Malnutrition, frailty, and sarcopenia in pancreatic cancer patients: assessments and interventions for the pancreatic surgeon

Noah S. Rozich, Caitlin E. Jones, Katherine T. Morris

Department of Surgery, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Contributions: (I) Conception and design: KT Morris, NS Rozich; (II) Administrative support: KT Morris; (III) Provision of study materials or patients: KT Morris; (IV) Collection and assembly of data: NS Rozich, CE Jones; (V) Data analysis and interpretation: NS Rozich, CE Jones; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Noah S. Rozich. Department of Surgery, University of Oklahoma Health Sciences Center Oklahoma City, OK, USA. Email: Noah-Rozich@ouhsc.edu.

Abstract: The objective of this article is to review the available literature examining the impact of malnutrition, frailty, and sarcopenia on surgical morbidity among pancreatic cancer patients. We examine definitions used to diagnose and quantify these conditions and review the differences between them with regards to preoperative assessment and postoperative outcomes. The most relevant scoring systems are summarized. Lastly, we summarize current knowledge regarding effectiveness of specific interventions aimed at malnutrition, frailty, and sarcopenia for patients undergoing pancreatic cancer surgery.

Keywords: Malnutrition; frailty; sarcopenia; pancreatic adenocarcinoma (PDAC); distal pancreatectomy (DP); pancreaticoduodenectomy (PD)

Received: 28 February 2018; Accepted: 27 February 2019; Published: 11 March 2019.

doi: 10.21037/apc.2019.02.01

View this article at: http://dx.doi.org/10.21037/apc.2019.02.01

Background

Morbidity rates following distal pancreatectomy (DP) average 35% (1), and rates following pancreaticoduodenectomy (PD) range from 38–44% (2-4). Studies have investigated numerous risk factors affecting morbidity. These range from patient-specific risk factors such as body mass index (BMI) (5), pancreatic duct size and parenchymal texture (6), to operative risk factors including anastomotic techniques (7) and intraoperative blood loss (8), and also include histopathologic factors such as tumor size, margin and lymph node status (4,9). There has been an increased emphasis on the potentially modifiable triad of patient specific risk factors of malnutrition, frailty, and sarcopenia as they relate to complications after oncologic surgery. Pancreatic cancer patients are at particular risk given they present at a median age of 71 years old (10). In addition, pancreatic cancer is specifically associated with fat malabsorption, elevated systemic inflammation, release of cachexia factors, and frank obstruction of the gastrointestinal tract, further increasing susceptibility to this triad of risk factors.

While malnutrition, frailty, and sarcopenia are related in important ways, they are independently measurable and have been shown to uniquely affect outcomes after surgery for pancreatic cancer. Although definitions of these three conditions have not been standardized, there is a general consensus that they all negatively impact surgical outcomes.

Methods

A literature search was conducted using the NCBI National Library of Medicine database. The search strategy was set up using a combination of the following keywords: “malnutrition”, “frailty”, and “sarcopenia” along with “pancreas cancer” or “surgery” or “distal pancreatectomy” or “pancreaticoduodenectomy” or “total pancreatectomy” or “outcomes” or “exercise” or “nutrition” or “prehabilitation” or “morbidity” or “complications” or “pancreatic fistula”. Studies from the modern era (2007–present) were preferentially selected, with older studies used primarily for historical reference and background information. Our primary focus were studies with level I evidence where available, however, many of the articles presented are level II or III evidence. Randomized trials, retrospective and prospective cohort studies, meta-analyses, and systematic reviews were all included. Case reports, expert opinion papers, and animal studies were excluded. Articles were restricted to those written in English. Unpublished data were not used. Available evidence used for this narrative review are presented selectively.

Malnutrition

Malnutrition is defined as a physiologic imbalance in energy and nutrients resulting from inadequate or improper intake of food. Disease related malnutrition can be distinguished from starvation related malnutrition by the presence of acute or chronic inflammation (11), and is important to consider when assessing how patients will tolerate or respond to various treatment modalities. Both surgical and cancer patients frequently suffer malnutrition and surgical outcomes are worse when malnutrition is present (12,13). Patients with pancreatic cancer are particularly vulnerable to malnutrition (13).

Assessment and implications

There are multiple ways to assess nutritional status. Albumin level and unintentional weight loss are single-factor assessments commonly used to evaluate nutritional status. Development continues on several multi-factor clinical scoring systems seeking more comprehensive methods for assessing nutritional status.

Albumin levels are used to estimate preoperative nutritional status, given the ease of quantitative measurement. Hypoalbuminemia is associated with poor wound healing, decreased collagen synthesis in wounds and impaired immune function (14,15). One limitation of this assessment is that it estimates mid- and long-term nutritional status only, as its half-life is approximately 20 days (16). In a retrospective review of 268 patients with pancreatic adenocarcinoma (PDAC) who underwent PD at a single institution in Japan, Kanda *et al.* (17) found hypoalbuminemia, defined as serum albumin <4.0 g/dL, to be a risk factor for developing post-operative pancreatic fistula (POPF) as well as an independent risk factor for all cause postoperative morbidity. This was confirmed by Fujiwara *et al.* (18), whose multivariate analysis found lower average serum albumin levels were an independent risk factor for developing a grade B or C fistula [International Study Group of Pancreatic Fistula (ISGPF) (19)]. Similarly, in a series of 143 pancreatic and periampullary cancer patients treated with either DP or PD, La Torre *et al.* found severe hypoalbuminemia (≤2.5 g/dL) was independently associated with increased morbidity (20).

Unintentional weight loss is common in cancer patients and is intimately related to malnutrition in the setting of cancer. A single-institution series from Germany including 408 pancreatic cancer patients who underwent PD found that patients with unintentional weight loss >10% of their previous body weight had higher operative, non-operative and overall complications compared to those with <10% weight loss (21). Patients with unintentional weight loss also had significantly lower albumin levels than those without weight loss. Loh *et al.* (22), in a study of 104 cancer patients of whom 53 had pancreatic cancer, confirmed this link, finding unintentional weight loss to be independently correlated with malnutrition.

Clinical scoring systems for quantifying malnutrition include the Malnutrition Universal Screening Tool (MUST), the Nutritional Risk Index (NRI), the Instant Nutritional Assessment (INA), the Prognostic Nutrition Index (PNI), and the abridged Patient Generated Subjective Global Assessment (aPG-SGA).

MUST scores, used in the previously mentioned study by Loh *et al.* to correlate unintentional weight loss and malnutrition, incorporates unintentional weight loss, BMI, and C-reactive protein (CRP) into a weighted score. Higher percentages of weight loss, lower BMI, and higher CRP values correlate with increasing severity of malnutrition. La Torre *et al.* (20) found that MUST scores ≥1 predict longer hospital stay, increased postoperative morbidity, and increased incidence of surgical site infections (SSI) in a study of 143 pancreatic cancer patients from Italy. A MUST score ≥1 was also found to be independently correlated with postoperative morbidity on multivariate analysis.

The NRI assessment includes both albumin level and weight loss to quantify nutritional status, while the INA score is calculated using albumin levels and blood lymphocyte count. Sierzega *et al.* (23) reported findings of a single institution study of 132 patients undergoing DP for pancreatic pathology (76 of whom had malignancy). An NRI score ≤100 was an independent risk factor for developing a POPF. Additionally, the rate of an abnormal INA was significantly higher in patients who developed POPF. A Japanese study found an NRI score ≤97.5 to be an independent risk factor for developing an SSI after PD (24).

