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# Effects of pancreatic and periampullar tumors, immunomodulation and surgical treatments on metabolism, systemic inflammatory response and outcomes

**SUMMARY OF DOCTORAL DISSERTATION**

Medicine and health sciences,
Medicine (M 001)

VILNIUS 2020

This doctoral dissertation was prepared at the Clinic of Gastroenterology, Nephrourology and Surgery, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, in 2015 – 2019.

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The dissertation will be defended at a public meeting of the Dissertation Defence Panel at 12:00 hour on 29th May, 2020, in the Fifth audience of Vilnius University Hospital Santaros Klinikos.

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VILNIAUS UNIVERSITETAS

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# Kasos ir periampulinių navikų, imunomoduliacijos ir operacinio gydymo įtaka ligonio medžiagų apykaitai, sisteminiam uždegiminiam atsakui ir gydymo išeitims

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## Abbreviations

Amino acids: phosphoserine (Phser), taurine (Tau), phosphoethanolamine (Pea), aspartate (Asp), threonine (Thr), serine (Ser), asparagine (Asn), glutamate (Glu), glutamine (Gln), sarcosine (Sarc), alpha-aminoadipic acid (Ama), glycine (Gly), alanine (Ala), citruline (Cit), alpha-aminobutyric acid (Aaba), valine (Val), cystine (Cys), methionine (Met), cysteine (Cyst), isoleucine (Ile), leucine (Leu), tyrosine (Tyr), beta-alanine (Bala), phenylalanine (Phe), beta-aminoisobutyricacid (Baiba), gamma-aminobutyric acid (Gaba), ethanolamine (Etha), hydroxylysine (Hlys), ornithine (Orn), lysine (Lys), 1-methylhistidine (1-Mhis), histidine (His), tryptophan (Trp), 3-methylhistidine (3MHis), anserine (Ans), carnosine (Car), arginine (Arg), hydroxyproline (Hpro), proline (Pro);

BIA – bioelectric impedance analysis;

BMI – body mass index;

CCI - Comprehensive Complication Index;

CDC – Clavien-Dindo classification;

CRP – C-reactive protein;

CT – computed tomography;

ERAS - Enhanced Recovery after Surgery;

ESPEN – the European Society for Clinical Nutrition and Metabolism;

FFMI - fat free mass index;

GC/MS – gas chromatography with mass spectrometry;

H1-NMR – proton nuclear magnetic resonance spectroscopy;

IL-6 – interleukin-6;

LC/MS – liquid chromatography with mass spectrometry;

LSMI - lumbar skeletal muscle index;

MAD median absolute deviation;

n.r. – normal ranges;

NRS 2002 - Nutritional risk screening 2002;

PDAC - pancreatic ductal adenocarcinoma;

PDR – pancreatuduodenal resection;

POD – post-operative day;

SD – standard deviation.

# INTRODUCTION

Worldwide mortality due to pancreatic cancer increased by 39.9% during the period of 2007 to 2017 [Roth GA et al, 2018] with the highest mortality registered in Eastern Europe and North America [McGuigan A et al, 2018]. In fight with this deadly disease, the main current issues are (1) there are no dominating modifiable risk factors, while known risk factors - smoking, obesity and insulin resistance - are growing in prevalence across the world [Kamisawa T et al, 2016]; (2) there are no validated biomarkers and sensitive methods for early diagnostics, even in patients at an increased risk timely diagnostics may be difficult [Urayama S, 2015]; (3) due to highly heterogenous nature and cancer cell plasticity, usual oncological treatments are ineffective in the majority of patients, while proper stratification measures for personalized approaches are missing [McGuigan A et al, 2018]; (4) the only curative option is surgical treatment, however, it is applicable to a minority of patients (up to 20%) and results in a substantial morbidity [Bozzetti F et al, 2007]; moreover, due to limited abilities to differentiate between malignant and benign lesions and due to frequently imprecise staging prior to surgery, a substantial number of patients with benign lesions (up to 25%) [McGuigan A et al., 2018] and those with disseminated unresectable cancer [Bathe OF et al, 2011] are subjected to potentially avoidable highly morbid surgeries; (5) nutritional impairments as sarcopenia and cachexia develop early and contribute to high morbidity, mortality and diminished quality of life of pancreatic cancer patients [Argilés JM et al, 2014; Peng P et al, 2012], however, diagnostics is insufficient and often masked by highly prevalent obesity [Joglekar S et al., 2015].

Metabolic and immune reprogramming are hallmark features in pancreatic ductal adenocarcinoma (PDAC) [Meseure D et al, 2014] leading to a rapid demise despite a relatively small tumor burden

[Zhan W et al, 2018]. The immune system plays a complex role in the development and progression of pancreatic cancer [Inman KS et al, 2014]. Inflammation can promote the formation of premalignant lesions and accelerate pancreatic cancer development. Conversely, pancreatic cancer is characterized by an immunosuppressive environment, which is thought to promote tumor progression and invasion. Inflammatory response is the main driving force behind cancer cachexia [Argilés JM et al, 2018; de Matos-Neto EM et al, 2015]. Besides, pancreatic surgeries are recognized as challenging and highly morbid interventions, leading to major changes in metabolism and nutritional status through the activation of an inflammatory cascade and the release of stress hormones and cytokines [Gianotti L et al, 2018]. Eventually, all these intricate pathogenetic elements - evolving cancer, derangements of local and systemic immune responses, metabolic and nutritional impairments - comprise a complex cycle of interrelated factors that determine the final prognosis of any patient with pancreatic cancer. Each of these elements have to be targeted with different treatments, hence, it is of crucial importance to identify and address all of them appropriately. Only comprehensive and personalized treatments may eventually change destinies of this highly complex and reluctant cancer.

**Aim of the study**

To evaluate the main pathogenetic aspects of pancreatic ductal adenocarcinoma (PDAC) and other periampullary tumors (including cancer biology, systemic inflammation, nutritional impairments), medical interventions (including immunonutrition, surgical treatment), their implications and impact on treatment outcomes.

**Tasks of the study**

1. To evaluate the characteristics of metabolism, nutritional status and systemic inflammation in patients with PDAC and periampullary tumors;
2. To determine the interrelations of metabolic, nutritional and inflammatory indicators and impairments and their impact on treatment outcomes and postoperative systemic inflammation;
3. To analyse tools and methods for screening and diagnostics of nutritional impairments and to compare conventional and experimental nutritional indicators and their interrelations;
4. To evaluate the impacts of immunonutrition on postoperative outcomes;
5. To make practical recommendations for perioperative management of patients with pancreatic cancer and periampullary tumors.

**Statements to be defended**

1. Characteristic findings of laboratory and instrumental investigations in patients with PDAC and periampullary tumors reflect cancer biology and systemic effects of cancer.
2. Combining of various biomarkers of cancer and systemic effects of cancer provides means to early and accurate diagnosis, prognosis, and selection of treatments.
3. Cancer biology and systemic effects of cancer have significant impacts on the outcomes in PDAC and periampullary tumors.
4. Body composition abnormalities as sarcopenia are an early sign of systemic effects in PDAC and periampullary tumors that may be diagnosed through LSMI measurement on CT.
5. Perioperative immunonutrition may improve outcomes in patients with PDAC.

**Practical and scientific significance**

Our study cohort consisted of patients with relatively better prognosis, i.e., patients, scheduled for pancreatoduodenal resection due to suspicion of non-advanced pancreatic cancer. Patients were randomly allocated into immunonutrition vs. control groups and stratified according to the final histological diagnosis into the groups of PDAC vs. other pancreatic tumors. After a comprehensive clinical description and phenotyping, a range of laboratory and instrumental investigations was applied to evaluate closely interrelated pathogenetic aspects of PDAC and periampullary tumors. Currently unsolved problems of clinical practice were given special consideration, including late and inaccurate diagnosis due to the lack of biomarkers, insufficient diagnostics and management of nutritional impairments, lack of personalized precision medicine solutions.

In this study, a quantitative plasma amino acid analysis was selected as an experimental metabolomic investigation to identify potential biomarkers. Amino acids are highly important in pancreatic cancer biology: many amino acids, including glutamine, proline [Olivares O et al, 2017], serine, glycine [Maddocks ODK et al, 2017] have been implicated in the pathogenesis of pancreatic cancer in recent years. Amino acids were identified as an important class of metabolites through a review of metabolomic studies [Tumas J et al, 2015; Tumas J et al, 2016]. A systematic review of metabolomic biomarkers in pancreatic cancer published at the time of writing this thesis confirmed the relevance of this choice: several hundred metabolites have been linked to pancreatic cancer, but the most consistent finding were changes in systemic amino acid concentrations, glutamate and histidine in particular [Long NP et al, 2018]. In this study, significant differences of eleven plasma amino acid concentrations in PDAC vs. periampullary tumors were detected. Novel, not described to the best of our knowledge findings

were revealed: some amino acids identified as potential biomarkers in this study have not been investigated in other published studies (Citr, Aaba, 3Mhis); correlation of three amino acid concentrations (Asn, Aaba, His) with cancer stages and characteristic pattern of amino acid concentrations in relation to cancer stage; correlation of plasma 3-methyl histidine, metabolite that is specific to skeletal muscle, with the diagnosis of PDAC. In addition, a statistically significant association was found between plasma Ala, Glu, Aaba, and Lys concentrations and nutritional impairments. A systematic analysis of published data was performed to assess the usage of amino acid assays in the diagnostics of pancreatic cancer and to identify factors that may lead to discordance of published findings, such as methodological gaps and issues of patients phenotyping and stratification.

Important and statistically significant differences of indicators of systemic inflammation were identified in patients with PDAC vs. other tumors and a characteristic pattern in PDAC was identified: prior to surgery, PDAC patients showed higher systemic inflammation (IL-6 levels), while after surgery PDAC patients had lower systemic inflammation with consistently lower interleukin-6 (IL-6) and C-reactive protein (CRP) levels. Statistically significant effects of systemic inflammation (IL-6 and CRP levels) on the frequency and severity of postoperative complications was determined. Regression equations showed significant effects of nutritional status indicators on postoperative CRP and IL-6 levels. Upon systematic analysis of published data and results of this dissertation, we may assume that serum concentrations of IL-6 measured before and after surgery may have significance (a) as a diagnostic biomarker for PDAC (in conjunction with other biomarkers); (b) as a prognostic biomarker for postoperative outcomes and overall survival, and (c) as a biomarker for cancer cachexia.

A range of investigations was used to evaluate nutritional status of patients, including surveys, anthropometric measurements, instrumental and laboratory investigations, with a combination of conventional, novel (CT method for lumbar skeletal mass index) and experimental methods (plasma amino acid levels). These investigations were used for screening and diagnostics of nutritional impairments. The aim of this work was to evaluate and compare various indicators of nutritional status and diagnostic tools of nutritional disorders and to assess effects of nutritional impairments on outcomes. In our study, nutritional screening tool NRS-2002, subjective indicators and anthropometric indicators, including body mass index (BMI), were not sufficiently sensitive in detecting patients with nutritional impairments. The most sensitive and easily applicable method in clinical practice was measurement of lumbar skeletal muscle index (LSMI) on CT. Decreased LSMI were identified in more than a half (52.5%) of patients studied. A systematic analysis of published data revealed a significant diversity: the incidence of sarcopenia was between 11.1% and 68.8% in published studies. Size of muscle mass depends on many factors, in particular age, gender, genetic factors, physical activity, general state and duration of illness [Baracos V et al, 2013]. However, abundance of methods and normal ranges used for analyses may have a significant effect on testing sensitivity. Finally, combination of instrumental and laboratory indicators (e.g., 3-methyl histidine plasma levels) may potentially improve the accuracy of the assays. At present, there are no studies combining different instrumental and laboratory indicators of nutritional status and comparing the relationships between these indicators.

