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INFLUENCE OF PREOPERATIVE NUTRITIONAL STATUS AND BODY COMPOSITION ON POSTOPERATIVE COMPLICATIONS AND CLINICAL OUTCOMES AFTER SURGERY IN PATIENTS WITH RESECTABLE PANCREATIC AND PERIAMPULLARY TUMOR

Wpływ przedoperacyjnego stanu odżywienia i składu ciała na występowanie powikłań pooperacyjnych u pacjentów po resekcji z powodu guzów trzustki i okołobrodawkowych

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A - Koncepcja i projekt badania, B - Gromadzenie i/lub zestawianie danych, C - Analiza i interpretacja danych, D - Napisanie artykułu, E - Krytyczne zrecenzowanie artykułu, F - Zatwierdzenie ostatecznej wersji artykułu

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Abstract (in Polish):
Cel pracy: Celem pracy była ocena prognostycznej wartości stanu odżywienia, wybranych parametrów klinicznych i składu ciała ocenionego metodą bioimpedancji elektrycznej, na wskaźniki pooperacyjne i ciężkość powikłań po operacji z powodu guzów trzustki i okołobrodawkowych.
Materiał i metody: Badanie obejmowało prospektywną analizę 56 pacjentów zakwalifikowanych do leczenia operacyjnego z powodu guza trzustki lub guzów okołobrodawkowych. Poważne powikłania występowały u 28.6% pacjentów. Oceniono wybrane parametry kliniczne, stan odżywienia oraz skład ciała przy użyciu bioimpedancji elektrycznej. Analizie poddano wpływ wymienionych czynników na występowanie powikłań pooperacyjnych.
Wyniki: Niedożywienie występowało u 76.8% pacjentów przed operacją, a 71.4% miało utratę masy ciała wynoszącą ≥5%. Na podstawie BMI określono, że 44.6% chorych miała nadmierną masę ciała. Nie wykazano istotnych statystycznie różnic pomiędzy przedoperacyjnymi parametrami stanu odżywienia, i składem ciała , a ciężkością powikłań pooperacyjnych (Clavien-Dindo ≥3). W analizie wielowymiarowej jedynymi istotnymi czynnikami wpływającymi na większe ryzyko występowania poważnych powikłań pooperacyjnych były hipoalbuminemia (p= .004) i brak cukrzycy (p= .032).
Wnioski: Guzy trzustki i okołobrodawkowe we wczesnym stadium mogą nie wpływać na występowanie istotnych zaburzeń składu ciała i tym samym nie powodować odchyleń w badaniu bioimpedancją elektryczną. Wykorzystanie przedoperacyjnych pomiarów składu ciała wykorzystując BIA jako czynników prognostycznych powikłań pooperacyjnych w u chorych we wczesnym stadium choroby wydaje się być ograniczone. Niedożywienie nie wpływało w istotny sposób na ryzyko występowania ciężkich powikłań po leczeniu chirurgicznym.

Abstract (in English):
Aim: The aim of our study was to evaluate the prognostic role of nutritional status, selected clinical parameters and body composition assessed by bioelectrical impedance on clinical outcomes and major complication after pancreatic surgery in oncological patients.
Material and methods: This is a prospective study including 56 patients who underwent resection due to pancreatic or periampullary tumors. The nutritional status, body weight loss, selected laboratory and body composition parameters were evaluated. We assessed their predictive value in relation to postoperative complications and clinical outcomes.
Results: 76.8% of the patients were malnourished, and 71.4% lost ≥5% of body weight before surgery. However, 44.6% of patients were overweight based on body mass index. Severe complications occurred in 28.6% patients. There were not any significant differences between the grade Clavien-Dindo≥3 group and grade 1-2 also no complication group in terms of bioimpedance and nutritional parameters. In multivariate analysis, the factors predictive of severe complications after pancreatic resection were hypoalbuminemia (p= .004) and absence of diabetes mellitus (p= .032).
Conclusions: Early-stage of pancreatic and periampullary tumors may not cause significant changes in body composition that can be detected by bioelectrical impedance analysis. The role of preoperative BIA's parameters assessment as indicators of postoperative outcomes in this group seems to be limited.

Keywords (in Polish): bioimpedancja elektryczna, rak trzustki, skład ciała, niedożywienie.

Keywords (in English): nutrition status, pancreatic tumor, body composition, bioelectrical impedance, pancreatic surgery.

