much higher in fatty acids compared to other parts of Europe.[114, 115] Furthermore, BMI has geographical variation with obese patients being more likely to get wound infections after open surgery.[116] Of the studies that included participants of any nutritional status, there was variation in average baseline BMI of participants from 19 in one Japanese based study[107] to

26.9 in the Lithuanian study[87] and 26.5 in the Australian study.[109] Two studies did not report baseline BMI of participants.[99, 102]

Figure 6: Geographical location of included studies. Each red dot represents an individual study included in this review.

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3.4.2 Year of publication

Publication year of included studies ranged from 2000 to 2020, with more studies published in the last ten years (Fig 7). This has implications for our review given advancements in surgical techniques and perioperative care during this time can influence complication rates. For example, the older study by Nakamura et al 2005[107] used total parenteral nutrition (TPN) for nutrition postoperatively, where early oral feeding is now recommended as standard care postoperatively.[53]

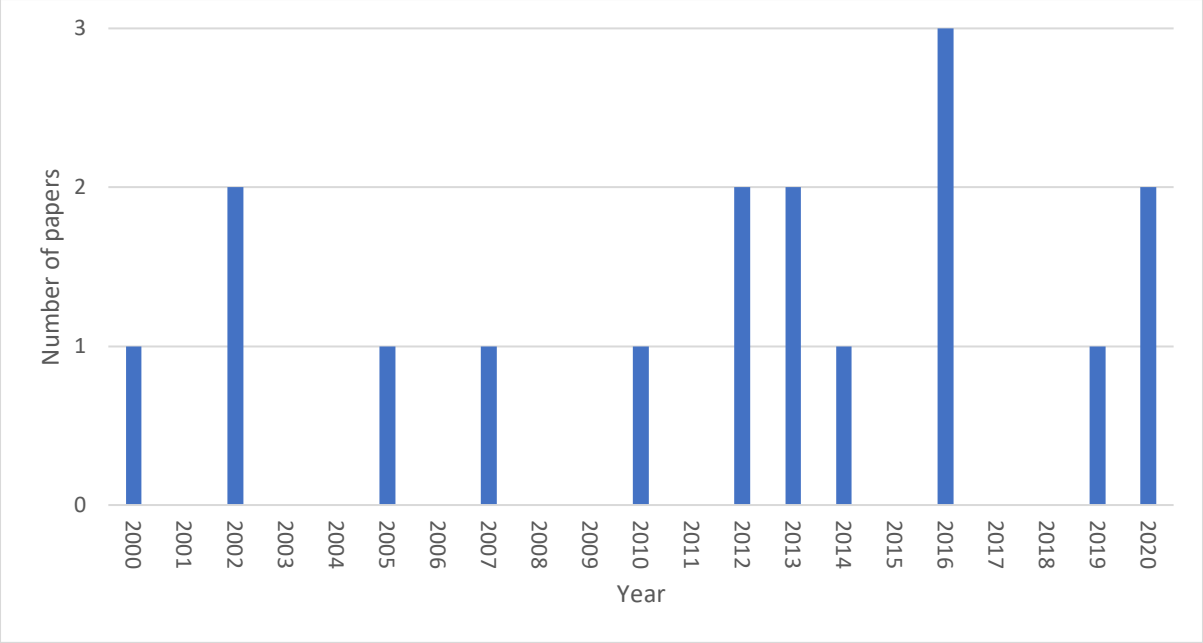

Figure 7: Graph showing year of publication of included studies.

3.4.3 Study Participants

The average participant age across all studies was in the 60s. Participant characteristics varied across studies with nine including patients only undergoing PD.[87, 88, 96-98, 101-103, 112] The other eight studies included patients undergoing PD as part of broader patient cohorts, with six studies including all patients undergoing GIT surgery[99, 104-106, 109, 111], one study including patients undergoing surgery for stomach and pancreatic cancer[100] and one study with patients undergoing surgery for stomach, pancreatic and oesophageal cancer.[107] Only PD patients were included in meta-analysis.

Cancer status also varied slightly across inclusion criteria in the studies. Of the eight studies with patients included in meta-analysis, three studies included patients with resectable pancreatic cancer for PD.[87, 88, 112] Aida et al[98] described 9/50 patients' diagnosis as 'other' and Suzuki et al 4/30,[102] in relation to the pancreas where all other included patients had cancer. Gianotti et al[104] included patients with 'neoplasms' and Shirikawa et al[96] describes curative PD for a 'lesion'. Silvestri et al[97] had 7/55 patients undergoing PD for benign disease. Studies included patients with varied pre-intervention nutritional status except three studies where all patients were well nourished[97, 104, 111] and two studies where all patients had poor nutritional status.[99, 105] Participant exclusion criteria varied slightly, where importantly three studies excluded patients with diabetes,[96, 100, 107] one study excluded those with insulin dependent

diabetes mellites[100] and one study excluded those with uncontrolled diabetes.[106] Of the studies included in meta-analysis only Shirikawa et al[96] excluded patients with diabetes.

3.4.4 Study interventions

In all studies, the nutritional intervention was oral IN except one which studied oral synbiotics for seven days preoperatively[103] and another which studied the dietary supplement Fortisip[106]. The duration of preoperative IN was three days in one study[111], five days in 11 studies,[87, 96-98, 100-102, 104, 105, 107, 109] seven days in three studies,[88, 99, 112] and one study had both a five day and two day group[100] (see appendix III for in-depth description of each studies nutritional intervention). In the majority of studies, the control group were instructed to have a normal diet preoperatively except those where patients were blinded with studies using an oral control solution of isocaloric isonitrogenous standard nutrition.[88, 105, 111] Various postoperative nutrition delivery modes were used across the studies with six studies not giving a clear description,[87, 88, 96, 101, 109, 112] three studies resuming oral intake as tolerated,[105, 106, 111] three studies using catheter jejunostomies,[98, 100, 103] one study using enteral nutrition via either a catheter jejunonstomy or a nasojejunal tube,[99] two studies using TPN,[97, 107] one study with either catheter jejunostomy or TPN depending on group allocation and another with either oral or enteral nutrition depending on group allocation.[104]

3.4.5 Outcomes measures

A wide range of outcome measures were used across the studies including serum markers related to immunity, inflammation, and nutrition; clinical complications; clinical nutrition status; questionnaires; and microorganisms present in mesenteric lymph nodes. The primary outcome measure was overall complications in three studies,[99, 105, 111] infectious complications in one study;[98] unclear in six studies;[87, 96, 97, 101, 102, 107] and hospital LOS in one study.[109] The study by Gianotti et al[104] used postoperative infection rate and hospital LOS as their primary outcome measures; while Gade et al[112] differed slightly with overall postoperative complications and hospital LOS. Giger et al's[100] primary outcome measure was serum c-reactive protein levels; Yokoyama et al[103] looked at detection of bacteria in mesenteric lymph nodes; Ashida et al[88] used serum concentrations of interleukin 6; and MacFie et al[106] looked at maintenance of preoperative weight. All studies with only PD patients included outcomes specific to complications of PD such as pancreatic fistula. Of the 17 studies, eight included an outcome measure pre and post nutrition intervention.[87, 88, 98, 100, 101, 106, 107, 112]

3.5 Review findings

Data for meta-analysis was able to be extracted from eight studies on preoperative IN supplementation before PD, including six RCTs and two quasi-experimental studies with remaining studies presented narratively. Two studies reported on the same patients, and data was therefore included once in meta-analysis.[87, 101] One additional study had a broader participant cohort but data specifically for PD patients was obtained from contact with authors and therefore included in meta-analysis.[104] In all forest plots the experimental group represents preoperative IN, with effect size reported as risk ratios and heterogeneity explored using the I^2 statistic.

3.5.1 Primary outcome measures

3.5.1.1 Overall infectious complications

All studies reported infectious complications. Data on the number of patients undergoing PD who received preoperative IN and experienced a postoperative infectious complication was extracted from six studies and included a total of 269 patients.[88, 96-98, 102, 104] Length of follow up for infectious complications in these six studies was 30 days postoperatively in one study,[98]14 days in one study,[88] 30 after discharge in one study,[104] and unclear in three studies.[63, 97, 102] Pooled results demonstrate that IN decreases the risk of postoperative infectious complications by 58% compared to control, which reached statistical significance (RR 0.42; 95% CI 0.28, 0.63; P = <0.0001; I^2 =0%; Figure 8).

In studies including only PD patients but not included in meta-analysis, one reported individual infectious complications where patients could be included more than once and found that when including each patient's most serious complication there was no difference between groups for infections,[112] two studies focused on severity of complications finding significantly less severe complications for the IN group,[87, 101] and the final study looked at preoperative synbiotics where no difference was found between groups for infectious complications (n=9/22 synbiotics vs 8/22 control; P = 0.757). The remaining six studies included patients having other major GIT operations receiving preoperative IN where data for PD could not be isolated, with three studies reporting less patients with infectious complications in the intervention group,[99, 100, 111] and three studies with no difference.[105, 107, 109] The final study provided no breakdown of complications.[106]

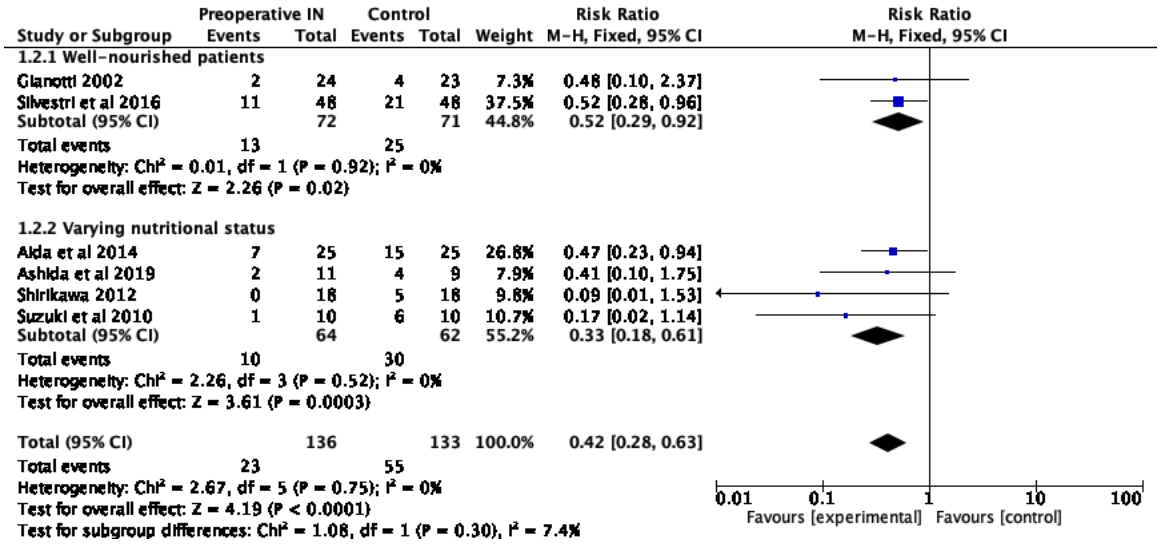

Figure 8: Comparison of preoperative IN vs control for patients undergoing PD on postoperative infectious complications, including subgroup analysis of well-nourished patients and those with varying nutritional status

3.5.1.1.1 Subgroup analysis (overall infectious complications for well-nourished patients)

Findings of two studies including all well-nourished patients, with a total of 143 patients, were pooled for infectious complications with results showing that IN decreases the risk by 48% compared to control, which reached statistical significance (RR 0.52; 95% CI 0.29, 0.92; P = 0.02; I^2 = 0%; Figure 8).[97, 104] One other study included only well-nourished patients, finding no difference between groups, however data on just PD patients was unavailable.[111] Braga et al[99] included only malnourished patients and found less infectious complications in the IN group, while Hubner et al[105] also included only patients at nutritional risk but found no difference between groups. The study by Barker et al[109] performed subgroup analysis of outcomes for well-nourished compared to malnourished patients and found that malnourished patients in the intervention group had shorter hospital LOS, less overall infectious complications and wound infections but all failed to reach statistical significance. The two studies by Tumas et al[87, 101] included only PD patients and compared severity of complications between well-nourished and malnourished patients in the IN group and found no difference.