Immuonutrition is recommended for patients undergoing pancreatoduodenectomy as it may reduce the incidence of infectious complications. However, studies on its effects on other outcome parameters produced contradictory findings, besides, it is currently unclear, which patient groups are most likely to benefit from

immunonutrition (e.g., those with PDAC vs. less aggressive pancreatic diseases or those with nutritional impairments vs. nutritionally normal). Importantly, Clavien-Dindo classification (CDC) was used for complication rating in all these studies. In this study, a recently developed Comprehensive Complication Index (CCI) was used for the assessment of postoperative complications. While CDC assesses only one of the most severe complications, CCI enables longitudinal estimation of all postoperative complications over a certain period of time [Slankamenac K et al, 2013] and may be especially sensitive in major and complex surgeries that are followed by prolonged recovery periods [de la Plaza Llamas R et al, 2018]. In this study, CCI enabled detection of significant effects of immunonutrition on the rate of severe and/or multiple complications in patients with PDAC, while the overall complication rate measured by either CDC or CCI did not differ between the groups. There are no studies of CCI usage in the evaluation of immunonutrition effects on complication rates in patients with PDAC or periampullary tumors to date. In conclusion, we may assume that patients with PDAC may experience greater benefits of immunonutrition as compared to patients with benign pancreatic diseases or less aggressive tumours.

The impacts of all investigated clinical parameters and indicators of laboratory and instrumental investigations on treatment outcomes were evaluated. The development of regression models revealed a significant overall effect of nutritional indicators on postoperative complications (CCI); the highest CCI indices were obtained in patients with sarcopenic obesity and in underweight patients with sarcopenia.

Finally, practical recommendations for diagnostics, prognostication, preoperative evaluation and management, treatment and outcome evaluation were developed.

**The presentation and approbation of the results**

**Publications:**

- Tumas J, Kvederaviciute K, Petrulionis M, Kurlinkus B, Rimkus A, Sakalauskaite G, Cicenas J, Sileikis A. Metabolomics in pancreatic cancer biomarkers research. Med Oncol. 2016 Dec;33(12):133. doi:10.1007/s12032-016-0853-6. Review.
- Tumas J, Baskirova I, Petrenas T, Norkuniene J, Strupas K, Sileikis A. Towards a Personalized Approach in Pancreatic Cancer Diagnostics Through Plasma Amino Acid Analysis. Anticancer Res. 2019 Apr;39(4):2035-2042. doi: 10.21873/anticanres.13314.
- Tumas J, Jasiūnas E, Strupas K, Šileikis A. Effects of Immunonutrition on Comprehensive Complication Index in Patients Undergoing Pancreatoduodenectomy. Medicina (Kaunas). 2020 Jan 24;56(2). doi: 10.3390/medicina56020052

**Presentations:**

- Poster: „Challenges and Opportunities of Contemporary Nutritional Evaluation in Patients Scheduled for Pancreatoduodenal Resection“ ‚Evolutionary medicine: pre-existing mechanisms and patterns of current health issues“. Vilnius, Lietuva 2016.
- Poster: “Nutritional evaluation and surgical outcome measures in patients scheduled for pancreatoduodenal resection (radiological view)“. 7th Baltic Congress of Radiology. Kaunas, Lietuva 2018.
- Oral presentation: “Nutritional evaluation and surgical outcome measures in patients scheduled for pancreatoduodenal resection“. 9th Congress of Baltic Association of Surgeons. Klaipėda, Lietuva 2018.
- Oral presentation: “Towards a Personalized Approach in Pancreatic Cancer Diagnostics Through Plasma Amino Acid Analysis”. Baltic metabolic group meeting. Riga, Latvija 2019.

**The structure and volume of the dissertation**

The dissertation contains the following chapters: Abbreviations, Introduction, Review of the literature, Materials and methods, Results, Discussion, Conclusions, Practical recommendations, List of publications and presentations, References (251), Acknowledgements. The volume of dissertation is 170 pages, it contains 15 figures and 36 tables. The dissertation is written in Lithuanian with a summary in English.

## MATERIALS AND METHODS

The study was approved by the relevant institutional review boards (Vilnius Regional Biomedical Research Committee permission 2016-01-12 No. 158200-16-810-341, the State Data Protection Inspectorate permission 2016-03-21 No. 2R-1807 (2.6-1). All consecutive patients (age range 18 to 85 years) scheduled for PDR at Vilnius University Hospital Santaros Klinikos between January 2016 and November 2018 were recruited into the study according to the inclusion/ exclusion criteria (Table 1). The patients were scheduled for surgeries after regular multidisciplinary team meetings. Standard pylorus-preserving PDR surgeries were performed by experienced tertiary-level pancreatic surgery team. All study participants provided informed consent.

**Table 1.** Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Patients 18-85 years age, scheduled for pancreatic surgery due to suspected pancreatic cancer | • Cancer stage ≥ *3 according to TNM classification of Malignant Tumours UICC (8th.ed.)*<br>• *The Eastern Cooperative Oncology Group (ECOG) grade ≥ 3.* |

Using simple randomization sequence (randomization envelopes), patients were randomized into nutritional intervention and control groups. Nutritional intervention group got intervention with nutritional supplements with immunomodulatory components (Cubitan® Nutricia 2 bottles daily with L-arginine 6.04 g/day, polyunsaturated fats 4 g/ day) for 5 days.

Nutritional status was evaluated in every patient one day before surgery in the control group or one day before the start of nutritional intervention in the nutritional intervention group. The following criteria were used to define malnutrition [Weimann A et al, 2017]: (1) BMI <18.5 kg / $m^2$, (2) Weight loss (unplanned): > 10% at any time, or > 5% in the last 3 months together with BMI <20 kg / $m^2$ for age <70 years or <22 kg / $m^2$ for age ≥ 70 years, or fat free mass index (FFMI) <15 kg / $m^2$ for women or <17 kg / $m^2$ for men. Nutritional evaluation included nutritional screening (NRS-2002), anthropometric measurements, bioelectrical impedance analysis (BIA) and lumbar skeletal mass index (LSMI) measurement on CT. Body weight and height were measured to within 0.1 kg and 0.5 cm, respectively. BMI was calculated and categorized according to the World Health Organization's classification of BMI. BIA was performed using InBody S10 according to manufacturer's recommendations and European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines [Cederholm T et al, 2017]. A list of variables for BIA was composed according to Grundmann and co-authors [Grundmann O et al, 2015]. Variables measured by BIA were as following: phase angle (n.r.: male >6, female >5), standardized phase angles according to age and gender, FFMI (n.r.: male ≥17 kg/m², female ≥15 kg/m²). High resolution CT images were performed routinely in every patient scheduled for pancreatic surgery. Cross-sectional area of muscle tissue was analysed in contrast-enhanced CT scans at the level of the third lumbar vertebra (L3) as described in Baracos et al, 2013 [Baracos V et al, 2013]. Skeletal muscle density was assessed by computing the mean

radiation attenuation of the entire muscle area at L3 in contrast enhanced CT scans and expressed in Hounsfield units. Muscle area was normalized for height in meters squared ($m^2$) and reported as lumbar skeletal muscle index (LSMI) (n.r.: male > 55 $cm^2/m^2$; female > 39 $cm^2/m^2$).

Fasting blood samples (5 ml) were collected just before surgery from antecubital veins into tubes containing lithium heparine according to a standard procedure. Samples were prepared for quantitative amino acid analysis according to routine procedure: plasma separated from the whole blood by centrifugation at 3,000 rpm at 4°C for 15 min, deproteinized with 5% sulfosalicylic acid and centrifuged at 3,000 rpm at 4°C for 15 min. Separated supernatant (400 µl) was filtered through 0.2 µm pore size cellulose acetate filters and stored at -80°C until analysis. After thawing, quantitative amino acid analysis was performed using Biochrom30+ amino acid analyzer (ion-exchange chromatography, ninhydrin post-column derivatization, single-point calibration). Norleucine was used as an internal standard and the method was certified by participation in the external quality assurance scheme (ERNDIM; https://erndim.org). Concentrations of 39 amino acids were measured and analysed.

For analyses of immune indicators (including CRP and IL-6), blood samples were collected from antecubital veins into tubes containing lithium heparine according to a standard procedure one day before the start of nutritional intervention in the nutritional intervention group, and for all patients prior to the surgery and at the 1st, 3rd and 5th postoperative days (POD). The first five PODs are the most important for the prediction and early detection of postoperative complications [Mokart D et al, 2005]. Samples were prepared according to routine procedure: plasma was separated from the whole blood by centrifugation at 3,000 rpm at 4°C for 15 min, deproteinized with 5% sulfosalicylic acid and centrifuged at 3,000 rpm at 4°C for 15 min. Separated supernatant (400 µl) was filtered

through 0.2 μm pore size cellulose acetate filters and stored at -80°C until analysis.

For each patient, a dataset of additional clinical and laboratory testing information was collected: demographics, medical history including risk factors (diabetes, obesity), cancer history, clinical evaluation and laboratory testing results, CT evaluation (including cancer staging). Establishment of the final diagnosis was guided by the histological investigation of specimens removed during surgery. For further analyses, de-identified data were used. The MIDAS archive was used for data capture and storage. The system automatically generated backups and data protection systems.

Surgical outcomes were assessed postoperatively for 30 days after surgery using Clavien-Dindo classification (CDC) and Comprehensive Complication Index (CCI).

**Statistical analysis**

Sample size calculator RAOSOFT (Raosoft, Inc.) was used to calculate sample size. Statistical analysis was performed using software packages: R statistical software package V 3.6.0 2019-04-26, ©The R Foundation for Statistical computing, R studio Version 1.2.1335 © 2009-2019 R Studio, Inc., IBM SPSS Statistics V.23. Interval and ratio variables were described by means and standard deviations (SD), by medians and median absolute deviation (MAD), by the first (Q1) and the third (Q3) quartiles. For verification of the normality of variables, we used Shapiro–Wilk and Kolmogorov–Smirnov (K–S) tests. Our variables, with rare exceptions, did not satisfied the condition of normality. Statistically significant relationships between related variables for the independent groups were determined using a number of nonparametric criteria, based on the $\chi^2$ criterion for the interval and ordinal variables: The Kruskal-Wallis test that is an extension of the Mann-Whitney U test to allow the comparison of more than two independent groups. For data

described in a four-digit (2 × 2) frequency table, Fisher's Exact test or exact $\chi$ 2 test were additionally calculated when at least one expected value was less than 5. The degree of linear dependencies of variables (correlation coefficients) of Kendall $\tau$-b was calculated for interval variables when the normality was not satisfied, and for the order variables. The dependency between variables was considered as statistically insignificant, when the two-sided p-value (Exact Sig.(2-sided), Approx Sig.) of all criteria in the category was higher or equal than the established significance level of 0.05 ($p \geq 0.05$) and statistically significant, when $p < 0.05$. The power of statistical tests was ß=0.95.

Models based on regression analysis were comprised to evaluate the effect of respective (independent) variables on derivative (dependent) variables. Median regression was the most suitable for the data (condition of normalcy not satisfied, presence of outliers, heteroscedasticity).

## RESULTS

The overall flow-chart of the study is presented in Figure 1. Ninety two patients, eligible for inclusion into the study, were randomized into nutritional intervention group (n = 40) and control group (n = 52). Four patients were excluded prior to surgery, 18 patients were excluded during surgery due to changes in scope or type of surgeries (surgeries other than PDR were performed: 11 patients had biliary bypass and gastrojejunostomy, 4 patients had pancreatectomy, tumor enucleation, segmental resection and distal pancreatic resection each).