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Stan odżywienia i skład ciała chorych z rakiem trzustki

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1. Introduction

Pancreatic cancer has poor prognosis and rates of resectability. About 92% of patients with pancreatic cancer and 55% of patients with ampullary carcinoma die within 5 years after resection [1]. The standard surgical procedures for periampullary and pancreatic malignancies are total pancreatectomy, distal pancreatectomy and pancreaticoduodenectomy (PD) which are associated with a high complications rate [2,3]. The major complications after pancreatic and periampullary operation include intra-abdominal abscess, sepsis, gastrointestinal fistula, bile leakage, haemorrhage, pancreatic fistula (POPF), delayed gastric emptying, surgical site infections (SSI) and death [4]. Currently, preoperative malnutrition, excess body weight loss, low albumin (ALB) and total protein (TP) level, BMI >25 also <18,5 kg/m2 and muscle wasting are among well-known metabolic risk factors of postoperative complications after pancreatic surgery [3-9]. Many different questionnaires were introduced to assess nutritional status (NS) in pancreatic cancer patients. The most common are Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA) and Nutrition Risk Screening 2002 (NRS 2002) [10]. As shown, in recent studies malnutrition occurs in 83% of patients with periampullary malignancies [11]. Postoperative pancreatic fistula is a well-known major complication after partial pancreatectomy [12,13]. The potential consequences of POPF are sepsis, longer hospital stay with increased treatment costs, and death. Patients with BMI ≥25 kg/m2, at older age and with increased intraabdominal fat thickness, soft pancreatic gland, small size pancreatic duct, and tumors of the papilla of Vater or neuroendocrine tumors are at high risk of POPF [4,14,15,16]. Although pancreatic cancer has a predilection for cachexia, surprisingly, overweight was reported in 41% of patients [17]. Some authors confirmed the relationship between BMI and POPF incidence but suggested focusing more attention on the role of abdominal fat distribution [18]. Patients with

POPF were more likely to have a higher visceral fat area (VFA) especially measured at the level of the coeliac trunk [18,19].

Determining body composition disorders and nutritional status impairments may be useful for postoperative complications risk assessment. It is important to assess the distribution of adipose tissue and the amount of muscle tissue. Previous studies showed that sarcopenia is associated with worse overall survival and higher complications rate after PD [8,20-24]. To assess muscle mass, adipose tissue and other body composition parameters, it is recommended to use data form bioelectrical impedance (BIA), computed tomography (CT), magnetic resonance imaging (MRI) or dual energy X-ray absorptiometry (DXA) measurements. Bioelectrical impedance is a non-invasive, portable, quick and bedside tool to assessed body composition. Most of BIA parameters (phase angle, extracellular water, total body water, fat free mass) are recognized as helpful in nutritional status assessment in surgical and critically ill patients [25-28]. There is a good agreement between low muscle mass calculated in computed tomography and BIA in critically ill patients [29-31]. However, BIA equations are population-specific. There is a considerable amount of research focusing on relationship between malnutrition and postoperative complications but there is paucity of data on BIA assessment and its role in patients with resectable pancreatic an periampullary tumors. The aim of our study was to evaluate the prognostic role of NS, selected clinical parameters and body composition assessed by BIA on clinical outcomes and major complication after pancreatic surgery in oncological patients.

2. Material and Methods

2.1. Study design

This is a prospective study which enrolled patients with resectable pancreatic or periampullary tumors who underwent surgical treatment in our institution. The study was approved by the local Ethics Committee. Patients with neoadjuvant chemotherapy, after palliative resection, with a history of other cancer treatment or major surgery during the last 5 years, and patients who had contraindications to body composition analysis (pregnancy, the presence of metal elements in the body, a cardiac pacemaker) were excluded. Clinical and nutritional parameters, body composition data were included in prospective database (presented in the tables).

Postoperative complications definitions

Postoperative complications were graded according to the Clavien-Dindo classification [32]. The grade 1 and 2 Clavien-Dindo complications were classified as mild, whereas the grade 3 through 5 were regarded severe. Postoperative pancreatic fistula was defined according to the International Study Group for Pancreatic Surgery (ISGPS) classification as B- patient in a generally stable condition with slight septic symptoms and having drainage persisting beyond 3 weeks, C - being in poor condition, with symptoms of sepsis or organ failure, the patient requiring surgical intervention and being in the intensive care unit or death [33].

Gastrointestinal fistula definition

Gastrointestinal fistula was defined as an abnormal opening that causes fluids from gastric or intestinal to be discharged through the lining of the other organ.

Nutritional status

For nutritional status assessment we used NRS-2002 and SGA, weight loss during the last 6 months, body mass index - actual BMI and usual BMI (before the diagnosis). The information of NS was collected between 1-3 days before the surgery. Based on cut-offs from WHO all patients were divided into group with BMI ≥25 kg/m^2 as overweight/obese and normal/underweight (BMI <25 kg/m^2). Using NRS 2002 we divided patients into group no-risk of malnutrition (<3 points) and risk of malnutrition (≥3 points).

Laboratory parameters

Biochemical markers including serum albumin and total protein level were evaluated. Blood samples were collected on the day before or in day of the surgery.