3.5.1.1.2 Subgroup analysis (overall infectious complications for patients of varying nutritional status)

Results of four studies, with a total of 126 patients, included patients of varying nutritional status and were pooled for infectious complications with results showing IN

reduces the risk of by 67% compared to control, which was statistically significant (RR 0.33; 95% CI 0.18, 0.61; P = 0.0003; I^2 = 0%; Figure 8).[88, 96, 98, 102] All four studies recruited patients regardless of their nutritional status. The minority of patients in the studies by Aida et al[98] and Ashida et al[88]were possibly malnourished, with 4/25 and 5/20 patients respectively, having more than ten per cent weight loss preoperatively. Shirakawa et al[96] and Suzuki et al[102] provided no data on patients' nutritional risk.

3.5.1.2 Wound infections

Findings of seven studies, with a total of 296 patients, were pooled for meta-analysis of postoperative wound infections with results demonstrating preoperative IN decreases the risk by 61% compared to control which was statistically significant (RR 0.39; 95% CI 0.2, 0.75; P = 0.005; I^2 = 0%; Figure 9). Definition of wound infection across these seven studies varied with two studies requiring purulent discharge and a bacterial culture,[96, 98] and two using the definition provided by guidelines from the Centers for Disease Control and Prevention (CDC).[88, 97] Gade et al[112] defined wound infection as leakage from the wound, while Gianotti et al[104] described redness or tenderness with discharge of pus. Suzuki et al[102] did not provide a clear definition. Wound dehiscience was included as a separate category in two studies.[104, 112]

Four studies where the PD patients could not be isolated, found less wound infections in the experimental IN group compared to control.[99, 105, 107, 111] The study looking at preoperative synbiotics found more patients developed wound infections in the experimental group compared to control (3/48 vs 2/48).[103] Four studies presented no specific results on wound infections.[87, 100, 101, 106]

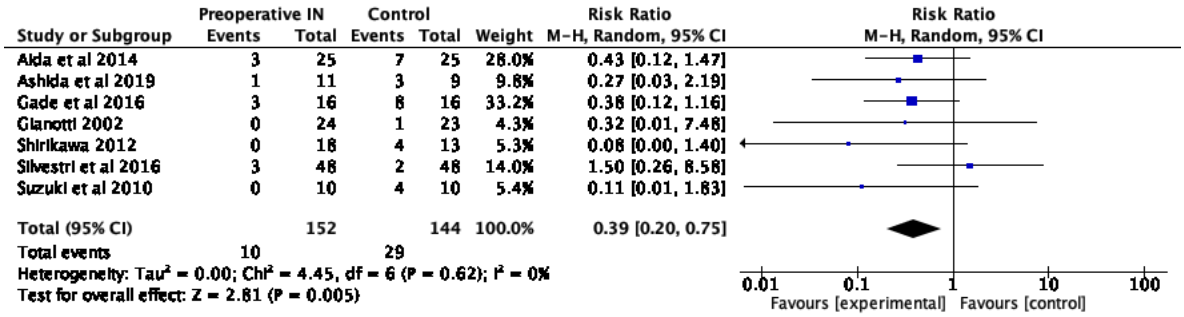

Figure 9: Comparison of preoperative IN vs control for patients undergoing PD on postoperative wound infections

3.5.1.3 Intrabdominal abscess

Seven studies reported on postoperative intrabdominal abscess in PD patients, with two studies finding no events in either experimental or control groups in a total of 56 patients,[88, 96] leaving five study results with a total of 248 patients to be pooled for meta-analysis.[97, 98, 102, 104, 112] Pooled results showed 49% less risk of intrabdominal abscess in the preoperative IN group compared to control which reached statistical significance (RR 0.51; CI 0.29, 0.92; P = 0.02; I^2 = 0%; Figure 10). Of the remaining studies, Giger-Pabst et al[111] found less patients developed intrabdominal abscess in the experimental preoperative IN groups (1/55) compared to control (2/53); as did Hubner et al[105] (4/73 vs (5/72); while Nakamura et al[107] had no events (0/12 vs 0/14), however PD patients data could not be isolated from these studies. The study by Yokoyama et al[103] looking at preoperative synbiotics found no difference between groups (2/22 vs 2/22). Six studies had no specific data for intrabdominal abscess complications.[87, 99-101, 106, 109]

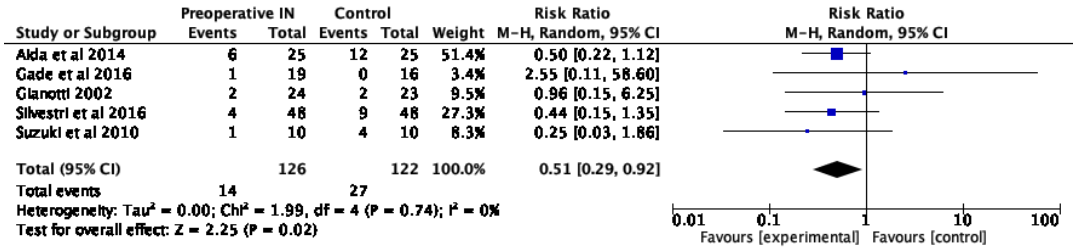

Figure 10: Comparison of preoperative IN vs control for patients undergoing PD on postoperative intrabdominal abscess

3.5.1.4 Sepsis

Results of four studies were pooled for meta-analysis of postoperative sepsis. In one study including 20 patients, no patients developed sepsis. In the other three studies with a total of 193 patients, IN was found to decrease the risk of sepsis by 67% compared to control, however this did not reach statistical significance (RR 0.33; 95% CI 0.005, 2.04;P = 0.23; I^2 = 0%; Figure 11). Two other studies presented sepsis data, but patients who underwent PD could not be isolated; with Giger-Pabst et al[111] and Hubner et al[105] finding more patients in the experimental preoperative IN group developed sepsis compared to control (1/55 vs 0/53; 2/73 vs 0/72). The study comparing preoperative Fortisip supplementation found more patients developed postoperative sepsis (6/24) compared to control (2/25).[106] Nine studies presented no specific data on sepsis.[87, 96, 99-103, 107, 109] Results in Gade et al[112] were unclear as numbers for sepsis and septic shock presented, with patients able to be included more than once.

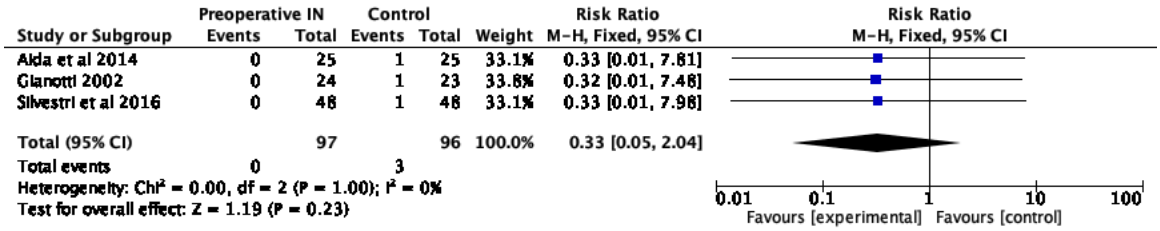

Figure 11: Comparison of preoperative IN vs control for patients undergoing PD on postoperative sepsis

3.5.1.4 Pneumonia

Seven studies reported on postoperative pneumonia in patients undergoing PD, with four studies and a total of 123 patients finding no events in experimental or control groups.[88, 96, 102, 104] Suzuki et al[102] stated they were collecting data on postoperative pneumonia, while Shirikawa et al[96] stated they were collecting data on all postoperative infections and therefore an assumption was made there were no incidences of pneumonia given none were presented in results. This left three studies with a total of 181 patients to be pooled for meta-analysis.[97, 98, 112] Although results showed preoperative IN reduced the risk of pneumonia by 61% compared to control, this did not reach statistical significance (RR 0.4; CI 0.10, 1.62; P = 0.20; I^2 = 12%; Figure 12). Of the remaining studies where PD patient data could not be isolated, two found less patients in the experimental group developed pneumonia compared to control,[99, 111] one found more patients in the experimental group,[105] and the other had no events in either group.[107] Yokoyama et al's[103] study on synbiotics found no difference between groups (1/22 vs 1/22) and all other studies presented no specific pneumonia data.[87, 100, 101, 106, 109]

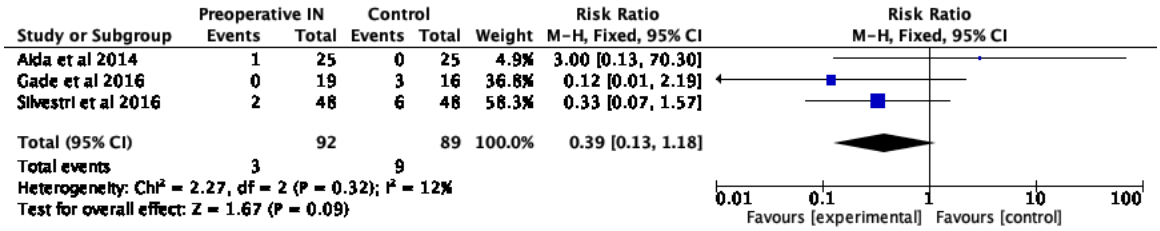

Figure 12: Comparison of preoperative IN vs control for patients undergoing PD on postoperative pneumonia

3.5.1.5 Mortality

All studies presented data on mortality. The protocol for this systematic review stated mortalities up to postoperative day 90 would be included, however included studies had

variable follow up duration. Three studies reported mortality up to postoperative day 30,[105, 111, 112] five studies up to 30 days post discharge,[87, 99, 101, 104, 109] one study up to 7 days postoperatively,[107] and eight studies were unclear regarding the duration.[88, 96-98, 100, 102, 103, 106] The articles by Tumas et al[87, 101] reported severity of complications using the Clavien-Dindo Classification. Mortality data was able to be extracted given Clavien Dindo grade five complications equate to death of a patient.

Of the studies where PD patient data could be extracted, four studies had no events in experimental or control groups.[88, 96, 98, 102] Results of four studies were therefore pooled for meta-analysis [87, 97, 104, 112] as data from the two studies by Tumas et al[87, 101] was included only once. Results suggested preoperative IN may reduce the risk of postoperative mortality by 20% compared to control however, this was not statistically significant (RR 0.78; CI 0.17, 3.57; P = 0.75; I^2 = 0%; Figure 13).

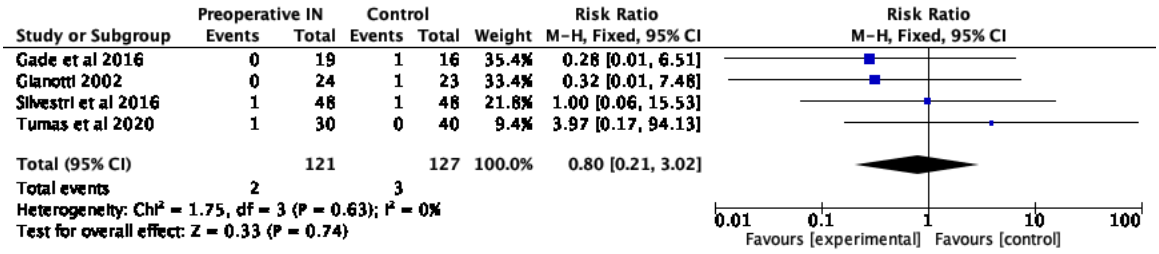

Figure 13: Comparison of preoperative IN vs control for patients undergoing PD on postoperative mortality

Results from remaining studies are presented narratively in Table 5 and could not be pooled as data on PD patients could not be isolated or the nutritional intervention differed. Two of these studies had more patient deaths in the control group,[99, 109] three studies had more deaths in the experimental group,[103, 105, 111] one study had one death in both experimental and control group,[106] and one study had no deaths in either group.[107] Within each study included in the narrative table, results reported no statistically significant difference in between groups for mortality.

