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Exploring the relation between preoperative physical functioning and the impact of major complications in patients following pancreatic resection

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Abstract

Background: This study aimed to evaluate the association between preoperative level of physical functioning and time to recovery of physical functioning, postoperative complications, and the impact of postoperative major complications in patients undergoing elective pancreatic resection. Additionally, prediction models to identify high-risk patients for developing a major complication were externally validated.

Methods: Perioperative data of patients who underwent pancreatic resection were analysed. Primary outcomes were time to recovery of physical functioning and postoperative major complications. Impact of a major complication was explored by evaluating its effect on time to recovery of physical functioning. Risk-prediction models were retrieved following a systematic review.

Results: Multivariable analysis (n = 63) showed that ASA grade III (OR 3.498) and preoperative platelet count (OR 1.005) were associated with major complications, whereas aerobic capacity (OR 0.347) was associated with time to recovery of physical functioning. Age, preoperative aerobic capacity, functional mobility, and perceived level of functional capacity were associated with the impact of a major complication. The AUC of two risk prediction models were 0.556 and 0.701.

Conclusion: Preoperative parameters of physical function were associated with postoperative outcomes and may be useful in outcome prediction, although future approaches should not only register the incidence of major complications but also take the impact of a complication on a patient's physical functioning into account.

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Introduction

Patients diagnosed with cancer in the pancreas often experience disease-related symptoms (e.g., loss of body mass, jaundice, loss of appetite, nausea), which also induce changes in skeletal muscle mass and in the function of a variety of organs leading to functional impairments.[1] Surgical resection is the only potentially curative modality. However, pancreatic resection is associated with a high risk of perioperative morbidity (36–60%) and mortality (2.9–3.5%).[2–4] Patients and their (in)formal caregivers should together make a well-informed decision about the risk-benefit ratio for undergoing major abdominal surgery with or without preoperative preventive interventions, and the options for additional or non-surgical cancer-directed treatment as a (palliative) alternative.[5,6] Several prediction models exist to preoperatively estimate the risk of postoperative morbidity and mortality,[7–9] which can be used to support decision-making with the patient and their (in)formal caregivers when considering pancreatic resection. However, there is a wide variability in the selection of preoperative factors and the definition of post-operative outcomes in risk models. Some have included operative factors (e.g., type of surgery, operation time, blood loss),[10,11] making them more difficult to utilize during preoperative counselling of patients. Other risk models focus merely on one specific type of complication, mostly pancreatic fistula.[12,13] Moreover, as external – pragmatic clinical – validation of available evidence-based risk models is scarce and risk models are thought to not outweigh the surgeon's assessment, they currently play a very limited role in clinical practice.[14,15]

Patient's tolerance for surgery depends on their ability to adapt to the stress of hospitalization (e.g. decreased physical activity[16]) and surgery (e.g. hormonal and metabolic disturbances[17]). Especially those patients developing a complication after pancreatic surgery should have enough reserve capacity to cope with the increased psychophysiological load.[18,19] Some studies have shown that preoperative aerobic capacity is associated with postoperative morbidity, mortality, and length of stay in patients undergoing pancreatic resection.[20–22] Besides aerobic capacity, also muscle strength, functional mobility, and the patient's physical activity level in daily life are considered as indicators for the adaptive capacity of the patient, as they are associated with postoperative time to recovery of physical functioning, morbidity, and mortality following major abdominal surgery.[23–25] If a patient has significant perioperative risk factors (e.g., low aerobic fitness, malnutrition, anemia), appropriate preoperative preventive interventions should be initiated by means of personalized multimodal prehabilitation. Optimizing a patient's psychophysiological reserves prior to surgery is increasingly considered beneficial for recovery functioning, as it reduces the risk for morbidity, and mortality following major abdominal surgery.[26,27] Furthermore, it is hypothesized that psychophysiological reserve capacity is associated with the impact of any complication, in which the impact of a post-operative event is expected to be lower in patients with higher levels of physical fitness. The first aim of this study was to evaluate the association between the preoperative level of physical functioning and postoperative outcomes in patients with pancreatic cancer opting for pancreatic resection. In addition, we aimed to assess the external validity of prediction models that have been developed to preoperatively identify patients with a higher risk for developing a major complication after pancreatic resection. The number of patients who develop complications after pancreatic resection is high and fitter patients might also develop a complication. It should be noted that fitter patients might demonstrate enhanced coping with a complication, reducing its impact and resulting in better postoperative outcomes. Hence, the final aim of the current study was to explore whether the patient's preoperative level of physical functioning was associated with the impact of major postoperative complications.

Methods

Study design

This single-center prospective cohort study evaluated post-operative outcomes (time to recovery of physical functioning, major complications and their impact) in patients with pancreatic or periampullary carcinoma undergoing elective pancreatic resection.

Participants

Patients with pancreatic tumors (adenocarcinoma of the pancreatic head, duodenum, ampulla of Vater, and lower bile duct, or neuro-endocrine tumors), primary benign tumors (e.g., intraductal papillary mucinous neoplasm of the pancreas), and metastases in the pancreas who were scheduled for curative pancreatic resection based on input from a multidisciplinary team of medical specialist (surgeons, oncologists, radiologists, pathologist, radiotherapist, gastroenterologists) at the Maastricht University Medical Center (Maastricht UMC+) between March 2016 and July 2018 were included. Exclusion criteria were pancreatic resection for acute or chronic pancreatitis (except when there was a suspicion for malignancy), a primary tumor outside the pancreas with only secondary involvement of the pancreas, pancreas preserving bile duct resection, and exploratory surgery without pancreas resection. Additionally, patients who had not undergone screening of physical functioning as part of preoperative assessment because of logistical issues, or those who were screened on their level of physical functioning, but did not opt for surgery, were excluded. All consecutive patients with no objection for using their usual care data for research purposes were included. The medical ethical committee of the Maastricht UMC + decided (reference number 15-4-234) that this study met the ethical policies of the Maastricht UMC+.