Body Composition analyses

Bioelectrical impedance measurements included fat-free mass (FFM), fat mass (FM), total body water (TBW), phase angle (PA) and body cell mass (BCM). Body composition evaluation by BIA is based on determination of fat free mass and fat tissue using low voltage and low current. The human body is composed of fatty tissue that does not conduct electricity, inversely than FFM which conducts electricity. In this study we used 50 kHz frequency. Body composition parameters were developed by the bioelectrical impedance analysis device the MALTRON, BIO-SCAN 920. Before BIA testing the patients had overnight or minimum 4 hour fasting period. BIA was performed with patients in horizontal position on a bed and legs and arms apart, not touching the body. Because, in other studies the level of FM and FFM between males and females is significantly different, for our analyses we also matched patients based on sex and made assumptions according to the ESPEN cut-offs: FFMI (male < 17 kg/m^2, female < 15 kg/m^2) [34]. The FMI cut-offs for males were <7.7 kg/m^2 and for females <5 kg/m^2 [35]. FFMI and FMI was calculated, respectively: FFMI = fat free mass [kg]/ (height [m])^2 and FM = fat mass [kg]/ (height [m])^2 .

2.2. Statistical analysis

Statistical analyses were performed in IBM SPSS Statistics 27.0. To compare groups by nominal data, Pearson's chi-square test or Fisher's exact test was performed if the expected number was lower than 5. Univariate and multivariate logistic regressions were performed to determine CD >3 predictors. The statistical tests were given a significance level of $p < 0.05$.

Relationship between two nominal variables

The relationship between two variables on the nominal and scale was analyzed in pairs in the form of contingency tables with the indication of frequency and shares. The dependence of the variables was examined using the Pearson chi-square test with Cramer's *V* measure of association.

Examine the differences between means

In the case of the number of groups above two and a continuous variable with a normal distribution, the Mann-Whitney U test was used to examine the means with rank biserial correlation coefficient as a measure of relationship.

3. Results

We enrolled 56 patients. The median of age was 64.5 years and 51.8% were males. Pancreatic tumor was recognized in 80.4% and tumors of the papilla of Vater in 19.6%. Histopathologically, adenocarcinoma, acinocellular carcinoma and signet ring cell carcinoma were diagnosed in 94.6%, 3.6% and 1.8%, respectively. Pancreaticoduodenectomy was performed in the majority of patients (75%), while distal pancreatectomy and total pancreatectomy were less common, in 16.1 % and 5.9% of cases, respectively.

The median BMI was 24.5 kg/m² and 44.6% patients had BMI ≥25. The median BMI before the diagnosis (usual) was 27.16 kg/m² . Based on NRS 2002, 76.8% patients had malnutrition or risk of malnutrition. The median level of serum albumin and total protein were 3.9g/dL and 6.8g/dL, respectively hypoalbuminemia was seen in 24.5% cases. Diabetes mellitus was recognized in 62.5% of patients.

Based on by BIA, we assessed median phase angle 7.45 Hz, fat mass (FM) in kilograms and percentage; 23.07 kg and 30.31%. For fat free mass (FFM), the median levels were 47.47kg and 69.37%. BIA measurements in our patients showed no significant disturbances in the body composition when we compared them to the healthy population [36].

3.1. Influence on preoperative nutritional status, BMI, body composition and weight loss on postoperative complications and clinical outcomes

Generally, patients were malnourished based on nutritional assessment questionnaires and weight loss parameters. However, the median BMI was borderline normal and overweight. BIA parameters did not show any significant disturbances in the body composition in patients before the surgery. Overall, postoperative complications occurred in 71.4% (n=40) of cases and severe (Clavien-Dindo ≥3) had 28.6% (n=16) of patients. Pancreatic fistulas occurred in 19.6% and septic complication in 41.1% cases.

One-year mortality after surgery was 26.8% in our patients and were not dependent on nutritional status assessed by NRS 2002. NRS ≥ 3 was associated with inconsiderable more incidence of overall surgical complications and has no influence on the type of postoperative complications but prolonged the length of stay in hospital 13 vs 9 days compare to no risk of malnutrition patients (p = .021). We observed that tumor location had no significant influence on the risk of malnutrition (p= .097). Table 1 demonstrates the selected clinical parameters and complication profile after pancreatic resection stratified according to the nutritional status assessed by NRS 2002.

Table 1. Postoperative outcomes and preoperative parameters according to nutritional status assessed by NRS 2002