Table 5: Comparison of postoperative mortality between experimental and control groups by study

Study	Experimental group	Control group
Braga et al[99]	1/50	2/50
Barker et al[109]	0/46	1/49
Giger-Pabst et al[111]	2/55	1/53
Hubner et al[105]	4/73	2/72
MacFie et al[106]	1/24	1/25
Nakamura et al[107]	0/12	0/14
Yokoyama et al[103]	1/22	0/22

3.5.1.6 Hospital LOS

Data on hospital LOS could not be pooled as only 1 study where PD patient data could be isolated presented results as mean number of days.[96] Findings are therefore presented narratively in Table 6. Eight of the studies found hospital LOS was less in the experimental nutritional supplementation group compared to control;[97, 99, 100, 104, 106, 109, 111, 112] three studies found longer hospital LOS in the experimental group,[96, 103, 107] and five studies did not report LOS.[87, 88, 98, 101, 102] One study reported conflicting results for LOS in their text compared to table.[105] There was a wide range in average hospital LOS from 7.1 days[109] to 49 days.[107]

Table 6: Comparison of experimental nutritional supplementation group vs control for patients undergoing major abdominal surgery on postoperative length of hospital stay

Study	Experimental (days)	Control (days)
Barker et al[109]	7.1 (4.1); mean (SD)	8.8 (6.5)
Braga et al[99]	13.2 (3.5); mean (SD)	15.3 (4.1)
Gade et al[112]	11 (6-30); median (range)	16 (8-30)
Gianotti et al[104]	15 (14-20); median (IQR)	16 (14-18)
Giger et al[100]	13.7 (2.3); mean (SD)	23.1 (3.6)
Giger-Pabst et al[111]	12 (4.9); mean (SD)	23.1 (3.6)
MacFie et al[106]	12 (mean)	13
Nakamura et al[107]	49 (18.3); mean (SD)	46.1 (15)
Shirikawa et al[96]	29 (13); mean (SD)	26 (12)

Study	Experimental (days)	Control (days)
Silvestri et al[97]	18.3 (6.8); median (IQR)	21.7
Yokoyama et al[103]	37 (6-103); median (range)	35 (15-19)

SD = standard deviation; IQR = interquartile range

3.5.1.7 Delayed gastric emptying

Four study results were pooled for meta-analysis of postoperative DGE where results showed preoperative IN may increase the risk by two per cent compared to control which was not statistically significant (RR1.02; CI 0.57,1.80; P = 0.95; I^2 = 0%; Figure 14). Of the remaining studies, two with broader patient groups where PD data could not be isolated presented findings with Braga et al[99] and Giger Pabst et al[111] having more events in the experimental group compared to control (3/50 vs 2/50 and 1/55 vs 0/53). The study on synbiotics by Yokoyama et al[103] had less events in the intervention group compared to control.

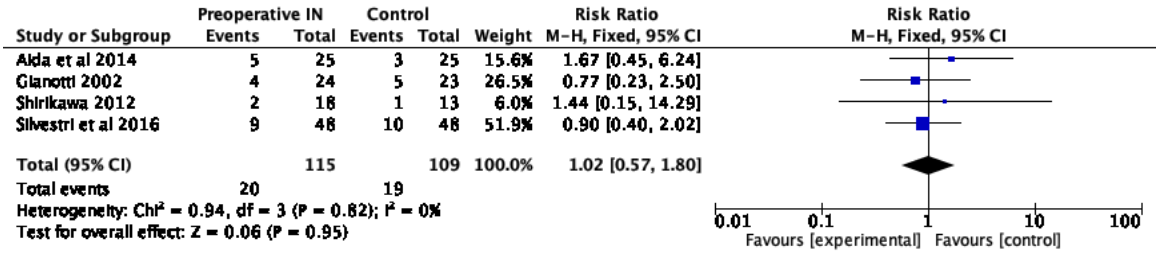

Figure 14: Comparison of preoperative IN vs control for patients undergoing PD on postoperative delayed gastric emptying

3.5.1.8 Pancreatic fistula

Data from eight studies was pooled for meta-analysis of postoperative pancreatic fistula, where results showed preoperative IN may reduce the risk by nine per cent, which was not statistically significant (RR 0.91; CI 0.64, 1.20; P = 0.59; I^2 = 0%; Figure 15).[88, 96-99, 102, 104, 112] In the study by Braga et al[99] pancreatic fistula complications were assumed to be from the patients who underwent PD, given this would not be an expected complication of the other included surgeries. The study by Yokoyama et al[103] on synbiotics found more patients developed pancreatic fistula in the experimental compared to control group (8/22 vs 3/22). Giger Pabst et al[111] found no difference between groups, where data could not be directly attributed to PD patients given inclusion of other surgeries where pancreatic fistula is a possible complication (1/55 vs 1/53). The remaining studies had no specific data on pancreatic fistula.[87, 100, 101, 105-107, 109]

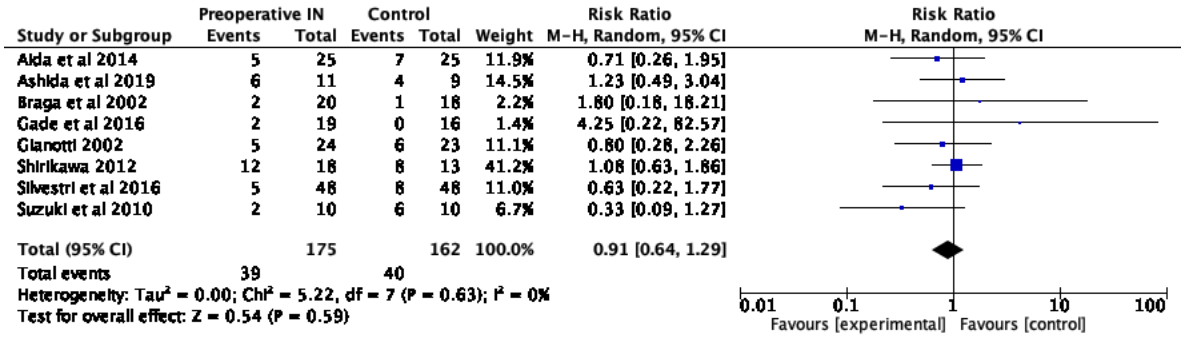

Figure 15: Comparison of preoperative IN vs control for patients undergoing PD on postoperative pancreatic fistula

3.5.1.9 Weight loss

In the systematic review protocol data for this study, the authors stated body weight data would be extracted, however none of the studies presented data at the specified time intervals. The study by Gade et al[112] was specific to PD patients and collected body weight data from baseline to one day before surgery and postoperative day 10, 20 and 30. They found no difference between the preoperative IN group and control at any time point. Median weight loss of more than six percent was identified in both groups at postoperative day 30. MacFie et al[106] included a broader group or surgeries and recorded patient weight at baseline, before surgery, at discharge and four weeks after discharge. The mean weight loss throughout the study period for the group who received preoperative standard ODS was four kilograms compared to three kilograms in the group who received no supplementation. Shirikawa et al[96] recorded bodyweight at baseline and until postoperative day seven and found no difference between preoperative IN and control.

3.5.1.10 Serum albumin levels

In the systematic review protocol data for this study, the authors stated serum albumin levels would be extracted, however none of the studies presented data at the specified time intervals although most presented baseline patient albumin levels. Studies that presented albumin levels at more than one time interval are presented narratively below (those in bold included only PD patients):

- **Aida et al[98]** reported no difference between the preoperative IN group and control for albumin levels throughout the duration of the study (data not presented).
- **Ashida et al[88]** reported albumin levels at baseline, before surgery and postoperative day (POD) 1, 4, 7 and 14 finding no difference between preoperative IN group and control.

- Barker et al[109] collected serum albumin levels where requested by the surgeon (data not presented) throughout the study period and found no significant difference between the preoperative IN group and control.
- Giger et al[100] presented albumin data for baseline and POD 1,3 and 7 however, no comparison was made between the IN and control group.
- **Giger-Pabst et al[111]** collected albumin data for before and after preoperative IN and found no difference between groups.
- MacFie et al[106] collected albumin levels before preoperative intervention, after preoperative intervention, at discharge and four weeks after discharge. Albumin levels increased by 1.8g/L after preoperative supplementation with a standard ODS compared to 0.1g/L for the control group. The difference between first and final measurement for the intervention group was -1.3g/L compared to 1g/L for the control group.
- Nakamura et al[107] presented albumin data for before and after IN, and POD 1,3 and 7 finding no significant difference between groups.
- **Shirikawa et al[96]** presented albumin data for baseline and POD 1,3 and 7 finding no significant difference between the preoperative IN group and control.

3.5.2 Secondary outcome measures

3.5.2.1 Anastomotic leak

Results of three studies were pooled for postoperative anastomotic leak after PD. Results showed the risk was reduced by 56% with use of preoperative IN compared to control but this did not reach statistical significance (RR 0.44; CI 0.17, 1.19; P = 0.11; I^2 =0%; Figure 16). Of the studies where PD patient data could not be isolated Braga et al[99] found less patients had an anastomotic leak in the preoperative IN group (3/50) compared to control (5/50); while Giger Pabst et al[111] and Hubner et al[105] found no difference (1/55 vs 1/53; 2/73 vs 2/72). All other studies had no specific data on anastomotic leak.

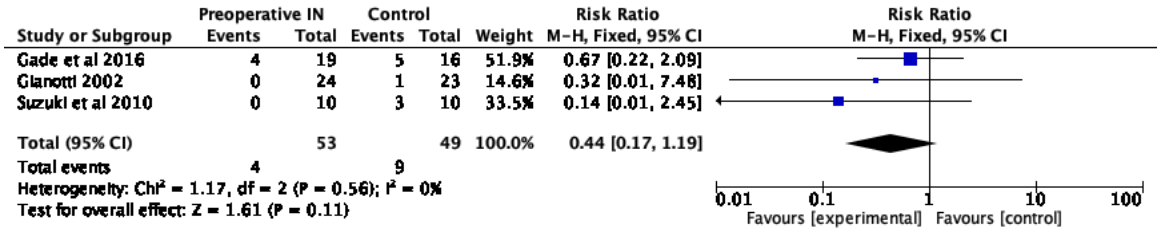

Figure 16: Comparison of preoperative IN vs control for patients undergoing PD on postoperative anastomotic leak

3.5.2.2 Haemorrhage

Four study results were pooled for meta-analysis of postoperative haemorrhage where preoperative IN was found to reduce the risk by 17% compared to control, however this was not statistically significant (RR 0.83; CI 0.31, 2.18; P = 0.70; I^2 = 0%; Figure 17). Of the other studies, three with broader patient groups where PD data could not be isolated, presented findings on postoperative haemorrhage with Braga et al[99] finding less events in the experimental group (0/50 vs 2/50); Hubner et al[105] and Nakamura et al[107] finding no difference (5/73 vs 5/72 and 1/12 vs 1/14).

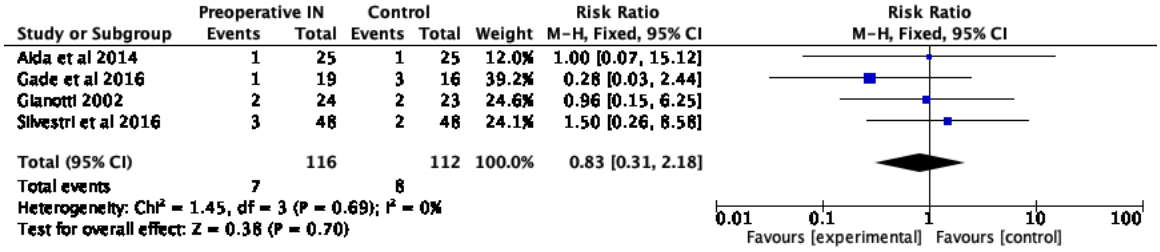

Figure 17: Comparison of preoperative IN vs control for patients undergoing PD on postoperative haemorrhage

3.5.2.3 Lymphocyte count, BMI and NRI

Data on serum lymphocyte number was planned to be extracted for prior to nutritional intervention, day before surgery, POD 1 and 7 however, this was not reported in any included articles. Three studies reported on other factors related to lymphocytes.[88, 98, 102] Aida et al[98] measured indices of lymphocyte stimulation and T helper (Th) 1 / Th2 lymphocyte differentiation prior to IN, before surgery, after surgery and POD 1, 3, 7 and 14 and found statistically significant higher levels of stimulated lymphocyte proliferation at POD 7 in the IN group and higher indicators of T helper 1 differentiation on POD 3. They proposed that IN can mitigate some of the effect of operative stress which changes Th1/Th2 balance towards Th2, therefore downregulating cell-mediated immunity and impairing host defence against pathogens. Suzuki et al[102] also measured indices of lymphocyte proliferation, Th1/Th2 differentiation and Th17 response prior to IN, before surgery, immediately after surgery and POD 1,3,7,14 and 21. They found significantly higher expression of Th1 cells and a shift in ratio towards Th1 on POD 3 and favourable Th17 response on POD 0,1,3 and 7 for the group that received preoperative IN, concluding a reduction in perioperative stress-induced immunosuppression. Finally, Ashida et al[88] measured serum CD4/8 T lymphocyte balance prior to immunonutrition, before surgery and POD 1,4,7 and 14 and found the rise of

CD4/8 lymphocyte balance was significantly higher in the IN group before surgery, however there was no proposed interpretation of this finding in the article.