Onodera's PNI (25), a verified nutritional risk score from

Japan, is composed of albumin level and lymphocyte count. Kanda *et al.* (17) found that a PNI <45 is an independent risk factor for postoperative complications and the development of ISGPF grade B or C fistula following DP and PD. This finding was confirmed in a study of 87 patients undergoing PD primarily for pancreatic or periampullary cancer (26). These investigators also compared the ratio of BMI to PNI (BMI/PNI ratio) in patients with POPF to those without fistulas, and found the BMI/PNI ratio was significantly higher among patients with fistulas. Interestingly, using receiver operating characteristic curve analysis, a BMI/PNI ratio of 0.5 was found to more accurately predict the occurrence of POPF than either BMI or PNI alone, and was found to have a sensitivity, specificity, and diagnostic accuracy of 73%, 74%, and 74%, respectively.

The Patient Generated Subjective Global Assessment (PG-SGA) score, a nutritional assessment specific to oncology patients, combines results from a patient questionnaire and a physical exam by a licensed clinician to determine functional nutritional status. Several studies have found it to be effective at identifying malnutrition (27,28). An abridged version of the score, aPG-SGA, was used by Vigano *et al.* (29), in a study of 207 cancer patients including those with pancreatic cancer, to identify malnourished patients. A score ≥9 was correlated with 12% longer hospital stay, more dose reductions in chemotherapy, and increased mortality. In contrast to the findings of many previously mentioned studies, a prospective study of 279 patients undergoing pancreatic resection by Probst *et al.* (30) did not find a significant correlation between complication rates and malnutrition scoring assessments. Each patient in this study was evaluated by 12 nutritional assessments, including NRI, SGA, and MUST, and none were found to be independent predictors of postoperative complications. The authors acknowledged the controversial findings, and suggest the prospective nature of their study and shorter enrollment period as possible reasons for the unexpected results. They note that the studies demonstrating significant links between malnutrition scores and surgical outcomes were retrospective and some had recruitment periods of up to 20 years, increasing the likelihood of confounders.

Intervention

The ability to optimize nutritional status pre- and post-operatively has the potential to decrease morbidity and improve outcomes. Nutritional support may be delivered by enteral or parenteral means, and may incorporate standard, enriched, or immune enriched formulas.

Several studies have investigated preoperative nutrition and the role it plays in reducing complication rates. Braga *et al.* (31) performed a prospective, double blind trial with 171 patients with stomach, colorectal, or pancreas cancer, with equal numbers of malnourished patients per group. Patients were randomized to receive either standard enteral formula or enriched (arginine, RNA, omega-3 fatty acids) formula along with a standard diet 7 days prior to surgery and received the same formula via jejunostomy tube starting 6 hours after surgery. Patients receiving enriched formula had significantly fewer infectious complications, 11% *vs.* 24%, P=0.02, regardless of preoperative nutritional status. Additionally, the enriched formula cohort had a shorter mean duration of antibiotic therapy when needed for treatment of infectious complications and shorter length of stay (LOS) compared to the standard formula cohort. In a separate randomized trial, Braga *et al.* (32) compared preoperative (7 days preoperative enriched formula followed by standard formula postoperatively) and perioperative (7 days preoperative enriched formula followed by enriched formula postoperatively) nutrition to standard (standard formula postoperatively only) nutrition in 150 malnourished patients with ≥10% weight loss. Pre- and perioperative groups had shorter LOS compared to the standard control group, and the perioperative group had significantly fewer complications than both the preoperative and control groups.

Nutritional support following major pancreatic resection for cancer is challenging, and attempts to improve it have had mixed results. The advent of total parenteral nutrition (TPN) offered the possibility to improve nutrition in malnourished patients who were unable to tolerate adequate enteral intake. However, a prospective study from Memorial Sloan Kettering in 1994 by Brennan *et al.* (33) randomized 117 patients with pancreatic cancer after resection to either receive adjuvant TPN or not receive it. The group that received TPN had higher rates of major complications, namely abscesses, obstruction, fistula, anastomotic leak, and reoperation, compared to those that did not receive TPN, leading the authors to recommend against routine application of TPN postoperatively following pancreatic resection.

Enteral nutrition therefore remains the modality of choice following resection for pancreatic cancer when possible. A systematic review from 2013 by Gerritsen *et al.* (34) found that patients fed with enteral nutrition after pancreatic surgery via oral route or gastrojejunostomy tube had shorter LOS than those fed with TPN. Additionally, those fed with oral nutrition returned to a normal diet faster than all other feeding methods. Complications were lowest in the jejunostomy tube and oral feeding cohorts; however, specific complications were not explicitly stated. Lassen *et al.* (35), in a randomized, multi-center trial, compared at-will oral feeding to enteral feeding via jejunostomy tubes in patients undergoing major abdominal surgery. The rate of major complications for the 453 patients, of whom 25% underwent PD or DP, were significantly lower in the at-will feeding group when compared to the jejunostomy tube group, 46% *vs.* 73%, P=0.012, respectively. Mean time to flatus and mean hospital LOS were both significantly shorter in the at-will feeding group. In a subgroup analysis, adjusting for the presence or absence of an upper gastrointestinal anastomosis, there was no significant difference in major complications between groups. This study suggests that, while at-will oral feeding is the preferred route of enteral feeding, jejunostomy tubes are comparable and provide a viable option when an oral diet isn't clinically feasible.

To address whether immune enriched formulas are superior to standard formula for post-operative enteral feeding, Klek *et al.* (36) performed a randomized, double-blinded study of 305 gastric or pancreatic cancer patients with malnutrition, defined by BMI <18 or unintended weight loss ≥10%, and randomized them to receive either immunomodulating formula or standard oligopeptide formula starting 6 hours postoperatively. "Immunomodulating" refers to the addition of essential nutrients and immune system influencing agents, such as omega-3-fatty acids, glutamine, arginine, nucleotides and anti-oxidants, to enteral or parenteral nutrition (37). Patients receiving the immunomodulating formula had significantly fewer infectious complications and lower overall morbidity when compared to the standard oligopeptide group. However, a recent meta-analysis by Probst *et al.* consisting of 83 randomized controlled trials of patients undergoing major abdominal surgery contradicts these findings (38). The authors performed a risk-of-bias assessment, and after excluding studies with high or unclear risk for bias, concluded that immunonutrition had no significant effect on mortality, overall complications, infectious complications or hospital LOS. Furthermore, the study found that industry-funded trials demonstrated a greater impact on these parameters when compared to non-industry trials. However, subgroup analyses supported the notion that malnourished patients, those with malignant disease, and those undergoing hepatopancreaticobiliary procedures did show benefit from immunonutritional intervention. Thus, while this and several other studies report conflicting results (39-41), perhaps immune enhanced nutrition may be beneficial in select groups of patients.

Based on this, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend 10–14 days of standard enteral nutrition preoperatively in malnourished patients, adding that immune enhanced enteral nutrition is preferable, regardless of nutritional status (42). The Enhanced Recovery After Surgery (ERAS) Society protocol for pancreatic cancer, however, stresses the initiation of a postoperative regular diet with stepwise advancement, and downgrades recommendations for enriched and preoperative nutrition to "weak" (43). A review from Bozzetti *et al.* (44) analyzing ESPEN guidelines and the ERAS Society protocol for pancreatic cancer concluded that, despite the ESPEN recommendations being generalized to all gastrointestinal surgery and potentially outdated, they were supported by the literature. Indeed, the authors recommended further integration of ESPEN and ERAS guidelines for optimal risk reduction in malnourished patients.

Summary

We recommend incorporation of preoperative albumin and percent of unintentional body weight lost into preoperative risk assessment. While it intuitively makes sense to incorporate assessment of inflammation via lymphocyte count or CRP levels into nutrition risk scores as is done in the MUST, INA, and PNI scores, the utility of doing so has not been confirmed in prospective studies of pancreatic cancer patients. All currently reported nutritional scores lack one potentially useful component or another. At this point, until a standard clinical scoring system is agreed upon, we recommend surgeons routinely use at least one assessment of malnutrition that can be reliably obtained in their patients.