The final diagnosis was obtained after histological investigation of surgical tissues; final diagnoses included: PDAC (n = 39), periampullary carcinoma (n = 11), other pancreatic tumors (n = 12) and chronic pancreatitis (n = 8) Other pancreatic tumors included

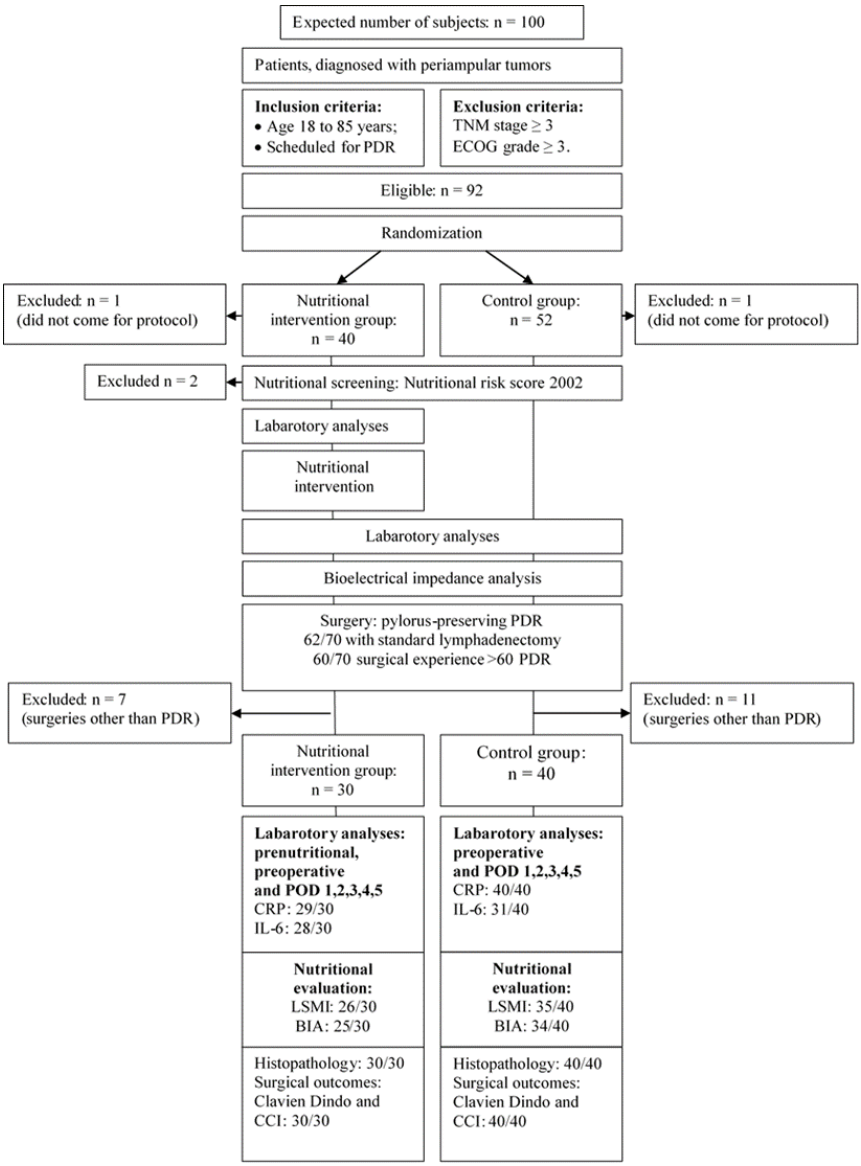



**Figure 1.** Study flow chart

neuroendocrine pancreatic cancer (n = 5), intraductal papillary mucinous neoplasm (n = 2), pseudopapillary solid tumor (n = 1), mucinous pancreatic adenocarcinoma (n = 1), acinar cell pancreatic cancer (n = 1), metastatic cancer (renal cellular carcinoma) (n = 1), pancreatic microcystic adenoma (n = 1). For further analyses, the patients were grouped into PDAC vs. other pancreatic tumors groups.

Prior to surgery, no differences of more than 30 clinical, nutritional evaluation and inflammatory parameters were detected in nutritional intervention vs. control groups. Besides, no differences in demographic and presurgical nutritional parameters were observed in groups of PDAC vs. other pancreatic tumors.

Nutritional screening and comprehensive nutritional evaluation were performed in all patients according to the protocol. Increased nutritional risk score 2002 (NRS-2002 ≥3 points) was identified in 15 patients (22.40%). 19 patients were determined as having severe nutritional risk (27.10% of all patients).

Majority of our cohort had BMI in the range of normal to overweight (61.4%, n = 43, BMI range 22.1 – 29.9 kg/m²), 14.3% (n = 10) of patients were underweight (BMI < 22 kg/m²), while 24.3% (n = 17) of patients were obese (BMI ≥ 30 kg/m²). Importantly, almost half of all patients (49.2%) had weight loss that was detected across all BMI ranges: 13 patients (18.8%) declared less than 5 percent loss, while 21 patients (30.4%) had ≥ 5 percent loss over the recent 3 months. Fifteen patients (21.4%) were diagnosed with cachexia. Weight loss and cachexia were not necessarily accompanied by anorexia (15.4%, n = 10) and reduced food intake (20%, n = 13).

Abnormal body composition phenotypes were measured by means of BIA and LSMI. LSMI below normal range was identified in 52.5% of patients (n = 32), decreased phase angle - in 39% of patients (n = 23), while decreased FFMI was detected in only 3.4% of patients (n = 2). Subjective indicator of muscle functional

impairment, fatigue, was reported by 6.2% of patients only (n = 4). Sarcopenia (defined in this study by reduced muscle mass and function) was detected in 17.9% of patients (n = 12). Importantly, while cachexia was predominantly diagnosed in underweight patients, sarcopenia was detected across all BMI categories and 11.7% of obese patients had sarcopenia (Figure 2).

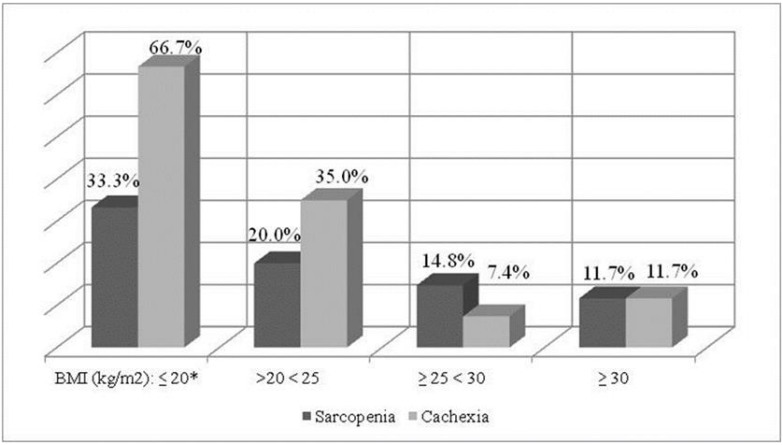



**Figure 2.** Incidence of sarcopenia and cachexia across BMI categories.

Inflammatory indicators were measured preoperatively and for five days after surgery. A sign of systemic inflammation, increased IL-6 prior to surgery, was detected in 57.9% of all patients (n = 33). There were no significant differences of postoperative CRP and IL-6 levels in nutritional intervention vs. control groups. However, statistically significant differences were identified in PDAC vs. other tumors groups and a characteristic pattern in PDAC was identified: prior to surgery, PDAC patients showed higher systemic inflammation (mean levels of IL-6 in PDAC were 5.33 ng/l vs. 3.49 ng/l in other tumors, p = 0.02, Kruskal - Wallis rank sum test). Conversely, after surgery PDAC patients showed lower systemic inflammation with consistently lower IL-6 and CRP levels: mean levels of IL-6 in PDAC were 73.47 ng/l vs.

104.5 ng/l in other tumors, p = 0.027; mean levels of CRP in PDAC were 123.5 mg/l vs. 150.3 mg/l in other tumors, p = 0.027, Kruskal - Wallis rank sum test.

Comparison of PDAC and other pancreatic tumor groups revealed statistically significant differences in plasma levels of 11 amino acids (Thr, Asn, Gln, Gly, Citr, Aaba, Cysth, Lys, His, 3MHis, Arg). Plasma levels of 3 amino acids (Asn, Aaba, His) significantly correlated with cancer stage: patients with advanced pancreatic cancer had lower concentrations of these amino acids (Table 2). Besides, characteristic patterns of plasma amino acid

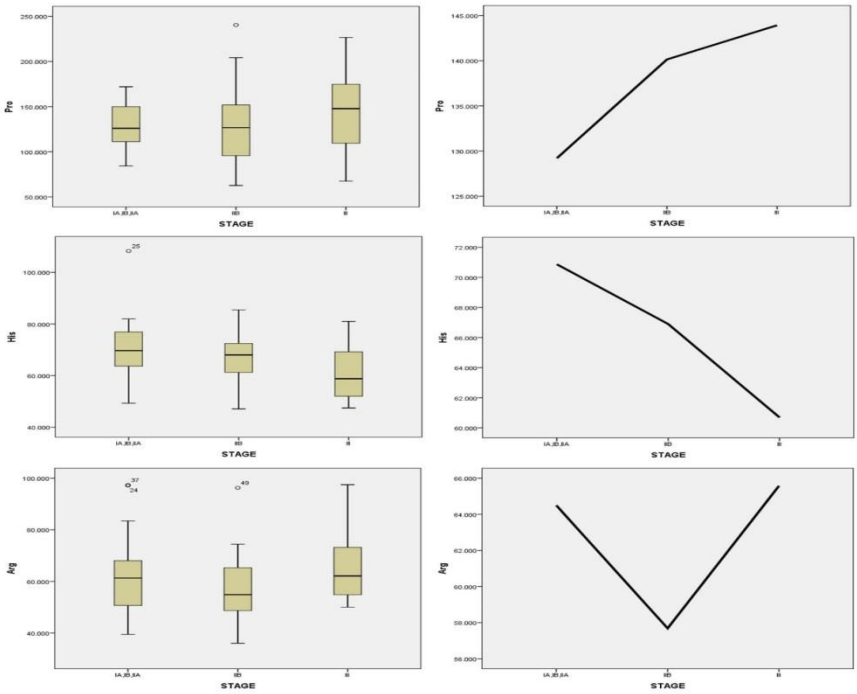



**Figure 3.** Plasma amino acid levels (medians) in relation to PDAC stage: Pro, His, Arg.

levels in relation to cancer stage were obtained: inverse relationship between His levels and cancer stage, direct relationship between Pro levels and cancer stage, U-shaped curve for a number of amino acids (Thr, Lys, Arg, Gly, Ser, Asn).

Significant differences of plasma levels of four amino acids (Ala, Gln, Aaba, Lys) in patients with impaired indicators of nutritional status (phase angle, LSMI) and nutritional impairments (sarcopenia) were identified (Table 2).