No studies recorded BMI at multiple time intervals however most reported baseline BMI except two studies. [99, 102]. NRI was not reported in any studies and was unable to be calculated from data within studies.

3.6 Summary of Findings

Summary of Findings (SoF) data was generated for primary outcomes of overall infectious complications, wound infections, DGE, pancreatic fistula and mortality (table 7). The certainty of evidence for overall infectious complications and wound infectious was determined as moderate. These outcomes were downgraded one level for risk of bias posed by pooled studies, due to lack of allocation concealment in the two included quasi-experimental studies and lack of blinding in multiple studies (see explanation section table 7).

Meta-analysis findings for DGE indicated no benefit of IN and the certainty of this finding is low. Reasons for downgrading this outcome included risk of bias, in addition to one level for imprecision. Lack of precision for this outcome was due to optimal information size (OIS) criterion not being met. Based on DGE affecting around 21% of PD patients postoperatively, around 579 patients per group would be required in a single trial to detect a 25% relative risk reduction with 80% power. However, the combined sample size for all studies on DGE was only 224. Pooled results for postoperative pancreatic fistula suggested no significant benefit with use of IN, with certainty of evidence determined as moderate. Downgrading by one level also occurred due to inclusion of quasi-experimental studies and lack of blinding.

Findings for mortality indicated no significant difference with use of IN, with certainty of this finding determined as moderate. A decision was made to not mark down for bias given the definitiveness of death/mortality making it unlikely lack of concealed allocation and blinding within included trials would affect determination of this outcome. Mortality was however downgraded one level for precision due to OIS criterion not being met. Based on postoperative mortality rates being near one percent, a significantly larger sample size would be required to detect any meaningful change with IN. Overall, the certainty of the evidence was moderate, with key areas of concern being lack of concealment

due to inclusion of quasi-experimental studies, lack of blinding in multiple studies and overall sample sizes being too small to detect meaningful change for DGE and mortality.

Table 7: Summary of Findings

Effect of preoperative immunonutrition on postoperative outcomes for patients undergoing pancreaticoduodenectomy for cancer

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control diet	Risk difference with Immunonutrition
Overall Infectious Complications	269 (4 RCTs; 2 quasi-experimental)	⊕⊕⊕◯ Moderate[a]	RR 0.42 (0.28 to 0.63)	414 per 1,000	240 fewer per 1,000 (298 fewer to 153 fewer)
Wound infections	296 (5 RCTs; 2 quasi-experimental)	⊕⊕⊕◯ Moderate[b]	RR 0.39 (0.20 to 0.75)	201 per 1,000	123 fewer per 1,000 (161 fewer to 50 fewer)
Delayed Gastric Emptying	224 (2 RCTs; 2 quasi-experimental)	⊕⊕◯◯ Low [c,d]	RR 1.02 (0.57 to 1.80)	174 per 1,000	3 more per 1,000 (75 fewer to 139 more)
Pancreatic fistula	337 (6 RCTs; 1 quasi-experimental)	⊕⊕⊕◯ Moderate[d]	RR 0.91 (0.64 to 1.29)	247 per 1,000	22 fewer per 1,000 (89 fewer to 72 more)
Mortality	248 (3 RCTs; 1 quasi-experimental)	⊕⊕⊕◯ Moderate[c]	RR 0.80 (0.21 to 3.02)	24 per 1,000	5 fewer per 1,000 (19 fewer to 48 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded level due to: lack of allocation concealment in two quasi-experimental studies (Shirakawa, Silvestri); lack of blinding in five studies (Aida, Gianotti, Shirakawa, Silvestri, Suzuki).
b. Downgraded level due to: lack of allocation concealment in two quasi-experimental studies (Shirakawa, Silvestri); lack of blinding in six studies (Aida, Gade, Gianotti, Shirakawa, Silvestri, Suzuki).
c. Downgraded two levels due to: lack of allocation concealment in two quasi-experimental studies (Shirakawa, Silvestri); lack of blinding in all four studies (Aida, Gianotti, Shirakawa, Silvestri) and optimal information size criterion not met
d. Downgraded one level due to: lack of allocation concealment in two quasi-experimental studies (Shirakawa, Silvestri); lack of blinding in six studies (Aida, Gade, Gianotti, Shirakawa, Silvestri, Suzuki).
e. Downgraded one level due to: optimal information size criterion not met

Chapter 4: Discussion and conclusion

4.1 Introduction

Chapter four critically explores the findings from this review in the context of existing knowledge to facilitate interpretation of the findings. Next, limitations of the evidence included in this review and review process are explored. The thesis is concluded followed by proposal of implications for clinical practice and future research.

4.2 General discussion

The objective of this systematic review was to identify, critique, extract and synthesis the best available evidence for the effectiveness of preoperative nutritional supplementation, such as IN, on postoperative complications such as infections and hospital LOS, for patients undergoing PD for cancer.

The findings from this review support the use of preoperative IN for five to seven days to improve outcomes for patients undergoing PD. Meta-analysis results show IN decreases the risk of overall infectious complications by 58%. Wound infection and intrabdominal abscess risk were also significantly reduced which may translate to decreased hospital LOS, however this data was only explored narratively due to clinical heterogeneity across studies.

No benefit on pancreatic fistula rates was identified. Findings for complications of sepsis, pneumonia, mortality and DGE showed no benefit with IN, but results are limited by small patient numbers. Overall, statistical heterogeneity was low across meta-analysis outcomes meaning the observed benefits of IN are likely more than could be expected from chance alone with consistent overlapping of confidence intervals. Given the specificity of PD and preoperative timing of IN, minimal clinical diversity was facilitated across studies that were pooled for results.

4.2.1 Immunonutrition and connection to the immune system

Immunonutrition formulas were created with specific nutrients including arginine, glutamine, omega three fatty acids and nucleotides which may modulate the immune and inflammatory process.[67] The immune system is a multilayered network to defend the body

against harmful agents. The first layer includes anatomical and physiological barriers such as intact skin, ciliary clearance in the respiratory tract, mucosal membranes, stomach acid and the commensal microbiome.[117] The next layer of defence is the innate or non-specific immune system which is independent of prior exposure and involves cells such as neutrophils, basophils, eosinophils, monocytes/macrophages and natural killer cells performing elimination through phagocytosis (cell ingestion of harmful agent) and cytotoxicity.[117] The final layer of defence is the sophisticated adaptive or acquired immune system which evolves over days and gives rise to immune memory to protect against repeat exposure. Components include humoral immunity which mainly involves B lymphocytes dealing with extracellular pathogens and cell-mediated immunity through T lymphocytes attacking intracellular pathogens.[117] T helper lymphocytes produce cytokines and participate in initiation and evolution of the immune response with Th1 stimulating the cell mediated immune response and Th2 the humoral response.

The aim was to collect data on lymphocyte counts which are a marker of nutritional status.[117] It was hoped this would provide further understanding on the effect of supplementation on the immune system, however no studies reported data. Two studies did measure Th1/Th2 ratios and found IN led to a shift towards the more favourable Th1 cell mediated immunity.[98, 102]The stress of surgery has been shown to depress Th1 which can be clinically significant when a postoperative infection arises and requires response,[118, 119] therefore use of IN which enhances Th1 response may in part explain why postoperative infection rates improved in our findings.

4.2.2 Nutrition and connection to infection

The link between infection and nutrition includes many factors in addition to providing energy for cells to function.[117] Components of IN include arginine and glutamine which are amino acids and therefore building blocks of protein. Protein-energy malnutrition affects immunity through energy deficiency and reduced carrier proteins such as retinol binding protein, transferrin, albumin and ceruloplasmin, which are essential for delivery of micronutrients including vitamin A, iron, zinc and copper to cells and components of the immune system.[120] The effect of nutrition on the inflammatory response is also important. Cytokines are key chemical signals in the inflammatory cascade, and micronutrients such as zinc and retinol can modify the intensity of responses to these cytokines.[120] Furthermore, essential fatty acids such as omega three, a component of IN, and their products of

metabolism are key building blocks of cell membranes and precursors for mediators of inflammation and immunity.[120] Another consideration is that nutrients can modulate cell injury from factors such as toxin mediated cell damage. Vitamin E and resolvins derived from omega 3 fatty acids are important antioxidants which can prevent further injury after infection.[120]

Multiple systematic reviews of perioperative IN for gastrointestinal surgery support use for improving outcomes such as hospital LOS and infectious complications.[121-123] The dose and duration of IN may affect outcomes. A previous systematic review suggested best outcomes are achieved with IN doses of 0.5-1 litre per day for five to seven days before surgery.[123] Only one study included in our review supplemented for less than five days and found no benefit of IN.[111] Timing of IN delivery is variable throughout the literature. Perioperative supplementation reduces complications and should be considered with evidence now supporting early oral feeding after surgery.[124] However, multiple systematic reviews have suggested best outcomes are achieved with preoperative supplementation emphasising this as the critical time period.[123, 125]

Immunonutrition is a feasible prehabilitation intervention, given only five days of supplementation are required to achieve benefit. Furthermore, hospital costs saved could be significant with the Australian based study included in this review reporting a cost saving of AUD1576 per patient in the preoperative IN group based on a five day course costing a total of AUD51.[109] These findings are generalisable to patients undergoing PD for cancer, although careful consideration needs to be given to patients with diabetes, given the potential effect on blood sugars which lead to one study included in meta-analysis excluding patients with diabetes.[96]

The aim was to include other forms of nutritional supplementation to clarify differences in effect, however only one study using a standard ODS and one using synbiotics was identified.[103, 106] Limited conclusions can be drawn from the ODS study given few patients underwent PD.[106] Meta-analysis findings of synbiotics (combination of probiotics and prebiotics) in GIT surgery patients indicate they may reduce infectious complications.[126] We identified only one study on synbiotics meeting inclusion criteria, where no difference was found between the synbiotic and control group.[103] Probiotics are made of live bacteria and can increase intestinal motility, stabilise the intestinal barrier and facilitate the innate

immune system.[127] Prebiotics serve as a nutritional source for probiotics, being a non-digestible dietary substance. Further studies are needed to clarify if any benefit exists for PD patients through preoperative use.

4.2.3 Patient factors contributing to infection in the postoperative setting

Development of postoperative infectious complications is multifactorial and includes both patient and operative factors, with many impacting aspects of the immune system. Infection risk increases with age, as does pancreatic cancer incidence, with the average age in all included studies being over sixty.[128] Aging is associated with increasing comorbidities and higher wound infection rates due to reduced nerve and blood supply to skin in addition to thinning of tissues with progressive loss of collagen.[129] Other risk factors for postoperative infections include smoking with mechanisms including vasoconstriction which affects blood supply and oxygenation of operated tissues, impaired immune bactericidal mechanisms and reduced collagen synthesis and deposition.[130] Males are also higher risk with reasons being unclear but theories include different profile in bacterial skin colonisation and testosterone affecting cell mediated immunity.[131, 132]

Postoperative infection risk also increases with hyperglycaemia in patients with diabetes which can impair immune responses through reducing neutrophil chemotaxis, affecting intracellular bacteriacidal activity and depressing cell mediated immunity.[133] Diabetic patients have higher rates of asymptomatic skin colonisation with staphylococcus aureus, particularly those who inject insulin daily, and vascular insufficiency which impairs blood flow and healing potential.[134]

Finally, head of pancreas lesions can have a compressive effect on the ampulla and bile duct, however preoperative biliary drainage increases the risk of complications, including wound infections. Biliary drainage can be necessary for bilirubin levels above 250umol/L, episodes of cholangitis and for neoadjuvant treatment.[82] Biliary drainage can allow a channel for bacteria from enteric contents and cause a severe inflammatory response in the bile duct during the lead up to surgery.[135] The impact of preoperative stenting on infectious complications was not explored in this study, however of note, around a quarter of patients included in meta-analysis developed a postoperative infection; with around half of patients having undergone preoperative stenting. This relationship and any impact of IN could be explored in subgroup analysis in future studies.