Variable	Total, *N*=56ǂ	Risk of malnutrition NRS ≥3 *n*= 43ǂ	No risk of malnutrition NRS <3 *n*= 13ǂ	*P*
Albumin level, g/dL n, (%) median (IQR)	3.9 (0.95) [*n*=53]	3.9 (1.35) [*n*=41]	4.25 (0.91) [*n*=12]	**.034**
Total protein level, g/dL, median (IQR)	6.80 (0.85) [*n*=53]	6.70 (0.70) [*n*=41]	7.10 (1.03) [*n*=12]	.053
CRP level, mg/L median (IQR)	2.3 (7.14) [*n*=54]	2.75 (10.90) [*n*=41]	1.4 (4.09) [*n*=12]	.105
Tumor histopathology, n (%):				
Adenocarcinoma	53 (94.6%)	41 (95.3%)	12 (92.3%)	
Acinocellulare	2 (3.6%)	1 (2.3%)	1 (7.7%)	.551*
Signet ring cell	1 (1.8%)	1 (2.3%)	0 (0.0%)	
Tumor location, n (%):				
Head of the pancreas	36 (64.3%)	28 (65.1%)	8 (61.5%)	
Body of the pancreas	4 (7.1%)	1 (2.3%)	3 (23.1%)	.097*
Tail of the pancreas	5 (8.9%)	4 (9.3%)	1 (7.7%)	
Papilla of Vater	11 (19.6%)	10 (23.3%)	1 (7.7%)	
Postoperative outcomes				
Surgical complications, n (%)	40 (71.4%)	31 (72.1%)	9 (69.2%)	1.000*
Relaparotomy, n (%)	10 (17.9%)	7 (16.3%)	3 (23.1%)	.682*
Postoperative 30-day mortality, n (%)	7 (12.5%)	4 (9.3%)	3 (23.1%)	.335*
Pancreatic fistula incidence, n (%)	11 (19.6%)	8 (18.6%)	3 (23.1%)	.705*
Pancreatic fistula grade: B vs C, n (% of N)	8 (14.3%) / 3 (5.4%)	6 (10.7%) / 2 (3.6%)	2 (3.6%) / 1 (1.8%) /	1.000*
Intraabdominal abscess, n (%)	7 (12.5%)	6 (14.0%)	1 (7.7%)	1.000*
Septic complications, n(%)	23 (41.1%)	18 (41.9%)	5 (38.5%)	1.000*
Hemorrhagic complications, n (%)	3 (5.4%)	3 (7.0%)	0 (0.0%)	1.000*
Gastrointestinal fistula, n (%)	1 (1.8%)	0 (0.0%)	1 (7.7%)	.232*
1 years survival, n (%)	41 (73.2%)	31 (72.1%)	10 (76.9%)	1.000*
LOS, day, median (IQR)	11.0 (12.5)	13.0 (14.0)	9.0 (6.0)	**.021**

* — Fisher's Exact Test; ǂ - for certain parameters the data for some patients was unavailable; in such cases, the non-standard group count is provided in "[ ]". Abbreviations: CRP – c-reactive protein, NRS – Nutritional Risk Score, LOS – length of stay.

Comparison on selected factors in patients with postoperative complications using Clavien-Dindo classification or without post-operative have been presented in table 2. There were no statistically significant differences in nutritional status and body composition parameters between patients with no/mild postoperative complications (Clavien-Dindo <3) and severe ones (Clavien-Dindo ≥3). However more patients with serious complications had hypoalbuminemia than with mild complications *(p= .012)* (Table 2). Surprisingly, the percent of weight loss was higher in people with Clavien-Dindo <3 than ≥3 (10.81% vs 5.29%, *p*= .040).

We did not find differences between median FFMI and Clavien-Dindo groups. For FMI, both men and women had a median value of body fat below normal (5.65 kg/m² and 4.15 kg/m²). The median usual BMI (before the diagnosis) were higher in patients without or mild complications than in severe complications group (27.42 kg/m² vs 25.79 kg/m²). Contrariwise, if we compare actual BMI (before the surgery, after diagnosis) between Clavien-Dindo groups. The results were not significantly *(p*= .420 and *p*= .717).

Table 2. Comparison on selected factors in patients with mild, serious or without post-operative complications using Clavien-Dindo classification

