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CARDIOPULMONARY EXERCISE TESTING FOR PREOPERATIVE RISK ASSESSMENT BEFORE PANCREATICODUODENECTOMY FOR CANCER.

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Abstract

Objective: Pancreaticoduodenectomy is the standard of care for tumours confined to the head of pancreas and can be undertaken with low operative mortality. The procedure has a high morbidity, particularly in older patient populations with pre-existing co-morbidities. This study evaluates the role of cardiopulmonary exercise testing (CPET) as a means of predicting post-operative morbidity and outcome in high-risk patients undergoing pancreaticoduodenectomy.

Methods: In a prospective cohort of consecutive patients undergoing pancreaticoduodenectomy, those aged over 65 years (or younger with co-morbidity) were categorized as high-risk and underwent preoperative assessment by CPET according to a pre-defined protocol. Data were collected on functional status, postoperative complications and survival.

Results: 143 patients underwent preoperative assessment of whom 50 were deemed low-risk for surgery per protocol. Of 93 high-risk patients 64 proceeded to surgery after preoperative CPET. Neither Anaerobic threshold (AT) nor maximal oxygen consumption ($\dot{V}O_{2}$ MAX) predicted patient mortality or morbidity. However ventilatory equivalent of carbon dioxide ($\dot{V}E/\dot{V}CO_{2}$) at AT was a predictive marker of postoperative mortality with an AUC of 0.84 (95% CI 0.63 to 1.00, p=0.020); a threshold of 41 was 75% sensitive and 95% specific (PPV 50%, NPV 98%). Above this threshold, raised $\dot{V}E/\dot{V}CO_{2}$ predicted poor long-term survival (HR 2.05, 95% CI: 1.09 to 3.86, p=0.026).

Conclusions: CPET is a useful adjunctive test for predicting post-operative outcome in patients being assessed for pancreaticoduodenectomy. Raised CPET-derived $\dot{V}E/\dot{V}CO_{2}$ predicts early post-operative death and poor long-term survival.

[Word count 238].

Introduction

Surgical resection is the standard of care for patients with tumours confined to the head of the pancreas [1-3]. An increasing number of reports attest that pancreaticoduodenectomy can be performed with low operative mortality [2, 4]. However, perioperative morbidity remains high and the risk-benefit ratio of complex resectional surgery must be carefully assessed [5]. Thus one of the principal thrusts of current pancreatic oncological surgery is towards optimal patient selection.

Detailed oncological staging can be undertaken with a combination of high-resolution cross-sectional imaging combined with endoscopic ultrasonography. Assessment of risk in terms of cardio-respiratory co-morbidity is an integral component of pre-operative assessment. This is particularly relevant when it is considered that pancreatic adenocarcinoma is predominantly a disease of later life and that patients assessed for resection may be at high risk for post-operative cardiac or pulmonary complications. Furthermore, postoperative complications may affect uptake of adjuvant chemotherapy potentially leading to adverse outcome [6].

Current methods of evaluating perioperative risk rely on tools comprising subjectively derived assessments of functional capacity, such as the Revised Cardiac Risk Index (RCRI) or the Physiological and Operative Severity Score for Enumeration of Morbidity and Mortality (POSSUM). These measures along with other forms of functional assessments (shuttle walk test, Duke's score) have been shown to be poor surrogates for functional cardiopulmonary assessment [7.8].

Cardiopulmonary exercise testing (CPET) provides an accurate and reliable non-invasive assessment of cardiopulmonary function. CPET-derived variables have been demonstrated to provide prognostic information relating to outcome following major intra-abdominal surgery [7, 9]. Despite validation in a heterogeneous general surgical population, its evaluation in pancreatic resectional surgery is very limited either in an exclusive cohort or as an independently-reported subgroup of a broader cohort.

Thus the aim of the present study is to assess the role of preoperative CPET for prediction of peri-operative outcome in a cohort of patients scheduled to undergo pancreaticoduodenectomy.

Methods

Study design

This was a single-centre prospective cohort study evaluating outcome in patients undergoing pancreaticoduodenectomy. Cardiopulmonary exercise testing (CPET) was utilised for preoperative risk assessment in protocol-defined high risk patients.