Perioperative TPN in pancreatic cancer patients following surgical resection increases complication rates and should not be routinely implemented. While postoperative enteral nutrition via PO diet seems ideal following PD according to the literature, in practice this is challenging for multiple reasons, including high rates of delayed gastric emptying, opioid-induced nausea, and patient motivation. The Lassen study (35) and Gerritsen review (34) discussed above demonstrate that, while enteral nutrition is clearly superior to TPN, route of delivery is less important. Immune-enriching enteral formula seems appropriate in malnourished patients, as level I evidence supports this practice. Preoperative enteral nutritional support in malnourished patients, alone or as part of a multi-modal pre-habilitation regimen, improves outcomes and should be considered by all centers.

Frailty

Frailty is defined as a clinical decline in physical and mental function with or without the presence of disease (45). However, one cannot assume that an older adult is frail based on chronologic age alone. Therefore, it is important to distinguish between chronologic age and functional or physiologic age. Frailty is distinguished from chronological aging by Mogal *et al.* (46) as a state of decreased physiologic reserve arising from deficits in multiple homeostatic systems accumulating to produce greater susceptibility and less resilience to physiologic stressors. Surgeons often rely on a patient's age to determine their ability to tolerate the stress of a major operation. Multiple other factors, including cardiac health, diabetes mellitus status, and neurologic deficits, however, have been shown to contribute more than age to a patient's physiologic reserve in terms of how they may respond to surgical stress. Rigorous assessments of frailty can be difficult to obtain, can lack consistency between different clinician assessments, and can be time-intensive in clinical settings.

Assessment and implications

Many attempts have been made to define and quantify frailty, including the Charlson Comorbidity Index (CACI), Fried's Frailty Index (FFI), and more recently the Modified Frailty Index (mFI). Dias-Santos *et al.* (47) utilized the age-adjusted CACI to assess correlation of this score with morbidity and mortality in 497 patients following resection for PDAC. The score accounts for acute and chronic conditions, such as previous myocardial infarction, dementia, diabetes, cancer, liver disease, and the presence of HIV/AIDS. The authors found that a CACI ≥4 increased the odds of postoperative complications by 52% (OR =1.52; 95% CI: 1.01–2.28, P=0.042). Additionally, CACI ≥ 4 doubled the odds of a LOS ≥10 days, and increased the odds of discharge to a rehabilitation facility by 6-fold. However, CACI does not include elements of functional status, and many of the comorbidities included in this index may be variably controlled in different patients, limiting its reliability.

The mFI is a model of frailty centered on the theory of accumulating deficits (48). The mFI is derived from the 70-point frailty index developed by the Canadian Study of Health and Aging (CSHA-FI), and substitutes items on the original CSHA-FI for corresponding variables from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database to create the mFI (49). In contrast to CACI, the variables in the mFI are derived from NSQIP data and therefore are generally only present if they have been recently documented. There are 11 different variables utilized in the mFI, including the presence of pre-existing chronic medical conditions, impaired sensorium, previous acute events such as myocardial infarction or stroke, and previous invasive intervention (see *Table S1*). Each item is allocated an equal weight of 1 point (46), and some studies divide the final score by 11 to obtain a ratio. Previous studies have demonstrated a score of 0.25 to be roughly the cutoff between "robust" and "frail" individuals (50-52). Mogal *et al.* (46) found that an mFI score ≥0.27 to be an independent predictor of major morbidity, classified by Clavien-Dindo grade III or IV, in patients following PD. Augustin *et al.* (53) performed a retrospective review of 13,020 patients from the ACS-NSQIP database who underwent PD or DP, and found on multivariate analysis that each 1-point increase in mFI score independently predicted Clavien-Dindo grade IV complications. Obeid *et al.* (49) found increasing mFI to be an independent predictor of Clavien-Dindo grade IV and V complications in colectomy patients, as well.

Components of the FFI include self-reported unintentional weight loss ≥10 lbs per year, height-adjusted slow gait speed, gender-adjusted grip strength, as well as self-reported patient exhaustion (54). Dale *et al.* (54) found that self-reported exhaustion, measured by at least one positive response to a two question exhaustion survey, independently predicts poor outcomes following PD, including complications classified as Clavien-Dindo grade III or higher, ICU admission, and increased hospital LOS. While self-reported exhaustion is easy to determine, it is subjective, and may be either under or over-reported by patients. Self-reported exhaustion has clinical utility if considered provisionally, but objective measurements are more consistent. However, in a prospective study of 104 patients undergoing PD, Sur *et al.* (55) found that Fried's exhaustion criteria independently predicted serious complications and increased hospital LOS. Furthermore, using receiver operating characteristic curve analysis, the authors found that combining radiographically defined sarcopenia with Fried's exhaustion criteria enhanced the ability of base clinical values, including age, BMI, American Society of Anesthesiologists score, and modified Charlson comorbidity score, to predict serious postoperative complications.

Intervention

Both frailty and sarcopenia (discussed below) have been proposed as potential comprehensive measurements of an individual's overall health status. As a consequence of their similarities, interventions affecting one are likely to affect the other. Interventions both for frailty and sarcopenia are discussed together, below.

Summary

Methods for assessing frailty, such as CACI, focus on the presence or absence of comorbid conditions, as opposed to their severity. Additionally, CACI lacks assessment of functional status. The FFI has self-reported exhaustion as a major component, which is subjective and vulnerable to bias. However, several level II studies suggest that self-reported exhaustion independently predicts major complications following surgery.

Abbreviated assessment methods, such as the mFI, risk over-simplifying a complex condition such as frailty. However, several studies show that complex assessments are less ideal for clinical screening (56-59) and are infrequently used by surgeons when assessing cancer patients (60). The mFI has been validated by level II studies. However, the score itself is based on the limited data fields within ACS-NSQIP, therefore potentially missing key variables. Even with these limitations, however, frailty scores can be used to improve pre-operative counseling and risk assessment. Finally, frailty scores may also be useful in identifying patients that would benefit from minimally invasive procedures as shown by Konstantinidis *et al.* (61), in a study of 1,038 patients undergoing DP.

Sarcopenia

Sarcopenia is defined as the loss of lean muscle mass (62). It is a distinct entity from cancer related weight loss and cachexia and is complementary to frailty assessments (63,64). Sarcopenia is also easily obtained and quantified. It is not surprising, therefore, that it is an area of interest in cancer research, especially as increasing reports have shown a correlation with poor postoperative outcomes and sarcopenia in cancer patients (65,66). Recently, investigators have recognized that sarcopenia may be present and at risk for under-diagnosis in overweight or obese individuals, and have coined the term sarcopenic obesity.

Assessment and implications

In a retrospective review of 763 PDAC patients undergoing resection at Johns Hopkins University, Amini *et al.* (67) compared sarcopenia defined by standard total psoas area (TPA) to total psoas volume (TPV). They found that sarcopenia defined by TPV was associated with increased hospital LOS and was an independent risk factor for major postoperative complications, specifically renal complications and bile leaks. Moreover, when stratified into quartiles based on TPV, those in the lowest quartile were found to have the highest rate of complications. Similarly, Joglekar *et al.* (68), in a retrospective review of 118 patients with PDAC undergoing resection, analyzed postoperative complications related to sarcopenia, quantified by Hounsfield Unit Average Calculation (HUAC) and Total Psoas Index (TPI) (*Table S1*). Sarcopenia quantified by TPI was independently predictive of hospital LOS, while the HUAC method was independently predictive of increase hospital LOS and ICU stay, delayed gastric emptying, cardiac, infectious, gastrointestinal, pulmonary, overall and major grade III (Common Toxicity Criteria for Adverse Events) complications.

