An investigation of the clinical utility of preoperative cardiopulmonary exercise testing in patients undergoing major pancreatic surgery.

by

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SUBMITTED IN FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF MEDICINE

to

THE UNIVERSITY OF GLASGOW

BASED ON RESEARCH CONDUCTED IN THE
UNIVERSITY DEPARTMENT OF SURGERY,
GLASGOW ROYAL INFIRMARY
AUGUST 2015

Pebbles on the beach.

Dedicated to LGCPVAIA.

SUMMARY OF THESIS

Pancreaticoduodenectomy with or without adjuvant chemotherapy remains the only modality of possible cure in patients with cancer involving the head of the pancreas and the periampullary region. While mortality rates after pancreaticoduodenectomy have improved considerably over the course of the last century, morbidity remains high. Patient selection is of paramount importance in ensuring that major surgery is offered to individuals who will most benefit from a pancreaticoduodenectomy. Moreover, identifying preoperative risk factors provides potential targets for prehabilitation and optimisation of the patient's physiology before undertaking surgery. In addition to this, early identification of patients who are likely to develop postoperative complications allows for better allocation of critical care resources and more aggressive management high risk patients.

Cardiopulmonary exercise testing is becoming an increasingly popular tool in the preoperative risk assessment of the surgical patient. However, very little work has been done to investigate the role of cardiopulmonary exercise testing in predicting complications after pancreaticoduodenectomy. The impact of jaundice, systemic inflammation and other preoperative clinicopathological characteristics on cardiopulmonary exercise physiology has not been studied in detail before in this cohort of patients.

The overall aim of the thesis was to examine the relationships between preoperative clinico-pathological characteristics including cardiopulmonary exercise physiology, obstructive jaundice, body composition and systemic inflammation and complications and the post-surgical systemic inflammatory response in patients undergoing pancreaticoduodenectomy.

Chapter 1 reviews the existing literature on preoperative cardiopulmonary exercise testing, the impact of obstructive jaundice, perioperative systemic inflammation and the importance of body composition in determining outcomes in patients undergoing major surgery with particular reference to pancreatic surgery.

Chapter 2 reports on the role of cardiopulmonary exercise testing in predicting postoperative complications after pancreaticoduodenectomy. The results demonstrate that patients with $\dot{V}_{O_2}$AT less than 10 ml/kg/min are more likely to develop a postoperative pancreatic fistula, stay longer in hospital and less likely to receive adjuvant therapy. These results emphasise the importance of aerobic fitness to recover from the operative stress of major surgery without significant morbidity. Cardiopulmonary exercise testing may prove useful in selecting patients for intensive prehabilitation programmes as well as for other optimisation measures to prepare them for major surgery.

Chapter 3 evaluates the relationship between cardiopulmonary exercise physiology and other clinicopathological characteristics of the patient. A detailed analysis of cardiopulmonary exercise test parameters in jaundiced versus non-jaundiced patients demonstrates that obstructive jaundice does not impair cardiopulmonary exercise physiology. This further supports emerging evidence in contemporary literature that jaundiced patients can proceed directly to surgery without preoperative biliary drainage. The results of this study also show an interesting inverse relationship between body mass index and anaerobic threshold which is analysed in more detail in Chapter 4.

Chapter 4 examines the relationship between preoperative cardiopulmonary exercise physiology and body composition in depth. All parameters measured at cardiopulmonary exercise test are compared against body composition and body mass index. The results of this chapter report that the current method of reporting $\dot{V}_{O_2}$, both at peak exercise and anaerobic threshold, is biased against obese subjects and advises caution in the interpretation of cardiopulmonary exercise test results in patients with a high BMI. This is particularly important as current evidence in literature suggests that postoperative outcomes in obese subjects are comparable to non-obese subjects while cardiopulmonary exercise test results are also abnormally low in this very same cohort of patients.

Chapter 5 analyses the relationship between preoperative clinico-pathological characteristics including systemic inflammation and the magnitude of the postoperative systemic inflammatory response. Obstructive jaundice appears to have an immunosuppressive effect while elevated preoperative CRP and hypoalbuminemia appear to have opposite effects with hypoalbuminemia resulting in a lower response while elevated CRP in the absence of hypoalbuminemia resulted in a greater postoperative systemic inflammatory response.

Chapter 6 evaluates the role of the early postoperative systemic inflammatory response in predicting complications after pancreaticoduodenectomy and aims to establish clinically relevant thresholds for C-Reactive Protein for the prediction of complications. The results of this chapter demonstrate that CRP levels as early as the second postoperative day are associated with complications. While post-operative CRP was useful in the prediction of infective complications, this was the case only in patients who did not develop a post-operative pancreatic fistula. The predictive ability of inflammatory markers for infectious complications was blunted in patients with a pancreatic fistula.

Chapter 7 summarises the findings of this thesis, their place in current literature and future directions. The results of this thesis add to the current knowledge regarding the complex pathophysiological abnormalities in patients undergoing pancreaticoduodenectomy, with specific emphasis on the interaction between cardiopulmonary exercise physiology, obstructive jaundice, systemic inflammation and postoperative outcomes.

The work presented in this thesis lays the foundations for further studies aimed at improving outcomes after pancreaticoduodenectomy through the development of individualised, goal-directed therapies that are initiated well before this morbid yet necessary operation is performed.

Contents

List of Figures

List of Tables

Acknowledgements

I would like to thank the following people, for their help, advice and encouragement:

Professor Donald C McMillan,
University Department of Surgery, Glasgow Royal Infirmary

Professor Paul Horgan,
University Department of Surgery, Glasgow Royal Infirmary

Declaration

I declare that the work presented in this thesis was carried out solely by me, as a clinical research fellow in the University Dept of Surgery, Royal Infirmary, Glasgow, except where indicated below:

Measurement of biochemical and haematological parameters was performed by the hospital laboratory service.

Cardiopulmonary exercise tests were performed by the Department of Respiratory Medicine at the Glasgow Royal Infirmary.

Statistical analysis was performed with the assistance of Prof Donald C McMillan, Academic Unit of Surgery, Royal Infirmary, Glasgow.

In addition, no work referred to in this thesis has been submitted in support of an application for another degree or qualification in this or any other university.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
AT	Anaerobic Threshold
AUC	Area Under Curve (in ROC analysis)
BMI	Body Mass Index
BP	Blood Pressure
CARS	Compensatory anti-inflammatory response syndrome
CECT	Contrast Enhanced Computerised Tomography
CI	Confidence Interval
COPD/COAD	Chronic Obstructive Pulmonary/Airway Disease
CPET	Cardiopulmonary exercise testing
CRP	C-reactive protein
CT	Computerised Tomography
DGE	Delayed Gastric Emptying
ECG	Electrocardiogram
ERCP	Endoscopic retrograde cholangio-pancreatography
ESPAC	European study group for pancreatic cancer
EUS	Endoscopic ultrasound
FEV	Forced Expired Volume
FVC	Forced Vital Capacity
GIMP	GNU Image Manipulation Program
mGPS	Modified Glasgow Prognostic Score
HDU	High Dependency Unit
HR	Heart Rate

HRR	Heart Rate Reserve
Hb	Haemoglobin
ICU	Intensive care unit
IPMN	Intraductal mucinous neoplasm of pancreas
IQR	Inter-quartile range
ISGPF	International study group for pancreatic fistula
ISGPS	International study group for pancreatic surgery
JVP	Jugular venous pulse
LBM	Lean body mass
MRI	Magnetic Resonance Imaging
NET	Neuro-endocrine tumour
NLR	Neutrophil-lymphocyte ratio
PBD	Preoperative Biliary Drainage
PET	Positron-emission tomography
POD	Postoperative Day
POPF	Post-Operative Pancreatic Fistula
POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity
PPH	Post Pancreatectomy Haemorrhage
PPS	POSSUM Physiology Score
RCRI	Revised Cardiac Risk Index
RER	Respiratory Exchange Ratio
ROC	Receiver Operating Characteristics
SIMD	Scottish Index of Multiple Deprivation
SIRS	Sytemic Inflammatory Response Syndrome
US	Ultrasound
WCC	White Cell Count
WHO	World Health Organisation

Chapter 1

Introduction

1.1 Pancreatic neoplasia

1.1.1 Epidemiology of pancreatic cancer

Tumours involving the head of the pancreas and the periampullary region account for a small proportion of gastrointestinal tumours. They may be broadly classified as benign and malignant. Most pancreatic neoplasia are malignant [Li et al. 2004].

