ORIGINAL ARTICLE

Influence of preoperative nutritional status on clinical outcomes after pancreatoduodenectomy

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Abstract

Background: This study investigated the clinical outcomes according to the preoperative nutritional status and to identify factors influencing long-term unrecovered nutritional status.

Methods: Data were prospectively collected from 355 patients who underwent PD between 2008 and 2014. Nutritional status was evaluated by Mini Nutrition Assessment (MNA) and patients were classified into group A (malnourished), group B (risk-of-malnutrition), or group C (well-nourished). MNA score, complications, body mass index (BMI), stool elastase level, biochemical parameters, and quality-of-life (QOL) were collected serially for 1 year.

Results: Preoperatively, 60 patients were categorized into group A, 224 into group B, and 71 into group C. Overall complication and pancreatic fistula were higher in groups A and B compared with group C (P = 0.003 vs P = 0.004). QOL, biochemical parameters, BMI and stool elastase level were lowest in group A preoperatively. BMI and stool elastase level remained low after surgery in all groups. Advanced age, low BMI, pre-existing diabetes mellitus, jaundice, exocrine insufficiency and adjuvant therapy were factors influencing long-term unrecovered nutritional status.

Conclusion: Preoperative malnourished patients suffer from poor clinical outcomes. Therefore, those with risk factors of malnutrition should be monitored and vigorous efforts are needed to improve their nutrition.

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Introduction

Pancreatoduodenectomy (PD) is a standard treatment for periampullary diseases.[1] With improved surgical techniques and perioperative care, surgical mortality has recently decreased.[1] However, there remains considerable morbidity owing to the complexity of the surgical procedure and characteristics of the involved organ.[1,2] In addition, preoperative nutritional status is a known risk factor for morbidity after abdominal surgery.[3,4] Thus, nutritional risk assessment scores are important for predicting complications after abdominal surgery, including pancreatectomy.[4–6] In a recent study, 83%–88% of patients with periampullary carcinoma prior to surgery were assessed to be moderately to severely malnourished per nutritional risk screening tools.[5] Moreover, low scores for nutritional risk correlated with poor postoperative outcomes.[5]

To date, most previous studies have focused on perioperative nutritional supplementation to improve nutritional status during perioperative periods, or early postoperative clinical outcomes in malnourished patients undergoing pancreatectomy.[2,4,6–8] In contrast, the importance of long-term nutritional outcomes and recovery status for malnourished patients is often overlooked. Patients who undergo PD frequently suffer from long-term impaired pancreatic exocrine and endocrine function, which

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may lead to long-term nutritional problems.[9–12] However, studies examining the effect of preoperative nutritional status on long-term clinical outcomes after PD are lacking. As such, prospective studies with long-term follow-up (as opposed to cross-sectional studies) are needed to identify nutritional recovery status and factors affecting unrecovered nutritional status after PD. To investigate nutritional status and recovery pattern over time, and identify important factors, this study evaluated clinical outcomes according to preoperative nutritional status after PD.

Materials and methods

Patients and data collection

This prospective study included patients who underwent PD for benign or malignant periampullary diseases at Seoul National University Hospital. Informed consent was obtained from all patients as required by the Institutional Review Board of Seoul National University Hospital (IRB No. 0801-030-232). Individuals with palliative resection, neo-adjuvant treatment, metastasis or recurrence, history of other abdominal procedures (such as gastrectomy or colectomy), or American Society of Anesthesiologists classification exceeding grade III were excluded from this study, as were individuals lacking Mini Nutrition Assessment (MNA) information.

Data were collected preoperatively and postoperatively at 3, 6, and 12 months. All patients were admitted to the hospital 36 h before surgery. The baseline preoperative data was evaluated just before the operation. All questionnaires were measured only after correction for jaundice, acute pancreatitis, or any symptoms. When the patients exhibited cholangitis, preoperative endoscopic or percutaneous transhepatic biliary drainage was performed. Only after liver function tests improved, were these patients enrolled in this study.

In order to diagnose diabetes mellitus (DM), tests were performed at preoperative, and postoperative 3, 6, 12 months, measuring fasting plasma glucose (FPG) and 2-h plasma glucose (2-h PG) values after a 75-g oral glucose tolerance test, as well as serum hemoglobin A1c (HbA1c). New-onset DM after surgery was diagnosed according to the American Diabetes Association guidelines (HbA1c $\geq$ 6.5, FPG $\geq$ 126 mg/dL, or 2-h PG $\geq$ 200 mg/dL).[13] Patients with DM diagnosed preoperatively (pre-existing DM) were excluded from the analysis in order to calculate the exact proportion of new-onset DM after surgery.

In this study, we also measured the proportion of BMI less than 18.5 kg/m^2, which is the reference value for underweight from the World Health Organization BMI classification.

Postoperative complications were graded by the Clavien–Dindo Classification.[14] In this study, a Clavien–Dindo Classification of more than grade II was considered to be a clinically relevant postoperative complication. Clinically relevant postoperative pancreatic fistula (POPF) were graded according to standards of the International Study Group on Pancreatic Fistula (ISGPF).[15] Delayed gastric emptying was defined by standards of the International Study Group of Pancreatic Surgery.[16]

Stool elastase level, the indicative index of pancreatic exocrine function, was measured with an Enzyme-Linked Immunosorbent Assay (BIOSERV Diagnostics, Rostock, Germany). Stool elastase less than 200 ng/mL was defined as insufficient pancreatic exocrine function, as healthy populations exhibit levels higher than 200 ng/mL.[10]

Biochemical nutritional markers including serum prealbumin, transferrin, albumin and total protein were collected to evaluate nutritional status.

A history of alcohol was defined as an intake of more than 10 g of alcohol per day for longer than 1 year.

Questionnaires related with nutritional status

Nutritional status was classified with the MNA,[17,18] which includes 16 questionnaires in four rubrics:[18] (1) anthropometric assessment including body mass index (BMI) and weight loss; (2) general assessment including independent living, medication, mobility and neuropsychological problems; (3) dietary assessment including loss of appetite and intake of protein, vegetables, fruit and fluids, as well as mode of feeding; (4) subjective assessment including self-view for nutritional status and comparison with the health status of other people of the same age. All answers have a numerical value, which is calculated into scores with a maximum of 28 points. Questionnaires were self-reported by patients. Nutritional status was classified by the following scores: well-nourished if greater than 22, at-risk-of malnutrition if between 15 and 21.5, and malnourished if less than 15.