Other studies have corroborated these findings in pancreatic cancer patients. Nishida *et al.* (69), in a retrospective review of 266 patients undergoing PD for cancer, found sarcopenia to be an independent risk factor for developing a clinically relevant ISGPF grade B or C fistula. Vugt *et al.* (70), in a retrospective review of 452 patients with a mixture of gastrointestinal malignancies (10% pancreatic/periampullary), found sarcopenia to be associated with increased complications and an increased hospital LOS. In both studies, sarcopenia was defined using cross-sectional psoas muscle area measured on computed tomography (CT) slices at the L3 vertebrae and quantified using the Skeletal Muscle Index (SMI). Interestingly, Vugt *et al.* also conducted a cost analysis and found sarcopenia to be independently associated with increased total hospital cost, both in patients with and without major complications.

However, there are reports of conflicting findings. Sui *et al.* (5), in a prospective study of 354 patients undergoing PD for cancer, found no difference in major complications between sarcopenic and non-sarcopenic patients. In fact, on univariate analysis, the POPF rate was higher in the non-sarcopenic patients. Sarcopenia, in that study, was again quantified by psoas muscle area estimated from CT slices at L3 and quantified using SMI. In a study from Johns Hopkins preceding the work of Amini *et al.* (67), Peng *et al.* (71) performed a study involving 557 patients undergoing resection of PDAC and found that sarcopenia, quantified by TPA, was not significantly predictive of hospital LOS, ICU stay, overall morbidity or major complications. It appears, therefore, that the method used to diagnose and quantify sarcopenia is important and may significantly influence complications rates. Further studies are needed to compare different methods for quantifying sarcopenia in pancreatic cancer patients to clarify these conflicting findings.

Sarcopenic obesity describes presence of sarcopenia in overweight or obese individuals. Interest in this area has increased as studies have emerged finding sarcopenic obesity as a prognostic factor in pancreatic cancer patients (64,72). While obesity is defined as BMI ≥30 kg/m^2 and increased BMI has been shown to correlate with increased morbidity and fistula rates following pancreas surgery (5,26,73), several studies have found central obesity and visceral fat area (VFA) to be a superior, independent predictor of complications and fistula rate following surgery (74,75). It is therefore important to consider central obesity in addition to BMI when analyzing sarcopenic obesity.

Sandini *et al.* (76), in a retrospective review of 124 patients who underwent PD, 75% with cancer, defined sarcopenia using total abdominal muscle area (TAMA) and obesity as BMI ≥25 kg/m^2. Additionally, they focused on total fat area and volume (TFA, TFV) and VFA and visceral fat volume (VFV). All muscle and adipose tissue measurements were calculated from preoperative CT slices at the level of L3. The authors found sarcopenic obesity to correlate with increase DGE, abscess formation, pulmonary and cardiac complications. VFA, VFV, and TFV were also found to predict higher rates of complications classified by Clavien-Dindo scores ≥3. Additionally, when controlling for confounders on multivariate analysis, higher VFA/TAMA ratio was independently predictive of increased postoperative complications.

In a study from the Mayo Clinic, Kirihara *et al.* (77) used preoperative CT slices at level of the L3 vertebrae to calculate skeletal muscle (SM) mass as a surrogate for sarcopenia and visceral (VAT) and subcutaneous adipose tissue (SAT) areas as adjuncts to quantify central obesity. The authors found decreased SM area and increased VAT area were independent risk factors for developing a clinically relevant pancreatic fistula. While their numbers were low, with only 7 of 173 patients having sarcopenic obesity (sarcopenia + BMI ≥30 kg/m^2), the clinically relevant fistula rate was 86% (6/7) in those with sarcopenic obesity versus 10% (16/166) in those without. Furthermore, using the results from their multivariable analysis, they created and compared several 2-factor predictive models for clinically relevant POPF, and the predictor with the highest concordance rate (C-index =0.959) was VAT + SM. This is significantly higher than established predictors such as BMI + pancreatic duct size (C-index =0.748) or pancreatic duct size + parenchymal texture (C-index =0.688), suggesting that sarcopenic obesity quantified by high VAT area and low SM area accurately predicts POPF.

Intervention

Incorporating frailty scores and measures of sarcopenia into comprehensive pre-habilitation programs is one possible direction for future studies. As discussed above, cancer patients are particularly vulnerable to both frailty and sarcopenia due to disease-induced catabolism and inflammation. Both conditions are linked to worse peri-operative outcomes, leading many investigators to test interventions aimed at improving both parameters. While there is little high-quality evidence testing such interventions in pancreatic cancer patients specifically, an emerging body of work suggests potential benefits to pre-operative programs incorporating exercise and nutritional support in frail and sarcopenic patients.

Data regarding physical activity and exercise improving postoperative morbidity in pancreatic cancer patients is limited. However, in a randomized, controlled trial from Denmark, Adamsen *et al.* studied 269 patients undergoing active treatment, including surgery, for various cancers, and compared an intensive exercise regimen to standard, non-structured activity (78). Outcomes included health-related quality of life (HRQoL), fatigue, treatment side effects, and general physical and emotional well-being and were determined via different questionnaires. The study found that regimented exercise significantly reduced fatigue, increased general physical and emotional well-being, and increased physical functioning. Interestingly, there was no significant improvement in HRQoL. A systematic review by Loughney *et al.* evaluating exercise training in cancer patients undergoing adjuvant chemotherapy after surgery found several level I studies noting significant improvement in domains of HRQoL following exercise intervention (79). The exercise regimens varied in length and intensity but generally consisted of aerobic and resistance training ranging from 6- to 17-week periods. The study found mixed results regarding the effects of exercise on cancer related fatigue.

Sebio Garcia *et al.* performed a random-effects meta-analysis focused on postoperative outcomes in lung cancer patients, comparing those that underwent preoperative exercise intervention to those that did not (80). A significant reduction in both hospital LOS and postoperative complications was found, however the authors note a substantial level of heterogeneity when comparing postoperative complications. The study included a systematic review of parameters where heterogeneity in the populations was too high to perform a meta-analysis, and when examining HRQoL, the study found no significant improvement in any major domains. In contrast, Mishra *et al.*, in a large Cochrane review, performed a meta-analysis specifically focused on HRQoL, consisting of 56 trials with 4,826 participants with cancer undergoing or scheduled to undergo treatment (81). The study found significant improvement in HRQoL with exercise intervention compared to control. Furthermore, the authors noted significant improvement in physical functioning, decreased fatigue, and improvements in various psychological aspects including decreased anxiety, depression, and sleep disturbances. Further emphasizing the benefit of preoperative exercise intervention, a meta-analysis by Santa Mina *et al.* showed a significant reduction in hospital LOS with preoperative exercise intervention compared to controls (82).

Protein supplementation is an integral part in building muscle and increasing strength, and therefore is important to incorporate into programs aimed at correcting deficits in these fields. In a prospective trial from the Netherlands, Tieland *et al.* randomized 65 frail individuals ≥65 years old to receive either protein supplementation drinks versus placebo drinks twice per day for 24 weeks and compared physical performance, muscle mass and strength over time (83). Frailty was defined using Fried's criteria. The study found that physical performance, assessed by the short physical performance battery, was significantly improved with protein supplementation versus placebo. However, SM mass, measured by dual energy X-ray absorptiometry (DXA) scan, handgrip strength, and muscle strength, measured by leg press and leg extension, were all similar between those with protein supplementation and those without.