Pancreatic ductal adenocarcinoma arising from the ductal epithelium of the exocrine part of the pancreas is the most common cancer of the pancreas. However, the head of the pancreas is anatomically related to several other epithelium lined structures that can also give rise to cancers. These include the distal common bile duct (cholangiocarcinoma), the duodenum (duodenal adenocarcinoma) and the ampulla (ampullary adenocarcinoma). Neuroendocrine tumours (NET) are a collection of a variety of neoplasia that originate from the endocrine portion of the pancreas. Other neoplasia such as intra-ductal papillary neoplasms (IPMN) as well as rare stromal tumours may also occur in this region. Occasionally, chronic pancreatitis may present with features similar to pancreatic cancer and can be morphologically, radiologically and histologically difficult to differentiate from cancer.

Pancreatic cancer is the tenth most common cancer in the UK but the fifth most common cause of cancer death. Only 21% survive beyond the first year and 5-year survival is 3% [CancerResearchUK 2011]. The majority of patients (80-85%) with pancreatic cancer present with inoperable disease [CancerResearchUK 2011; Sener et al. 1999].

In patients with resectable disease, surgery [Sener et al. 1999; Sohn et al. 2000; Geer et al. 1993] followed by adjuvant chemotherapy in selected patients [Neoptolemos et al. 2004; Neoptolemos et al. 2009] offers the only chance of a cure. However, major pancreatic surgery places significant physiological stresses on multiple organ systems. The ability of the cardiac and respiratory systems in

particular, to cope with the increased physiological demand placed by general anaesthesia and major pancreatic surgery plays an important role in determining outcome after surgery.

1.1.2 Aetiology of pancreatic cancer

Several factors have been identified as being associated with an increased risk of pancreatic cancer. The most important risk factor associated with increased incidence of pancreatic cancer is tobacco. Tobacco smoking has been reported to be associated with at least a 2-fold increased risk of pancreatic cancer and this risk increases to 5-fold in patients with over 40 pack-years of smoking [Raimondi et al. 2007; Iodice et al. 2008]. This increased risk persists for at least 10 years after cessation of smoking [Iodice et al. 2008].

The association between alcohol consumption and pancreatic cancer is less clear. While alcohol consumption on its own has not been shown to result in an increased risk of pancreatic cancer, the incidence of pancreatic cancer in heavy drinkers is greater than in the general population. This may be due to the confounding effect of cigarette smoking in this cohort of patients [Jiao et al. 2009; Rohrmann et al. 2009].

Obesity and high caloric intake have also been reported to be associated with increased risk of pancreatic cancer although the underlying mechanisms and the effects of confounding factors are poorly understood [Berrington de Gonzalez et al. 2003; Larsson et al. 2007; Li et al. 2009].

Other possible risk factors include increasing age, diet high in saturated fats, chronic pancreatitis, family history of pancreatic cancer and genetic abnormalities resulting in cancer syndromes [Raimondi et al. 2009; Maisonneuve et al. 2010]. It is of note that some of the important risk factors such as smoking, obesity, poor diet and increasing age may also be associated with other medical comorbidities including cardiorespiratory diseases that may have a significant impact on patient

fitness.

1.1.3 Clinical presentation

The anatomical location of the pancreas, deep within the retroperitoneum, surrounded by numerous vital blood vessels including the coeliac trunk and its branches, the superior mesenteric artery, portal vein and superior mesenteric vein as well as proximity to other viscera such as the stomach, duodenum, transverse colon results in early involvement of these structures even by relatively small tumours [Li et al. 2004]. Moreover, symptoms are often absent in the early stages and when present are too non-specific to help with diagnosis. Obstructive jaundice is the most common presenting symptom and painless, obstructive jaundice in an elderly patient should always raise the suspicion of a neoplastic process in the head of the pancreas or the periampullary region. Other non-specific symptoms include weight loss, early satiety, vomiting, fatigue and pain in the epigastrium or the back. Occasionally, the first presentation of a pancreatic neoplasm may be in the form of an episode of acute pancreatitis.

1.1.4 Diagnosis and staging

Initial assessment includes a thorough history, clinical examination and blood tests including full blood count, renal function tests, liver function tests and tumour markers, especially CA 19-9. However, definitive diagnosis requires cross-sectional imaging in the form of a contrast-enhanced computerised tomogram (CECT) of the abdomen using a pancreas-specific protocol (a modified form of the portal-venous phase). CECT of the pancreas when combined with CT Thorax also provides accurate information on staging of the disease with regards to metastasis and this can be supplemented by further imaging such as Positron Emission Tomography (PET-CT) or contrast-enhanced Magnetic Resonance Imaging (MRI) of the liver in specific cases. CECT-pancreas is also useful for assessing local

resectability with accurate information regarding vascular involvement. Endoscopic Ultrasound (EUS) is used in selected patients to assess vascular involvement and for obtaining tissue samples for histological examination. In jaundiced patients, endoscopic retrograde cholangio pancreatography (ERCP) may play a role in the alleviation of jaundice in patients with cholangitis by placing stents across the obstructed bile duct, obtaining accurate visualisation of the biliary anatomy as well as obtaining brushings from within the bile duct for cytological examination. However, the role routine preoperative biliary drainage is controversial and is discussed in more detail in Section 1.9.4.

1.1.5 Treatment of pancreatic cancer

Pancreaticoduodenectomy (followed by adjuvant chemotherapy in some cancers) offers the only chance of cure in patients with resectable pancreatic cancer who are fit enough to undergo surgery [Li et al. 2004] In patients with unresectable disease or who are not fit to undergo surgery, palliative chemotherapy plays a limited role in prolonging survival. Assessment of resectability of lesions of the head of the pancreas is discussed in the next section while the assessment of physiological fitness and the impact of comorbidity are discussed in detail in section 1.4 on page 15.

1.2 Surgical treatment of pancreatic cancer

Pancreaticoduodenectomy remains a technically challenging and complex surgical procedure. Excision of cancer of the head of the pancreas was first described as a two-stage operation by a German surgeon, Walther Kausch in 1909 at Augusta-Viktoria-Krankenhaus in Berlin-Schöneberg [Kausch 1912]. The operation was further popularised initially as a two-stage procedure by Allen Whipple [Whipple et al. 1935], an American surgeon, before evolving into the current single

stage operation by the 1950s [Whipple 1941; Whipple 1950].