Nutrition factors that increase postoperative infection rates include both obesity and malnutrition. Obesity leads to deficient collagen formation, impaired responsiveness of lymphocytes and relatively poor blood supply of subcutaneous fat tissue.[136] Malnutrition can affect immunity through mechanisms described earlier.[137] However, our study demonstrated that well-nourished patients also benefited from nutritional supplementation, with reduced infectious complications which correlates with findings of a previous review in surgical patients.[138] The nutritional reserve provided by supplementation may benefit all patients given the significant additional stress of PD and underlying catabolic state of this cancer cohort.

4.2.4 Operative factors contributing to infection in the postoperative setting

Patient factors that may be influenced by IN are the focus of this review, but operative factors that can affect postoperative outcomes need to be outlined to complete the picture. Pancreaticoduodenectomy causes extensive physiologic stress leading to fluid shift and systemic vasodilation.[29] Combined with blood loss and anaesthesia, this can result in intraoperative hypotension with reduced blood flow to anastomoses and impaired immune capacity. A delicate balance of fluid resuscitation is required to avoid subsequent oedema which can slow reconstruction during surgery and effect anastomotic integrity.[139] Intraoperative blood transfusions are used judiciously given they can increase infectious risk due to mediators in the transfusion which can interact with immune cell functions, leading to proinflammatory and immunosuppressive effects.[140] Infection risk also increases with longer duration surgery which likely reflects the complexity of the case and may increase potential exposure time to contamination or lead to decreased tissue concentration of prophylactic antibiotic.[131]

Open surgeries show higher rates of infectious complications, particularly wound infections, compared to minimally invasive approaches. Potential contributing factors include larger surface area of the wound and more pronounced proinflammatory response with impairment of the systemic immune function postoperatively.[141]Although minimally invasive approaches to PD, including laparoscopic and robotic surgery have been developed, the uptake compared to other surgeries is slower given the complexity of PD. Minimally invasive PD can reduce hospital LOS, postoperative haemorrhage and wound infection rates, but requires conversion to open in up to 40% of cases and has a mean additional operative time

of 71 minutes.[142] Furthermore, results are variable, with one study showing higher rates of complication related deaths.[143] Clinical experience of the operator, learning curve and concentration to high-volume centres are recognised as key factors for success and safety.[143]

4.2.5 Implications of developing postoperative infections and complications

Surgical complications have significant impact including the effect on patient quality of life, time spent in hospital and delay to further treatment such as chemotherapy.[121] In addition, they have financial implications with an additional $15,000 American dollars spent per patient for an infectious complication after PD.[139] Adjuvant chemotherapy after PD is now the standard of care following a landmark RCT comparing adjuvant gemcitabine to surgery alone which found overall five-year survival with chemotherapy was 20.7% compared to 10.4%.[144] Further studies now mean chemotherapy regimen is decided base on fitness and tumour location with mFOLFIRONOX used for very fit patients with tumours of the head, body and tail of pancreas; combination gemcitabine and capecitabine used for less fit patients and single agent (usually 5-Fu) used for periampullary tumours as there is insufficient evidence to use the same treatments as other pancreatic tumour locations.[7]

Commencement of chemotherapy is recommended at 6-8 weeks after PD.[145] Chemotherapy may be omitted or delayed an additional three weeks on average for patients with postoperative complications after PD, but this hasn't shown a significant impact on long-term survival.[145] However omitting or incomplete chemotherapy due to complications does appear to impact survival. In one study of patients with cancer who underwent PD, the overall median survival was 17 months[146]. Survival improved to 20 months for those who commenced adjuvant chemotherapy but was only 12 months for those who received no or incomplete chemotherapy due to any postoperative complications, highlighting the importance of reducing complications to improve survival.

Currently, the best predictors of surviving from pancreatic cancer are curative intent surgery, early cancer and complete (R0) resection.[147] None of these factors are influenced by adjuvant chemotherapy which also has poor uptake due to postoperative complications. This led to development of neoadjuvant or preoperative chemotherapy. Neoadjuvant chemotherapy risks include toxicity, immunosuppression, disease progression and further malnutrition which can affect uptake of subsequent curable surgery and rates of postoperative complications.[147] Four studies included in meta-analysis for this review excluded patients

who underwent neoadjuvant chemotherapy with no specified reason,[97, 99, 102, 104] while the remaining five made no comment.[87, 88, 96, 98, 112] Neoadjuvant chemotherapy is now an accepted treatment for patients with resectable pancreatic cancer as it may improve survival, but is the subject of ongoing clinical trials.[147] Given this recent change in clinical practice, data is needed on postoperative outcomes for patients who received IN and neoadjuvant chemotherapy.

Postoperative 30-day mortality after PD is near one percent in some centres, with the main causes being haemorrhage often secondary to pancreatic fistula, vascular injury and anastomotic leak.[148] No difference with use of IN was identified in this study, although findings were limited by small patient numbers. Importantly, to the best of our knowledge, no studies have looked at long term outcomes of survival following preoperative IN in cancer surgery which is potentially improved through reduced complications and increased chemotherapy uptake.

Although logically a reduction in infectious complications would translate to decrease hospital LOS, our study was unable to demonstrate this. Narrative findings suggest preoperative IN may reduce hospital LOS but meta-analysis was limited given variation in measures of central tendency across included studies. Length of stay is highly hospital and location dependent, with triggers for discharge being variable. In this study, average stay ranged from 7.1 to 49 days, which is not necessarily a reflection of additional days due to complications.

No effect on rates of DGE with use of IN was identified, with strength of findings limited by small patient numbers. Other systematic reviews on PD and IN, also with small patient numbers, have found no difference.[86, 125] One possibility is the underlying aetiology of DGE which is thought to be related to surgical factors (see section 1.2.3) as appose to patient and healing factors that could be optimised by IN.

No difference with use of IN on pancreatic fistula rates was identified in this study through pooled results of eight studies. A meta-analysis study of PD patients receiving IN also found no difference in fistula rates across four studies.[125] However, preoperative malnutrition has been recognised as a risk factor for postoperative pancreatic fistula meaning IN could, in theory, have some influence on rates.[50, 51] One explanation may again be the

impact of surgical factors or the definition of pancreatic fistula. Two studies included in this analysis pre-date the consensus definition released for pancreatic fistula which could have affected results.[99, 104] One of these studies required drain amylase five times greater than serum, where the consensus definition needs only three times greater, potentially leading to under reporting.[99] Pancreatic fistulas are now graded A, B and C where A has no clinical consequence and therefore, two studies included in our meta-analysis presented grade B and C only.[98, 102]

Overall, risk factors of PD postoperative complications are multifactorial and include operative factors such as longer surgery duration and patient factors such as comorbidities and nutritional status.[149, 150] Nutrition is linked to infection rates through its effects on immune cells, inflammation and response to cell injury. Results from our study support implementation of preoperative IN to reduce the number of postoperative infectious complications.

4.3 Limitations of the review

4.3.1 Limitations of the included studies

One limitation of the evidence in this review is inclusion of two quasi-experimental studies.[96, 97] The author decided this was reasonable given the number of studies on the topic was likely to be small, but all research of experimental design would inform the topic. Quasi-experimental design means there is no randomisation process, which is thought to increase bias by around 30%.[151] Although this reduces the strength of our findings, both quasi-experimental studies scored a total of 78% on critical appraisal, indicating reasonable quality.[96, 97] The two studies included a control group, but for Shirakawa et al[96] these were historic patients.

A key area of weakness for included studies was blinding, with only one study included in the meta-analysis clearly double blinded, where study participants, those delivering nutritional intervention and outcome assessors were all masked to treatment assignment.[105] Blinding is particularly important in RCTs to minimise bias of human expectation influencing findings.[152] Randomised trials that have not used blinding can show larger treatment effects than blinded studies.[151] Lack of blinding can influence outcomes with more subjectivity such as pain however, this review focused on objective clinical findings

which were clearly defined in all but two studies included in meta-analysis.[88, 101] There is possibly a small potential for subjectivity with infectious findings such as wound infection, but other outcomes such as mortality and hospital LOS are definitive.

Three studies utilised patient blinding through an isocaloric isonitrogenous solution for the control group.[88, 105, 111] Interestingly, these studies found no significant difference between groups for any clinical outcomes including infectious complications. An argument can be made that by blinding patients using control solutions in addition to normal diet, this is also a form of supplementation and may confound the identified effect of IN. A systematic review of IN where only studies with a control solution were included found a significant reduction in postoperative infections in patients undergoing major surgery, although when focusing on preoperative supplementation alone there were insufficient patients and studies to reach significance.[153] A further systematic review and meta-analysis compared preoperative IN to isocaloric isonitrogenous solutions and found no difference in infectious complications, implying they may offer an alternative to IN with similar clinical benefit.[154] Neither study was specific to PD. Certainly, blinding assessors is essential to study design for IN studies which was completed by only two studies in our meta-analysis.[99, 104]

Another key limitation of included studies was the small patient numbers. Out of studies included in meta-analysis, Silvestri et al[97] recruited the highest number of patients with 96. Sample size calculations within studies were mostly unclear or based on overall complications or total infectious complications and therefore insufficiently powered to detect significant change for outcomes such as mortality, anastomotic leak, or sub types of infection. A larger systematic review of IN in cancer patients having surgery found a significant reduction in respiratory tract infection, urinary tract infection, and anastomotic leak; in addition to overall infectious complications and wound infections.[67] Included in this review were 61 RCTs, allowing greater precision with results although it was not specific to preoperative timing of PD. A high volume centre for PD is around 20-40 cases per year,[155] making achieving high patient numbers for studies challenging and likely requiring multiple centres or further years of patient recruitment.

An important consideration for this review is any potential impact of industry funding to introduce bias, given favourable findings of IN studies would likely benefit businesses selling IN. Of the studies included in meta-analysis, four studies made a clear statement of no

industry funding,[87, 97, 101, 112] three were unclear,[96, 98, 102] and one was industry funded.[88] Gianotti et al[104] and Braga et al[99] clearly described the IN being donated by a company of interest. Industry funded RCTs on IN may be seven times more likely to report a positive result than non-industry funded.[156] Furthermore, a meta-analysis study of IN in major abdominal surgery found that non-industry funded studies found smaller and non-significant effects,[84] making this an important consideration when interpreting this reviews findings.

4.3.2 Limitations of the review process

A limitation of this review was multiple studies being excluded from meta-analysis due to heterogeneous patient characteristics which included surgery types other than PD. Despite multiple attempts to contact each author, data for PD patients was unable to be obtained except for Gainotti et al.[104] If more data was obtained, this could have increased patient numbers and added strength to the findings however, by allowing a broader criterion it facilitated a more thorough exploration and understanding of the topic.

Furthermore, two reviewers were only used for critical appraisal due to the review being part of a Masters programme. However, the author has confidence in the study search, study selection and data extraction that were undertaken. All processes are also transparently presented in this thesis.

Outcome measures of albumin, weight loss, BMI, lymphocytes and NRI chosen for this study were not included in any studies and require further consideration. Initially it was thought studies might be identified where long periods of preoperative nutritional supplementation occurred. However, most studies in this review supplemented for only five to seven days which is unlikely to significantly change these parameters. Albumin levels may be the most sensitive to nutritional supplementation however, significant change is likely only seen after weeks of supplementation.[157] These outcomes have more value at baseline for nutritional risk screening and comparing outcomes for well-nourished and malnourished patients.