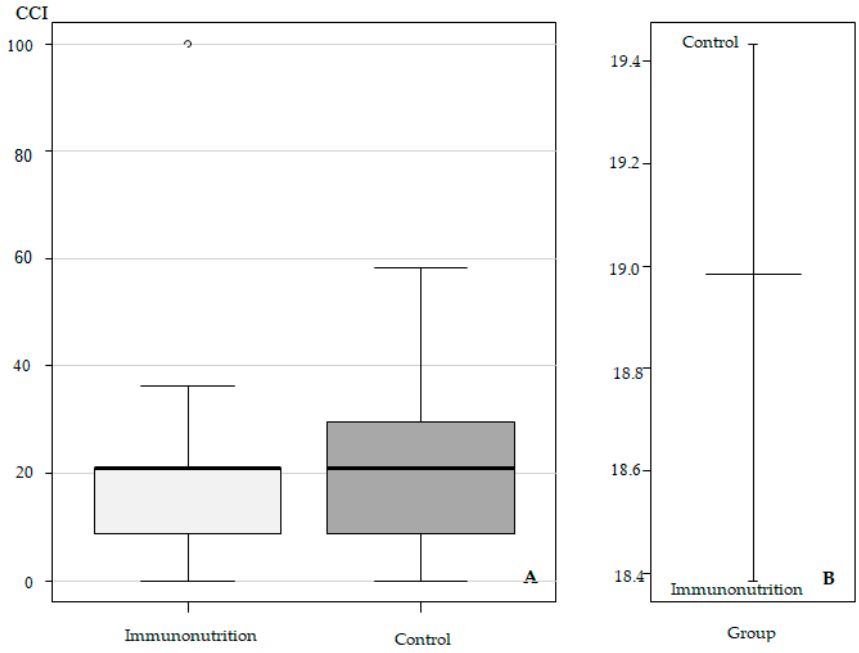
**Table 2.** Plasma amino acid levels in patients woith PDAC vs. other tumors.

| | **Diagnosis** | | | | | |
|---|---|---|---|---|---|---|
| | **PDAC** | | **Other tumors** | | | **Kruskal-Wallis test** |
| | **Mean (SD) µmol/l** | **Median µmol/l** | **Mean (SD) µmol/l** | **Median µmol/l** | **n.r. (µmol/l)** | **p-value** |
| Threonine (Thr) | 101,55 (28,44) | 93,32 | 117,19 (24,31) | 116,45 | 85-231 | **0,011** |
| Lysine (Lys) | 160,29 (36,12) | 154,47 | 181,12 (37,19) | 179,06 | 103-255 | **0,019** |
| Glycine (Gly) | 187,70 (41,92) | 178,99 | 216,34 (42,99) | 210,57 | 126-490 | **0,009** |
| Arginine (Arg) | 61,22 (14,93) | 58,36 | 76,14 (16,46) | 74,5 | 32-120 | **0,001** |
| Histidine (His) | 66,34 (11,59) | 66,5 | 73,11 (14,27) | 72,61 | 39-123 | **0,013** |
| Asparagine (Asn) | 47,70 (11,54) | 46,6 | 56,60 (14,68) | 52,87 | 37-92 | **0,023** |
| Glutamate (Glu) | 358,55 (154,17) | 404,34 | 452,05 (137,91) | 491,45 | 371-957 | **0,010** |
| Cystathionine (Cysth) | 1,89 (0,76) | 1,86 | 2,44 (1,22) | 2,22 | 0-5 | **0,045** |
| 3-Methylhistidine (3-Mhis) | 4,11 (1,14) | 4,07 | 5,99 (2,91) | 5,2 | 2-9 | **0,001** |
| Citruline (Citr) | 23,21 (6,51) | 23,84 | 31,35 (7,65) | 31,31 | 3-95 | **0,000** |
| α-aminobutyric a. (Aaba) | 18,22 (8,47) | 17,79 | 24,62 (6,70) | 25,42 | 9-37 | **0,002** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **PDAC stage** | | | | | | |
| | **Early (N0)** | | **Advanced (N1)** | | | |
| Histidine (His) | 72,30 (13,36) | 71,11 | 64,92 (9,43) | 61,74 | 39-123 | **0,019** |
| Asparagine (Asn) | 54,65 (13,35) | 52,94 | 46,83 (11,86) | 45,69 | 37-92 | **0,010** |
| α-aminobutyric a. (Aaba) | 23,55 (8,59) | 23,1 | 17,54 (7,60) | 17,73 | 9-37 | **0,008** |
| **Phase angle** | | | | | | |
| | **Normal** | | **Decreased** | | | |
| Alanine (Ala) | 334,77 (77,39) | 342,25 | 286,03 (62,16) | 288,52 | 200-579 | **0,019** |
| Glutamate (Glu) | 414,23 (161,43) | 472,13 | 332,58 (140,65) | 358,54 | 371-957 | **0,013** |
| α-aminobutyric a. (Aaba) | 23,05 (8,90) | 22,79 | 17,77 (7,76) | 19,11 | 9-37 | **0,034** |
| **Lumbar skeletal mass index (LSMI)** | | | | | | |
| | **Normal** | | **Decreased** | | | |
| Alanine (Ala) | 331,59 (65,68) | 332,17 | 290,56 (73,99) | 289,16 | 200-579 | **0,026** |
| Glutamate (Glu) | 432,72 (122,27) | 462,86 | 343,60 (175,93) | 381,03 | 371-957 | **0,027** |
| **Sarcopenia** | | | | | | |
| | **Absent** | | **Present** | | | |
| Lysine (Lys) | 172,50 (37,29) | 171,89 | 149,35 (34,36) | 145,72 | 103-255 | **0,027** |
| Glutamate (Glu) | 420,08 (135,67) | 435,62 | 274,39 (181,60) | 290,94 | 371-957 | **0,010** |

Surgical outcomes were assessed for 30 days after surgery using CDC and CCI. Overall, 81.4% of all patients experienced postoperative complications. 24 (34.3 %) of patients had severe complications (defined as CDC ≥ 3; CCI > 20.9), while 47.1% (n = 33) had mild complications (defined as CDC 1-2; CCI < 20.9).

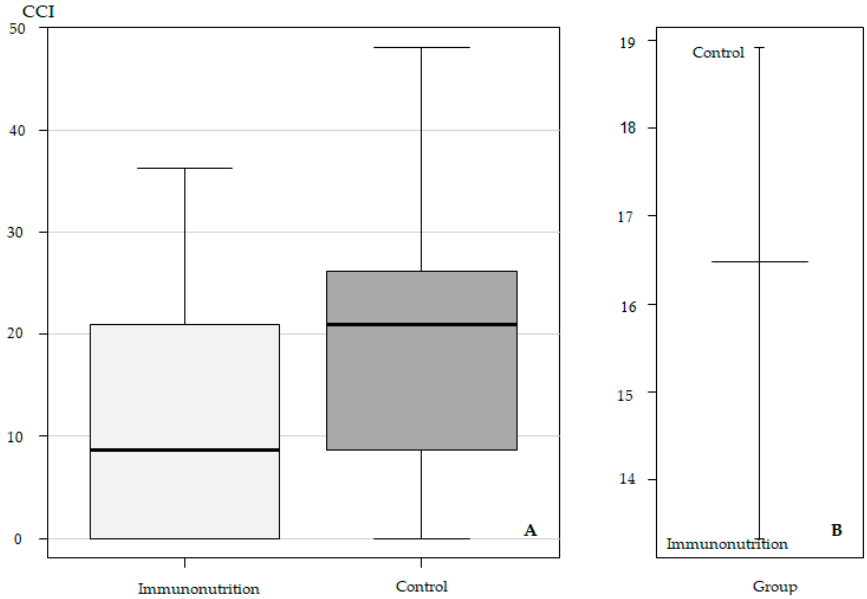
There were no statistically significant differences in the overall complication rates in immunonutrition vs. control groups (median CCI = 20.9 in both groups; Figure 4).




| | Group | | Total |
|---|---|---|---|
| | Immunonutrition | Control | |
| Mean | 18.39 | 19.43 | 18.98 |
| Median | 20.90 | 20.90 | 20.90 |
| SD | 19.01 | 14.88 | 16.65 |
| IQR | 12.20 | 20.90 | 17.00 |
| N | 30 | 40 | 70 |
| Kruskal-Wallis rank sum test: Chi-squared = 0.60314, p-value = 0.437 | | | |

**Figure 4.** Standard deviations (A) and mean (B) of the comprehensive complication index (CCI) in the immunonutrition vs. control groups.

In PDAC patients segregated according to immunonutrition, median CCI was 8.7 in the immunonutrition group (n = 17), while median CCI was 20.9 in the control group (n = 22); however, the difference was not statistically significant (p = 0.2) (Figure 5).




| | Group | | Total |
|---|---|---|---|
| | Immunonutrition | Control | |
| Mean | 13.34 | 18.92 | 16.49 |
| Median | 8.70 | 20.90 | 12.20 |
| SD | 12.01 | 13.14 | 12.81 |
| IQR | 20.90 | 17.00 | 14.70 |
| N | 17 | 22 | 39 |
| Kruskal-Wallis rank sum test: Chi-squared = 2, p-value = 0.2 | | | |

**Figure 5.** Standard deviations (A) and mean (B) of the comprehensive complication index (CCI) in PDAC patients: immunonutrition vs. control groups.

Evaluation of severe and/or multiple complications presented diverging results. Overall, 18.6% (n = 13) had CDC ≥ 3:13.3% (n = 4) of patients in the immunonutrition group and 22.5% (n = 9) in the control group; the difference between the groups was not statistically significant (p = 0.333). Overall, 34.3% (n = 24) of patients had CCI > 20.9:23.3% (n = 7) of patients in the immunonutrition group

and 42.5% (n = 17) in the control group; the difference between the groups was statistically significant (McNemar's chi-squared = 7.5, p = 0.006) (Figure 6). Even more significant differences of severe and/or multiple complication rates were obtained when PDAC patients were segregated into immunonutrition (n = 17) vs. control (n = 22) groups: CCI > 20.9 was found in 17.65% of patients in the immunonutrition group and in 45.45% of patients in the control group (McNemar's chi-squared = 4.3, p = 0.04) (Figure 7).

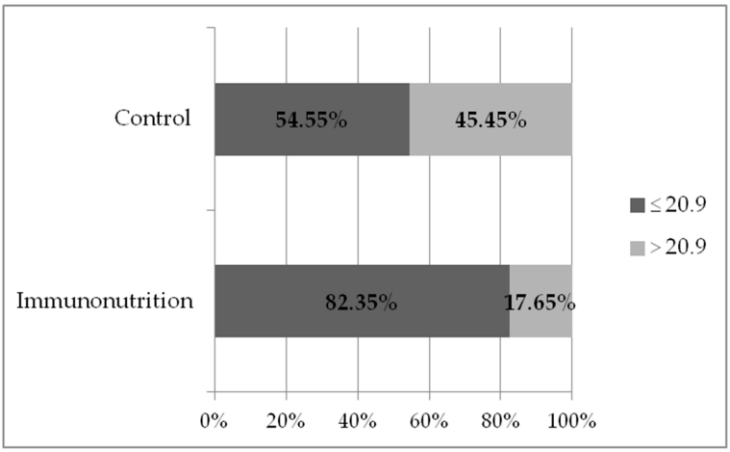



**Figure 6.** Rate of severe and/ or multiple complications (CCI > 20.9) in immunonutrition vs. control groups.

There were no significant differences in complication rate and severity in patients with cachexia/ sarcopenia vs. patients without these nutritional impairments. Interestingly, males had significantly higher overall complication rate (CCI = 21.75) as compared to females (CCI = 12.2; p = 0.03), although there were no statistically significant differences of postoperative inflammatory indicators between genders.

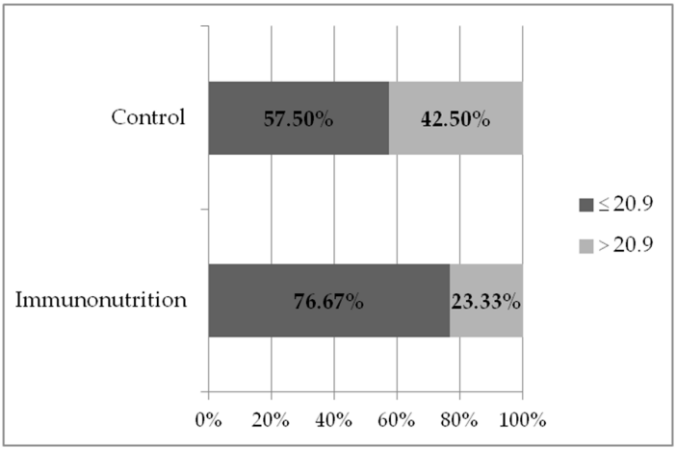



**Figure 7.** Rate of severe and/or multiple complications (CCI > 20.9) in PDAC patients, stratified to immunonutrition vs. control groups.