1.2.1 Resectability criteria

Resectable pancreatic cancer is defined as a tumour that does not involve the coeliac axis or the superior mesenteric artery and is not associated with distant metastatic disease [Li et al. 2004]. Tumours involving the portal vein or superior mesenteric vein are considered borderline resectable and can still be resected completely with en-bloc venous resection in selected cases [Fuhrman et al. 1996]. Neoadjuvant therapies such as chemotherapy with or without local radiotherapy [Gillen et al. 2010; Evans et al. 2008] and newer treatment modalities such as electroporation [Bower et al. 2011] and intra-peritoneal chemotherapy [Kamath et al. 2009] are the subject of ongoing clinical research. There is increasing evidence that some of these patients may be able to undergo potentially curative surgery after neo-adjuvant treatment [Gillen et al. 2010].

1.2.2 Operative technique

Pancreaticoduodenectomy is considered one of the most technically challenging operations on the gastrointestinal tract. While the procedure is carried out in a broadly similar fashion in all major centres, there remain some variations in perioperative care as well as some operative steps. The following is a description of the procedure as performed at the West of Scotland Pancreatic Unit.

A comprehensive preoperative evaluation was performed including staging of the disease for local resectability and absence of metastatic disease, assessment of patient fitness and anaesthetic review. All patients with suspected cancer were discussed at the pancreato-biliary multidisciplinary team meeting. Fully informed consent was obtained after discussion regarding treatment options, the details of a pancreaticoduodenectomy, expected perioperative course, potential risks and

follow-up care.

Patients received thrombo-prophylaxis on the night before surgery which was continued until discharge from hospital. General anaesthesia with complete muscle relaxation was used in all patients. Epidural analgesia was used routinely in patients during the early part of the study period while all patients in the later half of the study period received spinal diamorphine. Prophylactic antibiotics were administered at induction. The use of Octreotide, a somatostatin analogue, to reduce the incidence of postoperative pancreatic fistula is still under debate [Halloran et al. 2002; Li et al. 2004] . However, it was routinely used in all patients at our centre. Octreotide was administered intra-operatively (200 micrograms by subcutaneous injection at induction and repeated after 4 hours) and was continued for 5 days postoperatively (200 micrograms by subcutaneous injection administered three times a day).

A roof-top incision was made to enter the abdominal cavity. After assessing the peritoneal cavity and liver for absence of metastatic disease, an early assessment was made for local resectability. This involved complete Kocherisation of the duodenum to assess the retroperitoneum. Both the superior mesenteric artery and coeliac axis were assessed early for tumour involvement ('artery-first' approach) [Weitz et al. 2010]. The gastrocolic omentum was divided to enter the lesser sac. The superior mesenteric vein was identified and a retro-pancreatic tunnel was created between the pancreatic neck and the portal vein. If less than half the circumference of the superior mesenteric vein or portal vein was involved, an en-bloc resection was performed with vein repair at the same time. The hepatoduodenal ligament was dissected after a fundus-first cholecystectomy to isolate the common bile duct which was transected after ascertaining the hepatic artery anatomy. The gastro-duodenal artery was divided leaving a short segment on the common hepatic artery. This was done to facilitate mesenteric angiography and embolisation of this vessel in case of post-pancreatectomy haemorrhage. The stomach (classical Whipple) or the first part of the duodenum (pylorus-preserving pancreaticoduodenectomy) were divided using a stapling device. The pancreatic

neck was transected using Harmonic™ scalpel, diathermy or cold blade depending on surgeon's preference. The jejunum was divided at the first jejunal arcade and the jejunal mesentery was divided using the Harmonic ultrasonic scalpel. The retroportal lamina was divided preserving the superior mesenteric artery.

Reconstruction was performed as follows: either a pancreatico-jejunostomy was fashioned using 4-0 Biosyn™ sutures in a two-layer duct-to-mucosa technique or a pancreatico-gastrostomy was created using 3/0 Biosyn™ sutures placed in a similar manner. Hepatico-jejunostomy was performed using interrupted 4/0 Biosyn™ sutures. Gastro-jejunostomy or duodenojejunostomy (in pylorus-preserving pancreaticoduodenectomy) was performed using continuous 3/0 Polydioxanone (PDS™) sutures in 2-layers. One or two surgical drains were placed and the abdomen was closed after ensuring haemostasis.

1.2.3 Postoperative care

All patients were routinely admitted to the Surgical High Dependency Unit unless intra-operative events necessitated admission to the Intensive Care Unit. A standardised regimen of intravenous fluids, naso-jejunal feeding, mobilisation and physiotherapy was implemented in all patients. Standard physiological parameters including haemodynamic measurements, renal function and arterial blood gases were used to monitor adequate end organ perfusion. All patients received proton pump inhibitors and Octreotide. Patients were discharged to the general surgical ward as early as possible. Amylase content in the drain fluid was measured on the third post-operative day to aid in the diagnosis of post-operative pancreatic fistula. Surgical drains and naso-gastric/naso-jejunal tubes were removed at the surgeon's discretion. Patients were discharged when medically fit.

Histopathology reports were discussed at the multi-disciplinary team meeting for cancer patients and suitable patients were referred for adjuvant chemotherapy.

1.2.4 Complications

The incidence of complications after pancreaticoduodenectomy remains high in spite of a steady decline in postoperative mortality from over 40% in the 1950s to less than 5% in most large volume centres around the world [DeOliveira et al. 2006; Emick et al. 2006; Yeo et al. 1997; Winter et al. 2006; Teh et al. 2009; Gouma et al. 2000]. Accurate definitions and clinical severity grading are useful in comparing outcomes between centres as well as for research, audit and quality improvement purposes. The consensus definitions of the International Study Group for Pancreatic Surgery (ISGPS) and the Clavien-Dindo classification systems were used during the course of the studies reported here.

1.2.4.1 Postoperative pancreatic fistula

Postoperative pancreatic fistula is one of the most dreaded complications after a pancreaticoduodenectomy and can be associated with significant short-term morbidity as well as long-term disability. The reported incidence of postoperative pancreatic fistula varies from 2% to 30% after pancreaticoduodenectomy [Yeo et al. 1997; DeOliveira et al. 2006; Bassi et al. 2005a; Winter et al. 2007; Pratt et al. 2008a]. The variation in reported incidence has been largely due to lack of clear definition of what constituted a postoperative pancreatic fistula. It can be the result of breakdown or poor healing at the pancreatico-jejunostomy/ pancreatico-gastrostomy or may be the result of direct parenchymal leak unrelated to the anastomosis.

It is now generally accepted that 1 in 4 patients will develop a pancreatic fistula as defined by the International Study Group for Pancreatic Fistula (ISGPF) which has published a consensus statement on the definition and grading of postoperative pancreatic fistula [Bassi et al. 2005a]. A postoperative pancreatic fistula is defined as drain output of any measurable quantity after the third postoperative day with amylase content greater than three times the upper limit of the normal serum

Table 1.1: Postoperative pancreatic fistula: ISGPF definition.

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)†	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

Table 1.2: Postpancreatectomy haemorrhage: ISGPS definition.

Grade	A	B	C
Time of onset, location, severity and clinical impact of bleeding	Early, intra- or extraluminal, mild	Early, intra- or extraluminal, severe or Late, intra- or extraluminal, mild	Late, intra- or extraluminal, severe
Clinical condition	Well	Often well/ intermediate, very rarely life-threatening	Life-threatening, severely impaired
Diagnostic consequence	Observation, blood count, ultrasonography and, if necessary, computed tomography	Observation, blood count, ultrasonography, endoscopy, computed tomography, angiography	Angiography, endoscopy, computed tomography
Therapeutic consequence	No	Transfusion of fluid/blood, intermediate care unit (or ICU), therapeutic endoscopy,† embolization, relaparotomy for early PPH	Localization of bleeding, angiography and embolization, (endoscopy†) or relaparotomy, ICU

amylase value at the laboratory used for testing.