4.4 Conclusion

To the best of our knowledge, this is the first review specific to preoperative timing of nutritional interventions for PD patients. Nutritional interventions identified included IN, standard ODS and synbiotics. Seventeen studies were included, with eight on IN forming the

meta-analysis. Results demonstrate that IN for five to seven days prior to surgery, significantly reduces overall postoperative infectious complications, wound infections and intrabdominal abscesses. No difference was found for rates of pancreatic fistula. The findings of IN on other complications including other types of infections, anastomotic leak, DGE, haemorrhage and mortality was limited by the small number of studies and inconsistent reporting. Key limitations of studies in this review included the quasi-experimental design of two studies, small patient numbers, lack of blinding and possible influence of industry funding. Further research on IN using high quality RCT design and larger sample sizes, with consideration of long term follow up would allow better understanding of IN and if benefits translate to higher adjuvant chemotherapy completion and improved long-term survival.

4.5 Implication for practice

Currently there are multiple sets of guidelines for clinical practice in relation to PD which vary in recommendation. The European Society for Clinical Nutrition and Metabolism (ESPEN) practical guideline for nutrition in surgery state perioperative IN should be given to malnourished patients undergoing major surgery (grade B recommendation) and that there is no clear evidence for the sole use of IN versus standard ODS preoperatively however, IN can be preferred and administered five to seven days preoperatively when patients are not meeting energy demands from normal food.[124] The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines do not include reference to any recent literature.[55] Society guidelines from ERAS are specific to PD and state that IN is not recommended with high evidence level and strong grade of recommendation based on a large meta-analysis in abdominal surgery which demonstrated little benefit in non-industry funded trials.[82] They state specific evidence in pancreatic surgery is limited.[82]

The evidence in this review explored preoperative IN in PD much more extensively and could help inform these guidelines. Based on moderate certainty of evidence included in this systematic review, the author supports use of preoperative IN before PD to reduce postoperative infective complications. Statistical heterogeneity was low across studies making the observed benefit likely more than chance alone. Furthermore, the magnitude of effect was clinically significant with a 58% reduction in overall infectious complications.

The author therefore make a Grade B recommendation for use of preoperative IN before PD to reduce overall infectious complications for the following reasons: i) the findings

of this review demonstrated that preoperative IN for five to seven days (one litre per day) before PD reduces postoperative infectious complications; ii)immunonutrition is a feasible intervention which is accessible and low in cost. Previous cost analysis shows that perioperative IN for surgical patients equates to thousands of dollars saved per patient, based on reduction in infectious complications. [158, 159] Limited staff training would be required to implement this intervention and patient recruitment is easily accessible through preoperative outpatient clinics; iii) Immunonutrition is likely applicable to most patients awaiting PD for cancer as guidelines suggest oral intake as appose to other nutrition delivery modes. Our findings suggest that patients of any nutritional status, including well-nourished patients, benefit from IN to reduce infectious complications. Furthermore, IN benefit may result from a minimum of five days supplementation meaning it can be utilised even when time to surgery is short; iv) Immunonutrition poses little to no potential for harm and could empower patients during preoperative preparation. Palatability, tolerance and compliance need to be explored further.

4.6 Implication for research

There are multiple factors to consider for future research on preoperative IN for PD. More high-quality, strongly powered RCTs are required. Larger sample sizes may allow detection of significant differences in sub-categories of infections and postoperative mortality however, this could be challenging given study numbers may be small even at high-volume centres. Broader surgical patients could be included however, the authors recommend presenting supplementary data on outcomes based on surgery type. To reduce bias, future studies should be non-industry funded wherever possible and include blinding of at least the assessors to add strength to the body of evidence. Studies where patients are blinded using standard ODS for the control group would further clarify the effects of IN.

There needs to be more consistency in length of follow up for future studies given the duration for infectious complications in this study was variable (see section 3.5.1.1) along with mortality (see section 3.5.1.5). The author suggests postoperative infections be monitored until POD 30 and mortality until POD 90. Long term follow up would allow better understanding of preoperative nutritional supplementation on chemotherapy uptake and survival after PD. Compliance and palatability of IN also require further investigation.

The authors recommend future studies exploring outcomes for well-nourished compared to malnourished patients. Classification of nutritional status was variable across included studies with the study by Gianotti et al[104] defining well-nourished as less than 10% weight loss over the preceding six months whereas the study by Silvestri et al[97] used any one of 10% weight loss in last six months, BMI greater than 18, serum albumin greater than 3g/L or Karnofsky score greater than 60. The two studies by Tumas et al[87, 101] defined malnutrition as BMI <18.5, unplanned weight loss greater than 10% at any time or greater than five percent in the last three months together with BMI <20 for age <70 or <22 for those 70 years or older, or fat free mass index <15 for women or <17 for men; whereas Barker et al[109] used subjective global assessment (SGA) tool scores. A consistent definition is needed in future research and the author would suggest those proposed by ESPEN guidelines which are any one of weight loss 10-15 % within six months, BMI less than 18.5, SGA Grade C or nutritional risk screening >5 or serum albumin less than 30g/L with no evidence or hepatic or renal dysfunction.[124] These measures are all straightforward to obtain and would allow high sensitivity for detecting patients at nutritional risk.

Regarding recommendations for outcome measures in future studies, the author would suggest focusing on the clinical outcomes used in this review, with mean and standard deviation presented for hospital LOS. As described in section 3.5.1.2, wound infection definition varied across included studies. To ensure clarity in future studies the CDCs SSI definitions could be used.[160] A superficial incisional SSI is defined as occurring within 30 days of surgery, involves only skin or subcutaneous tissue and involves at least one of pain; swelling; erythema or heat. They also require one of purulent discharge; positive culture; or needing wound opening. Wound cellulitis and dehiscence would therefore be classified separately. Clear definitions are also provided for deep and organ space SSIs.

Serum nutritional markers and weight are unlikely to significantly change with supplementation for five to seven days and should be reserved for classifying patients at baseline as malnourished or well-nourished. Included studies were variable regarding if all grades of pancreatic fistula were included (see section 4.2.5). The authors would suggest future studies include only grade B and C in results given grade A have no clinical consequence.

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Appendices

Appendix I: Search strategies

Search in MEDLINE (via PubMed) conducted on 11th Feb 2021

Query	Records retrieved
"pancreaticoduodenectomy"[Mesh] OR "pancreatic neoplasms"[Mesh] OR "pancreatectomy"[Mesh] OR "pancreaticojejunostomy"[Mesh] OR Pancreaticoduodenectomy[Text Word] OR pancreatoduodenctom* [Text Word] OR Whipple*[Text Word] OR "pancrea* surgery"[Text Word] OR "pancreatoduodenal resection"[Text Word] OR duodenopancreatectom*[Text Word] OR "pancreatic tumour"[Text Word] OR "pancreatic ductal adenocarcinoma"[Text Word] AND "dietary supplements"[Mesh] OR nutrition*[Text Word] OR supplement*[Text Word] OR "nutrition* support"[Text Word] OR immunonutrition[Text Word] OR "diet therapy"[Text Word] OR synbiotics[Text Word] OR *nutrition[Text Word]	1965

Search in CINAHL (via EBSCO) conducted on 11th Feb 2021

Query	Records retrieved
MH pancreaticoduodenectomy OR MH pancreatectomy OR MH pancreaticojejunostomy OR MH "Pancreatic Neoplasms" OR Pancreat##oduodenectomy OR Whipple* OR "pancrea* surgery OR "pancreat##oduodenal resection OR duodenopancreatectom* OR "pancreatic tumo#r" OR pancreatic ductal adenocarcinoma AND MH "dietary supplements" OR nutrition* OR supplement* OR "nutrition* support" OR immunonutrition OR "diet therapy" OR synbiotics	476

Search in Scopus (via Elsevier) conducted on 11th Feb 2021

Query	Records retrieved
(pancreaticoduodenectomy OR “pancreatic neoplasms” OR “pancreatectomy” OR “pancreaticojejunostomy” OR pancreatoduodenctomy OR Whipple* OR “pancrea* surgery” OR "pancreatoduodenal resection” OR duodenopancreatectom* OR "pancreatic tumour" OR “pancreatic tumor” OR "pancreatic ductal adenocarcinoma") AND TITLE-ABS-KEY (“dietary supplements” OR nutrition* OR supplement* OR "nutrition* support" OR immunonutrition OR “diet therapy” OR synbiotics OR *nutrition)	3208

Search in Cochrane conducted on 11th Feb 2021

Query	Records retrieved
MeSH descriptor [pancreaticoduodenectomy] OR MeSH descriptor [pancreatectomy] OR MeSH descriptor [Pancreaticojejunostomy] OR Mesh descriptor [nutrition therapy] Using ‘Cochrane Reviews’ tab	145

Search in Cochrane Controlled Register of Trials (CENTRAL) conducted on 11th Feb 2021

Query	Records retrieved
MeSH descriptor [pancreaticoduodenectomy] OR MeSH descriptor [pancreatectomy] OR MeSH descriptor [Pancreaticojejunostomy] AND Mesh descriptor [nutrition therapy] Using ‘Trials’ tab	403

Search in World Health Organisation International Clinical Trials Registry Platform conducted on 11th Feb 2021 (included Australian New Zealand Clinical Trials Registry up to 19th April 2021 and ClinicalTrials.gov up to 19th April 2021)

Query	Records retrieved
Pancreaticoduodenectomy OR pancreatoduodenectomy OR pancreatic neoplasms OR pancreatectomy OR pancreaticojejunostomy OR pancreas surgery OR Whipple procedure OR pancreas surgery OR duodenopancreatectomy OR pancreatic ductal adenocarcinoma OR pancreatic tumour OR pancreatic tumor	4338 trials

Search in Australian Cancer Trials conducted on 11th Feb 2021

Query	Records retrieved
Cancer types explored: Pancreatic Biliary tree	 107 24

Appendix II: Studies ineligible following full text review

1. Akita H, Takahashi H, Asukai K, Tomokuni A, Wada H, Marukawa S, et al. The utility of nutritional supportive care with an eicosapentaenoic acid (EPA)-enriched nutrition agent during pre-operative chemoradiotherapy for pancreatic cancer: Prospective randomized control study. Clin Nutr ESPEN. 2019;33:148-53.

Reason for exclusion: Outcome - No postoperative outcome measures of interest

2. Barber MD, Preston T, McMillan DC, Slater C, Ross JA, Fearon KC. Modulation of the liver export protein synthetic response to feeding by an n-3 fatty-acid-enriched nutritional supplement is associated with anabolism in cachectic cancer patients. Clin Sci (Lond). 2004;106(4):359-64.

Reason for exclusion: Outcome - No postoperative outcome measures of interest

3. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L. Postoperative complications in gastrointestinal cancer patients: The joint role of the nutritional status and the nutritional support. Clinical Nutrition. 2007;26(6):698-709.

Reason for exclusion: Intervention - during postoperative period

4. Braga M, Bissolati M, Rocchetti S, Beneduce A, Pecorelli N, Di Carlo V. Oral preoperative antioxidants in pancreatic surgery: A double-blind, randomized, clinical trial. Nutrition. 2012;28(2):160-4.

Reason for exclusion: Intervention - less than 48 hours

5. Diepenhorst GM, van Ruler O, Besselink MG, van Santvoort HC, Wijnandts PR, Renooij W, et al. Influence of prophylactic probiotics and selective decontamination on bacterial translocation in patients undergoing pancreatic surgery: a randomized controlled trial. Shock. 2011;35(1):9-16.

Reason for exclusion: Intervention – postoperative nutrition differed between groups

6. Dobrila Dintinjana R, Guina T, Krznarić Z. Nutritional and pharmacologic support in patients with pancreatic cancer. Coll Antropol. 2008;32(2):505-8.

Reason for exclusion: Intervention – nutritional intervention started 4 week postoperatively

7. Gunerhan Y, Kokal N, Sahin UY, Uzun MA, Eksioglu-Demiralp E. Effect of preoperative IN and other nutrition models on cellular immune parameters. World Journal of Gastroenterology. 2009;15(4):467-72.

Reason for exclusion: Ineligible population – no response from authors regarding if any patients in study underwent PD or if data available.

8. Hamza N, Darwish A, O'Reilly DA, Denton J, Sheen AJ, Chang D, et al. Perioperative Enteral IN Modulates Systemic and Mucosal Immunity and the Inflammatory Response in Patients

With Periampullary Cancer Scheduled for Pancreaticoduodenectomy: A Randomized Clinical Trial. Pancreas. 2015;44(1):41-52.