Regression models were comprised to evaluate the effects of nutritional indicators on 24 variables. These models were used to evaluate the effects of individual indicators on the most important derivative variables. Regression model of the effects of nutritional indicators on the CCI showed $R^2$ coefficient = 0.7107435 (71.1 %). Analysis of individual groups of nutritional indicators indicated that the best model for CCI includes LSMI categorical + phase angle categorical + LSMI + sarcopenia, with $R^2$ coefficient = 0.3990847 (39.9 %). Regression model of the effects of nutritional indicators on the postoperative CRP levels (CRP median ~ LSMI categorical + phase angle categorical + LSMI + sarcopenia) showed $R^2$ coefficient = 0.3446631 (34.5 %). Regression model of the effects of nutritional indicators on the postoperative IL-6 levels (IL6 median ~ LSMI categorical + phase angle categorical + LSMI + sarcopenia) showed $R^2$ coefficient = 0.2701205 (27.01 %).

# DISCUSSION

Our study cohort consisted of patients with relatively better prognosis, i.e., patients, scheduled for PDR due to suspicion of non-advanced pancreatic cancer. Timely and appropriate perioperative nutritional management is highly important and may further improve outcomes in this group of patients. Although several guidelines on nutritional management were recently published, including those for patients undergoing pancreatic surgeries [Gianotti L et al, 2018], in oncology setting [Arends J et al, 2017] and intensive care [Taylor BE et al, 2016], specific recommendations for the overall nutritional management over the entire disease course in patients with pancreatic cancer were not as yet developed. All aforementioned guidelines have some differences, however, all of them may be applied to the same patient over his/ her disease course. Hence, it would be very important to have a multidisciplinary and holistic approach to pancreatic cancer nutritional management [DeLegge MH et al, 2013], covering all disease stages. Many relevant questions, including the best means for nutritional screening, relationships between various types and indicators of nutritional impairments, role of interventions, remain unanswered, precluding a clear guidance in a clinical setting.

Although to date the only validated tool for nutritional screening in surgical patients was NRS-2002 [Evans DC et al, 2014], in our study it was not sufficiently sensitive in detecting patients with nutritional impairments. Increased nutritional risk was identified in 22.4%, while cachexia was finally diagnosed in 41.4% of all patients. NRS-2002 mostly identified those patients who were already severely malnourished. Similar results were recently obtained in a large study of patients with various solid tumors: nutrition screening tools NRI, MUST and MST misclassified patients and were not sensitive enough to detect nutritional impairments [Orell-Kotikangas H et al, 2015]. Of importance, these nutritional screening tools were

not devised specifically for the detection of abnormal body composition phenotypes [Ní Bhuachalla ÉB et al, 2018].

In our cohort, patients distributed across all BMI categories. Importantly, while cachexia was predominantly diagnosed in underweight patients, sarcopenia was detected across all BMI categories and 11.7% of obese patients had sarcopenia. Thus, in the assessments of nutritional status, BMI measurements must be supplemented by other, more sensitive and accurate measures of nutritional status.

A high percentage of our patients reported recent weight loss (49.2%), including 17.8% with weight loss in the lower range (5-10%), that is still considered as significant according to recent guidelines [Cederholm T et al, 2017; Arends J et al, 2017]. In patients with lower weight, this loss may include several kilograms only and, consequently, may be rated as insignificant by some physicians [Muscaritoli M et al, 2016]. Weight loss was found in comparable numbers of patients in recently published studies (Table 3). Skeletal muscle is the body's main protein reserve that is rapidly depleting as cachexia develops; patients may lose as much as 75% of skeletal muscle mass throughout the course of cancer [Marinho R et al, 2018]. In our study, decreased LSMI was identified in 52.5% of patients, while decreased phase angle by BIA - in 39% and decreased FFMI - in 3.4% of patients only. In 13 recent publications and 4 systematic reviews and meta-analyses (Table 3), the rates of sarcopenia were highly diverse in study groups, ranging from 11.1% to 68.8%. Size of muscle mass depends on many factors, in particular age, gender, genetic factors, physical activity, general state and duration of illness [Baracos V et al, 2013]. However, abundance of methods and normal ranges used for analyses may have a significant effect on testing sensitivity (Table 4). Measurements of LSMI by CT were recently confirmed as the gold standard method for the identification of abnormal body composition phenotypes [Ní Bhuachalla ÉB et al, 2018]. A properly performed study can be very accurate, with error rates in the range of 0.4 - 1.5% [Baracos V et al, 2013].

**Table 2.** Rates of BMI categories and sarcopenia in published studies and in this study.

| Reference | Study, number of patients | Sarcopenia | Underweight | Overweight | Obese | Sarcopenic obesity | Weight loss |
|---|---|---|---|---|---|---|---|
| This study | Pancreatoduodenectomy ktomija, n = 70 | 52,5% | 14,3% | 38,6% | 24,3% | 12% | 49,2% |
| Di Sebastiano et al., 2013 | Pancreatic cancer, all stages, n = 50. | 48% | 10% | 30% | 2% | NA | NA |
| Cooper et al., 2015 | Pancreatic cancer, non-advanced, n = 89. | 52% | 1% | | 25% | NA | 62% |
| Joglekar et al., 2015 | Pancreatic cancer, non-advanced, n = 93. | 26,3% | | 32,1% | 31,3% | NA | |
| Pecorelli et al., 2016 | Pancreatic cancer, non-advanced, n = 202. | 65% | 7,9% | 27,2% | 5% | NA | 46% |
| Sahakyan et al., 2016 | Pancreatic cancer, non-advanced, n = 423. | NA | 5% | 37% | 13% | NA | NA |
| Mintziras et al.*, 2018 | PDAC, systematic review, 11 studies, n = 2997. | 45,4% (21,3 - 65,3% ) | NA | 11,6-58% | | 13% (0,6-25%) | NA |
| Tan et al., 2009 | Pancreatic cancer, advanced, n = 111. | 55,9% | NA | 39,6% | | 16,2% | NA |
| Gibson et al.*, 2015 | Gastrointestinal cancer, systematic review, 10 studies, n = 2584. | 27,3 – 66,7% | 0-12,3% | NA | NA | NA | NA |

Several systematic reviews and meta-analyses of studies in patients with various cancers [Joglekar S], gastrointestinal cancers [Levolger S et al, 2015; Gibson DJ et al, 2015], pancreatic cancer [Mintziras I et al, 2018] or those undergoing PDR [Ratnayake CB et al, 2018] revealed definite effects of sarcopenia on long-term and short-term treatment outcomes (Table 4). In this study, application of

regression models showed a high effect of nutritional impairments on postoperative outcomes; the highest value for prognostication was obtained through the inclusion of multiple, objective variables. With the epidemic of obesity spreading worldwide, nutritional disorders in obese or overweight patients, particularly sarcopenic obesity, is a problem of increasing importance. Obesity was identified in 2 - 31.3% of patients in recently published studies, while the incidence of sarcopenic obesity was in the range of 0.6% to 33.5% (Table 3). Wide ranges of incidences may be due to a variety of causes, including differences in patient samples and methodological issues. In this study, the incidence of sarcopenic obesity was 11.7%. Although only few studies have been performed to date, sarcopenic obesity was associated with significantly worse surgical and long-term outcomes (Table 4).

**Table 4.** Effects of sarcopenia and sarcopenic obesity on outcomes in published studies and this study.

| Reference | Study, number of patients | Method | Normal range | Sarcopenia | Sarcopenic obesity | Effects on outcomes |
|---|---|---|---|---|---|---|
| This study | Pancreatoduodenectomy, n = 70. | LSMI | Men > 55 $cm^2/m^2$; women > 39 $cm^2/m^2$. | 52,5% | 12% | Effects on the rate of postoperative complications. |
| Di Sebastiano et al., 2013 | Pancreatic cancer, all stages, n = 50. | LSMI | Men > 55,4 $cm^2/m^2$; Women > 38,9 $cm^2/m^2$. | 48% | NA | Significant effects on survival. |
| Danai et al., 2018 | Pancreatic cancer, all stages, n = 687. | LSMI | Men > 55,4 $cm^2/m^2$; Women > 38,9 $cm^2/m^2$. | 65% | 33,5% | No significant effects on survival. |
| Cloyd et al., 2018 | Pancreatic cancer, non-advanced, n = 127. | LSMI | Men > 55,4 $cm^2/m^2$; Women > 38,9 $cm^2/m^2$. | 63% | NA | Significant effects on survival. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cooper et al., 2015 | Pancreatic cancer, non-advanced, n = 89. | | Men > 55,4 $cm^2/m^2$; Women > 38,9 $cm^2/m^2$. | 52% | 23,6% | Significant effects on survival. |
| Okumura et al., 2015 | Pancreatic cancer, non-advanced, n = 230. | PMI | Percentiles. | 38,6% | NA | Significant effects on survival. |
| Peng et al., 2012 | Pancreatic cancer, non-advanced, n = 557. | TPA | Percentiles. | 33,3% | NA | Significant effects on survival. No significant effects on the rates of postoperative complications. |
| Amini et al., 2015 | Pancreatic cancer, non-advanced, n = 763. | TPA and TPV | Percentiles. | 25,1% (TPA); 19,9% (TPV). | 3,5% (TPA); 2,5% (TPV) | TPA method: effect of sarcopenia on the rate of postoperative complications; TPV method: effect of sarcopenia on the rate of postoperative complications and survival. |
| Choi et al., 2015 | Pancreatic cancer, advanced, n = 484. | LSMI | Percentiles. | 21,3% | NA | Significant effects on survival. |
| Joglekar et al., 2015 (b) | Pancreatic cancer, advanced, n = 228. | LSMI | Men > 43 $cm^2/m^2$ when BMI < 25, > 53 $cm^2/m^2$ when BMI >25; Women > 41 $cm^2/m^2$. | 60,5% | NA | No significant effects of sarcopenia on survival. Significant effects of sarcopenic obesity on survival. |
| Kays et al., 2018 | Pancreatic cancer, | LSMI | Men > 52,4 $cm^2/m^2$; | 49% | 11% | Significant effects on |

| | | | | | | |
|---|---|---|---|---|---|---|
| | advanced, n = 53. | | Women > 38,5 $cm^2/m^2$. | | | survival. |
| Ratnayake et al.*, 2018 | Pancreatectomy, systematic review, 13 studies, n = 3608. | Various | Various | NA | NA | No significant effects on the rate of postoperative complications. Significant effect on length of hospitalization. |
| Pecorelli et al., 2016 | Pancreatic cancer, non-advanced, n = 202. | TAMA | Men > 52,4 $cm^2/m^2$; Women > 38,5 $cm^2/m^2$. | 65% | NA | Significant effects on survival and the rate of postoperative complications. |
| Mintziras et al.*, 2018 | Pancreatic cancer, all stages, systematic review, 11 studies, n = 2297. | LSMI | Various | 45,4% (21,3 - 65,3%) | 13% (0,6 - 25%) | Significant effects of sarcopenia and sarcopenic obesity on survival. Significant effect of sarcopenic obesity on the rate of postoperative complications. |
| Tan et al., 2009 | Pancreatic cancer, advanced, n = 111. | LSMI | Men > 52,4 $cm^2/m^2$; Women > 38,5 $cm^2/m^2$. | 55,9% | 16,2% | Significant effects of sarcopenic obesity on survival. |
| Levolger et al.*, 2015 | Gastrointestinal cancers, systematic review, 13 studies, n = 2884. | Various | Various | 17 - 79% | NA | Significant effects on survival. |
| Joglekar et al.*, 2015(b) | Diverse cancers, systematic review, 14 studies. | Various | Various | 11,1 - 68,8% | NA | Significant effects on survival and the rate of postoperative complications. |

According to Enhanced Recovery after Surgery (ERAS) recommendations, patients undergoing pancreatoduodenectomy may receive immunonutrition for 5-7 days perioperatively (Evidence level: moderate, Recommendation grade: weak) [Lassen K et al, 2012]. However, it is currently unclear which patient groups are most likely to benefit from immunonutrition (e.g., those with PDAC vs. less aggressive pancreatic diseases or those vith nutritional impairments vs. nutritionally normal). The only meta-analysis investigating the effects of immunonutrition on patients undergoing pancreatoduodenectomy was recently published. Immunonutrition was found to reduce the rate of infectious complication and length of hospitalization, but had no effect on the overall complication rates, non-infectious complication rates, and postoperative mortality. Patients were not stratified according to diagnosis or nutritional state [Guan H et al, 2019]. Several randomized clinical studies included patients undergoing pancreatoduodenectomy and those with pancreatic or periampular cancers. These patient groups were also included into more general studies investigating patients undergoing gastrointestinal surgeries or those with gastrointestinal cancers (Table 5).