Quality-of-life (QOL) was measured using the global health status with QOL questionnaire from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30.[19] QOL questionnaires organized in a 7-point scale were self-reported by patients.

Abdominal pain was recorded in the medical charts as the chief complaint at the time of first diagnosis. Pancreatic pain was measured using the pain questionnaire EORTC QLQ-PAN26. The QLQ-PAN26 pancreatic pain scale items included presence of abdominal discomfort, back pain, pain during the night, and discomfort in certain positions. Pancreatic pain questionnaires were organized with a 4-point scale and high scores indicated greater pain.[19]

Transformation of raw scores into a 0–100 scale and adjustments of missing data were implemented according to the EORTC QLQ-C30 scoring manual.

Pancreatic enzyme replacement therapy (PERT)

PERT was performed when exocrine pancreatic insufficiency or exocrine insufficiency-related symptoms, such as steatorrhea, diarrhea, or weight loss were observed during the postoperative follow-up in the outpatient clinic. Pancreatin enteric-coated pellets at 40,000–80,000 units/meal were prescribed for PERT.

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Statistical analysis

Statistical analysis was performed with SPSS version 22.0 (IBM, Armonk, NY). All laboratory values were analyzed as continuous variables. Student's *t* test and ANOVA were performed for variables with normal distribution. Mann–Whitney U and Kruskal–Wallis tests were conducted for variables with non-normal distribution data. Categorical data described using values with percentages were compared with Pearson's chi-square or Fisher's exact tests. To better evaluate and reduce potential selection bias and confounding factors, propensity score matched analysis was performed. Changes over time between groups were analyzed by repeated measures ANOVA. Significance of *p* values (less than 0.05) and *post hoc* analyses were executed with Bonferroni correction.

Univariate and multivariate logistic regression analyses were used to determine risk factors for postoperative complications; *p* values less than 0.05 were included in the multivariate analysis using a logistic regression model.

Results

Enrolled patients

A total of 447 patients were enrolled between September 2008 and March 2014. Ninety-two patients were excluded: 82 patients had metastasis or recurrence, including microscopic metastasis, during the follow-up period from immediately after surgery to 1-year postoperatively (and were excluded due to the potential effects exerted on their nutritional status and QOL). Therefore, a total of 355 patients were included for short-term outcome analysis. A further 109 patients were subsequently excluded because of follow-up loss or unperformed MNA after PD. Finally, a total of 246 patients were included for long-term outcome analysis.

Demographic findings according to preoperative nutritional status

Demographics and characteristics of the included 355 patients are shown in Table 1. Two hundred and fifty-seven patients (72.4%) were diagnosed with malignant diseases, while 98 patients (27.6%) were diagnosed with benign diseases. Preoperatively, 71 patients (20.0%) were classified as malnourished, 224 patients (63.1%) exhibited at-risk-of-malnutrition, and 60 patients (16.9%) were well-nourished.

Postoperative complication according to preoperative nutritional status

A total of 141 cases (39.7%) of overall postoperative complication were observed. Complications deemed Clavien–Dindo Classification grade I were excluded in this study.

To control for the effects of confounding factors, propensity score matched analysis was performed with four pancreatic fistula risk factors: pancreatic texture, pancreatic duct size, estimated blood loss, and pathologic finding of disease.[20] Comparisons between propensity matched group A (well-nourished) and group B (risk-of-malnutrition and malnourished) at 1:3 ratios are shown in Table 2.

In multivariate analysis, malignant disease [odds ratio (OR) 1.948, 95% confidence interval (C.I.) 1.115–3.405, $P = 0.019$] and low MNA scores (malnourished, OR 3.033, 95% C.I. 1.360–6.761, $P = 0.007$; risk-of-malnutrition, OR 2.521, 95% C.I. 1.253–5.074, $P = 0.010$) were predictive factors of postoperative complication risk (Table 3).

Long-term nutritional outcomes

Recovery pattern of nutritional status after surgery

Nutritional status changes from preoperative to 12 months postoperative were as follows: malnourished [n = 71 (20.0%) to n = 20 (8.1%)], at risk-of-malnutrition [n = 224 (63.1%) to n = 143 (58.1%)], and well-nourished [n = 60 (16.9%) to n = 83 (33.7%), Fig. 1a].

Patients were categorized into three subgroups by nutritional status changes over time: 1) recovery, postoperative improvement in nutritional status compared with preoperative status; 2) aggravation, deterioration in nutritional status compared with preoperative status; and 3) persistent malnutrition, sustained malnutrition before and after surgery. Based on preoperative nutritional status, changes in nutrition postoperatively from 3 to 12 months were as follows: the recovery group (44.3%–68.7%) exhibited increased nutritional status as time passed, while the aggravation (45.5%–23.7%) and persistent malnutrition (10.2%–7.6%) groups gradually decreased over time (Fig. 1b). Nutritional status changes over time according to benign and malignant disease. The postoperative nutritional status of patients with benign disease was similar to their preoperative status (Fig. 1c), and the nutritional status of patients with malignant disease improved 1 year after surgery compared to preoperative levels (Fig. 1d).

Quality-of-life, BMI, exocrine function and biochemical markers of nutrition

Preoperative QOL scores were significantly lower in the malnourished group than in the risk-of-malnutrition or well-nourished groups (36.3 ± 26.5 vs. 57.7 ± 25.2 vs. 69.5 ± 18.5, respectively; $P < 0.001$). Twelve months after surgery, QOL levels increased in all groups and were higher compared with preoperative levels. Differences between the 3 groups were not statistically significant 1 year after surgery ($P = 0.634$, Fig. 2a). Stratified according to jaundice, pancreatic pain, abdominal pain and preoperative exocrine insufficiency similar tendencies were shown over time (Supplementary Fig. 1a–d). BMI decreased immediately after surgery in all groups and remained low 12 months after surgery compared with preoperative levels in all groups (21.3 ± 2.8 vs. 22.1 ± 2.5 vs. 24.5 ± 2.4, respectively; $P < 0.001$, Fig. 2b).