Three grades of postoperative pancreatic fistula have been defined based on clinical severity as described in Table 1.1 on page 10. Grade B and C fistulae are considered to be clinically significant as they alter patient management and are often associated with other secondary complications such as intra-abdominal sepsis, post-pancreatectomy haemorrhage or delayed gastric emptying. They may require further intervention (either radiological or operative) or prolonged critical care support.

1.2.4.2 Post-pancreatectomy haemorrhage

Post-pancreatectomy haemorrhage is reported to occur in 1 to 8% of patients undergoing pancreaticoduodenectomy. However, it accounts for 11% to 38% of mortality after pancreaticoduodenectomy [Wente et al. 2007]. Post-pancreatectomy haemorrhage may either be intra-luminal into the gastrointestinal tract or intra-abdominal into the peritoneal/retro-peritoneal space. Post-pancreatectomy haemorrhage may be from a number of potential sources although bleeding from the stump of the gastroduodenal artery is the most common cause. Other potential sources include suture lines at the anastomoses, gastric/duodenal ulcers or diffuse gastritis, pseudoaneurysms of the gastro-duodenal, splenic or rarely the hepatic artery or rarely, haemobilia.

Haemorrhage is often secondary to non-healing of the pancreatico-jejunal anastomosis leading to leakage of amylase-rich pancreatic juices into the retroperitoneum or secondary to intra-abdominal sepsis or bile leak [Tien et al. 2005; Koukoutsis et al. 2006; Choi et al. 2004; Balladur et al. 1996]. This can then lead to erosion of ligated blood vessels, most commonly the stump of the gastro-duodenal artery. Post-pancreatectomy haemorrhage is usually managed with angiographic embolisation of the bleeding vessel and surgical intervention is only rarely required. The grading of severity of post-pancreatectomy haemorrhage as described by the International Study Group of Pancreatic Surgery [Wente et al.

2007] is shown in Table 1.2 on page 10.

1.2.4.3 Clavien-Dindo classification of complications

A number of other adverse events may occur following pancreaticoduodenectomy including cardiopulmonary complications such as myocardial infarction, cardiac arrhythmias, pneumonia and pleural effusions, wound complications such as wound sepsis and dehiscence, intra-abdominal problems including intra-abdominal sepsis, leakage from the hepatico-jejunostomy or the gastro-jejunostomy, infected fluid collections, renal dysfunction, deep vein thrombosis, pulmonary embolism, etc. The Clavien-Dindo system grades the severity of complications based on the impact of the complication on the management of the patient and has been validated in large numbers of surgical patients [Clavien et al. 2009; Dindo et al. 2004]. The classification is summarised in Table 1.3 on page 13. and was used to grade complications in this thesis. Complications of grade 3 or greater are considered clinically significant as they require further procedures either under local or general anaesthesia, single or multiple organ support or result in death. However, grades 1 and 2 are managed with ward-based care including antibiotics, wound management, supplemental enteral or parenteral nutrition and similar interventions.

1.3 Adjuvant and neoadjuvant treatment

While surgery is the primary modality of curative treatment in patients with resectable pancreatic cancer, there is clear evidence that adjuvant chemotherapy improves survival and is now the standard of care for patients with pancreatic ductal adenocarcinoma.

Early randomised trials reported improved survival in patients with inoperable pancreatic cancer [Mallinson et al. 1980] as well as in patients who had undergone

TABLE 1.3: The Clavien-Dindo classification of surgical complications.

Grade	Description
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
	Grade III-a: - intervention not under general anaesthesia
	Grade III-b: - intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)‡ requiring HDU/ICU-management
	Grade IV-a: - single organ dysfunction (including dialysis)
	Grade IV-b: - multi organ dysfunction
Grade V	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

potentially curative surgery [Bakkevold et al. 1993b].

The European Study Group for Pancreatic Cancer (ESPAC) has conducted some of the largest randomised controlled trials of adjuvant chemotherapy and chemoradiotherapy versus observation after potentially curative surgery. They have reported that chemotherapy after surgery prolonged survival while chemoradiotherapy had a harmful effect [Neoptolemos et al. 2001; Neoptolemos et al. 2004; Neoptolemos et al. 2009; Neoptolemos et al. 2010].

The ESPAC-1 trial compared the use of chemotherapy with Fluorouracil and Folinic acid or chemoradiotherapy with 20Gy radiotherapy and 5-Fluorouracil (5-FU) versus observation only in patients who underwent potentially curative surgery for pancreatic ductal adenocarcinoma [Neoptolemos et al. 2004]. The 5-year survival rate in patients who received chemotherapy was 20% while it was 8% in patients who did not receive chemotherapy, demonstrating a clear survival benefit for adjuvant chemotherapy. However, adjuvant chemoradiotherapy resulted in 5-year survival dropping from 20% to 10% and has largely been abandoned in the adjuvant setting. The ESPAC-3 trial compared the efficacy of 5-FU and Folinic acid with Gemcitabine and reported that Gemcitabine was not superior to 5-FU/Folinic acid [Neoptolemos et al. 2010].

Oettle and co-workers reported on the results of a European multi-center, randomised controlled phase 3 trial comparing the results of surgery versus surgery and adjuvant chemotherapy with 6 cycles of gemcitabine in patients with pancreatic ductal adenocarcinoma [Oettle et al. 2007]. The median disease free survival in patient who received gemcitabine chemotherapy was 13.4 months while it was only 6.9 months in the surgery-only group. However, there was no difference in overall survival.

However, 25% to 50% of patients who undergo surgery for pancreatic ductal adenocarcinoma either do not receive or do not complete a full course of adjuvant chemotherapy [Sohn et al. 2000; Neoptolemos et al. 2004; Oettle et al. 2007]. A number of factors have been identified for the non-receipt of adjuvant therapy

including comorbidity, postoperative complications and favourable pathological features [Spitz et al. 1997; Aloia et al. 2007; Oettle et al. 2007; Merchant et al. 2009; Russ et al. 2009].

Increasingly, neo-adjuvant therapies are being used in patients with initially unresectable or 'borderline-resectable' cancers in an attempt to improve resectability. In a meta-analysis of 111 studies, Gillen and co-workers reported that approximately one-third of initially unresectable patients can be expected to have resectable tumours after neo-adjuvant treatment [Gillen et al. 2010]. The authors recommended that such patients should be actively included in neo-adjuvant protocols and re-staged for resection after treatment.

1.4 Preoperative risk stratification

Selection of patients suitable for potentially curative surgery not only depends on the resectability criteria that were discussed in section 1.2.1 but also on physiological fitness [Bilimoria et al. 2007; Sandroussi et al. 2010]. Major pancreatic surgery is associated with significant morbidity. Subjecting patients with poor physiological reserve to a pancreaticoduodenectomy is fraught with risk. High risk patients undergoing surgery are more likely to develop postoperative complications resulting in prolonged hospitalisation and poor quality of life with little difference in survival when compared to palliative treatment only. The risk of post-operative mortality is also increased.

1.4.1 Comorbidity

Comorbidity is defined as the presence of or the effect of other diseases that a patient has in addition to the primary disease of interest. Major pancreatic surgery requires the patient to have adequate reserve to cope not only with the increased

perioperative physiological demand but also with any adverse events that may occur.

The presence of comorbid conditions is associated with increased incidence of adverse outcomes in patients undergoing treatment for pancreatic cancer [Mann et al. 2010]. It can also limit the therapeutic options available due to the associated complications or side effects of surgery or adjuvant treatment [Sandroussi et al. 2010]. Patients with multiple comorbidities are more likely to have higher readmission rates, morbidity and mortality following discharge after pancreaticoduodenectomy [Teh et al. 2009].