Variable	All patients (n = 56)ǂ	Clavien-Dindo grade <3 No/Mild (n = 40)ǂ	Clavien-Dindo grade ≥3 Serious complications (n = 16)ǂ	p
Age [yr], median (IQR)	64.50 (9.00)	65.00 (10.75)	62.50 (9.25)	.188
BMI, median (IQR) [kg/m²]	24.50 (5.81)	24.44 (5.49)	25.29 (6.34)	.717
BMI ≥25, n(%)	25 (44.6%)	17 (42.5%)	8 (50.0%)	.610
Usual BMI median (IQR) [kg/m²]	27.16 (5.68)	27.42 (7.19)	25.79 (5.78)	.420
Usual_BMI ≥25 n(%)	36(64.3%)	28 (70%)	8 (50.0%)	.158
Risk of malnutrition NRS ≥3 N(%)	43 (76.8%)	30 (75.0%)	13 (81.3%)	.737*
Weight loss, median (IQR) [%]	9.03 (9.90)	10.81 (9.48)	5.29 (9.2)	**.040**
BCM, median (IQR) [kg]	25.39 (10.26) [n=45]	25.66 (10.86) [n=33]	25.19 (7.75) [n=12]	.980
PA, median (IQR) (50Hz)	7.45 (1.97) [n=46]	7.29 (1.53) [n=34]	8.06 (1.85) [n=12]	.206
FM, median (IQR) [kg]	23.07 (11.92) [n=45]	23.07 (12.29) [n=33]	21.60 (13.06) [n=12]	.457
FMI, median (IQR), [kg/m2]	8.01 (3.97) [n=45]	8.11 (3.14) [n=33]	7.9 (4.56) [n=12]	.729
Male, median < 7,7 kg/m2,[n;%]	5.65 (1.21) [n=12;26.7%]	5.86 (1.41) [n=9;27.3%]	5.22 (0.64) [n=3;25.0%]	.460
Female, median < 5 kg/m2,[n,%]	4.15 (0.56) [n=2;4.4%]	3.59 (0) [n=1;3.0%]	4.71 (0) [n=1;8.3%]	1.000
FM, median (IQR) [%]	30.31 (10.63)[n = 46]	30.31 (9.36)[n = 34]	29.90 (15.17)[n = 12]	.841
FFM, median (IQR) [kg]	47.47 (18.68)[n = 45]	47.47 (19.10)[n = 33]	46.82 (15.73)[n = 12]	.888
FFMI , median (IQR), [kg/m²]	16.95(3.2)[n=46]	16.8(3.4)[n=34]	17.05(1.25)[n=12]	.930
Male, median < 17 kg/m²,[n; %]	16.1 (2.1) [n=5, 10.9%]	16.1 (1.05) [n=3, 8.8%]	15.2 (1.4) [n=2, 16.7%]	1.000
Female, median < 15 kg/m²,[n; %]	14.3 (0.5) [n=14, 30.4%]	14.3(0.65) [n=6, 17.6%]	14.3(0) [n=1, 8.3%]	1.000
FFM, median (IQR) [%]	69.37 (9.98)[n = 46]	68.70 (9.38)[n = 34]	70.11 (13.57)[n = 12]	.745
Muscle mass, median (IQR), [kg]	20.94 (21.45)[n = 45]	20.94 (11.71)[n = 33]	21.03 (9.43)[n = 12]	.778
TBW, median (IQR) (L)	33.94 (14.02)[n = 45]	33.94 (14.36)[n = 33]	33.78 (4.94)[n = 12]	.898
TP median (IQR) [g/dL]	6.80 (0.85)[n = 53]	6.80 (0.70)[n = 37]	6.80 (2.35)[n = 16]	.662
Albumin median (IQR) (range) (g/dL)	3.90 (0.95)[n = 53]	3.90 (6.00)[n = 37)	3.45 (2.47)[n = 16]	.485
<3.5 n(%)	13 (24.5%)[n = 53]	5 (13.5%)[n = 37]	8 (50.0%)[n = 16]	**.012**
CRP, median (IQR) [mg/dL]	2.30 (7.14)[n = 54]	3.50 (19.425)[n = 38]	1.75 (2.13)[n = 16]	.073
Diabetes mellites [n,%]	35 (62.5%)	28 (70.0%)	7 (43.8%)	.067
LOS, median (IQR) (days)	11.00 (11.50)	11.00 (7.00)	18.00 (45.75)	.098

* — Fisher's Exact Test; ǂ - for certain parameters the data for some patients was unavailable; in such cases, the non-standard group count is provided in []. Abbreviations: BMI – body mass index, usual_BMI – body mass index before the diagnosis, NRS – Nutritional Risk Score, BCM – body mass cell, PA – phase angle, FM – fat mass, FMI – fat mass index (cut-offs for males were <7.7 kg / m² and for females <5 kg/ m²) FFMI [n;%] - means the percentage of people below FFMI cut-off value, FFM – fat-free mass, FFMI – fat-free mass index, TBW – total body water, TP – total protein, CRP – c-reactive protein, , LOS – length of stay.

In multivariate analysis (Table 3), the factors predictive of severe complications after pancreatic resection were hypoalbuminemia (p= .004) and absence of diabetes mellitus (p= .032)

Table 3.The results of logistic regression analyses for Clavien-Dindo ≥ 3 as dependent variable.

	Univariate analysis			Multivariate analysis		
Factors	**Exp. (*B*)**	**95% Cl**	***p***	**Exp. (*B*)**	**95% Cl**	***P***
DM	0.333	0.101 – 1.103	.072	0.201	0.046 – 0.874	.032
Alb < 3.5	6.400	1.643 – 24.927	.007	9.724	2.025 – 46.690	.004

A series of univariate logistic regression analyses revealed Alb <3.5 (p = .007) as a statistically significant predictor for CD ≥ 3 whereas DM's significance as a predictor approached statistical significance (p = .077). Thus, these two variables were selected as candidate predictors in multivariate logistic regression with entry method. According to the model, both DM and Alb ≥ 3.5 were statistically significant predictors of CD ≥3, namely decreased amount of albumin and ***negative*** DM increased the chance of CD ≥ 3. Abbreviations: DM – diabetes mellites, Alb – albumin level.