Stool elastase levels tended to decrease after surgery and were remained unrecovered in all groups 12 months after surgery (32.5 ± 32.2 ng/mL [malnourished], 56.5 ± 67.1 ng/mL [risk-of-

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Table 1 Demographics and characteristics according to preoperative nutritional status (between three groups)

Parameters	Overall (N = 355)	Well-nourished (N = 60)	Risk-of-malnutrition (N = 224)	Malnutrition (N = 71)	*P*-value
Age (mean ± SD, years)	61.8 ± 11.2	60.0 ± 11.2	61.4 ± 10.9	64.4 ± 11.7	0.017†
Sex					0.123
Male	210 (59.2%)	41 (68.3%)	133 (59.4%)	36 (50.7%)	
Female	145 (40.8%)	19 (31.7%)	91 (40.6%)	35 (49.3%)	
Diabetes mellitus					
Pre-existing	85 (23.9%)	9 (15.0%)	55 (24.6%)	27 (29.6%)	0.141
New diagnosed after surgery	87 (34.4%)	14 (28.6%)	59 (36.9%)	14 (31.8%)	0.526
Glucose tolerance test					
FPG (mean ± SD, mg/dL)	117.3 ± 38.5	110.9 ± 32.6	119.5 ± 41.2	115.9 ± 34.6	0.307
2-h PG (mean ± SD, mg/dL)	217.2 ± 85.7	202.9 ± 67.5	218.8 ± 91.3	226.5 ± 84.1	0.408
HbA1c (mean ± SD, %)	6.3 ± 1.1	6.1 ± 0.6	6.3 ± 1.1	6.4 ± 1.3	0.213
Pre-op BMI (mean ± SD, kg/m^2)	23.5 ± 2.9	26.0 ± 2.7	23.5 ± 2.6	21.3 ± 2.7	<0.001
Pre-op. BMI < 18.5 (kg/m^2)	14 (3.9%)	0 (0.0%)	4 (1.8%)	10 (14.1%)	<0.001*
Jaundice	118 (33.2%)	10 (16.7%)	80 (35.7%)	28 (39.4%)	0.010
Smoking (mean ± SD, pack year)	3.9 ± 11.7	2.9 ± 8.1	4.0 ± 12.3	4.4 ± 12.3	0.756
Alcohol history	62 (17.5%)	16 (26.7%)	39 (17.4%)	7 (9.9%)	0.041
Abdominal pain	105 (29.6%)	11 (18.3%)	69 (30.8%)	25 (35.2%)	0.087
Pancreatic pain (mean ± SD)	17.6 ± 19.9	11.7 ± 15.9	15.8 ± 19.1	27.8 ± 21.7	<0.001
Pre-op TPN use	15 (4.2%)	0 (0.0%)	10 (4.5%)	5 (7.0%)	0.114
Post-op Appetite- stimulants use	93 (26.2%)	6 (10.0%)	56 (25.0%)	31 (43.7%)	<0.001
Exocrine insufficiency	70 (41.7%)	8 (26.7%)	43 (43.0%)	19 (50.0%)	0.140
Operation					0.457
PD	42 (11.8%)	8 (13.3%)	23 (10.3%)	11 (15.5%)	
PPPD	313 (88.2%)	52 (86.7%)	201 (89.7%)	60 (84.5%)	
Diagnosis					0.001
Benign	98 (27.6%)	28 (46.7%)	56 (25.0%)	14 (19.7%)	
Malignancy	257 (72.4%)	32 (53.3%)	168 (75.0%)	57 (80.3%)	
Location					0.121
AoV	103 (29.0%)	15 (25.0)	66 (29.5%)	22 (31.0%)	
Distal CBD	79 (22.3%)	9 (15.0%)	48 (21.4%)	22 (31.0%)	
Pancreas	162 (45.6%)	32 (53.3%)	105 (46.9%)	25 (35.2%)	
Duodenum	11 (3.1%)	4 (6.7%)	5 (2.2%)	2 (2.8%)	
Cancer stage					0.269
Stage I	82 (31.9%)	14 (43.8%)	52 (31.0%)	16 (31.9%)	
Stage II	168 (65.4%)	17 (53.1%)	113 (67.3%)	38 (66.7%)	
Stage III	7 (2.7%)	1 (3.1%)	3 (1.8%)	3 (5.3%)	
Post-op HS (mean ± SD, day)	17 ± 7.9	16.2 ± 6.8	17.3 ± 7.9	17.6 ± 8.9	0.341†
Complication	141 (39.7%)	12 (20.0%)	95 (42.4%)	34 (47.9%)	0.002
PF	64 (18.0%)	4 (6.7%)	48 (21.4%)	12 (16.9%)	0.029
Wound	48 (13.5%)	6 (10.0%)	29 (12.9%)	13 (18.3%)	0.351
Fluid collection	30 (8.5%)	2 (3.3%)	20 (8.9%)	8 (11.3%)	0.244
DGE	27 (7.6%)	4 (6.7%)	19 (8.5%)	4 (5.6%)	0.808*
Bleeding	8 (2.3%)	0 (0.0%)	7 (3.1%)	1 (1.4%)	0.517*
Others	22 (6.2%)	2 (3.3%)	16 (7.2%)	4 (5.6%)	

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Table 1 (*continued*)

Parameters	Overall (N = 355)	Well-nourished (N = 60)	Risk-of-malnutrition (N = 224)	Malnutrition (N = 71)	*P*-value
Clavien–Dindo					0.679
Grade II	64 (45.4%)	4 (33.3%)	44 (46.3%)	16 (47.1%)	
Grade ≥ III	77 (54.6%)	8 (66.7%)	51 (53.7%)	18 (52.9%)	

Pre-op: Preoperative, FPG: fasting plasma glucose, 2-h PG: 2-h plasma glucose, HbA1c: serum hemoglobin A1c, BMI: body mass index, Pancreatic pain symptom score: using the European Organization for Research and Treatment of Cancer (EORTC) pancreatic module PAN 26, TPN: total parenteral nutrition, Post-op: Postoperative, PD: pancreatoduodenectomy, PPPD: pylorus preserving pancreatoduodenectomy, AoV: ampulla of vater, CBD: common bile duct, Postoperative HS: Postoperative hospital stay, PF: Pancreatic fistula, DGE: Delayed gastric emptying, *Fisher's exact test, † Kruskal–Wallis test.

malnutrition], 86.1 ± 136.7 ng/mL [well-nourished]; $P = 0.793$, Fig. 2c). Preoperatively, 73.3% of individuals in the well-nourished group, 57% in the risk-of-malnutrition group, and 50% in the malnourished group exhibited normal stool elastase levels ($P = 0.139$). Six and 12 months after surgery, less than 13% of patients exhibited normal stool elastase levels across all groups (Fig. 2d). Of the patients who received PERT, the nutritional status showed improvement in 41% of the patients, and remained constant in 33% (Supplementary Fig. 1e).