DeOliveira and co-workers reported that cardiovascular disease was a risk factor not only for overall morbidity but also for severity of complications after pancreaticoduodenectomy [DeOliveira et al. 2006]. Obesity is known to be associated with greater incidence and severity of postoperative complications [Benns et al. 2009]. However, existing methods of measuring the impact of comorbidity on physiological fitness are limited and do not adequately predict outcomes after major pancreatic surgery [Castro et al. 2009].

1.4.2 Risk stratification

Physiological fitness or reserve may be defined as the ability of the patient's organ systems to respond appropriately and adequately to the stress of surgery. Major surgery has a significant physiological impact on multiple organ systems, especially the cardiorespiratory system. The ability of the cardiorespiratory system as well as other organ systems including renal, gastrointestinal, hepatic, coagulatory and immunological systems to cope with major surgery and its sequelae plays a major role in determining postoperative outcomes. Therefore, accurate assessment of physiological fitness is important in patient selection, individualised risk prediction and consent, preoperative optimisation as well as perioperative management. A thorough clinical history of co-existing illnesses, general examination and review of

patient's medications is followed by more specialist testing to assess fitness. Numerous methods including individual tests and composite scores derived from physiological and biochemical variables have been used for risk assessment.

The Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) is one of the most used scores for risk-prediction in general surgery [Copeland et al. 1991]. It was devised by Copeland and co-workers as a method of predicting risk-adjusted mortality and morbidity rates for comparative audit between different surgical departments [Copeland et al. 1993] and individual surgeons [Copeland et al. 1995]. While some authors have reported it to be useful in predicting postoperative outcomes after pancreatic surgery [Pratt et al. 2008b] others have found that POSSUM was not a good risk prediction model in this group of patients [Khan et al. 2003; Kocher et al. 2005; Tamijmarane et al. 2008; Castro et al. 2009].

The physiology component of the POSSUM score (POSSUM Physiology Score, PPS) which takes into account comorbidities and specific preoperative biochemical parameters was used as an objective static measure of comorbidity in this thesis. The POSSUM Physiology Score has been reported to be associated with preoperative systemic inflammation and cancer-specific survival in patients who underwent potentially curative surgery for colorectal cancer [Richards et al. 2010]. The variables used in the calculation of the POSSUM Physiology Score are shown in Table 1.4 on page 18.

More recently, elevated preoperative systemic inflammation as measured by the modified Glasgow Prognostic Score (mGPS) has been reported to be associated with increased incidence of infective complications after colorectal surgery [Moyes et al. 2009] as well as oesophageal resections [Vashist et al. 2010].

POSSUM and other similar composite scores such as the APACHE II (Acute Physiology and Chronic Health Evaluation II) [Knaus et al. 1985] and Estimation of Physiologic Ability and Surgical Stress (E-PASS) [Haga et al. 1999; Hashimoto et al. 2010] have not found widespread use for risk prediction in pancreatic surgery.

TABLE 1.4: Variables used in the calculation of the POSSUM Physiology Score.

	Score			
Variable	1	2	4	8
Age	<61	61-70	>70	
Cardiac Signs	No failure	Diuretic, digoxin, antianginal, antiHT therapy	Peripheral oedema, warfarin, borderline cardiomegaly	Raised JVP, cardiomegaly
Respiratory	No dyspnoea	Dyspnoea on exertion	Limiting dyspnoea (one flight), moderate COAD	Dyspnoea at rest (rate>30/min), fibrosis or consolidation
ECG	Normal	AF rate 60-90		Other abnorm. rhythm, >4/min ectopics, Q-waves, ST/T-changes
Systolic-BP (mm Hg)	110 - 130	100 - 109 131 - 170	>170, 90 - 99	< 90
Pulse rate	50 - 80	40 - 49 81 -100	101 - 120	<40 > 120
Haemoglobin (g/dl)	13 - 16	11.5 - 12.9 16.1 - 17	10 - 11.4 17.1 - 18	<10 >18
White cell count ($x10^6$/l)	4 - 10	10.1 - 20 3.1 - 4	>20 <3	
Urea (mmol/l)	<7.6	7.6 - 10	10.1 - 15	>15
Sodium (mmol/l)	>135	131 - 135	126 - 130	<126
Potassium (mmol/l)	3.5 - 5	3.2 - 3.4 5.1 - 5.3	2.9 - 3.1 5.4 - 5.9	<2.9 >5.9
Glasgow Coma Scale	15	12 - 14	9 - 11	<9

While these scores are either useful for comparative audit between patient populations or in the case of APACHE II, for monitoring response to therapy in intensive care, they are of limited value when applied to individual patients.

1.4.3 Static versus dynamic testing

Conventional tests of cardiac and respiratory function assess either performance at rest or only one component of the cardiorespiratory system. These tests include electrocardiography, echocardiography, exercise tolerance testing, myocardial perfusion scan, pulmonary function tests including spirometry. However, none of these tests adequately measure the ability of the cardiopulmonary and circulatory systems to deliver oxygen to the tissues at times of increased demand. Patients with sub-clinical cardiopulmonary dysfunction or limitation cannot be identified on these tests alone. It is this group of patients who are most likely to be at greater risk of complications and who will most benefit from targeted prehabilitation. Moreover, composite score such as POSSUM do not provide information on the ability of the patient to cope with physiological stress or on how their risk may be mitigated before surgery. Cardiopulmonary exercise testing overcomes the limitations of the conventional static tests by providing a global assessment of the patient's oxygen delivery mechanisms at times of increased physiological demand.

1.4.4 Pancreas-specific risk factors

In addition to all of the above risk factors, post pancreatectomy complications are significantly associated with factors unique to pancreatic disease. Postoperative pancreatic fistula is one of the most dreaded complications after a pancreaticoduodenectomy and is discussed in more detail in Section 1.2.4.1. Soft pancreas texture, narrow pancreatic duct, pathology that does not obstruct the pancreatic duct such as ampullary or duodenal cancers are independent risk factors for pancreatic fistula [Pratt et al. 2008a]. These organ-specific risk factors are

independent of comorbidity and patient fitness [DeOliveira et al. 2006]. Lin and co-workers reported that in a study of 1891 patients undergoing pancreaticoduodenectomy, only soft pancreatic gland texture and coronary disease were related to postoperative pancreatic fistula on multivariate analysis [Lin et al. 2004].

Several studies have attempted to evaluate various surgical strategies in improving perioperative outcomes after pancreaticoduodenectomy. A prospective, multi-center, randomised controlled trial of 170 patients undergoing pancreaticoduodenectomy did not demonstrate any significant difference between a Whipple's classical pancreaticoduodenectomy and pylorus preserving pancreaticoduodenectomy [Tran et al. 2004]. A Cochrane review in 2008 reported on 7 randomised controlled trials comparing classical pancreaticoduodenectomy with pylorus-preserving pancreaticoduodenectomy and found no difference in morbidity, mortality or survival [Diener et al. 2008].

A prospective randomised trial comparing pancreaticogastrostomy versus pancreaticojejunostomy in patients undergoing pancreaticoduodenectomy reported that there was no difference in the incidence of overall complications or pancreatic fistula. However, patients who had a pancreaticogastrostomy had a significantly lower rate of biliary fistula, postoperative collections, delayed gastric emptying as well as lower incidence of multiple surgical complications [Bassi et al. 2005b]. A meta-analysis of eleven studies (one randomised trial, 2 non-randomised prospective trials and eight observational studies) appeared to show improved outcomes in patients undergoing pancreaticogastrostomy rather than a pancreaticojejunostomy [McKay et al. 2006]. However, an earlier trial by Yeo and co-workers failed to demonstrate any difference in outcomes between either technique [Yeo et al. 1995].