4. Discussion

Malnutrition

Using the NRS 2002 high preoperative nutritional assessment score had increased risk of complications after gastrointestinal cancer surgery [41]. The metabolic factors include poor nutritional status, very low or very high BMI, significant weight loss and low albumin level increasing the risk of postoperative complications in general surgery also in PC cancer [3,18,42,43]. Malnutrition may reduce the tolerance of oncological treatment and increase postoperative complications rate also LOS after pancreatic resection [11,37-39]. In Neeman et al. research, the serious complications (Clavien-Dindo ≥3) after pancreaticoduodenectomy occur in 19% of patients [23,40]. After distal pancreatectomy, 30% of patients had early postoperative complications and 22% POPF which was related to the degree of risk of malnutrition [3]. In our research - unexpectedly, postoperative mortality was 12.5%. In a study of patients undergoing pancreatoduodenectomy, malnutrition (MNA) was associated with more overall complications after pancreatic cancer surgery than in well-nourished patients. However, patients with good nutritional status had more often severe complications (Clavien-Dindo ≥3) than malnourished [6]. According to our study, no/mild postoperative complications (C-D <3) occurred in 71.4% of patients and 28.3% had severe complications (C-D≥ 3). The frequency and profile of the complications in this study group were not associated with nutritional status assessed by NRS 2002. However, patients with NRS ≥3 stayed longer in hospital (p= .021) and had lower level of albumin (p= .034). Likewise, Chen et al. revealed that nutritional status (NRS 2002, SGA and GLIM) was no associated with postoperative complications after pancreaticoduodenecomy [49].

Weight loss

Excessive weight loss is associated with significantly worse survival, prolonged hospital stay, reoperation and has been recognized as a good indicator of post-operative complications [3,10,50]. Although the study of PC with adenocarcinoma shows that the body weight loss >5% had no impact on survival based on multivariate analysis (hazard ratio, 1.32; 95% confidence interval, 0.76–2.30) but weight loss >10% was associated with worse survival (hazard ratio, 1.77; 95% confidence interval, 1.09–2.87) [50]. In our previous study we noticed an association between higher percent of body weight loss and lower level of TBW, FAT also increased value of ICW measured by BIA [51]. Additionally, weight loss in PC patients was related to FAT but not to FFM. Therefore, we hypothesized that in pancreatic cancer patients with increased BMI (usual) before cancer diagnosis, weight loss may be associated with mainly adipose tissue which may have an impact on the risk of postoperative complications. In our study weight loss was not associated with a significant loss of muscle mass, which plays an important role in the proper nutritional status and the risk of postoperative complications and clinical outcomes.

Body mass index

Body mass index is helpful parameter of nutritional assessment but not a sensitive indicator of malnutrition because it does not contain detailed data of body composition, muscle mass and fat distribution. Many studies showed that BMI≥25 kg/m² is an unfavourable prognostic factor in pancreatic surgery and is associated with more postoperative complications, POPF incidence and mortality [8,18,45]. In Mathur et al. study the preoperative BMI ≥30kg/m² was associated with worse survival (14 vs 18 months, p< .05) compared to patients with BMI ≤ 29kg/m² after pancreaticoduodenectomy [52]. Sarcopenic obesity had a significant impact on poorer survival compared to obese patients without sarcopenia (14 vs 23 months, *p*= .007) [24]. In advanced or metastatic PC, high BMI had impact on shorter OS - each increase in 5 units was associated with 21% relative risk of death using multivariable analysis (HR 1.21, 95% CI 1.06 – 1.41, p-value = 0.004) [53]. In addition, a higher BMI in patients undergoing chemotherapy for pancreatic cancer may influence longer overall survival. The adjusted hazard ratio (aHR); underweight vs. normal vs. overweight were 0.613 vs. 0.464 vs. 0.425, respectively. This protective effect was likely due to the better response to the oncological treatment [17]. In our study the median BMI was 24.44 kg/m² in patients with C-D grade <3 and BMI>25.29kg/m² in C-D ≥3 group. However did not notice any statistically significant differences in the severity of postoperative complications if the cut-off point was BMI 25 kg/m². Similarly, in Teolue et al. study of patients with pancreatic adenocarcinoma, there were no statistically significant differences in the 30-day mortality, rate of DGE and POPF and C-D ≥3 complications between obese and non-obese and groups [54]. The importance of BMI as a prognostic factor in patients with pancreatic cancer seems to be ambiguous and be associated with weight loss and body composition. .High BMI values may mask the current nutritional status and actual protein stores.