Compared with preoperative levels, serum transferrin (Fig. 2e), albumin, and total protein levels increased after surgery in all groups (Supplementary Fig. 1f and g). Notably, serum prealbumin level decreased immediately after surgery in all groups and remained low 12 months after surgery (Fig. 2f).

Influential factors for unrecovered nutritional status after surgery

To investigate factors affecting long-term unrecovered nutritional status after surgery, malnourished and well-nourished groups were compared. Mean age was significantly higher in the malnourished group than in the well-nourished group at 6 months ($P = 0.047$) and 12 months ($P = 0.025$) postoperative. Compared with preoperative values, BMI was significantly lower in the malnourished group than in the well-nourished group at 6 months ($P < 0.001$) and 12 months ($P < 0.001$) postoperative. More patients had undergone adjuvant treatment at 6 months postoperative ($P = 0.013$) in the malnourished group; however, nutritional status was comparable at 12 months postoperative. Finally, a tendency for higher incidence of pre-existing DM was observed in the malnourished group compared with the well-nourished group at 6 months (52.9% vs. 28.4%, $P = 0.052$) and 12 months (35.0% vs. 20.5%, $P = 0.168$, Table 4) postoperative.

Discussion

Malnutrition is a well-known risk factor for short-term postoperative outcomes after abdominal or gastrointestinal surgery.[3,4] However, studies examining whether preoperative malnutrition affects long-term nutritional recovery after pancreatic surgery are lacking. Moreover, patients who undergo PD frequently experience impaired pancreatic exocrine function that can affect long-term nutritional status.[9–11,21,22]

While several previous studies have assessed nutritional status using nutrition risk assessment tools, these studies were retrospective or cross-sectional.[3,23] Thus, prospective nutritional data were measured according to variable assessment tools or completely unavailable.[4–6,8]

The MNA, a single, rapid, and validated nutritional assessment tool without serum biochemical markers,[17] is comparable to other nutrition assessment tools for patients who undergo pancreatectomy. Sensitivity, specificity, and predictive values of MNA are 96%, 98%, and 97%, respectively.[17] Furthermore, the MNA tool has been proven to detect malnutrition before the occurrence of severe weight loss or decreased serum protein.[17] In this study, preoperative malnutrition and risk-of-malnutrition rates were approximately 80% as assessed using the MNA tool. In addition, the overall complication rate (Clavien–Dindo Classification of more than grade II) was approximately 40%. Notably, rates of overall complications (41.1% vs. 20.0%; $P = 0.003$) and clinically relevant POPF (23.9% vs. 6.7%; $P = 0.004$) were significantly higher in the malnourished and risk-of-malnutrition groups than in the well-nourished group after propensity score matched analysis. Many patients were malnourished or were at risk-of-malnutrition prior to surgery, and these preoperative nutritional issues may have influenced poor clinical outcomes, including complications such as POPF after surgery. These results suggest preoperative nutritional risk assessment and nutritional monitoring are needed for patients with periampullary disease.

In this study, malnutrition and risk-of-malnutrition rates were over 66%, 12 months after surgery. Furthermore, 12 months after surgery, we confirmed that over 30% of patients who were malnourished prior to surgery remained malnourished or had worsening nutritional status compared with preoperative assessment. However, in contrast to benign disease, the proportion of well-nourished nutrition status in the malignant disease group increased, from 12.5% preoperatively to 35.0% at postoperative 12 months. In subgroup analysis according to the type of malignancy, similar results were shown at postoperative

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Table 2 Comparison of clinical factors according to preoperative nutritional status (between two groups)

Parameters	Before PS Matching			After PS Matching	
	Control group Well-Nourished N = 60	Risk-of-malnutrition & Malnutrition N = 295	*P*-value	Risk-of-malnutrition & Malnutrition N = 180	*P*-value
Age (mean ± SD, years)	60.0 ± 11.2	62.2 ± 11.1	0.174†	62.6 ± 11.3	0.112†
Sex			0.113		0.357
Male	41 (68.3%)	169 (57.3%)		110 (61.1%)	
Female	19 (31.7%)	126 (42.7%)		70 (38.9%)	
BMI (mean ± SD, kg/m^2)	26.0 ± 2.7	23.0 ± 2.8	<0.001	23.1 ± 2.8	<0.001
Pre-op. HbA1c (mean ± SD, %)	6.1 ± 0.6	6.3 ± 1.1	0.118	6.7 ± 7.2	0.511
Exocrine insufficiency	8 (26.7%)	62 (44.9%)	0.066	35 (42.7%)	0.123
Operation			0.693		0.633
PD	8 (13.3%)	34 (11.5%)		18 (10.0%)	
PPPD	52 (86.7%)	261 (88.5%)		162 (90.0%)	
Diagnosis			<0.001		0.002
Benign	28 (46.7%)	70 (23.7%)		45 (25.0%)	
Malignancy	32 (53.3%)	225 (76.3%)		135 (75.0%)	
Diagnosis 2			0.050		1.000
PDAC or pancreatitis	6 (10.0%)	65 (22.0%)		18 (10.0%)	
Others	54 (90.0%)	230 (78.0%)		162 (90.0%)	
Operation time (minute)	324.5 ± 81.4	304.0 ± 81.9	0.078	299.5 ± 83.9	0.045
Pancreatic texture			0.353		0.335
Soft	46 (76.7%)	208 (70.5%)		150 (83.3%)	
Firm and hard	14 (23.3%)	87 (29.5%)		30 (16.7%)	
Pancreatic duct size (mean ± SD, mm)	3.3 ± 1.9	3.5 ± 2.6	0.962†	3.6 ± 2.7	0.920†
Complication	12 (20.0%)	129 (43.7%)	0.001	74 (41.1%)	0.003
Clinically relevant POPF	4 (6.7%)	60 (20.3%)	0.012	43 (23.9%)	0.004
Grade B	4 (100.0%)	58 (96.7%)		42 (97.7%)	
Grade C	0 (0.0%)	2 (3.3%)		1 (2.3%)	
Wound	6 (10.0%)	42 (14.2%)	0.382	24 (13.3%)	0.499
Fluid collection	2 (3.3%)	28 (9.5%)	0.118	15 (8.3%)	0.253*
Delayed gastric emptying	4 (6.7%)	23 (8.8%)	>0.999*	11 (6.1%)	>0.999
Bleeding	0 (0.0%)	8 (2.7%)	0.361*	4 (2.2%)	0.575*
Pulmonary	0 (0.0%)	7 (2.4%)	0.607*	5 (2.8%)	0.335*
CJ leak	1 (1.7%)	2 (0.7%)		0 (0.0%)	
Bowel obstruction	0 (0.0%)	3 (1.0%)		2 (1.1%)	
Others	2 (3.3%)	13 (4.4%)		7 (3.9%)	
Clavien–Dindo			0.380		0.465
Grade II	4 (33.3%)	60 (46.5%)		33 (44.6%)	
Grade III	6 (66.7%)	69 (53.5%)		41 (55.4%)	
Postoperative HS (mean ± SD, day)	16.2 ± 6.8	17.3 ± 8.1	0.292†	17.4 ± 8.2	0.297†

PS: propensity score, BMI: body mass index, PD: pancreatoduodenectomy, PPPD: pylorus preserving pancreatoduodenectomy, PDAC: Pancreatic ductal adenocarcinoma, POPF: Postoperative Pancreatic fistula, CJ leak: Choledochojejunostomy leak, HS: hospital stay. * Fisher's exect test. † Mann–Whitney test.