Study population

The study cohort comprised a consecutive series of patients undergoing pancreaticoduodenectomy at a tertiary hepatobiliary surgery referral centre. The study was undertaken over a 39-month period from 1st September 2007 to 31st December 2010. Staging of primary disease was undertaken using high-resolution, contrast-enhanced computed tomography together with endoscopic ultrasound (EUS) (and EUS-guided fine needle aspiration for cytological and biochemical analysis) in patients with cystic lesions. Patients presenting with obstructive jaundice routinely underwent endoscopic retrograde cholangiopancreatography (ERCP) with placement of an endobiliary stent or percutaneous trans-hepatic biliary drainage (PTBD).

Following clinical assessment, those individuals with pre-existing co-morbidity (definitions in disease descriptors section) or aged over 65 years were further assessed by preoperative CPET in compliance with a pre-defined hepato-pancreato-biliary unit protocol. These patients were classified as 'high-risk'. Younger individuals (≤65 years) with no significant pre-existing co-morbidity proceeded to surgery without preoperative CPET and were classified as the 'low-risk' group.

Patient-level data and disease descriptors

Baseline data were recorded for all patients including age, gender and preoperative haematological and biochemical profile which included full blood count, liver function tests, renal function tests and C reactive protein. Operative details (duration of surgery and intra-operative blood transfusion) were also recorded.

The primary outcome studied was postoperative mortality (defined as death within 30 days of operation). Secondary outcomes included in-hospital mortality occurring beyond the 30th postoperative day (time unlimited), intensive care unit (ICU – level III critical care) stay, high dependency unit (HDU – level II critical care) stay, overall hospital stay and longer-term survival with follow-up to four years. Long-term survival was also evaluated separately in patients who underwent preoperative assessment with CPET, but failed to undergo pancreatic resection either because of advanced disease or because they were deemed unfit for major surgery.

An enhanced set of data were obtained for patients undergoing CPET including self-reported history of smoking and preoperative co-morbidities. Preoperative co-morbidity was recorded at initial clinical assessment and included data on the following: cardiac – history of hypertension or ischaemic heart disease; diabetes mellitus (insulin dependent or otherwise); history of cerebrovascular disease; and, chronic obstructive airways disease or renal impairment (defined according to the National Institute for Health and Clinical Excellence guidance on chronic kidney disease) [10]. In this subset, preoperative functional status was assessed using the American Society of Anaesthesiologists (ASA) score and the six-point Revised Cardiac Risk Index (RCRI); including high-risk surgical procedure, history of ischaemic heart disease, history of heart failure, cerebrovascular disease, insulin dependent diabetes and preoperative serum creatinine concentration ≥177 µmol/L. Other predictors of postoperative risk including body mass index (BMI) and the Glasgow Prognostic Score (GPS) [11] were collected prospectively to permit comparison with CPET data.

Postoperative morbidity was defined using the International Study Group [11] for Pancreatic Surgery (ISGPS) classification for post-pancreaticoduodenectomy complications of postoperative pancreatic fistula (POPF) [12] delayed gastric emptying (DGE) [13] and post-pancreaticoduodenectomy haemorrhage (PPH) [14]. Cardiac complications included acute myocardial infarction (detection of a rise in serum troponin) and electrocardiographic (ECG) changes indicative of new ischaemia; congestive cardiac failure and, serious dysrhythmia resulting in compromised tissue perfusion and primary cardiac arrest. Pulmonary complications included pneumonia, pleural effusion and respiratory failure requiring ventilatory support. Renal complications included acute kidney injury defined as an increase in baseline creatinine of 1.5 fold and/or requirement for renal replacement therapy. Other recorded complications included confusion, cerebrovascular accidents, wound infections, thromboembolic events, intra-abdominal sepsis and interventions (radiological, endoscopic or surgical) which included return to theatre. Complications were recorded for the entire postoperative in-hospital period.

Data were recorded prospectively and analysed at completion of the study. All-cause mortality was determined using the Demographics Batch Service (DBS) to access the national electronic database of the UK NHS (National Health Service).