Combination therapy, utilizing nutritional optimization and exercise regimens, has promising findings when implemented in sarcopenic and frail adults. In a randomized, controlled trial from Japan, Kim *et al.* studied 155 women ≥75 years old defined as sarcopenic by several different methods, including appendicular SM mass measured by bioelectrical impedance, knee extension strength, walking speed, and BMI, to see if regular exercise, amino acid supplementation (AAS), or a combination would improve sarcopenia (84). The study randomized participants to intervention groups: exercise + AAS, exercise alone, AAS alone, and health education alone. Exercise consisted of a moderate intensity program consisting of 60-minute sessions twice per week for 3 months. Essential AAS was provided via packets of powder mixed with water or milk, 3 grams were taken twice daily for 3 months. The authors found that appendicular muscle mass and walking speed increased with exercise, AAS, and exercise + AAS groups, however muscle strength improved only in the exercise + AAS group. They concluded that a combination of nutritional supplementation with essential amino acids and regular exercise may improve sarcopenia in women.

Rosendahl *et al.* performed a randomized, blinded prospective trial in individuals aged ≥65 years with dependence in at least one activity of daily living (85). The authors randomized patients into 4 different combinations of groups with interventions of protein-enriched energy supplemented drinks and high-intensity exercise intervention compared to standard activity and protein-poor placebo drinks. Balance, gait ability, and lower-limb strength were compared between groups using the Berg Balance Scale, a 2.4-meter timed walking test, and a combination of leg press 1-repetition maximum and modified chair-stand test, respectively. The study found that exercise intervention, and not exercise combined with protein enriched nutrition or enriched nutrition alone, had significant improvement in gait speed, balance, and lower limb strength. Similarly, Arnarson *et al.* conducted a randomized, double-blind prospective trial of 161 Icelandic men and women between 65–91 years old randomized to receive whey protein or isocaloric carbohydrate drinks following a resistance-based exercise program (86). Lean body mass via DXA scan, muscle strength via knee extension and maximum voluntary quadriceps isometric contraction test, and physical function via timed up-and-go test and 6-minute walk-for-distance test, were used as primary endpoints. The authors found no difference between appendicular SM mass, quadriceps strength, and physical function between groups. However, all outcomes were significantly improved in both groups throughout the study, suggesting the exercise regimen and not the protein supplementation aided in the notable improvements in strength, SM composition, and physical function.

The notion of multimodal pre-habilitation programs in patients undergoing surgery is appealing, combining the positive effects of nutrition, exercise, education, counseling and stress-coping strategies. Studies have shown health benefits in non-surgical, frail patients undergoing multimodal care emphasizing exercise and nutritional supplementation (87). The concept is relatively novel, and few studies exist that show a benefit in cancer patients undergoing surgery. Minnella *et al.* analyzed the results of 3 studies from the same group, 1 pilot study and 2 randomized trials, resulting in a total of 185 participants scheduled for elective resection of colorectal cancer (88). The authors compared trimodal prehabilitation to postoperative trimodal rehabilitation. Both programs consisted of an exercise regimen, nutrition supplementation/education, and coping strategies for anxiety. Outcomes included estimates of functional capacity via 6-minute walk test and postoperative complications. The study found that patients who underwent prehabilitation had significantly increased functional capacity compared to the rehab/control group at every postoperative interval. However, they found no difference in postoperative complications between groups. This is still a developing area of research without evidence to support the implementation in pancreas cancer patients. The Society of Perioperative Assessment and Quality Improvement (SPAQI) acknowledges the potential benefits yet advocates for further studies before suggesting multimodal prehabilitation programs as standard of care (89).

Summary

Sarcopenia is an independent predictor of increased hospital LOS, increased complications and increased POPF rates in pancreas cancer patients after surgery. Sarcopenic obesity, as well as central obesity, are both predictive of worse outcomes following surgery. While other predictors of sarcopenia exist, such as grip strength, gait speed, and exhaustion level, these tests can be difficult and time consuming to evaluate, while calculating muscle and fat area and volume in preoperative CT scans is consistent and easily reproducible. Evaluating sarcopenia using TPV seems to more accurately predict complications compared to TPA, and should preferentially be used to estimate sarcopenia. Obesity is generally classified using BMI ≥30 kg/m^2, and extremes of BMI tend to correlate with increased complications and fistula rates. However, it is clear that BMI can inaccurately assess obesity in uncommon body types, such as extremes of height, age, and muscularity (90). Separate methods for estimating central obesity, such as using CT scans to calculate visceral and TFA and TFV, may enhance our ability to detect obese patients and more accurately risk stratify these individuals. Further prospective studies are needed to determine the accuracy of these methods for assessing central obesity and validate the predictive models that incorporate them, such as VAT + SM and VFA/TAMA.

There is a lack of evidence specifically addressing interventions aimed at improving frailty and sarcopenia in pancreatic cancer patients undergoing surgery. It is clear that regimented exercise programs in frail or sarcopenic individuals improve strength and functional capacity. The role of nutritional supplementation, specifically protein and amino acid-based formulas, is less clear. This is likely because frailty is not consistently defined across studies, allowing for inconsistencies with regard to treatment efficacy. Furthermore, evidence regarding subjective outcomes, such as HRQoL and fatigue, are subject to detection, attrition, and selection biases. However, frailty and sarcopenia have significant effects on outcomes in patients with PDAC, and therefore further study of interventions aimed at improving these parameters is critical.

Overall, available evidence suggests that malnutrition, sarcopenia and frailty are issues that are not only common among patients with pancreatic cancer, but also negatively affect outcomes for patients undergoing surgical treatment for pancreatic cancer. However, the true extent to which these parameters impact patients is limited by the quality of available data. A current limitation of the literature is the lack of prospective trials with *a priori* defined inclusion criteria for diagnosing malnutrition, sarcopenia and frailty. While many composite scores exist to diagnose and categorize these conditions, available studies are primarily retrospective in nature or focus on retrospective analysis of prospectively maintained databases. This potentially introduces bias when defining patient cohorts and limits the applicability of results. A prospective study designed with pre-determined endpoints for defining these conditions may improve our understanding of their impact on clinical outcomes and allow medical practitioners to better assess risk based on these criteria in a clinically relevant manner. Furthermore, variability in parameters used to define and assess these conditions as well as various types of bias that influence outcomes of current studies limits the applicability of available data. Future studies may consider focusing on prospectively obtained data in well-defined patient cohorts with a priori determined endpoints. As the fields of medicine and surgery become more specialized in the setting of a growing population of patients susceptible to these conditions, understanding how particular subsets of patients are impacted by these common yet deleterious conditions is increasingly important.

Acknowledgments

Funding: This work was supported in part by NIH-funded Ruth L. Kirschstein National Research Service Award (NRSA): T32 CA126607-10.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Yingbin Liu and Wei Gongi) for the series “The 8th Annual International Surgery Forum” published in *Annals of Pancreatic Cancer*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ apc.2019.02.01). The series “The 8th Annual International Surgery Forum” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Parikh PY, Lillemoe KD. Surgical management of pancreatic cancer--distal pancreatectomy. Semin Oncol 2015;42:110-22.
2. Behrman SW, Rush BT, Dilawari RA. A modern analysis of morbidity after pancreatic resection. Am Surg 2004;70:675-82; discussion 682-3.
3. Schmidt CM, Powell ES, Yiannoutsos CT, et al. Pancreaticoduodenectomy: a 20-year experience in 516 patients. Arch Surg 2004;139:718-25; discussion 725-7.
4. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg 2006;10:1199-210; discussion 1210-1.
5. Sui K, Okabayshi T, Iwata J, et al. Correlation between the skeletal muscle index and surgical outcomes of pancreaticoduodenectomy. Surg Today 2018;48:545-51.
6. Sugimoto M, Takahashi S, Kojima M, et al. In Patients with a Soft Pancreas, a Thick Parenchyma, a Small Duct, and Fatty Infiltration Are Significant Risks for Pancreatic Fistula After Pancreaticoduodenectomy. J Gastrointest Surg 2017;21:846-54.
7. Berger AC, Howard TJ, Kennedy EP, et al. Does type of pancreaticojejunostomy after pancreaticoduodenectomy decrease rate of pancreatic fistula? A randomized, prospective, dual-institution trial. J Am Coll Surg 2009;208:738-47; discussion 747-9.
8. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786-95.
9. Braga M, Capretti G, Pecorelli N, et al. A prognostic score to predict major complications after pancreaticoduodenectomy. Ann Surg 2011;254:702-7; discussion 707-8.
10. Yeo TP. Demographics, epidemiology, and inheritance of pancreatic ductal adenocarcinoma. Semin Oncol 2015;42:8-18.
11. Jensen GL, Compher C, Sullivan DH, et al. Recognizing malnutrition in adults: definitions and characteristics, screening, assessment, and team approach. JPEN J Parenter Enteral Nutr 2013;37:802-7.
12. Sungurtekin H, Sungurtekin U, Balci C, et al. The influence of nutritional status on complications after major intraabdominal surgery. J Am Coll Nutr 2004;23:227-32.
13. Bozzetti F. Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. Support Care Cancer 2009;17:279-84.
14. Rivadeneira DE, Grobmyer SR, Naama HA, et al. Malnutrition-induced macrophage apoptosis. Surgery 2001;129:617-25.