12 months for pancreatic cancer (37.3%) patients and for other periampullary cancers (34.1%). Indeed, surgical resection may have revised the cancer effect and improved the nutritional status.[24] Further studies would be expected to reveal the exact mechanisms of the anti-cancer effect of surgical treatment and the reasons for improvement of nutritional status.

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Table 3 Multivariate analysis of risk factors for postoperative complications, pancreatic fistula

Factors N = 355		Univariable analysis			Multivariable analysis		
		Exp.(B)	95% CI	*P*-value	Exp.(B)	95% CI	*P*-value
Complication							
Age	≥65 year	1.242	0.796–1.940	0.340			
Pre-existing DM		1.311	0.801–2.146	0.282			
Operation type	PPPD	1.753	0.865–3.552	0.119			
Pathology	Malignancy	2.402	1.433–4.026	0.001	1.948	1.115–3.405	0.019
BMI	<18.5 kg/m2	1.194	0.392–3.640	0.755			
Transfusion		2.179	0.854–5.560	0.103			
HbA1c	>7.5%	1.889	0.094–3.945	0.091			
Smoking		0.832	0.419–1.649	0.598			
Alcohol		1.519	0.822–2.806	0.182			
Jaundice		1.727	1.099–2.714	0.018	1.243	0.765–2.020	0.381
Abdominal pain		0.884	0.550–1.419	0.609			
Pancreatic pain		0.999	0.619–1.614	0.997			
EPI		1.086	0.567–2.078	0.804			
MNA score				0.003			0.014
	Malnutrition	3.676	1.676–8.062	0.001	3.033	1.360–6.761	0.007
	Risk-of-malnutrition	2.946	1.484–5.849	0.002	2.521	1.253–5.074	0.010

DM: diabetes mellitus, PPPD: pylorus preserving pancreatoduodenectomy, BMI: Body mass index, EPI: exocrine pancreatic insufficiency, MNA: Mini Nutrition Assessment, POPF: postoperative pancreatic fistula.

Pancreatic insufficiency after PD can result in malabsorption and weight loss.[9–11] Diagnosing pancreatic exocrine insufficiency after surgery is difficult and specific function tests are not routinely performed. Stool elastase measurement is widely used to screen pancreatic exocrine insufficiency.[10,11] Park *et al.* demonstrated that stool elastase levels decreased after pancreatectomy and remained low even 1 year after the absence of severe symptoms.[9] Onset of steatorrhea is a late symptom of pancreatic exocrine insufficiency, with many patients exhibiting significant malabsorption even with the absence of symptoms.[21] Previous studies reported that patients with decreased pancreatic exocrine insufficiency after PD existed, ranged 46–75%.[11,25] In this study, BMI and pancreatic exocrine function had not recovered to preoperative levels in any group 12 months after PD. However, despite malnourishment, stool elastase levels were not significantly different between the three groups after surgery.

In our study, PERT was administered to patients with postoperative exocrine insufficiency with related symptoms including steatorrhea, diarrhea, indigestion, or weight loss. Although PERT could be considered as a treatment for exocrine pancreatic insufficiency after pancreatectomy, most physicians do not perform continuous pancreatic exocrine function evaluation and patients often do not take the prescribed pancreatic enzyme regularly.[26] Two studies have suggested dosages and efficacy of PERT,[12,27] but validation has not been performed and the recommendations were not identical. In our study, nutritional status was recovered in 41% of the patients who received PERT, but 33% showed no change in nutritional status. It may be assumed that PERT provided some backup for pancreatic enzyme insufficiency, but it did not overcome the entire pancreatic enzyme insufficiency due to the pancreatic resection. As our study did not strictly control the dosage or duration of PERT, it would be difficult to maintain that the PERT was effective. In order to confirm the efficacy of PERT, further studies are needed to verify the dose and duration of PERT, such as through multicenter randomized controlled trials (RCT) including our ongoing RCT (NCT02127021). Furthermore, more sophisticated, individualized nutritional support, and multidisciplinary team consultation should be established for patients with severe or unrecovered malnutrition status.

QOL is considered to be of major importance in periampullary diseases; indeed, many studies reported QOL after PD. Previous studies showed that QOL after PD is similar to individuals who underwent laparoscopic cholecystectomy or healthy individuals.[28,29] However, other study reported deteriorating QOL after PD.[30] These conflicting results may vary greatly according to assessment tools employed, cross-sectional study design, or sample size. The QOL reference value (EORTC QLQ-C30) of the general population was 75, and the QOL score of the preoperative malnourished group in this study was 36.3, which was less than half of the reference value.[31] Although preoperative QOL scores were lowest in the malnourished group in our study, there was no significant difference between the three groups after