Cardiopulmonary exercise testing protocol

Preoperative cardiopulmonary exercise testing was carried out once the decision to undertake pancreaticoduodenectomy was made and patients met the inclusion criteria for CPET as per protocol. CPET results were available to clinicians prior to surgery. An established study protocol [15] was followed and the test was carried out and interpreted by two observers (a clinical scientist and an attending anaesthetist). CPET equipment (Ultima™ CardiO$_2$®, MedGraphics, Minnesota, USA) included an electronically braked cycle ergometer with a 12 lead ECG and a metabolic cart with a face mask for gas analyses. Calibration was carried out before each test for flow measurement and gas analysers.

The test was divided into four phases. The first phase involved a two to five minute rest period to ensure a respiratory exchange rate (RER) of less than 1. RER is the ratio of volume of carbon dioxide elimination ($\dot{V}CO_2$ L/min) to oxygen consumption ($\dot{V}O_2$ L/min). The second phase of unloaded cycling for three minutes was followed by the ramp phase in continuous increments maintaining greater than 60 revolutions per minute (RPM). The test ended with the recovery phase to allow the ECG and heart rate to return to baseline levels. The test was terminated if patients developed ECG changes (ST changes > 2.0 mm depression or > 3.0mm elevation, new dysrhythmia), near syncope or failed to maintain greater than 50 RPM.

Anaerobic threshold (AT) was determined using the modified V-slope method [16, 17] and confirmed by changes in ventilatory efficiency for oxygen ($\dot{V}_E/\dot{V}_{O_2}$) and end tidal values for oxygen (PET_{O_2}) in which $\dot{V}_E$ (L/min) is minute ventilation representing volume of gas expired per minute. Peak $\dot{V}_{O_2}$ was expressed as the highest mean oxygen consumption value ($\dot{V}_{O_2}$) obtained from 5 rolling breath to breath measures during the last part of the incremental ramp stage. The ventilatory equivalence for carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) was determined as the ratio of minute ventilation to carbon dioxide elimination ($\dot{V}_{CO_2}$) at AT.

Statistical methods

Per protocol analysis was performed using SPSS (16.0, full-version Chicago, IL.), with appropriate statistical tests for each variable type. As the purpose of the study was hypothesis generation, a value of $p < 0.05$ was regarded as significant, without correction for multiple testing. CPET (continuous) variables were evaluated using simple logistic regression to determine their potential prognostic value in predicting mortality or morbidity outcomes. Logistic regression models include a constant term and are reported as the exponential of the variable coefficient (the odds ratio). If more than one variable predicting an outcome then forward stepwise multiple variable regression was conducted. Significant CPET variables were further explored by plotting Receiver operating characteristic (ROC) curves to identify threshold values which discriminated effectively between patient groups with differing clinical outcomes.

Using these threshold values, survival analysis was conducted using the Kaplan Meier method to identify discrete groups with varying prognosis. Differences in survival curves were assessed using the log rank method as this gives equal weight to events at all points in time. Putative models were further evaluated using Cox regression.

The study was registered as a prospective audit with the Research and Innovation Division of the Central Manchester University Hospitals NHS Foundation Trust (reference number 1840).

Results

Over a 39-month period, from 1st September 2007 to 31st December 2010, 143 consecutive patients with operable pancreatic disease requiring pancreaticoduodenectomy were assessed for perioperative risk [Figure 1]. Per protocol, 93 patients were designated as 'high-risk' for preoperative assessment with CPET. Of these, 4 were unable to undergo CPET prior to surgery and proceeded to resection (in view of surgeon and patient preference) without CPET; 64 underwent pancreaticoduodenectomy following CPET and a further 25 did not proceed to resection - because of a combination of staging-detected advanced disease and/or co-morbidity. The 'low-risk' patient group comprised 50 patients all of whom underwent resection giving a total population of 118 undergoing pancreaticoduodenectomy.

Baseline characteristics and postoperative outcomes in these 118 patients are described in Table 1. No significant difference was noted between the low and high-risk groups in the incidence of preoperative obstructive jaundice, use of preoperative biliary drainage, preoperative bilirubin levels or postoperative ICU stay. The duration of HDU and hospital stay was significantly longer in the high-risk group.

An enhanced set of data collected in the high-risk CPET group is detailed in Table 2. Of the 64 consecutive pancreaticoduodenectomies, CPET was inadequate in 4 individuals leaving 60 patients contributing data to analyses.

Postoperative mortality

Early (30-day) and late (all in-hospital) postoperative deaths are reported in Table 1. Postoperative mortality was generally low with no significant difference between low and high-risk groups at 30 days (p=0.223). All post-operative deaths resulted from surgical complications.