Body composition parameters

In many studies data of body composition were collected based on computer tomography or magnetic resonance imaging [55]. Usually CT and MRI measurements were conducted a few weeks before the surgery. Therefore, they do not show actual data while the nutritional status of a patient with pancreatic cancer changes dynamically. The bioelectrical impedance is quick and lacks radiation exposure compared to the imaging methods. The importance of body composition measurements using BIA as an aid in assessing the risk of postoperative complications is contradictory in the hitherto published literature. Bioelectrical impedance was confirmed as a useful complementary tool to assess nutritional status which correlated with survival in cancer patients, especially in advanced stages [27,56-58]. The comprehensive review demonstrated the important prognostic significance of body composition parameters, particularly phase angle and fat free mass in oncological patients. Decreased levels of these indicators were associated with shorter OS and the occurrence of malnutrition [57]. Despite this, there are insufficient data of approved markers for predicting postoperative outcomes in pancreatic and periampullary tumors with respect to body composition. One of the most frequently described parameters of the BIA is phase angle (PA) and it was significantly lower in malnourished colorectal and pancreatic cancer patients and could be a potential nutritional indicator in advanced stage [57-59]. In older patients with cancer low PA parameters corresponded to decreased muscle strength, higher level of fatigue, anorexia, pain compared to normal PA [60]. Low PA correlated with fatigue, anorexia and poor nutritional status in colorectal and pancreatic cancer and older patients with cancer [60,66]. Similarly, Aslani et al. showed that PA correlated with nutritional status but was not associated with an increased rate of postoperative complications [66]. In our study, the median PA was 7.45 and we did not show any significant differences between the Clavien-Dindo <3 and ≥3 groups. In Lee et.al. study of critically ill patients some BIA's parameters as PhA, ECW and ECW/TBW differed significantly between the malnourished and well-nourished patient groups.. Mikamori et al. had indicated the importance of body compositions analysis using BIA in the long-term evaluation of changes in nutritional status after pancreaticoduodenectomy. The monitoring of ECW/TBW level allows for the assessment of changes in hydration associated with the occurrence of edema. Bioelectrical impedance may be helpful to assess changes in fat mass and fat-free mass especially in weight loss patients during postoperative period. This study showed a significant correlation between weight loss and a reduction in body fat 12 months after PD [26]. The parameters of muscle measured using BIA can be used to detect sarcopenia in oncological patients [61-64]. Sarcopenia at diagnosis was assessed as an independent prognosis factor of OS in advanced PC [22]. In PC patients the mean value of fat mass was 30.44% and fat-free mass was 69.37% before surgery [65]. Similar results were found in our study where FM was 30.31% and FFM was 69.37%. In PC patients following Whipple pancreaticoduodenectomy it was revealed that females had lower FM compared to healthy control group (p=.007) [66]. As it turns out, not only in our study the BIA parameters turned out to be statistically insignificant prognostic factors for the occurrence of postoperative complications. In Angrisani et al. research of patients undergoing PD the value of preoperative FFM, FFMI and PhA were no statistical significance lower in non-POPF group (BIVA) [67]. The FFMI index takes into account the lean body mass in relation to the height of the subject. When we used the cut-offs, FFMI median was higher in patients without serious complications than in Clavien-Dindo ≥3 (16.1 vs 15.2 kg/m2). Also more percent of men had low level of FFMI in Clavien-Dindo ≥3 group than patients with no/mild complications (16,7% vs 8,8%). In women we observed an inverse relationship – lower incidence of low level of FFMI in CD ≥3 than <3 (8.3% vs 17,6%). Nevertheless, the above differences were not statistically significant. For FMI, both men and women had a median value of body fat below normal (5.65 kg/m^2 and 4.15 kg/m^2). Both FM and FFM did not differ statistically between the groups with serious and no/mild postoperative complications. In Szafel et al. study of patients with colorectal cancer the BIA's parameters were not a good tool for screening nutritional status. Admittedly, men in stage I of colorectal cancer had increased FMI, SMMI, CEW/TBW (p< .05) compared to men in advanced stages (II-IV). However, the FM/FFM ratio did not differ. Women in early stages of colorectal cancer also had increased FMI,FFMI as well as FM/FFM compared to women in advanced stages (p< .05). Comparing women in stages I-II with women in stages III-IV only the FM (p <0.05) was statistically significant higher (25.5 ± 7.8 19.3 ± 6.2). The results highlight the need to distinguish between the sexes using the data from the bioelectrical impedance analysis. The researchers concluded that the ability of electrical bioimpedance to screen for malnutrition risk and detect cancer cachexia is insufficiently accurate compared to the NRS and SGA. Nonetheless, the monitoring of body composition changes in this group of patients may be beneficial and helpful [68]. In different study, the PhA <6° was positively correlated with incidence of postoperative complications and nutritional risk in patients after gastrointestinal surgery. Nevertheless, in multiple logistic regression analysis the phase angle was not statistically significant to develop postoperative complications (OR 95% CI 1.6 (0.7–3.8), p= .292) [69]. We also assume that the measurements from BIA, may be not enough sensitive to detect changes in body composition in pancreatic cancer patients who have developed malnutrition within the short period of last time. Probably, for this reason, in patients with an early stage of PC we did not notice the significant importance of BIA parameters on the incidence of postoperative complications. Our patients had no importance disturbances on body composition compare to the healthy populations from other publications. Therefore the BIA's parameters has been not a good predictors of postoperative outcomes in this group. The use of BIA may be helpful in monitoring changes in body composition over time and progression of malnutrition in pancreatic cancer patient. Additionally, the results should always be interpreted in relation to the remaining tests and the clinical condition of the patient. Future research should take into account the division into sex, standardization according to age, and height of patients. Additionally, it should include a detailed body composition analysis including visceral tissue. There are significant discrepancies in the literature in the terminology of FFMI, FMI, VAT, intraabdominal fat, trunk fat, visceral fat. There are no standardized cut-off points, and there is a need for studies on larger and heterogeneous populations (different race, age).