15. Reynolds JV, Redmond HP, Ueno N, et al. Impairment of macrophage activation and granuloma formation by protein deprivation in mice. Cell Immunol 1992;139:493-504.
16. Irvin TT, Hunt TK. Effect of malnutrition on colonic healing. Ann Surg 1974;180:765-72.
17. Kanda M, Fujii T, Kodera Y, et al. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg 2011;98:268-74.
18. Fujiwara Y, Shiba H, Shirai Y, et al. Perioperative serum albumin correlates with postoperative pancreatic fistula after pancreaticoduodenectomy. Anticancer Res 2015;35:499-503.
19. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8-13.
20. La Torre M, Ziparo V, Nigri G, et al. Malnutrition and pancreatic surgery: prevalence and outcomes. J Surg Oncol 2013;107:702-8.
21. Pausch T, Hartwig W, Hinz U, et al. Cachexia but not obesity worsens the postoperative outcome after pancreatoduodenectomy in pancreatic cancer. Surgery 2012;152:S81-8.
22. Loh KW, Vriens MR, Gerritsen A, et al. Unintentional weight loss is the most important indicator of malnutrition among surgical cancer patients. Neth J Med 2012;70:365-9.
23. Sierzega M, Niekowal B, Kulig J, et al. Nutritional status affects the rate of pancreatic fistula after distal pancreatectomy: a multivariate analysis of 132 patients. J Am Coll Surg 2007;205:52-9.
24. Shinkawa H, Takemura S, Uenishi T, et al. Nutritional risk index as an independent predictive factor for the development of surgical site infection after pancreaticoduodenectomy. Surg Today 2013;43:276-83.
25. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi 1984;85:1001-5.
26. Sato N, Tamura T, Minagawa N, et al. Preoperative body mass index-to-prognostic nutritional index ratio predicts pancreatic fistula after pancreaticoduodenectomy. Hepatobiliary Surg Nutr 2016;5:256-62.
27. Bauer J, Capra S, Ferguson M. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr 2002;56:779-85.
28. Velasco C, Garcia E, Rodriguez V, et al. Comparison of four nutritional screening tools to detect nutritional risk in hospitalized patients: a multicentre study. Eur J Clin Nutr 2011;65:269-74.
29. Vigano AL, di Tomasso J, Kilgour RD, et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. J Acad Nutr Diet 2014;114:1088-98.
30. Probst P, Haller S, Bruckner T, et al. Prospective trial to evaluate the prognostic value of different nutritional assessment scores in pancreatic surgery (NURIMAS Pancreas). Br J Surg 2017;104:1053-62.
31. Braga M, Gianotti L, Radaelli G, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg 1999;134:428-33.
32. Braga M, Gianotti L, Nespoli L, et al. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg 2002;137:174-80.
33. Brennan MF, Pisters PW, Posner M, et al. A prospective randomized trial of total parenteral nutrition after major pancreatic resection for malignancy. Ann Surg 1994;220:436-41; discussion 441-4.
34. Gerritsen A, Besselink MG, Gouma DJ, et al. Systematic review of five feeding routes after pancreatoduodenectomy. Br J Surg 2013;100:589-98; discussion 599.
35. Lassen K, Kjaeve J, Fetveit T, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. Ann Surg 2008;247:721-9.
36. Klek S, Sierzega M, Szybinski P, et al. The immunomodulating enteral nutrition in malnourished surgical patients - a prospective, randomized, double-blind clinical trial. Clin Nutr 2011;30:282-8.
37. Turczynowski W, Szczepanik AM, Klek S. Nutritional therapy and the immune system. Przegl Lek 2000;57:36-40.
38. Probst P, Ohmann S, Klaiber U, et al. Meta-analysis of immunonutrition in major abdominal surgery. Br J Surg 2017;104:1594-608.
39. Alivizatos V, Athanasopoulos P, Makris N, et al. Early postoperative glutamine-supplemented parenteral nutrition versus enteral immunonutrition in cancer patients undergoing major gastrointestinal surgery. J buon 2005;10:119-22.
40. Heyland DK, Novak F, Drover JW, et al. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. Jama 2001;286:944-53.
41. Helminen H, Raitanen M, Kellosalo J. Immunonutrition

in elective gastrointestinal surgery patients. Scand J Surg 2007;96:46-50.
42. Weimann A, Braga M, Harsanyi L, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr 2006;25:224-44.
43. Lassen K, Coolsen MM, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr 2012;31:817-30.
44. Bozzetti F, Mariani L. Perioperative nutritional support of patients undergoing pancreatic surgery in the age of ERAS. Nutrition 2014;30:1267-71.
45. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
46. Mogal H, Vermilion SA, Dodson R, et al. Modified Frailty Index Predicts Morbidity and Mortality After Pancreaticoduodenectomy. Ann Surg Oncol 2017;24:1714-21.
47. Dias-Santos D, Ferrone CR, Zheng H, et al. The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. Surgery 2015;157:881-7.
48. Velanovich V, Antoine H, Swartz A, et al. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res 2013;183:104-10.
49. Obeid NM, Azuh O, Reddy S, et al. Predictors of critical care-related complications in colectomy patients using the National Surgical Quality Improvement Program: exploring frailty and aggressive laparoscopic approaches. J Trauma Acute Care Surg 2012;72:878-83.
50. Tsiouris A, Hammoud ZT, Velanovich V, et al. A modified frailty index to assess morbidity and mortality after lobectomy. J Surg Res 2013;183:40-6.
51. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 2007;62:738-43.
52. Ali R, Schwalb JM, Nerenz DR, et al. Use of the modified frailty index to predict 30-day morbidity and mortality from spine surgery. J Neurosurg Spine 2016;25:537-41.
53. Augustin T, Burstein MD, Schneider EB, et al. Frailty predicts risk of life-threatening complications and mortality after pancreatic resections. Surgery 2016;160:987-96.
54. Dale W, Hemmerich J, Kamm A, et al. Geriatric assessment improves prediction of surgical outcomes in older adults undergoing pancreaticoduodenectomy: a prospective cohort study. Ann Surg 2014;259:960-5.
55. Sur MD, Namm JP, Hemmerich JA, et al. Radiographic Sarcopenia and Self-reported Exhaustion Independently Predict NSQIP Serious Complications After Pancreaticoduodenectomy in Older Adults. Ann Surg Oncol 2015;22:3897-904.
56. Extermann M, Aapro M, Bernabei R, et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG). Crit Rev Oncol Hematol 2005;55:241-52.
57. Ellis G, Whitehead MA, O'Neill D, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev 2017;9:CD006211.
58. Kothari A, Phillips S, Bretl T, et al. Components of geriatric assessments predict thoracic surgery outcomes. J Surg Res 2011;166:5-13.
59. Horgan AM, Leighl NB, Coate L, et al. Impact and feasibility of a comprehensive geriatric assessment in the oncology setting: a pilot study. Am J Clin Oncol 2012;35:322-8.
60. Ghignone F, van Leeuwen BL, Montroni I, et al. The assessment and management of older cancer patients: A SIOG surgical task force survey on surgeons' attitudes. Eur J Surg Oncol 2016;42:297-302.
61. Konstantinidis IT, Lewis A, Lee B, et al. Minimally invasive distal pancreatectomy: greatest benefit for the frail. Surg Endosc 2017;31:5234-40.
62. Cooper C, Dere W, Evans W, et al. Frailty and sarcopenia: definitions and outcome parameters. Osteoporos Int 2012;23:1839-48.
63. Baracos VE, Reiman T, Mourtzakis M, et al. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr 2010;91:1133s-7s.
64. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629-35.
65. Meza-Junco J, Montano-Loza AJ, Baracos VE, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. J Clin Gastroenterol 2013;47:861-70.
66. Voron T, Tselikas L, Pietrasz D, et al. Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma. Ann Surg 2015;261:1173-83.