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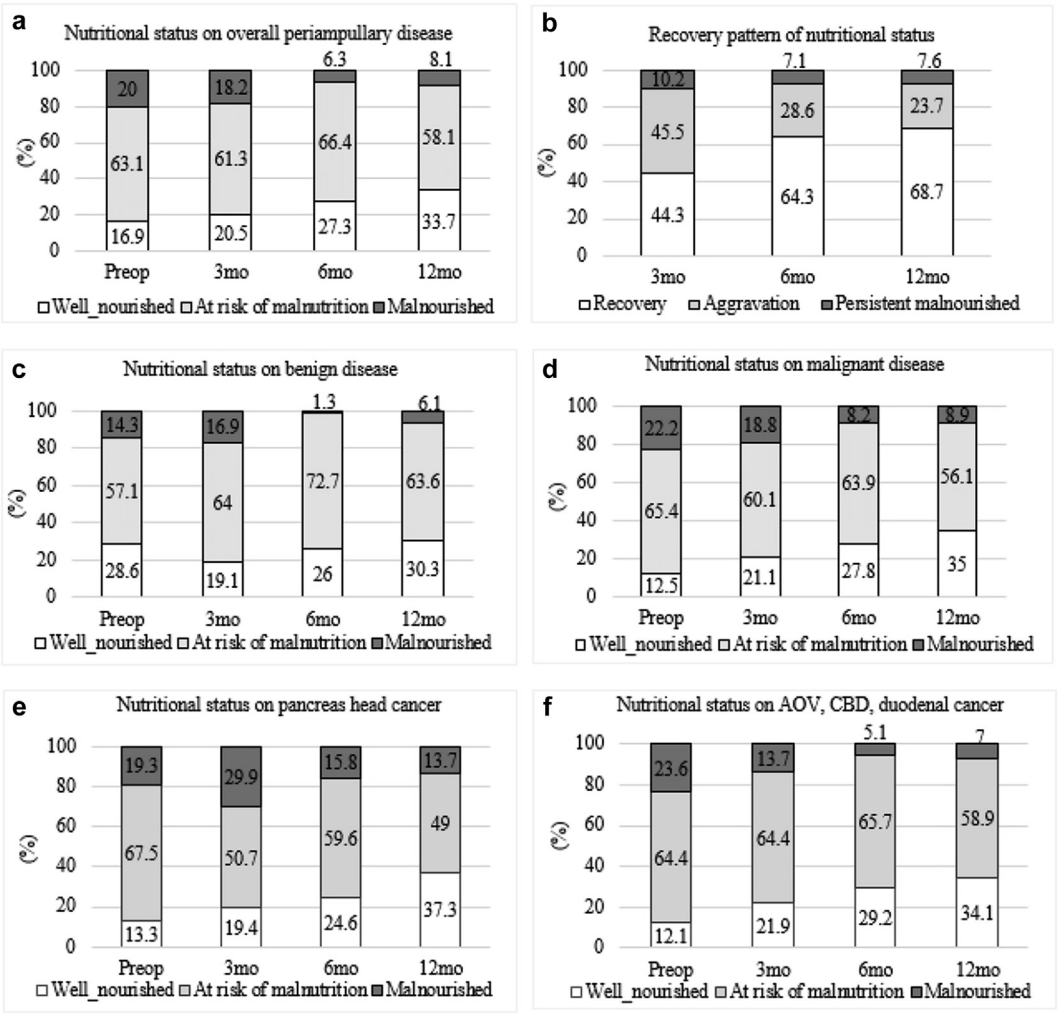


Figure 1 a) Change of nutritional status on overall periampullary disease, b) Recovery pattern of nutritional status after surgery, Recovery group: postoperative improvements in nutritional status compared to the preoperative period. Aggravation group: deterioration in nutritional status compared to the preoperative period. Persistent malnourished group: sustained malnutrition before and after surgery, c) Change of nutritional status on benign disease, d) Change of nutritional status on malignant disease, e) Change of nutritional status on pancreas head cancer, f) Change of nutritional status on ampulla of vater (AOV), common bile duct (CBD) and duodenal cancer

1 year and the QOL scores of all groups were close to the general population reference value.[31]

Biochemical nutritional marker analysis is a common method for assessing nutritional status. Serum albumin and prealbumin levels have been used to determine patients' nutritional status.[32] However, these biochemical nutritional markers are sometimes unreliable and should only be used as a subsidiary tool to supplement nutrition risk screening assessment. In this study, biochemical markers (with the exception of serum prealbumin) sharply increased after surgery compared with preoperative levels. However, prealbumin levels did not recover after surgery and exhibited a similar pattern with BMI. Therefore, serum prealbumin levels are considered to be a more reliable biochemical nutritional marker than other markers examined.

In this study, advanced age, preoperative low BMI, pre-existing DM, preoperative jaundice and adjuvant therapies were the influential factors for unrecovered nutritional status at 6 months postoperative, whereas only advanced age and preoperative low BMI and exocrine insufficiency were associated with unrecovered nutritional status at 12 months postoperative. Interestingly, while more patients in the malnourished group underwent adjuvant treatment at 6 months postoperative, their nutritional status was comparable 12 months after PD. Most cancer patients received active adjuvant therapies at postoperative 6 months, but completed such therapies within less than 1 year after surgery. There were only 2 cases of chemotherapy reduction, 1 for old age, the other for weakness, and the remaining patients all underwent scheduled treatment. Therefore, at 6 months after

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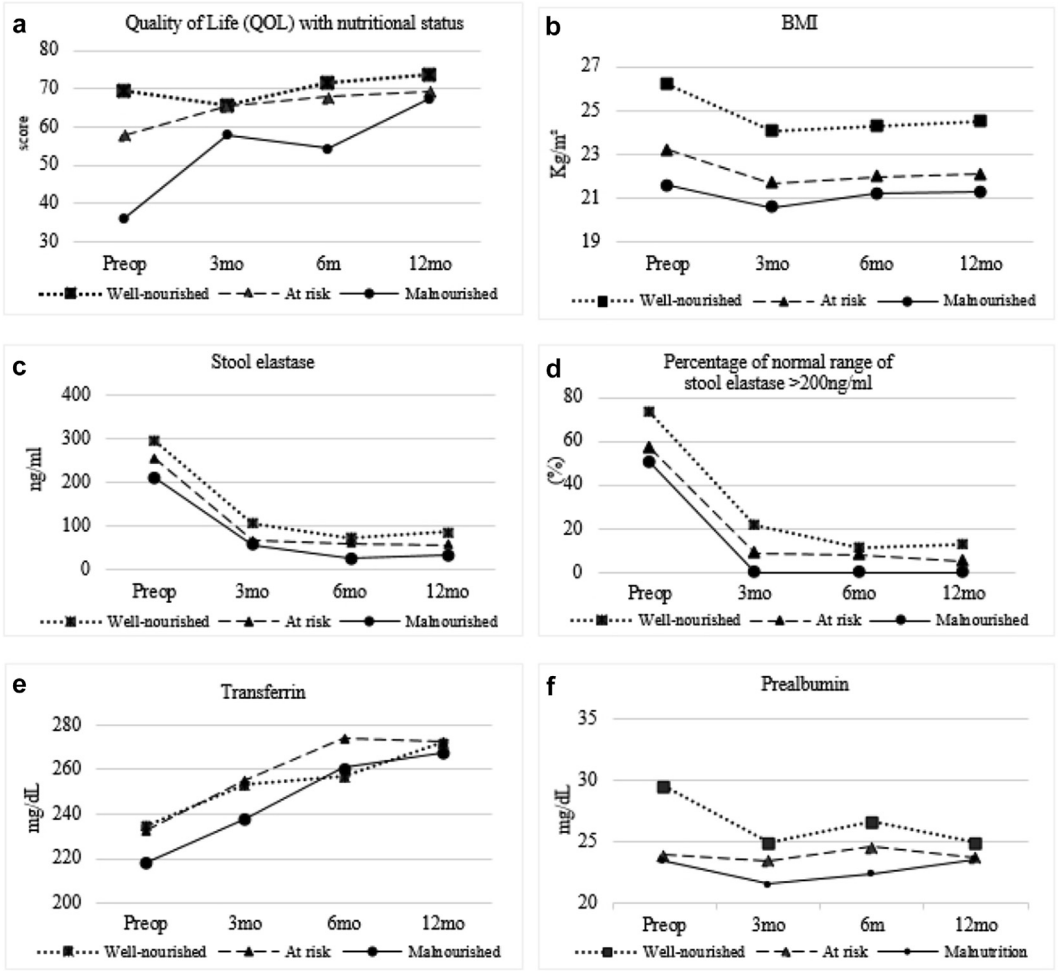