In spite of a lack of any clear evidence of efficacy, octreotide continues to be used in many centres including ours to reduce the incidence of postoperative pancreatic fistula. While some early randomised trials reported the benefits of octreotide in

decreasing the risk of postoperative pancreatic fistula [Montorsi et al. 1995; Nakatsuka et al. 2000], other more recent trials have not reproduced these results [Lowy et al. 1997; Yeo et al. 2000; Kollmar et al. 2008].

Surgical drains after pancreaticoduodenectomy have been a subject of considerable debate. A prospective randomised controlled trial of 179 patients in 2001 reported that intra-abdominal drains placed at the time of surgery did not reduce the incidence of complications [Conlon et al. 2001].

Two randomised trials comparing early versus delayed drain removal in patients with low risk of pancreatic fistula after pancreaticoduodenectomy reported that early drain removal was associated with lower incidence of pancreatic fistula, abdominal complications and pulmonary complications [Kawai et al. 2006; Bassi et al. 2010].

However, these pancreas-specific risk factors are not modifiable before surgery, have been studied extensively before and are not the subject of this thesis.

1.5 Cardiopulmonary exercise testing

1.5.1 Origins of preoperative cardiopulmonary exercise testing

The idea of measuring $\dot{V}_{O_2}$ (oxygen consumption) and v$\dot{V}_{CO_2}$ (expired carbon-dioxide) as a measure of cardiopulmonary response to exercise was described in the early twentieth century. In 1924, Hill and co-workers reported on adaptations made to an existing apparatus to allow measurement of oxygen consumption during exercise [Hill et al. 1924]. Their method involved the subject running while connected to a large bag slung on their back to collect expired gases. The subjects then returned to the laboratory where they were connected to a fairly large apparatus involving several more large bags and other equipment that filled

the most part of a large room. But the premise of their method remains unchanged to this date; to examine the response of the cardiopulmonary system to exercise. Such methods were refined by other physiologists to reduce the chance of errors and to devise more practical methods suitable for medical use [KATZ LN et al. 1934; Sutton et al. 1940].

One of the earliest attempts to apply these dynamic tests in surgical patients was reported by Starr and co-workers in 1945 [Starr et al. 1945]. They tried to devise a test that could assess respiratory function and oxygen utilisation in surgical patients before, immediately after and a week after surgery. They reported on the difficulties in obtaining reproducible results but suggested that a slow return to baseline of heart rate, respiratory rate and oxygen utilisation after surgery could identify patients who are slow to recover.

However, cardiopulmonary exercise testing in its current form where breath-by-breath analysis of gas exchange is combined with real-time electrocardiography during incremental exercise was devised and popularised by Karlman Wasserman and his team of physiologists. Wassermann and his team reported on the ventilatory response to exercise and how it may be used to identify cardiorespiratory disease in 1964 [Naimark et al. 1964]. The pioneering work on the detection of anaerobic threshold was also done by his team and applied in the assessment of patients with cardiac disease [Wasserman et al. 1964; Wasserman 1967; Wasserma.k et al. 1973].

The use of cardiopulmonary exercise testing as part of preoperative assessment was first reported by Older and co-workers. They conducted a prospective study of 187 patients over the age of 60 undergoing major abdominal surgery [Older et al. 1993]. All patients underwent a symptom-limited exercise test on a cycle ergometer with real-time 12-lead ECG monitoring. The average $\dot{V}_{O_2}$ across all patients was 12.4 ml/min/kg. There were a total of 11 deaths related to cardiovascular causes (5.9%) and 3 deaths due to non-cardiovascular causes. They reported that 10 out of the 11 deaths due to cardiovascular causes occurred in patients with

$\dot{V}_{O_2}AT < 11$ml/kg/min (n=55). Only one patient in the group with $\dot{V}_{O_2}AT \geq 11$ml/kg/min (n=132) died of cardiovascular complications (18% vs 0.8%, p<0.001). Eight out of the 10 patients in the low $\dot{V}_{O_2}$AT group who died also had evidence of myocardial ischaemia (p<0.01).

1.5.2 Cardiopulmonary exercise test methodology

FIGURE 1.1: ZAN-600 Cycle Erogmeter and CPET suite.
(Image from www.nspirehealth.com)

Cardiopulmonary exercise tests were performed in the Department of Respiratory Medicine at the Glasgow Royal Infirmary using the ZAN-600 CPET suite (nSpire Health, Longmont, CO 80501, USA). All tests were performed by specialised respiratory physiologists. Suitable equipment for cardiopulmonary resuscitation were available in the department in case of unexpected problems. The department was situated within the main hospital premises and therefore was easily accessible to the hospital cardiac arrest team. All patients were fully informed of the steps involved in the procedure, the reasons for performing the test as well as the risks involved.

Spirometry was performed in all patients prior to cardiopulmonary exercise testing. Capillary blood gases were measured in all patients after the test. The gas and flow analysis equipment were calibrated prior to every test. An electronically braked cycle ergometer was used to increase resistance to pedalling in preset increments. A tight-fitting face mask was placed on the patient covering the nose and the mouth. Breath-by-breath gas analysis and 12-lead electrocardiography were displayed in real-time to the investigator allowing measurement of several cardiac and respiratory parameters as they changed during exercise.

The test started with an initial 3-minute rest period to allow measurement of baseline parameters. This was followed by an incremental work-load test that involved the patient pedalling at approximately 60 revolutions per minute while the resistance to pedalling was gradually increased in preset increments. The test was terminated when patients reached volitional fatigue (maximal exercise tolerance), significant ischaemic changes on ECG or for other safety reasons.

The oxygen consumption at this point (considered 'peak' exercise capacity) is called $\dot{V}_{O_2}$Peak. This is different from $\dot{V}_{O_2}$Max which is identified by the plateauing of the increasing $\dot{V}_{O_2}$ when the physiological limits of oxygen consumption are met in an individual. $\dot{V}_{O_2}$Max is only observed in very fit individuals or well-trained athletes. This seldom happens in surgical patients and $\dot{V}_{O_2}$Peak is used as a surrogate for $\dot{V}_{O_2}$Max.

The list of parameters measured is provided in Tables 1.5 and 1.6 on page 29. A detailed description of these parameters is provided in Section 1.6.