In meta-analyses and systematic reviews evaluating the impact of immunonutrition on patients undergoing gastrointestinal surgery, two studies found an effect on rate of infectious complications and length of hospitalization [Wong CS et al, 2016; Marimuthu K et al, 2012], while in one meta-analysis with the largest number of subjects effect on the overall complication rates was also identified [Mazaki T et al, 2015]. Three meta-analyses and systematic reviews investigated the effects of immunonutrition in patients with various gastrointestinal cancers; in two of them, immunonutrition had effects not only on the rates of infectious complications and length of hospitalization, but also on the overall complication rates [Yan X et al, 2017; Song GM et al, 2015]. Immunonutrition was found to be cost-effective in surgical patients with gastrointestinal cancers (i.e., this intervention may reduce treatment costs due to lower complication rates) [Reis AM et al, 2016].

**Table 5.** Overview of published data on the use of immunonutrition in various patient groups.

| Publication | Number of patients | Patient population | Study design | Outcome measures | Study results |
|---|---|---|---|---|---|
| Miyauchi Y, 2019 [17] | 60 | Pancreato-duoden-ectomy. | Prospective, randomized. Perioperative or preoperative immunonutrition. | Immune functions, rate of postoperative complications. | No significant differences between the groups. RR 0.76 [0.46-1.28] |
| Silvestri S, 2016 [18] | 54 | Pancreato-duoden-ectomy; patients without malnutri-tion | Case-control. Immunonutrition preoperatively. | Mortality, overall complication rate, rates of individual complications, length of hospitalization. | Lower rate of infectious complications and shorter duration of hospitalization in the immunonutrition group. RR 0.87 [0.56-1.36] |
| Suzuki D, 2010 [7] | 30 | Pancreato-duoden-ectomy. | Randomized, three branches: perioperative immunonutrition, postoperative immunonutrition, control. | Immune functions; rate of infectious complications. | Statistically significant differences of immune functions and rates of infectious complications, RR 0.29 [0.08-1.05] in comparisons of perioperative immunonutrition vs. other groups. |
| Gade J, 2016 [19] | 35 | Pancreatic cancer | Randomized case-control. | Rate of postoperative complications, length of hospitalization, changes of body weight and general clinical status. | No significant differences between the groups. RR 0.70 [0.51-0.95] |

| | | | | | |
|---|---|---|---|---|---|
| Martin RC, 2017 [20] | 71 | Pancreatic cancer | Randomized case-control. Preoperative immunonutrition. | Overall complication rate and rate of infectious complications, length of hospitalization, risk of malnutrition postoperatively, serum albumin. | Lower rate of postoperative complications, RR 0.50 [0.24-1.05], shorter duration of hospitalization, lower risk of malnutrition and less of a decrease of serum albumin in the immunonutrition group. |
| Hamza N, 2015 [8] | 37 | Periampullar tumours | Randomized case-control. Perioperative immunonutrition. | Immune functions. | Statistically significant differences of immune functions in the immunonutrition group. RR 0.83 [0.32-2.15] |
| Guan H*, 2019 [16] | 299 | Pancreato-duoden-ectomy | Meta-analysis; four randomized clinical trials included. | | Immunonutrition decreases rate of infectious complications, RR 0.58 [0.37–0.92] and length of hospitalization; no effect on the overall complication rate, RR 0.81 [0.62–1.05], rate of non-infectious complications, RR 0.94 [0.69, 1.28] and postoperative mortality. |
| Hübner M, 2012 [9] | 152 | Gastro-intestinal surgery | Randomized case-control, preoperative immunonutrition, patients with malnutrition. | Rate of postoperative complications, infectious complications, length of hospitalization. | No significant differences between the groups. RR 0.95 [0.76-1.19] |
| Burden S*, 2012 [22] | 1585 | Gastro-intestinal surgery | Meta-analysis; thirteen clinical trials included. | | Immunonutrition decreases the overall complication rate, RR 0.67 [0.53- 0.84], and rate of infectious complications. |

| | | | | | |
|---|---|---|---|---|---|
| Hegazi RA*, 2014 [23] | 1456 | Gastro-intestinal surgery | Meta-analysis and systematic review; immunonutrition vs. standard nutritional management and immunonutrition vs. control (no nutritional management). 17 clinical trials included. | | Immunonutrition and standard nutritional management decreases rate of infectious complications, OR 0.49 [0.29-0.83] and length of hospitalization. No significant differences between immunonutrition and standard nutritional management. |
| Reis AM*, 2016 [24] | | Gastro-intestinal surgery | Systematic review; cost-effectiveness of immunonutrition. Six randomized clinical trials included. | | Immunonutrition may reduce costs of treatment due to decreased rate of complications. |
| Klek S (a), 2014 [25] | 776 | Gastro-intestinal surgery | Randomized clinical trial; enteral and parenteral immunonutrition. Patients with or without malnutrition. | Rate of postoperative complications, length of hospitalization. | No significant differences in patients without malnutrition. Statistically significant differences in patients with malnutrition when enteral immunonutrition is given, but no differences with parenteral immunonutrition. |
| Wong CS *, 2016 [26] | 2016 | Gastro-intestinal surgery | Systematic review; 19 randomized clinical trials included. | | Immunonutrition decreases rate of infectious complications and length of hospitalization; no effect on the overall complication rate and postoperative mortality. |
| Marimuthu K*, 2012 [27] | 2496 | Gastro-intestinal surgery | Meta-analysis; 26 randomized clinical trials included. | | Immunonutrition decreases rate of infectious complications, RR 0.64 [0.55 - 0.74] |

| | | | | |
|---|---|---|---|---|
| | | | | and length of hospitalization; no effect on the overall noninfectious complication rate, RR 0.82 [0.71- 0.95] and postoperative mortality. |
| Mazaki T*, 2015 [28] | 7572 | Gastro-intestinal surgery | Meta-analysis. Comparison of enteral and parenteral immunonutrition, enteral and parenteral standard nutritional management. 74 clinical trials included. | Enteral immunonutrition is the most effective in decreasing overall complication rate, OR 0.75 [0.58–0.95], postoperative mortality, rates of wound infections, intraabdominal abscess and sepsis. Parenteral immunonutrition is the most effective in decreasing rates of pneumonia and urinary tract infections. The worst outcomes are obtained with standard parenteral nutritional management. |
| Yan X*, 2016 [29] | 3854 | Gastro-intestinal cancers | Meta-analysis; 30 randomized clinical trials included. | Enteral immunonutrition decreases rates of infectious, RR 0.69 [0.48-0.98] and non-infectious complications, RR 0.72 [0.61-0.84], length of hospitalization. |
| Song GM*, 2015 [30] | | Gastro-intestinal cancers | Meta-analysis, systematic review; 27 randomized clinical trials included. | Immunonutrition pre-, peri- or postoperatively decreases rate of infectious complications, RR 0.58 [0.43–0.78]. Besides, perioperative |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | immunonutrition decreases rate of non-infectious complications, perioperative or postoperative immunonutrition decreases length of hospitalization. |
| Adiamah A*, 2019 [31] | 1387 | Gastro-intestinal cancers | Meta-analysis, systematic review; 16 randomized clinical trials included. | | Immunonutrition decreases rate of infectious complications, OR 0.52 [0.38, 0.71] and length of hospitalization, no effect on the rate of non-infectious complications, OR 0.98 [0.73, 1.33] and postoperative mortality. |
| Klek S (b), 2010 [32] | 305 | Gastro-intestinal cancers | Randomized clinical trial. Postoperative immunonutrition, patients with malnutrition. | Rate of postoperative complications, length of hospitalization, postoperative mortality. | Immunonutrition decreases rate of infectious complications, OR 0.84 [0.42-1.69] and overall complication rate, OR 0.67 [0.35–1.27], length of hospitalization and postoperative mortality. |

*Meta-analyses and systematic reviews.

Importantly, CDC was used for complication rating in all these studies. The CDC is an excellent and easy to apply system for grouping and grading complications, that is validated and used worldwide. However, while CDC assesses only one of the most severe complications, CCI enables longitudinal estimation of all postoperative complications over a certain period of time

[Slankamenac K et al, 2013]. This tool may be especially sensitive in major and complex surgeries that are followed by prolonged recovery periods [de la Plaza Llamas R et al, 2018]. In this study, CCI enabled detection of significant effects of immunonutrition on the rate of severe and/or multiple complications in patients with PDAC, undergoing pancreatuduodenal resection, while the overall complication rate measured by either CDC or CCI did not differ between the groups. Although there are no studies of CCI usage in the evaluation of immunonutrition effects on complication rates, CCI demonstrated increased sensitivity and superiority over traditionally reported morbidity endpoints in a recent clinical trial on patients undergoing pancreatoduodenectomy [Slankamenac K et al, 2014]. CCI was also successfully used to evaluate postoperative complication rate in patients undergoing laparoscopic vs. open pancreatoduodenectomy [Poves I et al, 2018]. In several other studies CCI was found to be more strongly correlated with length of hospitalization in gastric surgery patients [Kim TH et al, 2018] and a valid tool to assess the overall burden of complications in patients undergoing HIPEC treatment [Dumitra S et al, 2018].

In this study, patients were stratified according to the diagnosis (PDAC vs. other pancreatic tumours) and presence of malnutrition. Interestingly, significant effects of immunonutrition on the rate of severe and/or multiple complications were observed in patients with PDAC, while nutritional status was not a determining factor for the efficacy of immunonutrition. Importantly, PDAC patients displayed significant preoperative and postoperative disturbances of the indicators of systemic inflammation. Metabolic and immune reprogramming are important hallmarks of pancreatic cancer. Cancerous tissue is characterized by a complex and dynamic secretion of various pro-inflammatory and anti-inflammatory cytokines that co-modulate the microenvironment promoting carcinogenesis and metastasis [Ying H et al, 2016; Inman KS et al, 2014]. One of the best-studied cytokines with carcinogenesis-

promoting activity is IL-6, whose secretion is mediated, among other factors, by activation of the Kras signaling pathway and hypoxic microenvironment [Holmer R et al, 2014]. According to the results of this and other studies (Table 5), patients with PDAC may experience greater benefits of immunonutrition as compared to patients with benign pancreatic diseases or less agressive tumours.