In high-risk patients, simple logistic regression analyses identified $\dot{V}_E/\dot{V}_{CO_2}$ to be the CPET parameter most strongly associated with 30-day mortality (OR: 1.35, 95%CI: 1.03 to 1.77, p=0.030). Simple regression did not reveal any other CPET markers associated with early postoperative death (see Table 3). For in-hospital mortality, simple logistic regression similarly fitted $\dot{V}E/\dot{V}CO_2$ (1.26 (95% CI: 1.06 to 1.53, p=0.013).

The Receiver Operating Characteristic (ROC) curves of $\dot{V}E/\dot{V}CO_2$ for 30-day and all in-hospital postoperative mortality are shown in Figure 2. For 30-day mortality, the AUC was 0.95 (95% CI: 0.89 to 1.02, p=0.030) with 100% sensitivity and 92% specificity. For all in-hospital mortality, the AUC was 0.84 (95% CI: 0.63 to 1.07, p=0.020). Given the small number of deaths at 30-days, in hospital mortality was considered a more informative variable. A cut-off at 41.0 provided test sensitivity of 75% (95% CI: 0.30 to 0.95), specificity of 93% (95% CI: 0.85 to 0.98), PPV of 50% (95% CI: 0.19 to 0.81) and NPV of 98% (95% CI: 0.90 to 0.99). Thus a negative result effectively ruled out 30-day hospital mortality, while one in two patients above threshold died before discharge.

Amongst traditional pre-operative markers (ASA, RCRI, BMI, GPS and obstructive jaundice), none were statistically significant predictors of 30-day or in-hospital mortality. However, all 5 in-hospital deaths occurred in patients with ASA=3 (p=0.087 exact test).

Postoperative morbidity

No CPET preoperative variable was a significant predictor (p<0.05) of complications using simple logistic regression (Table 3). However obstructive jaundice was associated with cardiopulmonary complications (OR: 5.40, 95%CI: 1.66 to 17.56, p=.005)

ISGPS defined post-pancreatectomy complications

ISGPS defined complications of postoperative pancreatic fistula (POPF), post-pancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE) are reported in Table 2. Neither CPET nor other preoperative variables predicted ISGPS defined complications.

Survival

The median period of follow-up for all 143 patients undergoing assessment for resection was 1057 days (424 to 1657). For the 118 patients undergoing pancreaticoduodenectomy the median follow-up period was 997 days (424 to 1596).

Survival analysis (Kaplan Meier) identified discrete survival patterns using the CPET threshold value for $\dot{V}_E/\dot{V}_{CO_2}$ of 41 [Figure 3]. Patients above this threshold had a substantially poorer survival than patients below this threshold (HR 2.05, 95% CI: 1.09 to 3.86, p=0.026). For comparison the lower risk patient groups (not-undergoing CPET) are shown, with better survival due to lower age and associated risk markers.

Histologic sub-types [ductal adenocarcinoma 27 (41%), ampullary 13 (20%), intraductal papillary mucinous neoplasm 5 (7%), distal duct cholangiocarcinoma 3 (5%), duodenal adenocarcinoma 3 (5%), chronic pancreatitis 3 (5%) neuro-endocrine tumour 2 (3%), metastatic seminoma 1 (2%), metastatic renal cancer 1 (2%), autoimmune pancreatitis 2 (3%), benign adenoma 3 (5%) and benign distal bile duct stricture 1 (2%)] showed no correlation with outcome (Log-Rank Mantel Cox test *P = 0.72*). However, ductal adenocarcinoma was associated with a worse survival when compared to all other tumour types (Log-Rank Mantel Cox Test *P* = 0.001).

Discussion

This study reports an exploratory prospective cohort of high-risk patients undergoing pancreaticoduodenectomy with CPET for preoperative risk assessment. CPET-derived $\dot{V}E/\dot{V}CO_2$ ratio at AT with a cut-off at 41 was the best predictor of postoperative in-hospital mortality and long-term survival in this high-risk pancreaticoduodenectomy population. Commonly used risk markers including ASA, RCRI, and BMI were not predictive of adverse outcome in this cohort, although this may be due to small numbers of events.