1.5.3 Measuring the anaerobic threshold

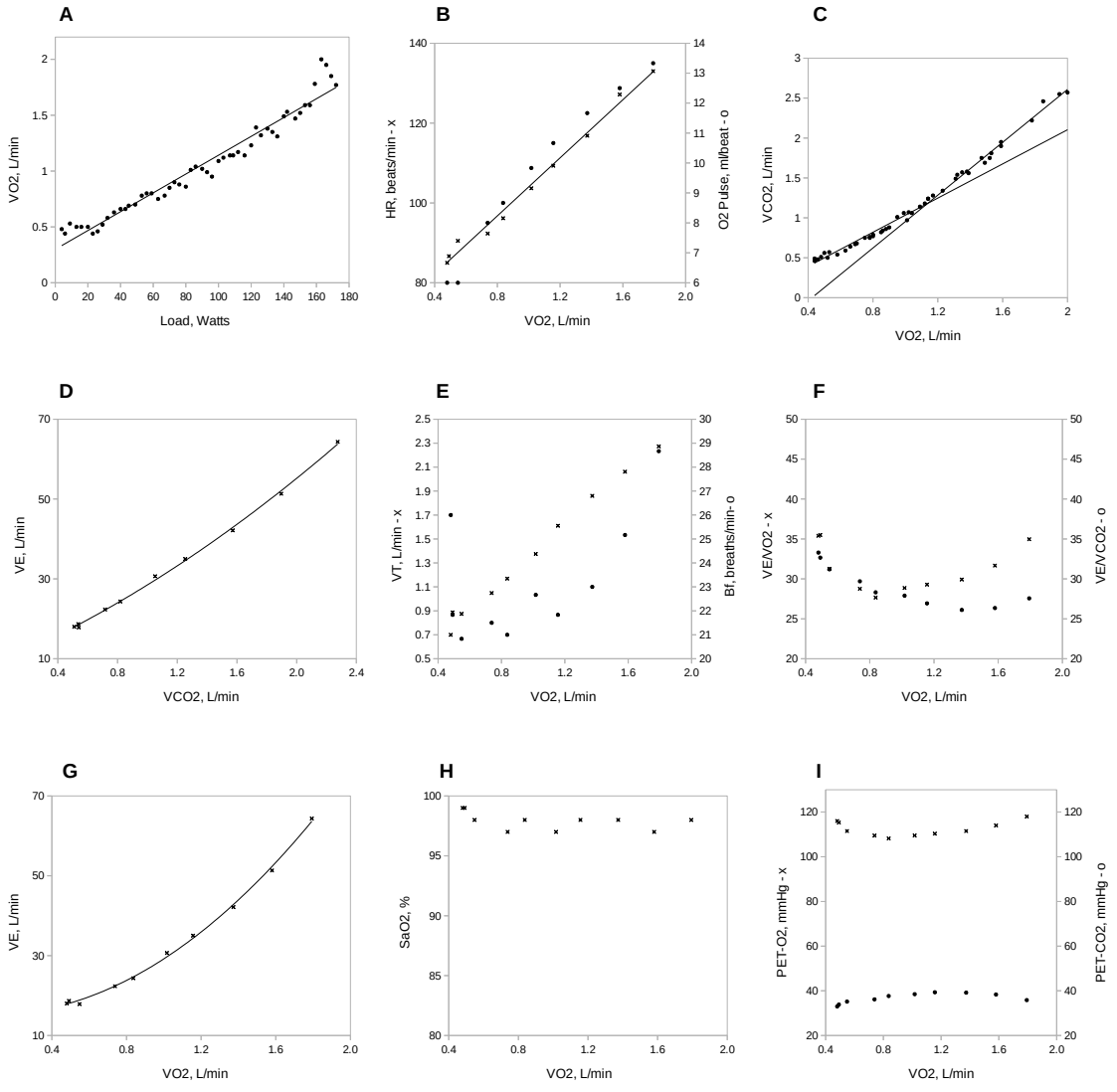


FIGURE 1.2: 9-panel view of trending parameters during cardiopulmonary exercise.

The anaerobic threshold (variously described as the lactate threshold or ventilatory threshold) is the point during exercise when oxygen demand by exercising skeletal muscle outstrips supply. Therefore, muscle tissues use anaerobic respiration to supplement aerobic respiration to continue generation of ATP. The resulting

metabolic lactic acidosis is almost immediately compensated by the bicarbonate buffer as below:

$$H^+ + HCO3^- \Longleftrightarrow H_2CO_3 \Longleftrightarrow H_2O + CO_2 \tag{1.1}$$

The resulting excess CO_2 is exhaled and is one of many parameters measured during cardiopulmonary exercise testing. This transition from aerobic to anaerobic respiration may be determined using the V-slope method [Sue et al. 1988] or the ventilatory equivalents method [Beaver et al. 1986]. Most centres, like ours, use both methods supplemented by information from a variety of other parameters to enable accurate determination of the anaerobic threshold. This approach is also recommended by the American Thoracic Society/American College of Chest Physicians Statement on cardiopulmonary exercise testing ["ATS/ACCP Statement on Cardiopulmonary Exercise Testing" 2003].

The software presents a standard 9-panel view of trending plots of various parameters measured during incremental exercise. All of these trends are taken into consideration rather than any one particular parameter value in determining the overall outcome of the test. A sample 9-panel view derived from parameters belonging to one of the patients studied is shown in Figure 1.2. The data used to generate these plots is included in Appendix C.

1.5.3.1 V-slope method

During aerobic phase of exercise, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ share a linear relationship as shown in the left half of Figure 1.3 on page 27. However, as anaerobic respiration starts to supplement aerobic respiration, $\dot{V}_{CO_2}$ increases disproportionate to $\dot{V}_{O_2}$ as a direct result of the respiratory buffer described in equation 1.1 on page 26. This results in a distinct difference in the slope of the relationship between $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during aerobic exercise (Line A) versus during anaerobic exercise (Line B). The point at which the two slopes intersect is the anaerobic threshold and the $\dot{V}_{O_2}$ at this point

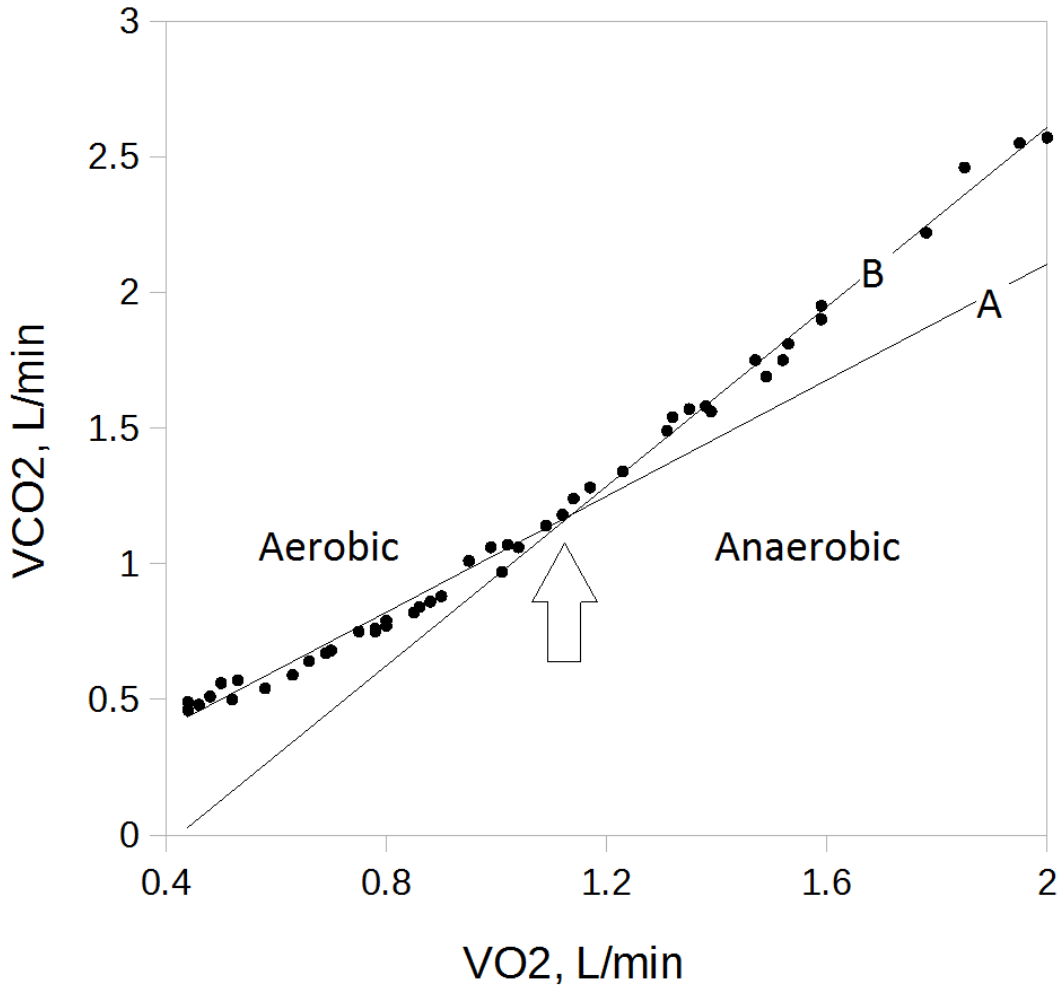


FIGURE 1.3: Determination of $\dot{V}_{O_2}$AT by the V-slope method.

in exercise is commonly referred to as the anaerobic threshold or $\dot{V}_{O_2}$AT.