Patient journey

Patients scheduled for curative pancreatic resection were consecutively referred to the outpatient physical therapy department by the hepato-pancreatic-biliary (HPB) surgeon or clinical nurse specialist for screening of physical functioning as part of multidisciplinary preoperative assessment. A hospital physical therapist with expertise in the hepato-pancreato-biliary (HPB) surgical field conducted the preoperative screening. The preoperative screening included tests to estimate the patient's aerobic capacity (modified steep ramp test [SRT], a short-time maximal exercise test on a cycle ergometer), muscle strength (handgrip strength [HGS]), functional mobility (five times sit-to-stand [FTSTS] test, timed up-and-go [TUG] test, and 2-minute walking test [2MWT]), and perceived level of functional capacity to perform activities of daily life (veterans-specific activity questionnaire [VSAQ] and Duke activity status index [DASI], both expressed in metabolic equivalents of task [METs]). An extensive description of the used measurement protocols for the preoperative screening of physical functioning is provided in the online Supplementary File 1.

All patients were educated (verbally and by using information leaflets) regarding the importance of an adequate preoperative level of physical functioning, and were advised to stay physically active throughout the pre- and postoperative phase. All patients were routinely admitted one day prior to surgery to the HPB surgical ward. Postoperatively, patients were admitted to the HPB surgical ward as soon as possible, unless admission to the intensive care unit was warranted due to intra-operative events or postoperative complications. All patients received postoperative physical therapy once a day (starting at postoperative day 1) focusing on airway clearing exercises and regaining functional independence by early mobilisation, adapted to the individual patient's needs and progress.[28–30] Recovery of physical functioning was monitored using the modified Iowa level of assistance scale (mILAS), scoring on the ability to perform five functional tasks.[31,32] Patients were discharged when analgesia, wound healing, organ functions, laboratory parameters, dietary intake, and recovery of physical functioning (mILAS) were considered adequate by the clinical team.

Pre- and postoperative outcomes, including monitoring of the patient's level of physical functioning

Preoperative clinical data collected from all patients consisted of patient demographics and anthropometrics (e.g., age, sex, body height, body mass), comorbidities, American Society of Anesthesiologists (ASA) grade, functional status (scored on the eastern cooperative oncology group [ECOG] scale[33]), smoking status, chronic steroid use, preoperative sepsis, preoperative interventions (e.g., neoadjuvant treatment, biliary drainage, nutritional support), preoperative blood parameters (e.g., hemoglobin concentration, white blood cell count, platelet count, creatinine level, albumin level), and preoperative level of physical functioning (e.g., aerobic capacity, handgrip strength, functional mobility, and perceived level of functional capacity to perform activities of daily life). These preoperative variables were selected based on a literature search[34–36] and usual care procedures as applied by the department of HPB surgery and department of physical therapy.

Postoperative data included pathology-specific information, surgical procedures, time to recovery of physical functioning, postoperative complications, and length of hospital stay. Time to recovery of physical functioning was defined as the time between the day of surgery and the day at which patients reached a mILAS score of 0 (in days). Time to recovery of physical functioning was also dichotomized according to the median time to recovery of physical functioning. Postoperative complications were classified following the criteria of the international study group for pancreatic surgery (ISGPS) for pancreatic fistula,[37] delayed gastric emptying,[38] hemorrhage,[39] and chyle leakage.[40] Biliary leakage was classified according to the definition of the international study group of liver surgery.[41] The incidence of postoperative complications as *events* were graded using the Clavien-Dindo classification.[42] Complications graded with I or II were defined as minor and complications between III and V were defined as major. *Impact* of these events, especially the major complications, was explored by calculating composite endpoints.

Selection of risk models to predict risk for major complications

The transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline was used for the external validation of available risk models.[43] A systematic literature search was performed in PubMed to identify cohort studies developing models to predict the risk for major complications following pancreatic resection published within the last ten years (Supplemental File 2). Studies were included when they (i) comprised a study population of patients (>18 years) undergoing elective pancreatic resection, (ii) evaluated preoperative patient-related risk factors in relation to postoperative morbidity, (iii) provided quantitative indicators concerning the association between preoperative patient-related variables and postoperative morbidity, and (iv) proposed a clinically interpretable risk-model. Studies were excluded when they merely predicted one particular complication (e.g., pancreatic fistula) or used intraoperative predictors. The study selection process is available in the online Supplementary File 2.

Association between preoperative physical functioning and the impact of postoperative major complications

The *impact* of a major complication was explored by evaluating its effect on time to recovery of physical functioning. Hereto, two composite endpoints were defined to enable the comparison of two subgroups of patients with a different impact of a major complication. One group of patients with a major complication and a time to recovery of physical functioning *above* its median value in this study cohort (*higher impact*) and a group of patients with a major complication and a time to recovery of physical functioning *below* its median value (*lower impact*). To explore whether a patient's preoperative level of physical functioning was associated with the impact of a major postoperative complication, preoperative characteristics were compared between the two subgroups.