There are a number of potential limitations when interpreting these findings. As in any hypothesis generating study, the findings should undergo external validation by other investigators in similar patient cohorts. The $\dot{V}E/\dot{V}CO_2$ threshold was determined for a high-risk cohort of pancreaticoduodenectomy patients and was limited by a low event rate in postoperative mortality: further evaluation in a larger cohort would be required to validate the utility of this marker of postoperative mortality. Another potential limitation is the lack of blinding of CPET results to clinicians: the availability of results to inform decision making potentially undermines the strength of association between variables and outcome measures, although it is unlikely that CPET findings modified surgical decisions since their importance was not known at the time that patients underwent surgery.

An important bias in accurate preoperative evaluation of cardiopulmonary function is introduced by the presence of malignant obstructive jaundice. Obstructive jaundice is known to adversely affect global cardiac function [18]. As increase in cardiac output remains the predominant mechanism of meeting increased oxygen demands following major abdominal surgery [19], the clinical impact of obstructive jaundice on postoperative outcomes in the context of pancreatic surgery remains unclear [20, 21].

Further the subjective dichotomisation of patients into “high” and “low” risk means that CPET was not utilised in a group designated as low risk. The reason for this is that CPET data from other studies indicates that the validity of this test is maximal in assessing high-risk patients [22] but it should be acknowledged that if the test had been applied to all patients different results may have been obtained.

In complex pancreatic resectional surgery, intra-operative factors including host-specific features (such as texture of pancreas, calibre of pancreatic duct), histology-related features (such as whether resection is for pancreatic ductal adenocarcinoma or other disease) and operator specific features (such as surgeon and hospital volume) have an important and profound influence on outcome. Pre-operative CPET will not substitute for these important predictors but rather helps inform the decision on patient selection.

Despite these shortcomings, a CPET-derived variable provided an adequate predictor of mortality-related outcomes to augment the decision-making process, by predicting early and long-term survival. A $\dot{V}_E/\dot{V}_{CO_2}$, threshold of 41 as a predictor of postoperative and long-term survival is similar to the findings of Carlisle and colleagues, reporting $\dot{V}_E/\dot{V}_{CO_2}$ above 42 as the strongest predictor of 30 day and mid-term survival following elective abdominal aortic aneurysm repair [22].

Our findings suggest that functional capacity as assessed by $\dot{V}_E/\dot{V}_{CO_2}$ is a strong predictor of early and late postoperative outcome and may have a greater role to play than primary pancreatic pathology or resectability of cancer alone.

Although it is clear that CPET-derived functional assessment outperforms other methods as a predictor of post-operative and long-term survival, its clinical utility in pancreaticoduodenectomy lies in acting as an adjunct to other forms of assessment and in allowing clinician and patient to make a more informed decision about the relative risks and benefits of surgery.

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Table 1: Outcome from 118 pancreatic resections

	All patients	High risk group*	Low risk group	p-value
N	118	68	50	-
Age in years	61 (36 – 80)	68 (45 – 80)	53 (36 – 65)	<0.001
Sex (male/female)	67/51	41/27	26/24	0.37
Obstructive jaundice	71 (60%)	44 (65%)	27 (54%)	0.24
Preoperative biliary drainage	70/71 (99%)	44/44 (100%)	26/27 (96%)	0.17
Preoperative Bilirubin (μmol/L)	10 (2 – 323)	10.5 (2 – 216)	9.5 (2 – 323)	0.87
ICU stay in days#	0 (0 – 194)	0 (0 – 194)	0 (0 – 24)	0.10
HDU stay in days	5 (0 – 32)	5 (0 – 32)	4 (1 – 19)	0.003
Hospital stay in days	16 (3 – 194)	18 (3 – 194)	13.5 (9 – 53)	0.005
<30 day postoperative mortality	2 (1.7%)	2 (2.9%)	0 (0%)	0.22
In-hospital postoperative mortality	5 (4.2%)	5 (7.4%)	0 (0%)	0.051

Data presented as median (range) or count (%) unless otherwise indicated. The Mann-Whitney U test was used for continuous- and exact test for categorical variables. *ICU*, Intensive care Unit; *HDU,* High dependency Unit. *Includes 64 patients undergoing resection with preoperative CPET and 4 patients qualifying for CPET but not undertaken. 25 patients assessed as unfit for surgery following CPET are not included in this table (median age 69, range 60-84, sex M/F 15/10). # With few ITU admissions postoperatively [14/118 patients (11.7% patients)], the median value was zero.