Reason for exclusion: Intervention – post operative nutrition differed between groups

9. Ijmker-Hemink VE, Wanten GJA, de Nes LCF, van den Berg MGA. Effect of a Preoperative Home-Delivered, Protein-Rich Meal Service to Improve Protein Intake in Surgical Patients: A Randomized Controlled Trial. Journal of Parenteral and Enteral Nutrition. 2020.

Reason for exclusion: Ineligible population – contacted author and only 1 patient in study underwent PD.

10. Jo S, Choi SH, Heo JS, Kim EM, Min MS, Choi DW, et al. 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. 2006;30(11):1974-82; discussion 83-4.

Reason for exclusion: Intervention – parenteral administration of nutritional intervention

11. Kabata P, Jastrzębski T, Kąkol M, Król K, Bobowicz M, Kosowska A, et al. Preoperative nutritional support in cancer patients with no clinical signs of malnutrition—prospective randomized controlled trial. Supportive Care in Cancer. 2015;23(2):365-70.

Reason for exclusion: Ineligible population – only 1 patient in intervention group underwent PD, none in control group

12. Klapdor S, Richter E, Klapdor R. Vitamin D status and per-oral vitamin D supplementation in patients suffering from chronic pancreatitis and pancreatic cancer disease. Anticancer Res. 2012;32(5):1991-8.

Reason for exclusion: Intervention – postoperative nutritional supplementation only

13. Klapdor S, Richter E, Klapdor R. Fat soluble vitamins in pancreatic diseases results of studies of serum concentrations of 25(OH)D and on supplementation with vitamin D. Ernahrungs Umschau. 2012;59(8):436-41.

Reason for exclusion: Outcomes – no relevant outcome measures

14. Klek S, Kulig J, Sierzega M, Szybinski P, Szczepanek K, Kubisz A, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: A prospective, randomized, clinical trial. Annals of Surgery. 2008;248(2):212-20.

Reason for exclusion: Intervention – postoperative nutritional supplementation only

15. McCarter MD, Gentilini OD, Gomez ME, Daly JM. Preoperative oral supplement with immunonutrients in cancer patients. Journal of Parenteral and Enteral Nutrition. 1998;22(4):206-11.

Reason for exclusion: Intervention – no control group

16. Miyauchi Y, Furukawa K, Suzuki D, Yoshitomi H, Takayashiki T, Kuboki S, et al. Additional effect of perioperative, compared with preoperative, IN after pancreaticoduodenectomy: A randomized, controlled trial. Int J Surg. 2019;61:69-75.
Reason for exclusion: Intervention – postoperative nutrition differed between groups
17. Nomura T, Tsuchiya Y, Nashimoto A, Yabusaki H, Takii Y, Nakagawa S, et al. Probiotics reduce infectious complications after pancreaticoduodenectomy. Hepatogastroenterology. 2007;54(75):661-3.
Reason for exclusion: Intervention – postoperative nutrition differed between groups
18. Rautalahti MT, Virtamo JRK, Taylor PR, Heinonen OP, Albanes D, Haukka JK, et al. The effects of supplementation with α-tocopherol and β-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer. 1999;86(1):37-42.
Reason for exclusion: Outcomes – no postoperative outcome measures
19. Senkal M, Haaker R, Linseisen J, Wolfram G, Homann HH, Stehle P. Preoperative oral supplementation with long-chain Ω-3 fatty acids beneficially alters phospholipid fatty acid patterns in liver, gut mucosa, and tumor tissue. Journal of Parenteral and Enteral Nutrition. 2005;29(4):236-40.
Reason for exclusion: Ineligible population – contacted authors and no patients underwent PD.
20. Słotwinski R, Olszewski WL, Słodkowski M, Lech G, Zaleska M, Kędziora S, et al. The up-regulation of pro-apoptotic signalling systems in peripheral blood lymphocytes of malnourished patients with pancreatic cancer after preoperative enteral immune-enhancing diet (IN). Przeglad Gastroenterologiczny. 2011;6(3):154-9.
Reason for exclusion: Outcomes – no relevant outcome measures
21. Słotwiński R, Olszewski W, Słodkowski M, Lech G, Zaleska M, Kędziora S, et al. Apoptosis in lymphocytes of pancreatic cancer patients: influence of preoperative enteral IN and extensive surgery. Arch Immunol Ther Exp (Warsz). 2011;59(5):385-97.
Reason for exclusion: Outcomes – no relevant outcome measures
22. Słotwiński R, Olszewski WL, Słodkowski M, Lech G, Zaleska M, Kędziora S, et al. The effect of enteral immune-enhancing diet (IN) on the apoptotic signaling pathways of peripheral blood lymphocytes in patients after pancreatic cancer surgery. Central-European Journal of Immunology. 2010;35(2):90-3.
Reason for exclusion: Outcomes – no relevant outcome measures
23. Słotwiński R, Olszewski WL, Słodkowski M, Lech G, Zaleska M, Kędziora S, et al. The anti-apoptotic impact of IN in pancreatic cancer patients is questionable. Przeglad Gastroenterologiczny. 2010;5(5):266-73.

Reason for exclusion: Outcomes – no relevant outcome measures

24. Słotwiński R, Olszewski WL, Słodkowski M, Lech G, Zaleska M, Wójcik Z, et al. Immunomodulatory influence of early enteral IN on the dynamics of changes in the cellular immune response after pancreatic resection for cancer. Central-European Journal of Immunology. 2007;32(3):147-54.

Reason for exclusion: Intervention – postoperative nutritional supplementation only

25. Sommacal HM, Bersch VP, Vitola SP, Osvaldt AB. Perioperative Synbiotics Decrease Postoperative Complications in Periampullary Neoplasms: A Randomized, Double-Blind Clinical Trial. Nutrition & Cancer. 2015;67(3):457-62.

Reason for exclusion: Intervention – postoperative nutrition differed between groups

26. Tsujinaka T, Hirao M, Fujitani K, Mishima H, Ikenaga M, Sawamura T, et al. Effect of preoperative IN on body composition in patients undergoing abdominal cancer surgery. Surg Today. 2007;37(2):118-21

Reason for exclusion: Ineligible population – no patients underwent PD

27. Vashi P, Popiel B, Lammersfeld C, Gupta D. Outcomes of systematic nutritional assessment and medical nutrition therapy in pancreatic cancer. Pancreas. 2015;44(5):750-5.

Reason for exclusion: Ineligible study design – retrospective. Also, no postoperative outcome measures.

28. Werner K, Küllenberg de Gaudry D, Taylor LA, Keck T, Unger C, Hopt UT, et al. Dietary supplementation with n-3-fatty acids in patients with pancreatic cancer and cachexia: marine phospholipids versus fish oil - a randomized controlled double-blind trial. Lipids Health Dis. 2017;16(1):104.

Reason for exclusion: Outcomes – surgery and postoperative outcomes not included

29. Wigmore SJ, Fearon KC, Maingay JP, Ross JA. Down-regulation of the acute-phase response in patients with pancreatic cancer cachexia receiving oral eicosapentaenoic acid is mediated via suppression of interleukin-6. Clin Sci (Lond). 1997;92(2):215-21.

Reason for exclusion: Outcomes – no postoperative outcome measures.

30. Xu J, Zhong Y, Jing D, Wu Z. Preoperative enteral IN improves postoperative outcome in patients with gastrointestinal cancer. World Journal of Surgery. 2006;30(7):1284-9.

Reason for exclusion: ineligible population – no patients underwent PD

Appendix III: Characteristics of included studies

Table: Characteristics of Included Studies - Quasi-Experimental Study Form

Study	Country	Setting/ context	Participant characteristics	Groups	Outcomes measured	Results
Shirakawa et al. 2012 [96]	Japan	Elective surgery	Consecutive patients scheduled for PD.	Group 1 (n=18): Oral IN for 5 days preoperatively (750mL/day) in addition to normal diet. Postoperative: unclear. Oral feeding started POD 5. Group 2 (n=13): Normal diet: Postoperative: as per group 1.	Infectious complications, SIRS, pancreatic fistula. Serum markers at POD 1, 3 and 7 (WBC, CRP, total protein, albumin, bilirubin, amylase, GPT, BUN and creatinine. Change in body weight and APACHE-II score.	Significantly lower incisional wound infections in group 1 (0 vs 30.8%), higher GPT levels and lower change in total APACHE-II score. No significant difference in other outcomes.
Silvestri et al. 2016 [97]	Italy	Elective surgery	Well-nourished patients (defined as any one of <10% weight loss in last 6 months, BMI >18 kg/m2, serum albumin >3g/L,	Group 1 (n=48): Oral IN for 5 days preoperatively (750mL/day) in addition to normal diet. Postoperative care included TPN from POD 1 with oral diet reintroduced from POD 5. Group 2 (n=48): consecutive patients submitted for PD with	Overall postoperative morbidity, need for second laparotomy, mortality, pancreatic fistula, haemorrhage, DGE, infectious complications and hospital LOS.	Significantly less infectious complications in group 1 (22.9% vs 43.7%) and shorter hospital LOS (18.3 +/- 6.8 days vs 21.7 +/- 8.3). No significant difference in other outcomes.

			Karnofsky score >60) planned for PD for cancer and chronic pancreatitis.	normal diet preoperatively. Postoperative care as for group 1.		

PD=pancreaticoduodenectomy; IN=IN; POD=postoperative day; SIRS = systemic inflammatory response syndrome; WBC=white blood cells; CRP=c-reactive protein; GPT=glutamic pyruvic transaminate; BUN=blood urea nitrogen; APACHE=acute physiology and chronic health evaluation; BMI=body mass index; TPN=total parenteral nutrition; DGE=delayed gastric emptying

Table: Characteristics of Included Studies - Randomised Controlled Trial Form

Study	Country	Setting/ context	Participant characteristics	Groups	Outcomes measured	Results
Aida et al. 2014[98]	Japan	Elective surgery	Patients undergoing PD or PPPD	Group 1 (n=25): oral IN for 5 days preoperatively (1,000 kcal/day), in addition to a 50% reduction in regular food (1,000 kcal/day). Postoperative: nutrition via gastrostomy catheter to jejunum with standard formula started at 20mL/hr on POD 1 and increased by 20mL/day. Oral intake recommenced on POD 5. Group 2 (n=25): normal diet (2,000 kcal/day). Postoperative diet as for group 1.	Infectious complications, mortality, pancreatic fistula (Grade B and C), DGE, haemorrhage, chylorus ascites. Serum marker prior to IN, POD -1, POD 0 and PODs 1,3,7 and 14: Con A, PHA, IL6, PGE_2, serum fatty acid composition (EPA and EPA/AA ratio), Th1/Th2 differentiation.	Significantly less infectious complications for group 1(28% vs 60%), lower IL-6 levels on POD 0, higher Con A and PHA on POD 7, higher EPA and EPA/AA ratio after supplementation and on POD 1 and 3, lower PGE_2 levels on POD 1. No significant difference in non-infectious complications.
Ashida et al 2019[88]	Japan	Elective surgery	Patients undergoing PD for cancer	Group 1 (n=11): Oral IN for 7 days preoperatively (600 kcal/day) in addition to 1,200 kcal/day of regular food. Postoperative: unclear	Serum IL-6, IL-1beta, TNF-alpha prior to intervention, before surgery and POD 1,4,7 and 14; nutritional status on POD 0 (CD4/8 T lymphocyte	No significant difference between groups for IL-6, serum albumin, transferrin, IL1-1, TNF-alpha, overall morbidity or infectious complications.