Table 1 Demographics, preoperative characteristics, and postoperative outcomes of the study cohort (n = 63)

	All
Demographics	
Sex ratio (M:F)	31:32
Age (years)[a]	68 (26–85)
<70	33 (52.4)
≥70	30 (47.6)
BMI (kg/m^2)[a]	25.6 (19.1–39.3)
Normal (18.5–24.9)	27 (42.9)
Overweight (25.0–29.9)	30 (47.6)
Obese (≥30.0)	6 (9.5)
ASA	
Grade I–II	46 (73.0)
Grade ≥ III	17 (27.0)
Comorbidities	
None	15 (23.8)
1 comorbidity	14 (22.2)
≥2 comorbidities	34 (54.0)
Cardiac	17 (27.0)
Vascular	24 (38.1)
Pulmonary	12 (19.0)
Diabetes	6 (9.5)
Gastrointestinal	13 (20.6)
Neurological	8 (12.7)
Functional status	
Independent	49 (77.8)
Dependent	14 (22.2)
Current smoking	
No	51 (81.0)
Yes	12 (19.0)
Chronic steroid use	
No	63 (100.0)
Yes	0 (0.0)
Preoperative sepsis	
No	63 (100.0)
Yes	0 (0.0)
Biliary drainage	
No	31 (49.2)
Yes	32 (50.8)
Additional nutrition	
No	37 (49.2)
Yes	26 (41.3)
Neoadjuvant treatment	
No	59 (93.7)
Yes	4 (6.3)

(*continued on next column*)

Table 1 (*continued*)

	All
Preoperative physical functioning[a]	
SRT (WR_{peak})	173.0 (56.0–308.0)
SRT (WR_{peak}/kg)	2.29 (0.92–4.12)
HGS (kg)	31.0 (15.0–68.0)
FTSTS test (s)	8.25 (3.69–30.5)
TUG test (s)	5.32 (3.32–21.25)
2MWT (m)	172.0 (55.0–245.0)
VSAQ (MET)	8.0 (2.0–12.0)
DASI (MET)	6.6 (3.1–9.9)
Laboratory values	All
Hemoglobin (g/dL)[a]	12.5 (7.0–16.4)
Thrombocytes (10^3 cells/mm^3)[a]	278 (141–683)
WBC (10^3 cells/mm^3)[a]	8.4 (1.1–18.0)
Creatinine (mg/dL) ≥1.4	2 (3.2)
Albumin (g/dL) ≤3.4	29 (46.0)
Operative characteristics	
Type of surgery	
PPPD	43 (68.3)
Whipple	4 (6.3)
Distal pancreatectomy	13 (20.6)
Other	3 (4.8)
Histologic diagnosis	
Adenocarcinoma	42 (66.7)
Neuroendocrine tumors	10 (15.9)
Benign cystic lesions	6 (9.5)
Other	5 (7.9)
Postoperative outcomes	
No complications	19 (30.2)
Grade I–II	17 (27.0)
Grade III	13 (20.6)
Grade IV	11 (17.5)
Grade V	3 (4.8)
Pancreatic fistula	
None	51 (81.0)
Grade A	0 (0.0)
Grade B	11 (17.5)
Grade C	1 (1.6)
Delayed gastric emptying	
None or grade A	48 (76.2)
Grade B	5 (7.9)
Grade C	10 (15.9)
Hemorrhage	
None or grade A	55 (87.3)
Grade B	7 (11.1)
Grade C	1 (1.6)

(*continued on next page*)

Table 1 (*continued*)

	All
Biliary leakage	
None of grade A	57 (90.5)
Grade B	5 (7.9)
Grade C	1 (1.6)
Chyle leakage	
None	52 (82.5)
Grade A	5 (7.9)
Grade B	6 (9.5)
Grade C	0 (0.0)
Wound infection	5 (7.9)
Pneumonia	7 (11.1)
Cardiac arrhythmias	2 (3.2)
Reintervention	24 (38.1)
Admission to ICU	14 (22.2)
Length of hospital stay[a]	14 (6–78)
Time to recovery of physical functioning[a]	6.5 (1–49)

Abbreviations: ASA = American Society of Anesthesiologists; BMI = body mass index; DASI = Duke activity status index; FTSTS = five times sit-to-stand; HGS = hand grip strength; ICU=Intensive care unit; MET = metabolic equivalent of task; PPPD = pylorus-preserving pancreaticoduodenectomy; SRT = steep ramp test; TUG = timed up-and-go; VSAQ = veterans-specific activity questionnaire; WBC = white blood cells; WR_{peak} = peak work rate; 2MWT = two-minute walk test.
[a] Values are expressed as median (range).