Table 2: Preoperative characteristics and postoperative outcomes for 64 patients who had resection after cardiopulmonary exercise testing

	No. of patients*
Age (years)†	64 (45-80)
Sex ratio (M : F)	38:26
Time between CPET and operation (days)†	13 (1–209)
Body mass index (kg/m^2)†	26 (15–44)
ASA score†	3 (1–3)
Revised Cardiac Risk Index†	1 (1–3)
Glasgow Prognostic Score	0 (1-2)
Obstructive Jaundice	43 (67%)
Surgical procedure	
Whipple	57 (89%)
Subtotal pancreatectomy (“Extended” Whipple)	2 (3%)
Whipple + liver + Gall bladder resection	1 (2%)
Whipple + Portal vein resection	1 (2%)
Total pancreatectomy	3 (5%)
Postoperative outcomes	
Cardiac complications	15 (23%)
Pulmonary complications	24 (38%)
Cardiopulmonary complications	32 (50%)
All complications	41 (64%)
Return to theatre	3 (5)
DGE (ISGPS grade, A=4, B=11, C=5)	20 (31.2%)
PF (ISGPS grade, A=3, B=12, C=1)	16 (25%)
PPH (ISGPS grade, A=0, B=5, C=0)	5 (7.8%)
ICU stay (days) †	0 (0–194)
HDU stay (days)†	5 (0–23)
Hospital stay (days)†	18 (3–194)

*With percentages in parentheses unless indicated otherwise; †values are median (range). CPET, cardiopulmonary exercise testing; ASA, American Society of Anaesthesiologists; COPD, chronic obstructive pulmonary disease; ISGPS, International Study Group for Pancreatic Surgery; *DGE,* Delayed Gastric Emptying; *PF,* post-pancreatectomy fistula; *PPH,* Post-pancreatectomy haemorrhage; ICU, intensive care unit; HDU, high-dependency unit.

Table 3: Evaluation of CPET variables and post-operative mortality and morbidity

	Odds Ratio	**95%CI**	**p**
In Hospital Mortality			
AT	0.90	(0.52 to 1.53)	0.69
$\dot{V}E/\dot{V}CO_2$	1.26	(1.05 to 1.52)	0.013
$\dot{V}O_2$ MAX	1.03	(0.77 to 1.37)	0.86
30-day Mortality			
AT	1.23	(0.72 to 2.11)	0.45
$\dot{V}E/\dot{V}CO_2$	1.35	(1.03 to 1.77)	0.030
$\dot{V}O_2$ MAX	1.32	(0.91 to 1.93)	0.14
Cardiopulmonary Complication			
AT	1.05	(0.82 to 1.34)	0.68
$\dot{V}E/\dot{V}CO_2$	0.98	(0.90 to 1.07)	0.63
$\dot{V}O_2$ MAX	1.00	(0.86 to 1.17)	0.98
Any Complication			
AT	1.07	(0.83 to 1.39)	0.60
$\dot{V}E/\dot{V}CO_2$	0.97	(0.89 to 1.07)	0.56
$\dot{V}O_2$ MAX	1.00	(0.86 to 1.18)	0.96