67. Amini N, Spolverato G, Gupta R, et al. Impact Total Psoas Volume on Short- and Long-Term Outcomes in Patients Undergoing Curative Resection for Pancreatic Adenocarcinoma: a New Tool to Assess Sarcopenia. J Gastrointest Surg 2015;19:1593-602.
68. Joglekar S, Asghar A, Mott SL, et al. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. J Surg Oncol 2015;111:771-5.
69. Nishida Y, Kato Y, Kudo M, et al. Preoperative Sarcopenia Strongly Influences the Risk of Postoperative Pancreatic Fistula Formation After Pancreaticoduodenectomy. J Gastrointest Surg 2016;20:1586-94.
70. van Vugt JLA, Buettner S, Levolger S, et al. Low skeletal muscle mass is associated with increased hospital expenditure in patients undergoing cancer surgery of the alimentary tract. PLoS One 2017;12:e0186547.
71. Peng P, Hyder O, Firoozmand A, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg 2012;16:1478-86.
72. Tan BH, Birdsell LA, Martin L, et al. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009;15:6973-9.
73. Rosso E, Casnedi S, Pessaux P, et al. The role of "fatty pancreas" and of BMI in the occurrence of pancreatic fistula after pancreaticoduodenectomy. J Gastrointest Surg 2009;13:1845-51.
74. House MG, Fong Y, Arnaoutakis DJ, et al. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. J Gastrointest Surg 2008;12:270-8.
75. Park CM, Park JS, Cho ES, et al. The effect of visceral fat mass on pancreatic fistula after pancreaticoduodenectomy. J Invest Surg 2012;25:169-73.
76. Sandini M, Bernasconi DP, Fior D, et al. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer. Nutrition 2016;32:1231-7.
77. Kirihara Y, Takahashi N, Hashimoto Y, et al. Prediction of pancreatic anastomotic failure after pancreatoduodenectomy: the use of preoperative, quantitative computed tomography to measure remnant pancreatic volume and body composition. Ann Surg 2013;257:512-9.
78. Adamsen L, Quist M, Andersen C, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. Bmj 2009;339:b3410.
79. Loughney L, West MA, Kemp GJ, et al. Exercise intervention in people with cancer undergoing adjuvant cancer treatment following surgery: A systematic review. Eur J Surg Oncol 2015;41:1590-602.
80. Sebio Garcia R, Yanez Brage MI, Gimenez Moolhuyzen E, et al. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2016;23:486-97.
81. Mishra SI, Scherer RW, Snyder C, et al. Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database Syst Rev 2012;(8):CD008465.
82. Santa Mina D, Clarke H, Ritvo P, et al. Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. Physiotherapy 2014;100:196-207.
83. Tieland M, van de Rest O, Dirks ML, et al. Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial. J Am Med Dir Assoc 2012;13:720-6.
84. Kim HK, Suzuki T, Saito K, et al. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. J Am Geriatr Soc 2012;60:16-23.
85. Rosendahl E, Lindelof N, Littbrand H, et al. High-intensity functional exercise program and protein-enriched energy supplement for older persons dependent in activities of daily living: a randomised controlled trial. Aust J Physiother 2006;52:105-13.
86. Arnarson A, Gudny Geirsdottir O, Ramel A, et al. Effects of whey proteins and carbohydrates on the efficacy of resistance training in elderly people: double blind, randomised controlled trial. Eur J Clin Nutr 2013;67:821-6.
87. Tarazona-Santabalbina FJ, Gomez-Cabrera MC, Perez-Ros P, et al. A Multicomponent Exercise Intervention that Reverses Frailty and Improves Cognition, Emotion, and Social Networking in the Community-Dwelling Frail Elderly: A Randomized Clinical Trial. J Am Med Dir Assoc 2016;17:426-33.
88. Minnella EM, Bousquet-Dion G, Awasthi R, et al. Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. Acta Oncol 2017;56:295-300.
89. Alvarez-Nebreda ML, Bentov N, Urman RD, et al. Recommendations for preoperative management of frailty

from the Society for Perioperative Assessment and Quality Improvement (SPAQI). J Clin Anesth 2018;47:33-42.
90. Moore EC, Pories WJ. The BMI: Is It Time to Scratch for a More Accurate Assessment of Metabolic Dysfunction? Curr Obes Rep 2014;3:286-90.

doi: 10.21037/apc.2019.02.01
Cite this article as: Rozich NS, Jones CE, Morris KT. Malnutrition, frailty, and sarcopenia in pancreatic cancer patients: assessments and interventions for the pancreatic surgeon. Ann Pancreat Cancer 2019;2:3.