Figure 2 a) Changes in quality of life according to preoperative nutritional status, b) changes in body mass index (BMI) according to preoperative nutritional status, c) changes in stool elastase levels according to nutritional status, d) percent of normal pancreatic exocrine function according to nutritional status, e) changes in serum transferrin according to preoperative nutritional status, f) changes in serum prealbumin according to preoperative nutritional status

surgery, adjuvant therapies were a factor that may potentially have affected nutritional status, but these did not seem to affect nutritional status 12 months after surgery because adjuvant therapies had already been completed.[9]

This study has some limitations. First, the results cannot be directly applied to other countries because there are many discrepancies in demographic findings such as BMI and eating habits, across different countries and regions. Second, the type, dose, and indication for PERT differed from previous studies and were not strictly controlled. Third, as long-term survivors increase after PD, studies evaluating more long-term (>1 year) nutritional outcomes of patients are still needed.

Despite such limitations, there are several clinically significant findings of this study. Indeed, this prospective study is the largest clinical report of long-term nutritional status after PD based on validated nutritional screening tools. The current study identified malnutrition to be highly associated with postoperative complications. Moreover, our findings provide long-term clinical outcomes according to nutritional status and identify several influential factors for long-term unrecovered nutritional status after PD (advanced age, preoperative low BMI, pre-existing DM, jaundice, preoperative exocrine pancreatic insufficiency and adjuvant therapies), thus yielding important information for improving the nutritional status of patients.

In conclusion, preoperative malnutrition is highly associated with postoperative complications. In addition, advanced age, preoperative low BMI, pre-existing DM, jaundice, exocrine pancreatic insufficiency and adjuvant therapies are probable influencing factors for long-term unrecovered nutritional status after PD. Vigorous efforts including nutritional monitoring with nutritional risk assessment, PERT, regular dietary counseling and education for adequate nutrition intake are needed to improve

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Table 4 Influential factors of non-nutritional recovery after surgery

Factors	Postoperative 6 months			Postoperative 12 months		
	Well-nourished (N = 74)	Malnourished (N = 17)	*P-value*	Well-nourished (N = 83)	Malnourished (N = 20)	*P-value*
Age	60.8 ± 8.2	63.9 ± 10.9	0.047*	59.4 ± 8.7	63.5 ± 13.9	0.025*
Comorbidity			0.698			0.101
One or more	43 (58.1%)	9 (52.9%)		37 (44.6%)	13 (65.6%)	
Pre-op BMI(mean ± SD, kg/m^2)	24.8 ± 2.4	21.7 ± 3.1	<0.001	24.9 ± 2.5	21.0 ± 2.4	<0.001*
Pre-op DM	21 (28.4%)	9 (52.9%)	0.052	17 (20.5%)	7 (35.0%)	0.168
Smoking	11 (14.9%)	1 (5.9%)	0.452	3 (3.6%)	3 (15.0%)	0.086
Alcohol history	15 (20.3%)	0 (0.0%)	0.064	18 (21.7%)	2 (10.0%)	0.349
Jaundice	23 (31.1%)	11 (64.7%)	0.010	31 (37.35)	11 (55.0%)	0.149
Operation			>0.999			0.733
PD	8 (10.8%)	2 (11.8%)		12 (14.5%)	2 (10.0%)	
PPPD	66 (89.2%)	15 (88.2%)		71 (85.5%)	18 (90.0%)	
Malignancy	54 (73.0%)	16 (94.1%)	0.107	63 (75.9%)	16 (80.0%)	0.778
Complication (+)	33 (44.6%)	8 (47.1%)	>0.999	27 (32.5%)	7 (35.0%)	>0.999
Pancreatic fistula (+)	17 (23.0%)	2 (11.8%)	0.353	17 (20.5%)	3 (15.0%)	0.757
Pre-op. Exocrine insufficiency	11 (28.9%)	4 (66.7%)	0.159	13 (31.0%)	4 (80.0%)	0.051
Postoperative PERT	35 (74.5%)	12 (25.5%)		34 (72.3%)	13 (27.7%)	
> 6 months	3 (8.6%)	5 (41.7%)	0.047	4 (11.8%)	4 (30.8%)	0.118
3 months–6 months	13 (37.1%)	3 (25.0%)		15 (44.1%)	2 (15.4%)	
< 3 months	19 (54.3%)	4 (33.3%)		15 (44.1%)	7 (53.8%)	
Dietician consultation	59 (79.7%)	17 (100.0%)	0.064	69 (83.1%)	17 (85.0%)	>0.999
Adjuvant treatment	32 (43.2%)	12 (70.6%)	0.042	41 (49.4%)	10 (50.0%)	0.961
Chemo therapy only	5 (6.8%)	0 (0.0%)		8 (9.6%)	1 (5.0%)	
Radiation therapy only	2 (2.7%)	0 (0.0%)		1 (1.2%)	0 (0.0%)	
Chemo + Radiation therapy	25 (33.8%)	12 (70.6%)		32 (38.6%)	9 (45.0%)	

Pre-op: preoperative, BMI: body mass index, DM: diabetes mellitus, PERT: pancreatic enzyme replacement therapy (Pancreatin enteric-coated pellets 40,000–80,000 units/meal), PD: pancreatoduodenectomy, PPPD: pylorus preserving pancreatoduodenectomy, *Mann–Whitney test.

patient nutrition and clinical outcomes before and after PD, especially in preoperatively malnourished patients and those exhibiting risk factors for malnutrition. In addition, further prospective trials are needed to identify optimal methods of nutritional support in the malnourished patients after pancreatectomy.