Statistical analysis

The Statistical Package for the Social Sciences for Windows (version 23.0; IBM, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. For continuous variables, normality was tested with the Kolmogorov–Smirnov test. Missing preoperative laboratory values or results on preoperative physical functioning tests were imputed using multiple imputation with ten iterations for each imputation. To analyse the association between preoperative level of physical functioning and postoperative outcomes, the Mann–Whitney U test was used for continuous variables and Fisher's exact test was used for categorical variables. All variables with *P*-values <0.05 in univariate analysis were included in a multivariable logistic regression model with backward stepwise elimination (with ten events per variable). A combination of conventional and physical functioning predictors were chosen based on level of statistical significance and expert opinion. To evaluate the performance of the available risk models, discrimination and calibration of the risk scores were assessed for each model.[44] Receiver operating characteristics (ROC) curve analysis was performed, and the discriminative ability of the prediction models was quantified as the area under the curve (AUC). The model's calibration evaluates the agreement between the observed probability and predicted probability of postoperative complications, and is illustrated using a calibration plot. A regression coefficient of 1 and an intercept of zero represents perfect calibration of the model. To explore the impact of a major complication, the two subgroups of patients with a different impact of a major complication were compared using the Mann–Whitney U test for the continuous variables and the Fisher's exact test for categorical variables. A *P*-value <0.05 was considered statistically significant.

Results

Pre- and postoperative outcomes with monitoring of the patient's level of physical functioning

A total of 79 patients diagnosed with pancreatic or periampullary carcinoma and opting for resection with preoperative assessment of physical functioning between February 2016 and July 2018 were considered for the study. Sixteen patients (20.3%) were excluded retrospectively, as intraoperative findings resulted in no surgical resection being performed. Hence, 63 patients (79.7%) were available for analysis following pancreatic resection. Mean ± SD time between preoperative screening of physical functioning and surgery was 23.6 ± 21.0 days. Patient demographics, preoperative variables, and postoperative outcomes of the study cohort are listed in Table 1. Fig. 1 gives an illustrative overview of the pre-and postoperative level of physical functioning of three individual patients following pancreatic resection for pancreatic cancer. A total of 44 patients (69.8%) developed a complication of which major complications (Clavien-Dindo classification ≥ III) occurred in 27 patients (42.9%). The median time to recovery of physical functioning was 6.5 days (range 1–49) and median length of hospital stay was 14 days (range 6–78 days).

Univariable analysis (Table 2) demonstrated that age, ASA grade (III versus I–II), and preoperative platelet count (10^3 cells/mm^3) were associated with the occurrence of major complications ($P < 0.05$). Multivariable logistic regression with stepwise elimination yielded a model including two variables predicting these events. ASA grade III versus I–II (odds ratio [OR] of 1.498; 95% confidence interval [CI] of 1.033–11.852; $P = 0.044$) and preoperative platelet count (OR of 1.005 per 10^3 cells/mm^3; 95% CI of 1.000–1.010; $P = 0.038$) (Table 3). The AUC for this model was 0.740 (95% CI 0.617 to 0.863; $P = 0.001$). Furthermore, univariable analysis for recovery of physical functioning showed that age, aerobic capacity (relative SRT performance, WR_{peak} in W/kg), functional mobility (2MWT distance, in m), preoperative perceived level of functional capacity to perform ADL (VSAQ and DASI, both in METs), and preoperative white blood cell count (10^3 cells/mm^3) were associated with mILAS-data for time to recovery of physical functioning (Table 2). Multivariable logistic regression with stepwise elimination starting with three variables (age in years, SRT performance in W/kg, and 2MWT distance in m) yielded a model predicting time to recovery of physical functioning above its median value in this study cohort from relative SRT performance (OR of 0.347; 95% CI

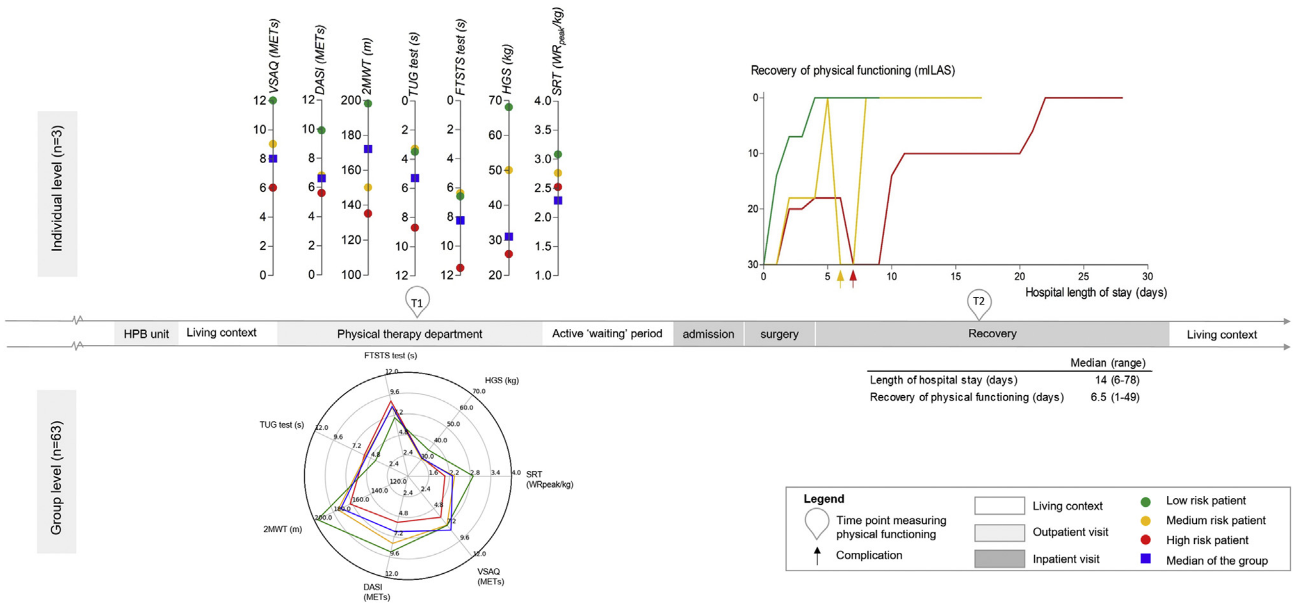

Figure 1 Illustrative overview of the pre-and postoperative level of physical functioning of individual patients (n = 3) with pancreatic cancer following pancreatic resection

0.141–0.854; $P = 0.021$). The AUC for relative SRT performance was 0.680 (95% CI 0.545 to 0.815; $P = 0.014$).