Figure 1: Flowchart

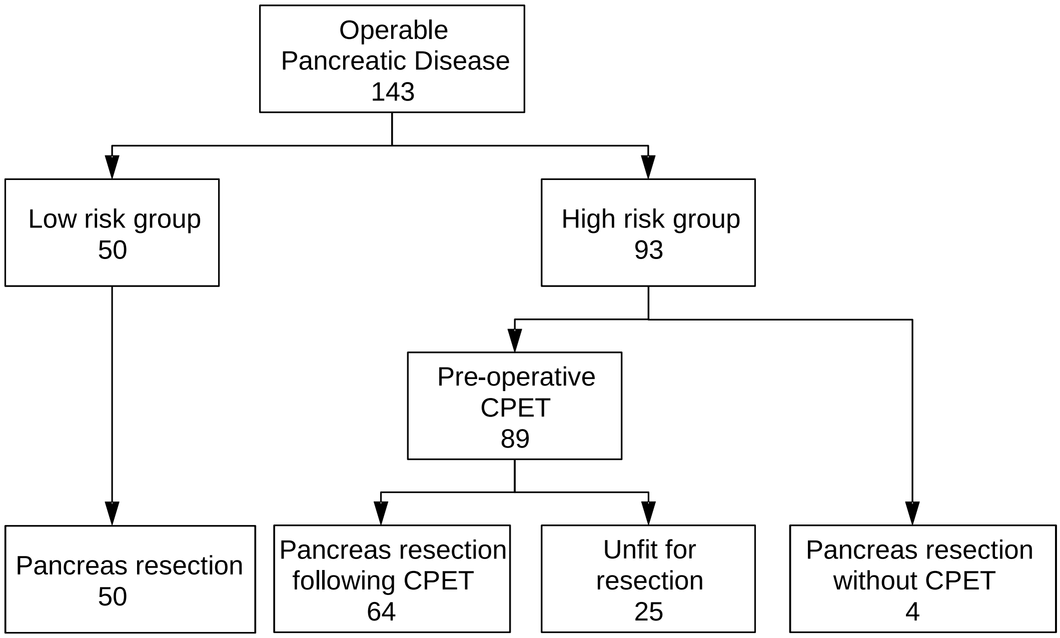


Figure 1: Flow diagram showing patient inclusion. Patients aged 65 years or less without co-morbidity were classified as low risk. The high-risk group comprised patients older than 65 years or younger patients with co-morbidity. Four patients in the high-risk group who deviated from the protocol by undergoing pancreaticoduodenectomy without cardiopulmonary exercise training (CPET) were excluded from the analysis. Following risk assessment with CPET, 25 patients were unfit for surgery, either due to advanced disease (12) or on basis of perioperative risk (13).

Figure 2: ROC curves for $\dot{V}_E/\dot{V}_{CO_2}$ as a predictor of postoperative (30-day) and in-hospital mortality