				Group 2 (n=9): Oral control solution of isocaloric isonitrogenous standard nutrition (600kcal/day) for 7 days preoperatively in addition to 1,200 kcal/day of normal diet. Postoperative: unclear.	balance, serum albumin, prealbumin, transferrin and the EPA/arachidonic acid [AA] ratio); overall morbidity; infectious complications (pancreatic fistula - grades A, B and C, SSIs pneumonia, bacteraemia, UTI, SIRS, sepsis).	Reduction curve of serum prealbumin levels in group 1 were significantly smaller POD 0. EPA/AA ratio significantly increased on POD 0,1 and 4 compared with POD 7 in group 1 and compared to group 2 Rise curve of CD4/8 lymphocyte balance significantly larger POD 0 in group 1
Barker et al 2013[109]	Australia	Elective surgery	All patients undergoing GIT surgery (n = 3/95:PD surgery)	Group 1 (n=46): Oral IN for 5 days preoperatively (711mL/day). Postoperative: unclear: 'as per normal clinical treatment management pathways at the hospital.' Group 2 (n=49): normal diet. Postoperative: as for group 1	LOS, infectious and non-infectious complications, antibiotics use and ICU admission and mortality.	No significant difference between groups. Trend towards shorter LOS, less overall complications, reduced antibiotic use and fewer wound infections in group 1.
Braga et al 2002[99]	Italy	Elective surgery	Malnourished patients (weight loss	Group 1 (n=50): Oral IN for 7 days preoperatively (1 litre/day) in addition to normal diet.	Mortality, Infectious complications, haemorrhage, anastomotic leak, renal	Significantly less complications in group 1 (18%) and group 2 (28%) vs group 3 (48%) and

			>/= 10%) undergoing major GIT surgery for malignancy (n = 28/100 with pancreatic cancer).	Postoperatively: enteral IN. *group excluded from analysis Group 2 (n=50): Oral IN for 7 days preoperatively (1 litre/day) in addition to normal diet. Postoperatively: standard enteral nutrition Group 3 (n=50): Normal diet preoperatively. Postoperatively: standard enteral nutrition.	dysfunction, hepatic dysfunction, pancreatic fistula, DGE, multiple organ dysfunction, hospital LOS.	shorter hospital length of stay in group 1 (13.2 days) and 2 (12 days) vs group 3 (15.3 days).
Gade et al 2016[112]	Denmark	Elective surgery	Patients undergoing pancreatic surgery (included total pancreatectomy and distal pancreatectomy) for cancer.	Group 1 (n=19): Oral IN for 7 days preoperatively (1.5g protein/kg) between normal meals. Postoperative: unclear. Group 2 (n=16): Standard preoperative care for department including nutritional assessment and advice from nurses about nutritional supplements. Postoperative: unclear	Overall postoperative complications, LOS, severity of complications, infectious complications, functional capability questionnaire; body weight prior to intervention, before surgery and POD 10, 20 and 30.	Number of patients with >/= 3 postoperative complications was significantly larger in the control group. No difference between groups for all other outcomes.

Gianotti et al 2002[104]	Italy	Elective surgery	Patients scheduled for major GIT surgery for cancer with <10% weight loss in past 6 months (n= 47/204 undergoing PD)	Group 1 (n=102): Oral IN for 5 days preoperatively (1 L/day) in addition to normal diet. Postoperatively: normal diet. Group 2 (n=101): Oral IN for 5 days preoperatively (1 L/day) in addition to normal diet. Postoperatively: Enteral IN until resumed normal diet. *Group excluded from analysis. Group 3 (n=102): Normal diet pre and postoperatively.	Mortality, Infectious complications, haemorrhage, anastomotic leak, renal dysfunction, hepatic dysfunction, pancreatic fistula, DGE, multiple organ dysfunction, hospital LOS.	Significantly less complications in group 1 (13.7%) and group 2 (15.8%) vs group 3 (30.4%) and shorter hospital LOS in group 1 (11.6 days) and 2 (12.2 days) vs group 3 (14 days).
Giger-Pabst et al. 2013[111]	Switzerland	Elective surgery	Well-nourished patients (defined as NRS score <3) undergoing major GIT surgery for cancer (n =	Group 1 (n=55): Oral IN for 3 days preoperatively (750mL/day) in addition to normal diet. Postoperative: IV fluids and electrolytes until resumed adequate oral intake. Group 2 (n=53): Isocaloric and isonitrogenous placebo for 3 days preoperatively (750mL/day) in	Full physical exam, body weight, BMI, NRS and ECOG performance status 7 days preoperatively. Serum WBC, RBC, liver and kidney function, albumin, prealbumin, total protein, glucose, CRP and electrolytes 7 days and 1 day before surgery. All	No difference between groups for outcomes.

			14/108: pancreatic cancer).	addition to normal diet. Postoperative: as for group 1	postoperative complications including infectious complications. Hospital LOS.	
Giger et al. 2007[100]	Switzerland	Elective surgery	Patients undergoing major surgery for stomach or pancreatic cancer (n = 34/46 with pancreatic or periampullary cancer).	Group 1 (n=14): Oral IN for 5 days preoperatively (1L/day). Postoperative: enteral IN for 7 days via catheter jejunostomy with oral food reintroduced POD 3-5. Group 2 (n=17): Oral IN for 2 days preoperatively (1L/day). Postoperative: as for group 1. Group 3 (n= 15): Normal diet. Postoperative: as for group 1.	Infectious complications. Serum nutritional parameters day before surgery and POD 1,3 and 7 (protein, albumin, prealbumin and transferrin). Serum inflammatory markers day before surgery, intraoperatively and POD 1,2,3 and 7 (CRP, leucocytes, neopterin, IL-6 and TNF).	Less overall complications and infectious complications in group 1 and 2 vs group 3. Significantly shorter ICU LOS and hospital LOS in group 1 and 2 vs group 3. Significantly lower CRP levels in group 1 and 2 vs group 3 on POD 7, lower TNF on POD 1 and 3 in group 1 and 2 vs group 3.
Hübner et al 2012[105]	Switzerland	Elective surgery	Patients at nutritional risk (>/=3 on NRS) scheduled for major GIT surgery for benign or malignant	Group 1 (n=73): Oral IN for 5 days preoperatively (3 times daily). Postoperatively: Normal diet. Group 2 (n=72): Oral control formula (isocaloric iso-nitrogenous standard oral feed) 3 times daily for 5 days preoperatively. Postoperatively: Normal diet.	Overall complication rate, infectious complications, SIRS, ICU and hospital LOS and postoperative stress response (serum IL-6 and IL-10 levels 2 hours after surgery and POD 1 and 2).	No significant difference between groups for all outcomes.

			disease (n=34/145 underwent pancreatic resections).			
MacFie et al 2000[106]	England	Elective surgery	Patients scheduled for major GIT surgery (n = 3/100 underwent hepatobiliary surgery).	Group 1 (n=24): Standard oral dietary supplement (Fortisip, minimum 400mL daily) from enrolment in study to day before surgery in addition to normal diet. Postoperative: Oral dietary supplement (Fortisip) for minimum 7 days in addition to normal diet. *Group excluded from analysis Group 2 (n=24): As for group 1 preoperatively. Postoperatively: normal diet only. Group 3 (n=27): Normal diet preoperatively. Postoperatively: as for group 1. *Group excluded from analysis	Nutritional markers on entry to study, prior to surgery, day of discharge from hospital and 4 weeks post discharge (weight loss, BMI, Handgrip strength, midarm circumference, triceps skinfold thickness, albumin). Total postoperative complications, septic complications, mortality, mean hospital LOS. Hospital anxiety and depression questionnaire preoperatively and 4 weeks post discharge. Questionnaire to assess activity, level of independence and general	No difference between groups in all outcome measures.

				Group 4 (n=25): Normal diet pre and postoperatively.	quality of life 6 months postoperatively.	
Nakamura et al 2005[107]	Japan	Elective surgery	Patients undergoing surgery for bile duct cancer (n=10), pancreatic cancer (n=7), gastric cancer (n=5) or oesophageal cancer (n=4).	Group 1 (n=12): Oral IN for 5 days preoperatively (1 L/day). Postoperatively: Standard TPN after surgery, enteral nutrition through jejunostomy catheter started POD 3. Oral food intake started POD 7. Group 2 (n=14): Normal diet preoperatively. Postoperatively: as for group 1.	Serum markers before supplementation, day of surgery; POD 1,3 and 7: fatty acids, TXB2, PGE_2, transferrin, RBP, prealbumin, albumin, TNF, IL-6, IL-8, TNF receptors I and II, high-sensitivity CRP, AAG, PMN-elastase. Hospital LOS. Complications: Postoperative haemorrhage, infection, failure of sutures, mortality	Statistically significant: increase in w-3 fatty acids and rapid turnover proteins in group 1 at POD 0; TXB2 and ratio of w-6 fatty acids to w-3 fatty acids lower at POD 0 in group 1 than before supplementation; inflammatory markers and cytokine receptors lower in group 1 compared to group 2; on POD 1 and 3 decrease in PMN-elastase and IL-8 in group 1. No difference between groups for hospital LOS or complications.
Suzuki et al 2010[102]	Japan	Elective surgery	Patients scheduled for PD for cancer.	Group 1 (n=10): Oral IN for 5 days preoperatively (1000kcal/day) in addition to half normal diet. Postoperative: enteral infusion via catheter jejunostomy of IN.	All postoperative complications. Serum Con-A, PSLP, NKCA, Th1/Th2 differentiation and T17 response on preoperative day	Significantly lower infectious complications in group 1 (10%) compared to group 2 (60%) and group 3 (60%). Significantly higher Con-A, PSLP, NKCA,

				Group 2 (n=10): Normal diet preoperatively. Postoperative: as for group 1 Group 3 (n=10): Normal diet preoperatively. Postoperative: TPN *group excluded in analysis	6, day before surgery and POD 0,1,3,7,14 and 21.	Th1/Th2 differentiation and Th17 response in group 1.
Tumas et al 2020.[87, 101]	Lithuania	Elective surgery	Patients scheduled for PPPD for suspected pancreatic cancer.	Group 1 (n=30): Oral IN for 5 days preoperatively in addition to usual preoperative nutritional management (preoperative nutritional screening and supplementation with standard normocaloric formula for those at high nutritional risk). Postoperative: enteral nutrition until POD 4-5. Group 2 (n=40): usual preoperative nutritional management as defined in group 1.	Preoperative nutritional evaluation (before intervention in group 1 and 1 day before surgery in group 2): NRS , anthropometric measurements, bioelectrical impedance analysis, lumbar skeletal muscle index, BMI. Inflammatory markers (IL-6 and CRP) before nutritional intervention and POD 1,3 and 5. CCI	41.4% of all participants diagnosed with cachexia. Significantly less severe complications for group 1 (CCI >20.9: 23.3% vs 42.5%) No difference between groups for complications rates or for complications among malnourished patients. No difference between groups for inflammatory markers.

Yokoyama et al 2016[103]	Japan	Elective surgery	All patients scheduled to undergo PD for cancer or chronic pancreatitis.	Group 1: Oral synbiotics for 7 days preoperatively (1 x 80mL bottle of Yakult 400 with living Lactobacillus casei strain Shirota; 1 x 100mL bottle MILMIL S which contained living Bifidobacterium breve strain Yakult; and 15g of galacto-oligosaccharides). Postoperative enteral feeding entering jejunum including synbiotics until POD 14. Group 2: Standard preoperative diet. Postoperative nutrition as for group 1.	Microorganisims present in MLN harvested at laparotomy and after the resection. Serum microorganisims prior to surgery and on POD 1. Serum inflammatory markers (WBC count; neutrophil count; CRP prior to surgery and POD 1,3 and 7). Mortality, pancreatic fistula, DGE, Infectious complications, hospital LOS.	No significant difference between group with detection of microorganisms in MLN or serum, complications or hospital LOS. Statistically significant higher serum postoperative inflammatory markers in group 1.

PD=pancreaticoduodenectomy; PPPD=pylorus preserving pancreaticoduodenctomy; IN=IN; DGE=delayed gastric emptying; POD=postoperative day; Con A=concanavalin A stimulated lymphocyte proliferation; PHA=phytohemagglutinin stimulated lymphocyte proliferation; IL=interleukin; PGE2=prostaglandin E_2; EPA=eicosapentaenoic acid; AA=arachidonic acid; Th=T helper; TNF=tumor necrosis factor; SSI=surgical site infection; UTI=urinary tract infection; SIRS=systemic inflammatory response syndrome; GIT=gastrointestinal; LOS=length of stay;ICU=intensive care unit; NRS=nutrition risk score; ECOG=Eastern Cooperative Oncology Group; WBC=white blood cell; RBC=red blood cell; CRP=c-reactive protein; BMI=body mass index; TXB2=thromboxane B2; RBP=retinol-binding protein; AAG=alpha 1 acid glycoprotein; PSLP=phytohemagglutinin stimulated lymphocyte proliferation; NKCA=natural killer cell activity; CCI=comprehensive complication index; MLN=mesenteric lymph