Selection and performance of risk prediction models

Three preoperative risk prediction models for pancreatic surgery were identified in the literature (Supplemental File 2, Table 1).[8,9,34] The number of predictors ranged from five to ten (Supplemental File 2, Table 2). One model could not be validated because of insufficient information, even after contacting the authors.[8] The authors closed the online risk prediction tool, as it was based on "outdated information". Hence, two models[9,32] were externally validated within the present study cohort. The models had a discriminative ability (AUC) of 0.701 (0.565–0.838)[9] and 0.556 (0.413–0.698),[32] respectively. The calibration plots showed a poor agreement between the observed and predicted probabilities, and both models - on average - underestimated the risk of major complications in the present study cohort (Fig. 2).

Composite outcomes

In total, 27 patients (42.9%) developed a major complication, of which 22 patients (81.5%) experienced a time to recovery of physical functioning *above* its median value (n = 19) or deceased (n = 3) (composite endpoint 1), whereas five of these patients (18.5%) experienced a time to recovery of physical functioning *below* its median value (composite endpoint 2). When preoperative demographics and level of physical functioning data were clustered according to composite endpoints (Table 4), a clinically relevant and statistically significant difference between both groups was observed in age (years), preoperative aerobic capacity (relative SRT performance, meaning the absolute SRT performance in Watt normalized for the patient's body mass [W/kg]), functional mobility (2MWT, in m), and perceived level of functional capacity to perform activities of daily life (DASI, in METs) ($P < 0.05$).

Discussion

In this study, we found that conventional factors (ASA grade III and platelet count) were associated with developing major complications, whereas aerobic capacity (SRT performance) was associated with time to recovery of physical functioning. External validation of two available preoperative prediction models for the risk of major complications demonstrated moderate-to-good ability to discriminate between individuals with and without a major complication. However, these prediction models underestimated the risk for major complications in the current study population. Explorative analysis demonstrated that age and preoperative physical functioning might be related with the *impact* of a major complication for a patient.

The current study confirms that preoperative tests of physical functioning (SRT and 2MWT) were associated with time to recovery of physical functioning (Table 2). This is congruent with other studies evaluating the relation between preoperative performance-based tests of physical functioning and postoperative time to recovery of physical functioning in similar patient populations.[23,24] Conventional preoperative factors (ASA grade III and preoperative platelet count) were associated with the development of postoperative major complications (Table 2). The presence of preoperative thrombocytosis (increased platelet count >500 × 10^9/L) has been shown to be associated with morbidity after distal pancreatectomy[34] and

Table 2 Preoperative variables and postoperative outcomes with frequency of complications according to Clavien-Dindo and time to recovery of physical functioning according to the modified Iowa level of assistance scale