Table S1 Summary of scoring systems

Scoring system	Method	Value meaning	Findings	Advantages/disadvantages
Measures of malnutrition				
MUST (Malnutrition Universal Screening Tool)	BMI (kg/m^2) • 0 points >20.0 • 1 point =18.5–20.0 • 2 points <18.5 Unintentional weight loss (in 3–6 months) • 0 points =5% • 1 point >5% to <10% • 2 points =10% Acute disease effect (CRP) • 2 points ≥6 mg/dL	0 =low risk 1 =medium risk ≥2 =high risk	La Torre *et al.* (20) found MUST score ≥1 increased operative morbidity, SSI, and LOS for patients undergoing PD/DP. ≥1 was independently associated with postoperative morbidity on multivariate analysis	Advantages •Easy to calculate • Incorporates weight loss and inflammation Disadvantages • Potential over-diagnosis of malnutrition • Does not incorporate albumin levels
NRI (Nutritional Risk Index)	[1.519× serum albumin (g/L)] +41.7× (present weight/ usual weight more than 6 months before admission)	>100= well nourished 97.5–100= mildly malnourished 83.5–97.5= moderately malnourished <83.5= severely malnourished	Sierzega *et al.* (23) found patients s/p DP with NRI ≤100 had higher POPF rates and was independently predictive of POPF on multivariable analysis; Shinkawa *et al.* (24) ≤97.5 independent risk for SSI after PD	Advantages • Easy to calculate • Objective data Disadvantages • No measure of inflammation • Based on retrospective studies • Unclear if more informative than serum albumin alone
PNI (Onodera's Prognostic Nutritional Index)	[10× serum albumin (g/Dl)] + 0.005× total lymphocyte count (per mm^3)	≥50= normal 45–49= mild malnutrition 40–44= moderate malnutrition <40= serious malnutrition	Kanda *et al.* (17) found PNI <45 had higher POPF and morbidity; Sato *et al.* (26) found PNI as independent POPF risk factor; high BMI/PNI predicts POPF	Advantages • Objective data • Strong correlation with POPF in multiple studies Disadvantages • Doesn't incorporate unintended weight loss • No component of functional capacity
aPG-SGA (Abridged Patient-generated Subjective Global Assessment)	Weight loss 0–5 Food intake 0–4 GI symptoms 0–24 Functional status 0–3	0–1: no problems 2–8: no critical need of intervention but may benefit ≥9: critical need for intervention	Vigano *et al.* (29) score ≥9, 12% increase LOS, more dose reductions in chemo, increased mortality	Advantages • Easy to use/calculate • Aspects of functional status incorporated into score Disadvantage • Susceptible to discrepancies across providers/institutions
INA (Instant Nutritional Assessment)	Albumin ≥3.5 g/dL, lymphocyte ≥1,500 cell/mm^3 = well nourished Albumin ≥3.5 g/dL, lymphocyte <1,500 cell/mm^3 = mildly malnourished Albumin <3.5 g/dL, lymphocyte ≥1,500 cell/mm^3 = moderate malnourished Albumin <3.5 g/dL, lymphocyte <1,500 cell/mm^3 = severely malnourished		Sierzega *et al.* (23): higher abnormal INA in patients with POPF	Advantages • Easy to use/calculate • Objective data used • Incorporates inflammatory markers Disadvantages • Doesn't incorporate unintended weight loss • No markers of functional reserve
Measures of frailty				
CACI (Charlson Comorbidity Index)	1 point per diagnosis • Myocardial infarct; congestive heart failure; peripheral vascular disease; cerebrovascular disease; dementia; chronic pulmonary disease; connective tissue disease; ulcer disease; mild liver disease; diabetes 2 points per diagnosis • Hemiplegia; mod-severe renal disease; diabetes w/ end organ damage; any tumor; leukemia; lymphoma 3 points per diagnosis • Mod -severe liver disease 6 points per diagnosis • Metastatic solid tumor AIDS + 1 point for each decade >40 years old	10-year survival =0.983^($e^{CCI \times 0.9}$), where CCI = Charlson Comorbidity Index Dias-Santos *et al.* (47): cut-off: <4 or ≥4 AND <6 or ≥6	Dias-Santos *et al.* (47) • CACI ≥4 doubled odds of early mortality, and increased odds postoperative complications by 52%, doubled the odds of duration of stay ≥10 d, and increased odds of discharge to rehabilitation facility by 6-fold • CACI ≥6 tripled odds early mortality	Advantages • Extensively used and studied • Correlates with mortality • Relatively easy to calculate Disadvantages • No measure of functional status • No clinical lab values • Comorbid conditions may be variably controlled in patients
Fried's Frailty Index	Shrinking • Unintentional weight loss (≥10 lbs or ≥5% of body weight in prior year) Weakness assessed by grip strength (average of 3 trials, dominant hand) • Men: • ≤29 kg for BMI ≤24 • ≤30 kg for BMI 24.1–26 • ≤30 kg for BMI 26.1–28 • ≤32 kg for BMI >28 • Women: • ≤17 kg for BMI ≤23 • ≤17.3 kg for BMI 23.1–26 • ≤18 kg for BMI 26.1–29 Poor endurance and energy • Self-report "3–4 days/week" or "most of the time" to the question: "I felt everything I did was an effort" Slowness (time to walk 15 feet) • Men: • ≥7 seconds for height ≤173 cm • ≥6 seconds for height >173 cm • Women: • ≥7 seconds for height ≤159 cm • ≥6 seconds for height >159 cm Low physical activity* • ≤270 kcal of physical activity on • Activity scale/wk	Number of criteria met: • 0= robust • 1–2= pre-frail • ≥3= frail	Dale *et al.* (54) Self-reported exhaustion component associated with major complications, admission to SICU, increased LOS Sur *et al.* (55) Fried's exhaustion predicted NSQIP serious complications and readmission	Advantages • Incorporates measures of functional reserve and objective data • Self-reported exhaustion independently correlates with morbidity •Widely used Disadvantages • Subjective components, hard to standardize • No incorporation of comorbid conditions
mFI (Modified Frailty Index)	1 point per diagnosis • Non-independent functional status • History of diabetes mellitus • History of either chronic obstructive pulmonary disease or pneumonia • History of congestive heart failure • History of myocardial infarction • History of percutaneous coronary intervention, cardiac surgery, or angina • Hypertension requiring the use of medications • Peripheral vascular disease or rest pain • Impaired sensorium • Transient ischemic attack; cerebrovascular accident with deficit	1 point for presence of each, divided by 11 May be represented as whole Numbers on scale of 1–11 Augustin *et al.* (53) or stepwise increases from 0–1.0 Augustin *et al.* (53): • 0= not frail • 1–2= low frailty • 3–4= intermediate frailty • ≥5= frail	Mogal *et al.* (46): Increasing mFI associated with higher incidence of any complication, major complication, 30-day mortality mFI ≥0.27 independent preoperative predictor of any complication, major postoperative morbidity, and 30-day mortality Augustin *et al.* (53): cardiac, pulmonary, renal complications increased linearly with increased frailty; increased LOS, Clavien-Dindo grade 4 complications each 1 point increase in mFI associated with significantly greater odds of Clavien-Dindo grade 4 complications	Advantages • Based on NSQIP data (comorbidities documented only if severity recently documented) • Incorporates comorbid conditions • Easy to calculate • Multiple studies show correlation with morbidity Disadvantages • No measure of functional capacity or strength • Score not completely standardized (some use 1–11, some use 0–1.0 ratio)
Measures of sarcopenia				
TPA (Total Psoas Area)	At the level of L3 vertebrae semi-automated fashion with manual outlining of psoas muscle border	HU 30–110 excludes vasculature and fatty infiltration	Peng *et al.* (71) found sarcopenia by TPA NOT to be associated with LOS, ICU stay, overall morbidity or major complications	Advantages • Easy to calculate • Reliable data Disadvantages • Doesn't correlate with complications as well as other methods (TPV)
TPV (Total Psoas Volume)	At the level of L3 vertebrae semi-automated fashion with manual outlining of psoas muscle border 3 measurements performed for a total of 55cm psoas muscle length	HU 30–110 excludes vasculature and fatty infiltration	Amini *et al.* (67) found sarcopenia by TPV associated with increased LOS, independent risk factor for major postop complications	Advantages • Easy to calculate • Reliable data • Correlates better with postop complications Disadvantages • More involved calculation
TPI (Total Psoas Index)	At the level of L3 vertebrae semi-automated fashion with manual outlining of psoas muscle border TPI = (right psoas area + left psoas area)/(height^2) normalized measured psoas area for height of the patient	HU 30-110 excludes vasculature and fatty infiltration	Joglekar *et al.* (68) found sarcopenia by TPI independently predictive of LOS	Advantages • Easy to calculate • Reliable data Disadvantages • Not commonly used • Doesn't correlate with complications or morbidity
HUAC (Hounsfield Unit Average Calculation)	Right Hounsfield unit calculation (RHUC) = (right Hounsfield unit × right psoas area)/(total psoas area) Left Hounsfield unit calculation (LHUC) = (left Hounsfield unit × left psoas area)/(total psoas area) HUAC = (RHUC + LHUC)/2	HU measured at the level of L3 vertebrae	Joglekar *et al.* (68) found sarcopenia by HUAC was independently predictive of LOS, ICU stay, DGE, cardiac, infectious, GI, pulmonary, and overall and major complications	Advantages • Reliably calculated • Correlates strongly with many postoperative outcomes Disadvantages • More complicated calculation • Not commonly used/studied

*, kcal/week = [activity-specific MET (kcal/kg × hour)] × [duration per session (min)/60 min] × [body weight (kg)] × [number of sessions in the last 2 wk/2] × [number of months per year activity was done. SSI, surgical site infection; LOS, length of stay; GI, gastrointestinal; ICU, intensive care unit.