Effect of immunonutrition on patients with nutritional impairments vs. nutritionally normal is also unclear. In a study by Braga et al., the highest clinical benefits were observed in patients at a high risk or with an established malnutrition [Braga M et al, 2013, several studies by Klek et al also identified benefits of immunonutrition in patients with malnutrition [Klek S et al, 2014; Klek S et al, 2011]. Martin et al. study found that patients receiving preoperative immunonutrition had a lower risk of malnutrition and a lower reduction in serum albumin after surgery [Martin RC et al, 2017]. However, in a study by Silvestri et al, immunonutrition reduced rate of infectious complications and length of hospitalization in patients without any nutritional impairments [Silvestri S et al, 2016], whereas Hübner et al did not identified any differences in patients with malnutrition vs. those without nutritional impairments [Hübner M et al, 2012].

In patients with pancreatic cancer, amino acids were the most frequently distinguished metabolite biomarker class in both targeted and untargeted studies of body fluid metabolomics [Long NP et al, 2018]. In this study, characteristic plasma amino acid biomarker profiles were identified for discrimination between pancreatic cancer histological types (PDAC vs. other periampullary tumors) and stages (in patients with PDAC). The deadliest of all pancreatic cancer histological types, PDAC, could be discriminated from other pancreatic tumors, encompassing variable group of pathologies.

Many studies to date revealed potential plasma amino acid biomarkers for pancreatic cancer diagnostics. A limited number of studies investigated patient groups with various disorders that may

present with pancreatic tumor (e.g., benign pancreatic lesions or various pancreatic cancer subtypes). Most frequently, amino acid concentrations in healthy controls vs. pancreatic cancer patients were analyzed. Some major trends could be identified in these studies (Table 6). The most concordant findings include decreased plasma concentrations of His, Val, Gln, Ala, Pro, Asn, Tyr, Lys in patients with pancreatic cancer vs. healthy controls and decreased concentrations of Gln, Ala, His, Pro, Asn, Thr, Lys in patients with pancreatic cancer vs. chronic pancreatitis. This study reveals the same trends of characteristic amino acid concentration profiles in PDAC vs. other periampullary tumors. Small number of studies preclude comparisons between rare pancreatic tumour lesion groups.

Unfortunately, discordant study results are also common (e.g., Arg, Glu, Ile, Leu in Table 6). The reasons for these discrepancies may be variable, including differences in metods and study design, biological heterogeneity of pancreatic cancer and variable clinical parameters of patients. A range of methods is applied in amino acid studies, including both untargeted semi-quantitative (e.g., H1-NMR or GC/MS-based) and targeted quantitative (e.g., LC/MS-based) approaches. Limited sensitivity of H1-NMR may present difficulties in identifying subtle metabolite concentration changes, especially decrease of concentrations [He X et al, 2017]. Indeed, in all discordant pairs of findings in Table 6, at least one of the results was obtained using H1-NMR.

Dynamic changes of amino acid concentrations in relation to disease progression were described for branched-chain amino acids (BCAA). In a study by Mayers et al [Mayers JR et al, 2014], elevation of BCAA concentrations was identified in plasma samples, collected 2 to 5 years prior to pancreatic cancer diagnosis, but not later. Plasma concentrations of BCAA are directly associated with muscle mass in healthy subjects [Jourdan C et al, 2012], and could be a sign of cancer-associated muscle wasting in patients with early pancreatic cancer in a study by Mayers et al. Besides, plasma BCAA

**Table 6.** Concordance of blood-based AA analyses in (1) patients with pancreatic cancer vs. healthy controls and in (2) patients with pancreatic cancer vs. chronic pancreatitis.

| Amino acid | PC vs. HC | | | | | | | PC vs. benign or CP | | | Concordance : PC vs. HC | Concordance : PC vs. CP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Methods** | HPLC/ESI-MS, quantitative | GC-MS, semi-quantitative | GC-MS/MS, quantitative | H1 NMR, semi-quantitative | H1 NMR, semi-quantitative | LC-MS and GC-MS | H1 NMR, semi-quantitative | GC-MS, semi-quantitative | H1 NMR, semi-quantitative | | | |
| **Authors** | Fukutake et al., 2015 | Kobayashi et al., 2013 | Hirata et al., 2017 | OuYang et al., 2011 | Zhang et al., 2012 | Xie et al., 2014 | Batte et al., 2011 | Mayerle et al., 2018 (30) | Zhang et al., 2012 (28) | | | |
| Ala | ↓ | | | | ↓ | | | ↓ | ↓ | | ++ | ++ |
| Arg | ↓ | | | | | | ↑ | ↓ | | | | D |
| His | ↓ | ↓ | ↓ | | ↓ | | | ↓ | ↓ | | ++++ | ++ |
| Pro | ↓ | | | | | ↓ | ↓ | ↓ | | | ++ | ++ |
| Asn | ↓ | ↓ | | | | | ↓ | ↓ | | | ++ | ++ |
| Glu | | | | | ↓ | ↑ | ↑ | | ↓ | | D | D |
| Gln | | ↓ | | | ↓ | ↓ | ↓ | ↓ | ↓ | | +++ | +++ |
| Tyr | ↓ | ↓ | | | | | | | ↓ | | ++ | |
| Thr | ↓ | | | | | | ↓ | ↓ | | | | ++ |
| Lys | ↓ | | | | ↓ | | ↓ | | ↓ | | ++ | ++ |
| Ile | | | | ↑ | ↓ | | | | ↓ | | D | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Leu | ↓ | | | ↑ | ↓ | | | | ↓ | D | |
| Val | ↓ | | ↓ | | ↓ | | ↓ | | | ↓ | ++++ |
| Met | ↓ | ↓ | | | | | | | | | ++ |

*Only 4 aminoacids were investigated.

levels increase in prediabetes and diabetes, presumably due to insulin resistance in skeletal muscle [Guasch-Ferré M et al, 2016]. Patients with cancer cachexia usually have diminished BCAA concentrations [Kitagawa M et al, 2017]. In this study, plasma concentrations of 3-MHis, a specific biomarker of muscle, showed the same direction of differences between these groups.

In our study, significant differences of plasma His concentrations in relation to PDAC stage were observed, with diminishing levels from stage I towards stage IV. Of major importance, concentrations of other amino acids, including Thr, Lys, Arg, Gly, Ser, Asn, obtained U-shaped curve across cancer stages. This observation may also explain some discordant results of different studies: when study groups include variable proportions of different cancer stages, results may not be comparable. The same applies to comparisons of patients with early vs. advanced cancer stages.

## CONCLUSIONS

1. Quantitative analysis of plasma amino acids may be important in the diagnostics of PDAC vs. other periampullary tumors: significant differences of eleven amino acid concentrations (Thr, Asn, Gln, Gly, Citr, Aaba, Cysth, Lys, His, 3MHis, Arg) in PDAC vs. other periampullary tumors, correlation of three amino acid concentrations (Asn, Aaba, His) with cancer stages, characteristic patterns of amino acid concentrations in relation to cancer stage, correlation of 3-methyl histidine - a specific

skeletal muscle metabolite - with PDAC diagnosis were identified.

2. Perioperative measurement of systemic inflammatory response indicators may be relevant (a) as a diagnostic biomarker for PDAC (significant differences of IL-6 and CRP concentrations), (b) as a prognostic biomarker (effects of IL-6 and CRP on postoperative complications) and (c) as a biomarker of cancer cachexia (significant effects of nutritional status indicators on postoperative IL-6 and CRP concentrations).
3. Perioperative immunonutrition may reduce the incidence of severe and / or multiple complications, in particular for patients with PDAC, presumably due to major immune derrangements in PDAC.
4. Comprehensive Complication Index (CCI) is more sensitive than Clavien-Dindo Classification (CDC) in the assessment of postoperative complication rates: statistically significant effects of immunonutrition on the rate of severe and / or multiple complications was identified using CCI, but not CDC.
5. Nutritional screening tool NRS-2002, subjective indicators and anthropometric indicators, including BMI, are not sufficiently sensitive in detecting nutritional impairments in patients with PDAC or periampullary tumors; the most sensitive and easily applicable in clinical practice method is a measurement of lumbar skeletal muscle index (LSMI) on CT, diminished LSMI was identified in the largest proportion of patients studied (52.5%).
6. In PDAC and periampullary tumors, laboratory parameters (plasma amino acid levels, systemic inflammation indicators) and instrumental measures (investigations of body composition and nutritional status) are closely interrelated, reflect cancer biology and systemic effects of cancer and have significant impacts on outcomes.

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# SANTRAUKA

Šiame darbe tirta neselektyvi, įprastinėje klinikinėje praktikoje gydomų pacientų grupė, taikant išsamų klinikinį pacientų apibūdinimą, klinikinėje praktikoje naudojamus ir kai kuriuos eksperimentinius tyrimų metodus įvairiems tampriai susijusiems PDAC ir kitų periampulinių navikų patogenezės aspektams tirti. Ypatingas dėmesys skirtas dabartinėms neišspręstoms klinikinės praktikos problemoms - vėlyvai ir netiksliai diagnostikai, nepakankamai mitybinių sutrikimų diagnostikai ir gydymui, individualizuotos tiksliosios medicinos sprendimų stokai. Pagrindinis tyrimo tikslas - įvertinti PDAC ir kitų periampulinių navikų patogenezės aspektų (vėžio biologijos, sisteminio uždegimo, mitybos sutrikimų) ir medicininių intervencijų (imunomitybinio, chirurginio gydymo) sąsajas ir įtaką ligonio išeitims.

Šiame tyrime kaip eksperimentinis metabolominis tyrimas galimų biožymenų identifikavimui pasirinktas kiekybinis aminorūgščių tyrimas kraujo plazmoje. Aminorūgštys labai svarbios kasos vėžio biologijoje: pastaraisiais metais nustatytas ne tik gliutamino, bet ir kitų aminorūgščių, įskaitant proliną [Olivares O et al, 2017], seriną, gliciną [Maddocks ODK et al, 2017] vaidmuo kasos vėžio biologijoje. Be to, aminorūgščių kaip svarbios metabolitų grupės tyrimų vaidmuo nustatytas, parengus metabolominių tyrimų kasos vėžio srityje apžvalgą [Tumas J (a); Tumas J (b)]. Disertacijos rengimo metu publikuota sisteminė metabolominių kasos vėžio biožymenų apžvalga patvirtino šio pasirinkimo tikslingumą: nustatytos kelių šimtų įvairių metabolitų ir jų grupių sąsajos su kasos vėžiu, tačiau dažniausiai stebėta sąsaja su sisteminėmis aminorūgščių koncentracijomis, ypač gliutamatu bei histidinu [Long NP et al, 2018]. Atlikus kiekybinį aminorūgščių kraujo plazmoje tyrimą, šioje disertacijoje nustatyti reikšmingi vienuolikos aminorūgščių koncentracijų pakitimai, lyginant PDAC ir kitų periampulinių navikų grupes. Šiame darbe gauta naujų, iki šiol nepublikuotų duomenų: kai

kurios šioje disertacijoje tirtos ir kaip galimi biožymenys identifikuotos aminorūgštys nebuvo tiriamos kituose publikuotuose tyrimuose (Citr, Aaba, 3Mhis); nustatyta trijų aminorūgščių koncentracijų (Asn, Aaba, His) kraujo plazmoje koreliacija su vėžio stadijomis ir kai kurių aminorūgščių koncentracijų būdinga dinamika, priklausomai nuo vėžio stadijos; nustatyta 3-metilo histidino – specifinio skeleto raumenų metabolito – koncentracijų koreliacija su PDAC diagnoze. Be to, rasta statistiškai reikšminga sąsaja tarp Ala, Glu, Aaba ir Lys koncentracijų sumažėjimo ir mitybinių sutrikimų. Atlikus sisteminę iki šiol publikuotų duomenų analizę, įvertintas aminorūgščių tyrimų panaudojimas kasos vėžio diagnostikoje ir identifikuoti diskordantinius duomenis galimai įtakojantys veiksniai – metodologiniai tyrimų trūkumai ir skirtumai bei pacientų fenotipavimo ir skirstymo problemos.