	Major complications[a]			Time to recovery of physical functioning[b]		
	Present (n = 27)	Absent (n = 36)	*P*	≥7 days (n = 33)	≤6 days (n = 30)	*P*
Sex ratio (M:F)	15:12	16:20	0.450	18:15	13:17	0.453
Age (years)[c]	72.0 (26.0–85.0)	63.5 (37.0–78.0)	**0.032**	71.0 (26.0–85.0)	65.5 (37.0–78.0)	**0.035**
<70	10 (37.0)	23 (63.9)	**0.044**	14 (42.4)	19 (63.3)	0.131
≥70	17 (63.0)	13 (36.1)		19 (57.6)	11 (36.7)	
BMI (kg/m^2)[c]	26.1 (19.1–39.3)	24.5 (20.6–35.2)	0.743	26.2 (19.1–39.3)	24.7 (20.6–31.6)	0.148
Normal (18.5–24.9)	10 (37.0)	17 (47.2)	0.466	11 (33.3)	16 (53.3)	0.146
Overweight (25.0–29.9)	13 (48.1)	17 (47.2)		17 (51.1)	13 (43.3)	
Obese (≥30.0)	4 (14.8)	2 (5.6)		5 (15.2)	1 (3.3)	
ASA			**0.046**			0.268
Grade I–II	16 (59.3)	30 (83.3)		22 (66.7)	24 (80.0)	
Grade ≥ III	11 (40.7)	6 (16.7)		11 (33.3)	6 (20.0)	
Comorbidities			0.078			0.093
None	4 (14.8)	11 (30.6)		5 (15.2)	10 (33.3)	
1 comorbidity	4 (14.8)	10 (27.8)		6 (18.2)	8 (26.7)	
≥2 comorbidities	19 (70.4)	15 (41.7)		22 (66.7)	12 (40.0)	
Functional status			0.124			0.373
Independent	18 (66.7)	31 (86.1)		24 (72.7)	25 (83.3)	
Dependent	9 (33.3)	5 (13.9)		9 (27.3)	5 (16.7)	
Current smoking			0.531			0.202
No	23 (85.2)	28 (77.8)		29 (87.9)	22 (73.3)	
Yes	4 (14.8)	8 (22.2)		4 (12.1)	8 (26.7)	
Biliary drainage			0.801			1.000
No	14 (51.9)	17 (47.2)		16 (48.5)	15 (50.0)	
Yes	13 (48.1)	19 (52.8)		17 (51.5)	15 (50.0)	
Additional nutrition			1.000			0.306
No	16 (59.3)	21 (58.3)		17 (51.5)	20 (66.7)	
Yes	11 (40.7)	15 (41.7)		16 (48.5)	10 (33.3)	
Neoadjuvant treatment			0.629			0.340
No	26 (96.3)	33 (91.7)		32 (97.0)	27 (90.0)	
Yes	1 (3.7)	3 (8.3)		1 (3.0)	3 (10.0)	
Physical functioning[c]						
SRT (WR_{peak})	168.0 (67.0–301.0)	183.5 (56.0–308.0)	0.128	169.0 (67.0–301.0)	184.0 (56.0–308.0)	0.091
SRT (WR_{peak}/kg)	2.21 (0.92–4.12)	2.3 (0.92–3.89)	0.161	2.21 (0.92–3.26)	2.56 (0.92–4.12)	**0.013**
HGS (kg)	32.0 (15.0–59.0)	30.5 (17.0–68.0)	0.844	31.0 (15.0–59.0)	30.5 (17.0–68.0)	0.899
FTSTS test (s)	8.66 (4.78–28.93)	8.16 (3.69–30.50)	0.501	9.09 (3.69–28.93)	7.38 (4.63–30.50)	0.072
TUG test (s)	4.91 (3.32–21.25)	5.45 (3.53–19.41)	0.409	5.81 (3.32–21.25)	4.58 (3.53–19.41)	0.135
2MWT (m)	165.0 (55.0–240.0)	175.0 (55.0–245.0)	0.144	163.0 (55.0–195.0)	177.0 (55.0–245.0)	**0.010**
VSAQ (MET)	8.0 (3.0–11.0)	8.0 (2.0–12.0)	0.397	7.0 (3.0–11.0)	9.0 (2.0–12.0)	**0.032**
DASI (MET)	6.3 (3.1–9.9)	7.3 (3.6–9.9)	0.103	6.3 (3.1–9.9)	7.3 (3.6–9.9)	**0.045**
Laboratory values						
Hemoglobin (g/dL)[c]	12.3 (7.0–15.7)	12.7 (9.7–16.4)	0.146	12.5 (7.0–16.4)	12.6 (9.72–15.6)	0.997
Platelet count (10^3 cells/mm^3)[c]	310 (183–683)	248 (141–467)	**0.019**	286 (141–683)	258 (167–467)	0.333
WBC (10^3 cells/mm^3)[a]	9.8 (4.3–18.0)	8.0 (1.1–16.6)	0.318	9.8 (1.1–18.0)	7.6 (5.5–14.0)	**0.043**

Table 2 (*continued*)

	Major complications[a]			Time to recovery of physical functioning[b]		
	Present (n = 27)	**Absent (n = 36)**	***P***	**≥7 days (n = 33)**	**≤6 days (n = 30)**	***P***
Creatinine (mg/dL) ≥1.4	2.0 (7.4)	0 (0.0)	0.180	2 (6.1)	0 (0.0)	0.493
Albumin (g/dL) ≤3.4	13 (48.1)	16 (44.4)	0.803	17 (51.5)	12 (40.0)	0.450

Abbreviations: ASA = American Society of Anesthesiologists; BMI = body mass index; DASI = Duke activity status index; FTSTS = five times sit-to-stand; HGS = hand grip strength; MET = metabolic equivalent of task; SRT = steep ramp test; TUG = timed up-and-go; VSAQ = veterans-specific activity questionnaire; WBC = white blood cells; WR_{peak} = peak work rate; 2MWT = two-minute walk test.
P values <0.05 was considered statistically significant which are mentioned in bold.
[a] Major complications are complications with Clavien-Dindo grade ≥ III.
[b] Median time to recovery of physical functioning in the current study cohort equaled 6.5 days.
[c] Values are expressed as median (range).

Table 3 Multivariable logistic regression for major complications and recovery of physical functioning above its median value in the current study cohort

	Covariate	Regression coefficient	OR	(95% CI interval)	AUC	*P*
Major complication (Clavien-Dindo grade ≥ III)	ASA grade III	1.252	3.498	(1.033–11.852)	0.620	**0.044**
	Platelet count (10^3 cells/mm^3)	0.005	1.005	(1.000–1.010)	0.673	**0.038**
Time to recovery of physical functioning (≥7 days)	SRT (WR_{peak}/kg)	−1.058	0.347	(0.141–0.854)	0.680	**0.021**

Abbreviations: ASA = American Society of Anesthesiologists; AUC = area under the curve; CI = confidence interval; SRT = steep ramp test; WR_{peak} = peak work rate.
P values <0.05 was considered statistically significant which are mentioned in bold.