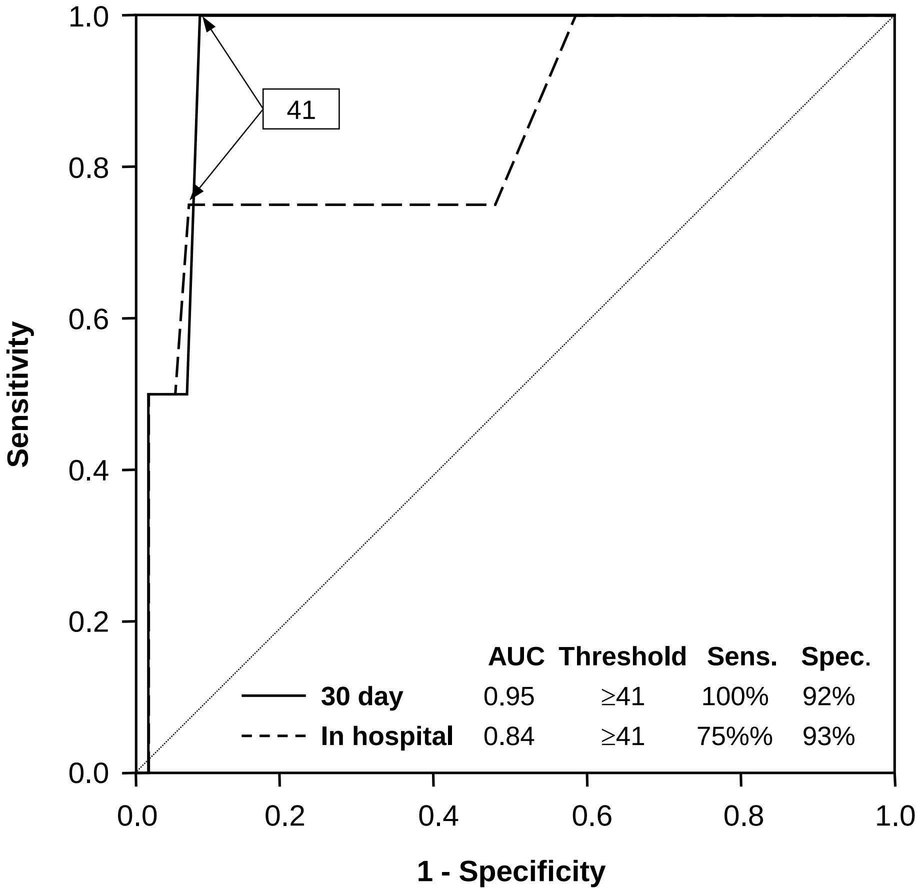
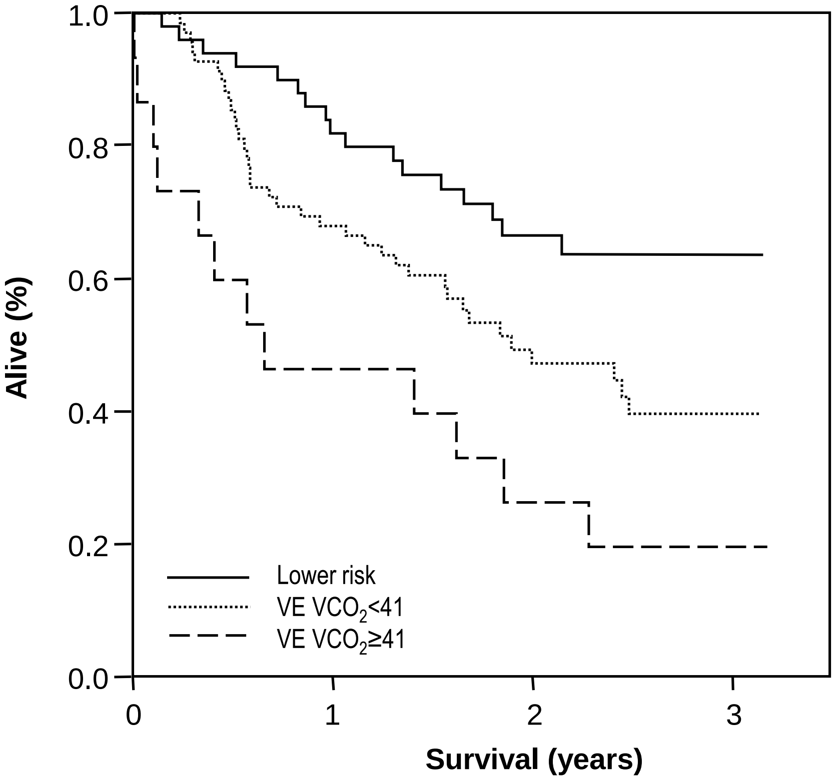


Figure 2: Receiver operating characteristic (ROC) curves for ventilatory equivalence of carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$), demonstrating the optimal cut-off for 30-day and all in-hospital mortality in patients who underwent resection after cardiopulmonary exercise testing. For 30-day mortality the area under the curve (AUC) was 0.95; sensitivity and specificity were 100 and 92 per cent respectively at a cut-off threshold of 41. For in-hospital death the AUC was 0.84; sensitivity and specificity were 75 and 93 per cent respectively at a cut-off threshold of 41.

Figure 3: Survival (Kaplan Meier) of the study cohort



	Number at risk			
Year	0	1	2	3
Low risk	50	41	27	16
High-risk $\dot{V}$ E/$\dot{V}$ CO_2 <41	69	47	23	10
High-risk $\dot{V}$ E/$\dot{V}$ CO_2 ≥41	15	7	4	2

Group		Log rank test
(1)	Low risk	(1) vs. (2), p=0.033
(2)	High-risk $\dot{V}$ E/$\dot{V}$ CO_2 <41	(2) vs. (3), p=0.022
(3)	High-risk $\dot{V}$ E/$\dot{V}$ CO_2 ≥41	(3) vs. (1), p<0.001

Figure 3: Kaplan Meier survival characteristics of all patients groups: the curves displayed are truncated when less than 10% of the cohort remains. The low-risk resection group represented individuals younger than 65 years of age, with no co-morbidity (50). High-risk group included individuals with pre-existing co-morbidity or age 65 years and over. 89 of these high-risk patients underwent preoperative CPET evaluation with 64 proceeding to resection. The remaining 25 patients were deemed inoperable either due to high operative risk (13) or advanced disease (12). CPET was inadequate in 4 patients undergoing resection and one patient with advanced disease. 84 patients providing data for survival analyses.