Tiriant sisteminio uždegiminio atsako (SUA) rodiklius (IL-6, IL-10, TNF-α, CRB) prieš ir po operacijos, nustatyti svarbūs ir statistiškai reikšmingi skirtumai tarp tiriamųjų grupių: prieš operaciją PDAC grupės tiriamiesiems nustatyti didesni SUA rodikliai (IL-6 koncentracijos), tuo tarpu po operacijos PDAC grupės pacientams nustatyti žemesni SUA rodikliai, lyginant su kitų periampulinių navikų grupe (IL-6 ir CRB koncentracijos serume). Nustatyta statistiškai reikšminga IL-6 ir CRB koncentracijų priklausomybė nuo komplikacijų dažnio ir sunkumo, o sudarius regresijos lygtis nustatyta reikšminga mitybos būklės rodiklių įtaka pooperacinėms CRB ir IL-6 koncentracijoms. Įvertinę šios disertacijos ir publikuotus duomenis galime daryti prielaidą, kad prieš operaciją ir po jos matuojamos IL-6 koncentracijos serume gali turėti svarbią reikšmę (a) kaip PDAC diagnostinis žymuo (kartu su kitais biožymenimis diferencijuojant PDAC ir kitus kasos navikus), (b) kaip prognostinis žymuo, susijęs su pooperacinių komplikacijų vystymusi ir bendra išgyvenamumo prognoze ir (c) kaip vėžio kacheksijos žymuo.

Šioje disertacijoje naudoti įvairūs mitybinės būklės tyrimai – apklausos, antropometriniai matavimai, instrumentiniai ir

laboratoriniai tyrimai. Šie tyrimai taikyti mitybinių sutrikimų patikrai bei diagnostikai, derinant klinikinėje praktikoje dažnai naudojamus ir naujus (KT metodas skeleto raumenų masės vertinimui) ar eksperimentinius (aminorūgščių koncentracijos plazmoje) tyrimų metodus. Darbo tikslas – įvertinti ir palyginti įvairius mitybos būklės rodiklius bei mitybinių sutrikimų diagnostikos įrankius, mitybos sutrikimų įtaką paciento išeitims ir sudaryti rekomendacijas dėl sergančių kasos vėžiu pacientų mitybinės būklės ištyrimo. Nustatyta, kad mitybinių sutrikimų patikros įrankis NRS 2002, subjektyvūs rodikliai ir antropometriniai matavimai (įskaitant KMI) yra nepakankamai jautrūs mitybinių sutrikimų diagnostikai sergančiųjų PDAC ir kitais periampuliniais navikais grupėje. Jautriausias ir klinikinėje praktikoje lengvai pritaikomas metodas – KT matuojamas juosmens skeleto raumenų indeksas (LSMI). LSMI rodiklio sumažėjimas nustatytas didžiausiai daliai (52,5%) tirtų pacientų. Atlikus sisteminę publikuotų duomenų analizę, nustatyta ženkli įvairovė: sarkopenijos dažnis tiriamųjų grupėse buvo nuo 11,1% iki 68,8%. Šią įvairovę gali įtakoti daug veiksnių (pvz., tiriamųjų amžius, lytis, fizinis aktyvumas ir kt.), tačiau svarbios ir metodologinės priežastys: taikomi skirtingi tyrimų metodai, tyrimų standartizavimo ir normos ribų validavimo stoka ir kt. Tyrimų tikslumą galimai pagerintų instrumentinių tyrimų derinimas su laboratoriniais rodikliais (pvz., 3-metilo histidino koncentracija plazmoje), atspindinčiais skeleto raumenų apykaitą: šioje disertacijoje nustatyta statistiškai reikšminga priklausomybė tarp 3MHis koncentracijų ir PDAC diagnozės. Šiuo metu tyrimų, kuriuose būtų derinami skirtingi instrumentiniai ir laboratoriniai mitybinės būklės rodikliai ir lyginamos šių rodiklių priklausomybės, nėra.

Nors imunomitybiniai preparatai rekomenduojami pacientams, kuriems atliekama pankreatoduodeninės rezekcijos operacija, nes gali sumažinti infekcinių komplikacijų dažnį, poveikis kitiems išeičių parametrams šiuo metu vis dar nėra aiškus. Be to, šiuo metu dar

neaišku, kuriems pacientams imunomityba yra veiksmingiausia (pvz., pacientams su vėžio diagnoze, turintiems mitybinių sutrikimų ir pan.). Šioje disertacijoje komplikacijų vertinimui panaudotas neseniai sukurtas jautresnis už įprastinę Clavien-Dindo klasifikaciją (CDC) įrankis, Išsamus komplikacijų indeksas (CCI), ir nustatytas statistiškai reikšmingas imunomitybos poveikis sunkių ir/ ar dauginių komplikacijų dažniui, vertinant pooperacines komplikacijas pagal CCI, bet ne CDC. Be to, nustatytas didesnis imunomitybos poveikis sunkių ir/ ar dauginių komplikacijų dažniui pacientams su PDAC, tačiau mitybiniai sutrikimai neturėjo įtakos imunomitybos poveikiui. Taigi, galime daryti prielaidą, kad imunomitybos poveikis pacientams su PDAC gali būti stipresnis dėl ženklesnių imuninės sistemos sutrikimų, tačiau šiuos radinius reikėtų patvirtinti, atliekant platesnės apimties tyrimus.

Vertintos visų tirtų klinikinių parametrų, laboratorinių ir instrumentinių rodiklių sąsajos su gydymo išeitimis. Sudarius regresijos lygtis, nustatyta didelė bendra mitybos būklės rodiklių įtaka komplikacijų dažniui ir sunkumui (CCI); didžiausi CCI indeksai stebėti pacientams su sarkopeniniu nutukimu ir nepakankamo svorio pacientams su sarkopenija. Apibendrinus šios disertacijos ir publikuotus duomenis, sudarytos praktinės diagnostikos, gydymo parinkimo ir prognozavimo, priešoperacinio ištyrimo ir paruošimo, gydymo ir išeičių vertinimo rekomendacijos.

**Darbo tikslas**

Įvertinti kasos duktalinės adenokarcinomos (PDAC) ir kitų periampulinių navikų pagrindinius patogenezės aspektus (įskaitant vėžio biologiją, sisteminį uždegimą, mitybos sutrikimus), medicinines intervencijas (įskaitant imunomitybą, chirurginį gydymą), jų sąsajas ir įtaką ligonio išeitims.

**Darbo uždaviniai**

1. Nustatyti sergančiųjų PDAC ir kitais periampuliniais navikais medžiagų apykaitos, mitybinės būklės ir uždegiminių rodiklių ypatumus;
2. Nustatyti medžiagų apykaitos, mitybinės būklės ir uždegiminių rodiklių sąsajas su gydymo išeitimis ir pooperaciniais uždegiminiais rodikliais;
3. Atlikti mitybinės būklės rodiklių bei mitybinių sutrikimų diagnostikos įrankių analizę, palyginti klinikinėje praktikoje naudojamus ir eksperimentinius rodiklius ir jų sąsajas;
4. Įvertinti mitybinio paruošimo, naudojant papildus su imunomoduliaciniais komponentais, įtaką pooperacinėms išeitims;
5. Sudaryti sergančiųjų kasos vėžiu ir kitais periampuliniais navikais perioperacinio ištyrimo ir gydymo rekomendacijas.

**Ginamieji teiginiai**

1. Sergantiems PDAC ir kitais periampuliniais navikais būdingi laboratoriniais ir instrumentiniais tyrimų metodais nustatomi pakitimai, atspindintys vėžio biologijos ir sisteminius vėžio poveikius.
2. Ankstyvai ir tiksliai diagnostikai, prognozavimui ir gydymo parinkimui svarbu derinti įvairius vėžio biologijos ir sisteminius vėžio poveikius atspindinčius biožymenis.
3. Vėžio biologijos ir sisteminiai vėžio poveikiai reikšmingai įtakoja sergančiųjų PDAC ir kitais periampuliniais navikais išeitis.
4. Kūno sandaros kitimai (sarkopenija) – ankstyvas PDAC ir kitų periampulinių navikų simptomas, o KT metodai padeda anksti diagnozuoti kūno sandaros pakitimus ir mitybinius sutrikimus.
5. Perioperaciniame laikotarpyje paskirta imunomityba gali pagerinti sergančiųjų PDAC ir kitais periampuliniais navikais išeitis.

**Išvados:**

1. Kiekybinis aminorūgščių tyrimas gali būti svarbus, diferencijuojant PDAC ir kitus periampulinius navikus: nustatyti reikšmingi vienuolikos aminorūgščių (Thr, Asn, Gln, Gly, Citr, Aaba, Cysth, Lys, His, 3MHis, Arg) koncentracijų pokyčiai, lyginant PDAC ir kitų periampulinių navikų grupes, trijų aminorūgščių koncentracijų (Asn, Aaba, His) kraujo plazmoje koreliacija su vėžio stadijomis, kai kurių aminorūgščių koncentracijų būdinga dinamika, priklausomai nuo vėžio stadijos, 3-metilo histidino – specifinio skeleto raumenų metabolito – koncentracijų koreliacija su PDAC diagnoze.
2. Sisteminio uždegiminio atsako rodiklių matavimas prieš ir po operacijos gali turėti svarbią reikšmę kaip (a) diagnostinis PDAC žymuo (nustatyti reikšmingi IL-6 ir CRB koncentracijų skirtumai, lyginant su kitų periampulinių navikų grupe), (b) prognostinis žymuo (nustatyta IL-6 ir CRB koncentracijų sąsaja su pooperacinių komplikacijų dažniu) ir (c) vėžio kacheksijos žymuo (nustatyta reikšminga mitybos būklės rodiklių įtaka pooperacinėms IL-6 ir CRB koncentracijoms).
3. Perioperaciniame laikotarpyje paskirti papildai su imunomoduliaciniais komponentais gali sumažinti sunkių ir/ ar dauginių komplikacijų dažnį ir gali būti ypač naudingi pacientams su PDAC, galimai dėl ženklesnių imuninės sistemos sutrikimų.
4. Išsamus komplikacijų indeksas (CCI) pasižymi didesniu jautrumu, lyginant su Clavien-Dindo klasifikacija (CDC), vertinant pooperacinių komplikacijų dažnius: nustatytas statistiškai reikšmingas imunomitybos poveikis sunkių ir/ ar dauginių komplikacijų dažniui, vertinant pooperacines komplikacijas pagal CCI, bet ne CDC.
5. Mitybinių sutrikimų patikros įrankis NRS 2002, subjektyvūs rodikliai ir antropometriniai matavimai (įskaitant KMI) nepakankamai jautrūs mitybinių sutrikimų diagnostikai

sergančiųjų PDAC ir kitais periampuliniais navikais grupėje, o jautriausias ir klinikinėje praktikoje lengvai pritaikomas metodas – KT matuojamas juosmens skeleto raumenų indeksas (LSMI), kurio sumažėjimas nustatytas didžiausiai daliai (52,5%) tirtų pacientų.

6. Tampriai patogenezėje susiję, vėžio biologijos ir sisteminius poveikius atspindintys laboratorinių (aminorūgščių koncentracijos plazmoje, sisteminio uždegiminio atsako rodikliai) ir instrumentinių tyrimų (kūnos sandaros tyrimų ir mitybinės būklės) rodikliai koreliuoja tarpusavyje ir įtakoja gydymo išeitis.

# CURRICULUM VITAE

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| Advanced resuscitation in trauma, Crisis Research Center, Vilnius, Lithuania. | 2012 |

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| --- |
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