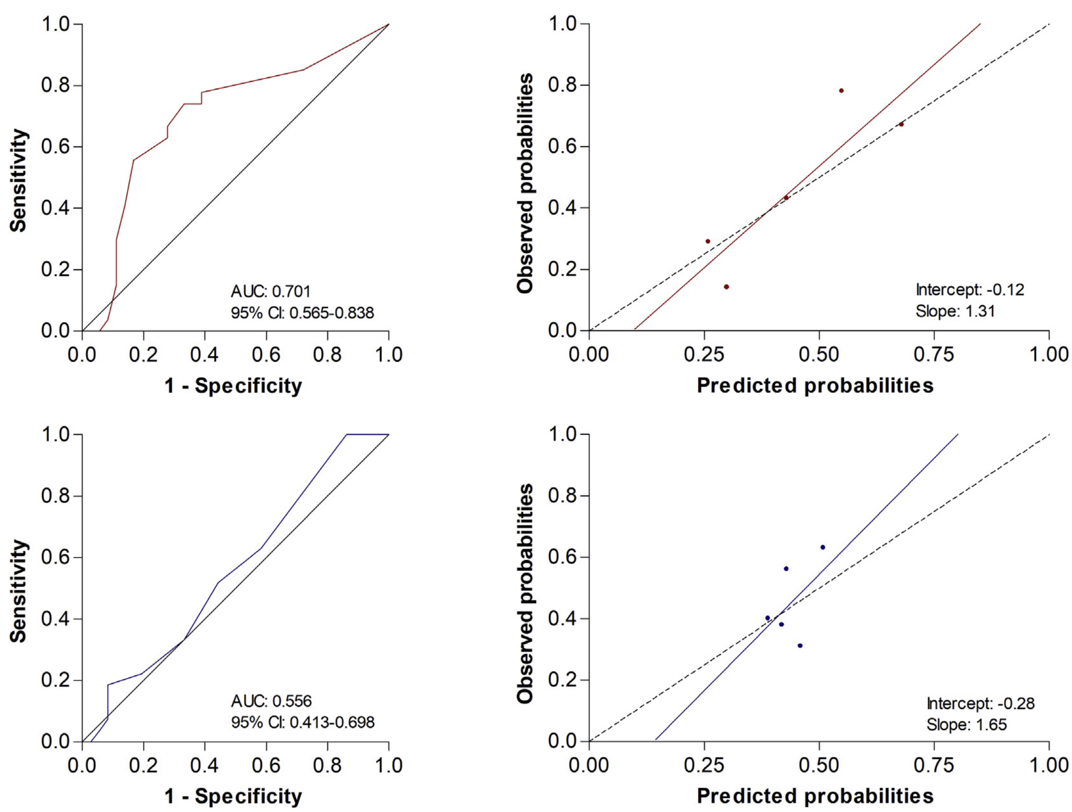

Figure 2 Performance of risk prediction models for major morbidity demonstrated by ROC curve and calibration curves for risk prediction model of Wiltberger *et al.*[9] (upper panel) and Kelly *et al.*[34] (lower panel)

Table 4 Demographics and level of physical functioning of patients undergoing pancreatic resection with a higher (composite endpoint 1) and lower (composite endpoint 2) impact of a major complications

	Composite endpoint 1[a]	Composite endpoint 2[b]	
	Present (n = 22)	Present (n = 5)	*P*
Sex ratio (M:F)	11:11	4:1	0.342
Age (years)[c]	73.0 (26.0–85.0)	61.0 (56.0–72.0)	**0.026**
<70	6 (27.3)	4 (80.0)	**0.015**
≥70	16 (72.2)	1 (20.0)	
BMI (kg/m^2)[c]	26.1 (19.1–39.3)	24.7 (20.8–26.7)	0.525
Normal (18.5–24.9)	7 (31.8)	3 (60.0)	
Overweight (25.0–29.9)	11 (50.0)	2 (40.0)	
Obese (≥30.0)	4 (18.2)	0 (0.0)	
ASA			0.370
Grade I–II	14 (63.6)	2 (40.0)	
Grade ≥ III	8 (36.4)	3 (60.0)	
Comorbidities			1.000
None	3 (13.6)	1 (20.0)	
1 comorbidity	3 (13.6)	1 (20.0)	
≥2 comorbidities	16 (72.7)	3 (60.0)	
Functional status			0.636
Independent	14 (63.6)	4 (80.0)	
Dependent	8 (36.4)	1 (20.0)	
Physical functioning[c]			
SRT (WR_{peak})	160.0 (67.0–301.00)	201.0 (162.0–239.0)	0.062
SRT (WR_{peak}/kg)	2.07 (0.92–3.13)	2.89 (1.87–4.12)	**0.047**
HGS (kg)	31.0 (15.0–59.0)	36.0 (29.0–56.0)	0.277
FTSTS test (s)	8.91 (4.78–28.93)	6.94 (5.44–14.07)	0.314
TUG test (s)	5.61 (3.32–21.25)	4.16 (3.59–4.44)	0.063
2MWT (m)	162.0 (55.0–193.0)	197.0 (175.0–240.0)	**0.001**
VSAQ (MET)	5.5 (3.0–11.0)	9.0 (8.0–11.0)	0.091
DASI (MET)	6.1 (3.1–9.0)	7.3 (5.9–9.9)	**0.049**
Complication grade			0.255
Grade IIIa	9 (40.9)	3 (60.0)	
Grade IIIb	0 (0.0)	1 (20.0)	
Grade IV	10 (45.5)	1 (20.0)	
Grade V	3 (13.6)	0 (0.0)	