Diabetes mellitus

In our study, we observed a higher proportion of patients with diabetes in the group with Clavien-Dindo grade <3 than in the group with severe complications (C-D≥3). Patients with preoperatively diagnosed diabetes had a higher risk of anastomotic leaks (OR 2.407; 95% CI 1.837–3.155; p < .001), surgical site infections (OR 1.979; 95% CI 1.636–2.394; p < .001) urinary complications (OR 1.687; 95% CI 1.210–2.353; p = .002) after colorectal surgery [70]. Although diabetes is a known factor that increases the risk of perioperative complications in a variety of oncological surgeries, this impact on early outcomes after pancreatic resection is still ambiguous. Toriola et al. found association with diabetes and decreased survival in pancreatic cancer patients. The multivariable-adjusted HR for mortality comparing participants with diabetes to those without was 1.52 (95% CI=1.14–2.04, p <.01) [71]. Patients with periampullary and pancreatic head adenocarcinoma presents DM before the surgery had no significant increased risk of POPF compare to non-DM (29% vs 25.5%, p= .68) and 90 days mortality (3.2% vs. 1.3%, p= .63). Nevertheless, in multivariate analysis diabetes had negative impact on 3-years survival (OS: HR, 2.61 [1.14-5.98] p= . 22) and 5-year survival (5 year OS: HR, 2.55; p= .04). Pancreatic consistency assessed as *soft* was present in 29.6% of patients with DM and *firm* pancreas had 70.4%. In non-DM group 35.9% had soft pancreas and 64.1% had firm pancreas [72]. In Zhang et al. study of PC patients with POPF 77.8% cases present soft pancreas, but only 5.56 % of patients had DM. In multivariate logistic regression analysis no diabetes (OR 30.235 95% CI 1.924-475.097, p= .015) and soft pancreas (OR 44.931 95% CI 1.754-42.486, p< .001) were an independent prognostic factor for pancreatic fistula [73]. Likewise, in our study, absence of diabetes mellitus was the risk factor of severe complications (p= .032). Regarding to above studies PC patients with DM present more incidence of hard pancreas, which may have a protective effect against the proteolytic influence of pancreatic enzymes (in the case of a soft pancreas) [71-73].

Hypoalbuminemia

In this study, hypoalbuminemia was the only metabolic risk factor of severe complications after pancreatic resection. In multivariate analysis, low preoperative albumin level (<3.5g/dL) was a factor predictive of severe complications after pancreatic resection (p= .004). In oncological surgery, hypoalbuminemia is associated with postoperative complications and poor tissue healing [48]. Preoperative low albumin level (<4g/dL) was associated with higher postoperative complications ratio in patients with adenocarcinoma (40.3% versus 25.5%; p< .05) [10]. Also in Rungsakulkij et al. study, the preoperative hypoalbuminemia was an independent factor associated with serious postoperative complications (Clavien-Dindo grade 3-5) after PD [47].

This study has several limitations. Firstly, the study group was quite small and heterogeneous including patients with pancreatic and duodenal cancer. Secondly, the calculations did not account for surgical risk factors such as soft pancreas or small pancreatic duct. And last but not least, the observed mortality in the period of study was relatively high compared to what was reported in recent series. This excess postoperative mortality seems to be just coincidental. On the other hand, overall mortality of pancreatic resection over the last 5 years remains below 6%.

Conclusion

In summary, resectable peri-ampullary and pancreatic tumors might not cause early measurable disturbances in body composition. Despite the fact that nutritional status did not significantly affect the occurrence of postoperative complications, it was associated with a higher risk of hypoalbuminemia. We have demonstrated that low albumin levels increase the risk of complications. Therefore, assessing the risk of malnutrition and identifying risk factors for malnutrition are important before surgery. The role of preoperative BIA measurement seems to be limited in early-stage PC patients but can be helpful to deepen the nutritional status assessment. Nevertheless, it seems that BIA may be a sensitive indicator for monitoring changes in body composition in the postoperative period. The important factors contributing to serious postoperative complications and clinical outcomes are low albumin levels and the absence of diabetes.

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Ethical standards

All human and animal studies have been approved by the Bioethical Commission of the Medical University of Warsaw; Approval Code: KB/172/2018, Approval Date: 08/10/2018 and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All persons gave their informed consent prior to their inclusion in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

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