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Conflict of interest

None declared.

References

1. Cameron JL, Riall TS, Coleman J, Belcher KA. (2006) One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 244:10–15.
2. House MG, Fong Y, Arnaoutakis DJ, Sharma R, Winston CB, Protic M *et al*. (2008) Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. *J Gastrointest Surg* 12:270–278.
3. Carey S, Storey D, Biankin AV, Martin D, Young J, Allman-Farinelli M. (2011) Long term nutritional status and quality of life following major upper gastrointestinal surgery - a cross-sectional study. *Clin Nutr* 30: 774–779.
4. Schiesser M, Kirchhoff P, Muller MK, Schafer M, Clavien PA. (2009) The correlation of nutrition risk index, nutrition risk score, and bioimpedance analysis with postoperative complications in patients undergoing gastrointestinal surgery. *Surgery* 145:519–526.
5. La Torre M, Ziparo V, Nigri G, Cavallini M, Balducci G, Ramacciato G. (2013) Malnutrition and pancreatic surgery: prevalence and outcomes. *J Surg Oncol* 107:702–708.
6. Shinkawa H, Takemura S, Uenishi T, Sakae M, Ohata K, Urata Y *et al*. (2013) Nutritional risk index as an independent predictive factor for the development of surgical site infection after pancreaticoduodenectomy. *Surg Today* 43:276–283.
7. Goonetilleke KS, Siriwardena AK. (2006) Systematic review of peri-operative nutritional supplementation in patients undergoing pancreaticoduodenectomy. *JOP* 7:5–13.

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8. Hwang SE, Jung MJ, Cho BH, Yu HC. (2014) Clinical feasibility and nutritional effects of early oral feeding after pancreaticoduodenectomy. *Korean J Hepatobiliary Pancreat Surg* 18:84–89.
9. Park JW, Jang JY, Kim EJ, Kang MJ, Kwon W, Chang YR *et al*. (2013) Effects of pancreatectomy on nutritional state, pancreatic function and quality of life. *Br J Surg* 100:1064–1070.
10. Dominguez-Munoz JE, Hieronymus C, Sauerbruch T, Malfertheiner P. (1995) Fecal elastase test: evaluation of a new noninvasive pancreatic function test. *Am J Gastroenterol* 90:1834–1837.
11. Matsumoto J, Traverso LW. (2006) Exocrine function following the whipple operation as assessed by stool elastase. *J Gastrointest Surg* 10:1225–1229.
12. Gubergrits N, Malecka-Panas E, Lehman GA, Vasileva G, Shen Y, Sander-Struckmeier S *et al*. (2011) A 6-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. *Aliment Pharmacol Ther* 33:1152–1161.
13. American Diabetes A. (2015) (3) Initial evaluation and diabetes management planning. *Diabetes Care* 38:S17–S19.
14. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al*. (2009) The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 250:187–196.
15. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*. (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13.
16. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR *et al*. (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 142:761–768.
17. Guigoz Y. (2006) The Mini Nutritional Assessment (MNA) review of the literature–What does it tell us? *J Nutr Health Aging* 10:466–485. discussion 485–467.
18. Park HK, Lim BK, Choi SH, Lee HR, Lee DS. (2009) Verification of the appropriateness when a shortened version of the mini nutritional assessment (MNA) is applied for determining the malnutrition state of elderly patients. *J Korean Soc Parenter Enter Nutr* 2:13–18.
19. Fitzsimmons D, Johnson CD, George S, Payne S, Sandberg AA, Bassi C *et al*. (1999) Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. *Eur J Cancer* 35:939–941.
20. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM, Jr.. (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 216:1–14.
21. Schnelldorfer T, Lewin DN, Adams DB. (2007) Operative management of chronic pancreatitis: longterm results in 372 patients. *J Am Coll Surg* 204:1039–1045. discussion 1045–1037.
22. van Berge Henegouwen MI, Moojen TM, van Gulik TM, Rauws EA, Obertop H, Gouma DJ. (1998) Postoperative weight gain after standard Whipple's procedure versus pylorus-preserving pancreatoduodenectomy: the influence of tumour status. *Br J Surg* 85:922–926.
23. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. (2011) Nutritional predictors of postoperative outcome in pancreatic cancer. *Br J Surg* 98:268–274.
24. Nicolini A, Ferrari P, Masoni MC, Fini M, Pagani S, Giampietro O *et al*. (2013) Malnutrition, anorexia and cachexia in cancer patients: a mini-review on pathogenesis and treatment. *Biomed Pharmacother* 67:807–817.
25. Bartel MJ, Asbun H, Stauffer J, Raimondo M. (2015) Pancreatic exocrine insufficiency in pancreatic cancer: a review of the literature. *Dig Liver Dis* 47:1013–1020.
26. Sikkens EC, Cahen DL, van Eijck C, Kuipers EJ, Bruno MJ. (2012) Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. *Pancreatology* 12:71–73.
27. Whitcomb DC, Lehman GA, Vasileva G, Malecka-Panas E, Gubergrits N, Shen Y *et al*. (2010) Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. *Am J Gastroenterol* 105:2276–2286.
28. McLeod RS. (1999) Quality of life, nutritional status and gastrointestinal hormone profile following the Whipple procedure. *Ann Oncol* 10:281–284.
29. Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman J *et al*. (2000) Quality of life and outcomes after pancreaticoduodenectomy. *Ann Surg* 231:890–898.
30. Rees JR, Macefield RC, Blencowe NS, Alderson D, Finch-Jones MD, Blazeby JM. (2013) A prospective study of patient reported outcomes in pancreatic and peri-ampullary malignancy. *World J Surg* 37:2443–2453.
31. Hinz A, Singer S, Brahler E. (2014) European reference values for the quality of life questionnaire EORTC QLQ-C30: results of a German investigation and a summarizing analysis of six European general population normative studies. *Acta Oncol* 53:958–965.
32. Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H *et al*. (2016) Malnutrition: laboratory markers vs nutritional assessment. *Gastroenterol Rep (Oxf)* 4:272–280.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.hpb.2018.05.004.

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