Abbreviations: ASA = American Society of Anesthesiologists; BMI = body mass index; DASI = Duke activity status index; FTSTS = five times sit-to-stand; HGS = handgrip strength; MET = metabolic equivalent of task; SRT = steep ramp test; TUG = timed up-and-go; VSAQ = veterans-specific activity questionnaire; WR_{peak} = peak work rate; 2MWT = two-minute walk test.
P values <0.05 was considered statistically significant which are mentioned in bold.
[a] Major complication and a time to recovery of physical functioning *above* its median value (≥7 days, *higher* impact).
[b] Major complication and a time to recovery of physical functioning *below* its median value (≤6 days, *lower* impact).
[c] Values are expressed as median (range).

pancreaticoduodenectomy[8] in previous studies. Surprisingly, (estimated) aerobic capacity was not related with the development of a postoperative complication in the present study, which is not in line with findings from other studies.[20–22] The group without a major complication had a tendency to a higher absolute and relative preoperative WR_{peak} at the SRT compared to the group who experienced a major complication (Table 2). One possible explanation could be the type of test that was used to estimate aerobic capacity: a SRT instead of a cardiopulmonary exercise test (the gold standard). Although, we did not find the same association between preoperative performance-tests of physical functioning and major complications as established in other studies.[25,45] A post hoc analysis was performed to evaluate differences in postoperative outcomes between patients who underwent pancreaticoduodenectomy (n = 47) and patients who underwent distal pancreatectomy (n = 13). By doing so differences were found in time to recovery of physical functioning (7.5 versus 4.0 days, respectively; $P = 0.055$), complication incidence (78.7% versus 46.2%, respectively; $P = 0.035$), major complications (48.9% versus 23.1%, respectively; $P = 0.122$), and length of hospital stay (14.5 days versus 9.0 days, respectively; $P = 0.049$). In future observational studies these findings should be taken into account, preferably already in the setup of the studies in order to have sufficient power to introduce different types of surgery in the analysis. Furthermore, it is also of interest to study the association between the preoperative (natural) course (change scores) of physical fitness and physical activity level of the patient (improved, stable, declined) and postoperative outcomes, or to assess the effect of a preoperative exercise intervention combined with nutritional support.

A limited number of useful clinical models is currently available in the literature to predict major complications in patients undergoing pancreatic resection (Supplemental file 2, Table 1). Performance of prediction models is often lower in the external validation cohort compared to the cohort in which the prediction model was developed.[46] This might be attributed to (i) the context in which the risk-prediction model is developed and validated (e.g. hospital-specific care pathways and protocols), (ii) heterogeneity in defining (major) complications (Clavien-Dindo $\geq$ III) in the different prediction models,[9,34] (iii) the type of surgery for which the risk-prediction model was developed, and (iv) methodology and sample size considerations (e.g. the impact of sample size and the number of events on the performance of prognostic models[47]). The model of Kelly *et al.*[34] was externally validated on all types of pancreatic surgery in the current study cohort, whereas it was developed merely for patients undergoing a distal pancreatectomy. The latter could be a possible explanation of its low predictive performance in the present cohort. The usefulness of the model of Wiltberger *et al.*[9] in daily clinical practice was further evaluated in a post-hoc analysis. The positive predictive value was 64.3% and the negative predicted value was 74.3%. The positive predictive value is relatively low; thus, only a small proportion of those considered at risk actually develop complications. Available models in the literature merely contain conventional predictors (e.g. age, comorbidities) for postoperative major complications. Predictors related to preoperative physical functioning (e.g. aerobic capacity) should be added to further improve the accuracy of preoperative risk stratification. Furthermore, the assessment of muscle mass with the use of computed tomographyin in combination with performance-based tests may provide additive risk prediction accuracy and the ability to develop targeted preoperative interventions.[48]

Concerning the impact of a major complication, its relation with time to recovery of physical functioning was explored. There was an independent statistically significant difference between age and level of physical functioning between patients who experienced a major complication with a delayed recovery of physical functioning compared to patients who experienced a major complication without a delayed recovery of physical functioning (Table 4). Patients who were younger, patients with a higher preoperative level of physical functioning (SRT and 2WMT performances), and patients with a higher perceived level of functional capacity to perform activities of daily life (DASI) were more likely to better cope with a major postoperative complication. Present study results are in line with a post-hoc analysis from Hulzebos *et al.*[49] The study reported that patients who received preoperative inspiratory muscle training seemed to cope better with postoperative pneumonia compared to patients in the usual care-group (without this type of training), as their median hospitalization was shorter (11.5 versus 13.0 days, respectively).[49] Hence, fitter patients might be more resistant and might cope better with the negative effects of postoperative complications. However, results in the current study showed a large range in preoperative physical functioning in patients experiencing major complications that had a time to recovery of physical functioning above its median value in the current study cohort. Nevertheless, it is hypothesized that a postoperative complication has less impact in fitter patients. Further research is required to investigate this hypothesis, as well as to look for alternatives outcome measures for evaluating the impact of a postoperative complication.

In conclusion, preoperative prediction of postoperative outcomes is feasible but needs another approach, as existing risk prediction models to predict major complications in patients undergoing major pancreatic surgery may have a limited role in clinical practice given their predictive performance. Only conventional predictors are used in currently available models and the current study shows that there might be room for improvement by also including variables of preoperative physical functioning. Furthermore, it is debatable whether optimal outcome measures are used by evaluating the incidence of complications without taking its impact into account.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.09.010.