1.5.3.2 Ventilatory equivalents method

The ventilatory equivalents method of determining $\dot{V}_{O_2}$AT involves plotting $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ against time, exercise load or $\dot{V}_{O_2}$. The point at which $\dot{V}_E/\dot{V}_{O_2}$ increases while $\dot{V}_E/\dot{V}_{CO_2}$ stays the same or decreases is the anaerobic threshold and this can be seen in Fig. 1.2F. Most respiratory physiologists including those at our centre use both methods as well as other trends during exercise to determine the anaerobic threshold as well as its validity.

1.6 Description of CPET parameters

1.6.1 Exercise load

The most common form of cardiopulmonary exercise testing for clinical use involves a cycle ergometer with steadily increasing resistance delivered through electric braking. This allows accurate measurement of work load in Watts. The relationship between $\dot{V}_{O_2}$ and work rate is usually linear and the slope of this relationship is independent of sex, age or height. An abnormality in this relationship is usually due to cardiopulmonary or circulatory causes.

1.6.2 Minute ventilation, $\dot{V}_E$

Minute ventilation or respiratory minute volume ($\dot{V}_E$) is the volume of air that is inhaled/expired in a minute.

$$\dot{V}_E = \dot{V}_T \times Bf \tag{1.2}$$

where $\dot{V}_T$ = Tidal Volume and Bf = Breathing Frequency.

Increasing $\dot{V}_E$ is one of the main mechanisms involved in increasing oxygen delivery during exercise. It is also an important factor in clearing CO_2 from the blood.

1.6.3 Oxygen Uptake, $\dot{V}_{O_2}$

$\dot{V}_{O_2}$ or oxygen uptake is measured breath-by-breath using digital analysis of the inspired and expired gases. This is then averaged, usually over time, to smooth-out any significant breath-by-breath variation. $\dot{V}_{O_2}$ increases with increasing work load and is influenced by several factors that have a role in the transport and utilisation of oxygen. These may be broadly classified as cardiac, pulmonary, circulatory and tissue factors. Some of the factors are encompassed in the following formula for

Table 1.5: Parameters measured at spirometry.

Parameter	Units	Description
FVC	litres	Forced Vital Capacity
FEV1	litres	Forced Expiratory Volume in 1 second
FEV1/FVC	%	Tiffeneau-Pinelli index

Table 1.6: Common parameters measured at cardiopulmonary exercise testing.

Parameter	Units	Description
Load	Watts	Exercise Workload
$\dot{V}_E$	litres/min	Ventilatory Equivalent
Vt	litres	Tidal volume
$\dot{V}_{O_2}$	litres/min	Absolute Oxygen uptake/consumption
$\dot{V}_{O_2}$/kg	ml//kg/min	Corrected Oxygen uptake/consumption
$\dot{V}_E/\dot{V}_{O_2}$		Ventilatory Equivalent for O_2
$\dot{V}_{CO_2}$	litres/min	Carbon-dioxide output
$\dot{V}_E/\dot{V}_{CO_2}$		Ventilatory Equivalent for CO_2
RER		Respiratory Exchange Ratio
PET_{O_2}	mmHg	End Tidal O_2
PET_{CO_2}	mmHg	End Tidal CO_2
O_2Pulse	ml/beat	Oxygen pulse
HR	beats/min	Heart Rate
B_f	resps/min	Breathing Frequency

$\dot{V}_{O_2}$.

$$\dot{V}_{O_2} = CaO_2 \times Cardiac\ Output \tag{1.3}$$

where CaO_2 is O_2 content per ml of blood and is defined by,

$$CaO_2 = Haemoglobin \times 1.34 \times SaO_2 \tag{1.4}$$

and cardiac output, the primary cardiac factor that influences $\dot{V}_{O_2}$, is:

$$Cardiac\ Output = Stroke\ Volume \times Heart\ Rate \tag{1.5}$$

Stroke volume is in turn influenced by ventricular function and end-diastolic volumes. The heart rate response to exercise is discussed in section 1.6.8 on page 32.

Pulmonary gas exchange plays an important role in the oxygenation of blood and removal of CO_2 and is influenced by numerous factors, the detailed discussion of which is beyond the scope of this chapter. However, ventilation, pulmonary blood flow, gas-exchange across the alveolar membrane and ventilation-perfusion mismatches (V/Q mismatch) all play an important role in determining the response of the lungs to exercise.

The quality of the peripheral circulation, both anatomical and its physiologic response to exercise which involves redistribution of blood flow to exercising muscle, has an important role in increasing availability of oxygen. The oxygen carrying capacity of blood determined by haemoglobin concentration, its saturation and the O_2 dissociation curve as well as the ability of tissues to extract and utilise oxygen are equally important factors that influence $\dot{V}_{O_2}$.

1.6.4 Oxygen pulse, O_2Pulse

O_2Pulse is defined as the oxygen uptake per heart beat.

$$O_2Pulse = \frac{\dot{V}_{O_2}}{Heart\ rate} \tag{1.6}$$

While some authors have suggested that oxygen pulse may be a surrogate for stroke volume others disagree. The clinical application of oxygen pulse in surgical patients remains unclear.

1.6.5 Respiratory Exchange Ratio, RER

The ratio of $\dot{V}_{CO_2}/\dot{V}_{O_2}$ is called the Respiratory Exchange Ratio. An RER greater that 1.0 may be caused either by lactic acidosis or due to hyperventilation. The RER is also a marker of the fuel being used for metabolism with RER less than 1.0 indicating mixed fuel source in the form of carbohydrate and fat while an RER of 1.0 or greater indicates a primarily carbohydrate source.

1.6.6 Ventilatory Equivalent for O_2 and CO_2, $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$

The changes in $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ during exercise provide valuable information regarding the ventilatory response to exercise. Both $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ tend to decrease initially during exercise. However, as the anaerobic threshold is passed, $\dot{V}_E/\dot{V}_{O_2}$ starts increasing before $\dot{V}_E/\dot{V}_{CO_2}$. This change in direction is yet another method to confirm the anaerobic threshold. $\dot{V}_E/\dot{V}_{CO_2}$ eventually starts increasing as respiratory compensation of metabolic acidosis results in increased $\dot{V}_E$.

1.6.7 End-tidal O_2 and CO_2, $P_{ET_{O_2}}$, PET_{CO_2}

PET_{O_2} and PET_{CO_2} are the partial pressures of O_2 and CO_2 at the end of an exhaled breath and are closely related to P_aO_2 and P_aCO_2 respectively. PET_{CO_2} is dependent on pulmonary gas-exchange which is in turn influenced by the right ventricular output, pulmonary blood flow and alveolar gas exchange. The changes in $P_{ET_{O_2}}$ and PET_{CO_2} during exercise help identify ventilation-perfusion mismatch as well as hyperventilation.

1.6.8 Heart Rate, HR

The heart rate response during exercise in healthy individuals is a linear function of $\dot{V}_{O_2}$ increasing linearly with increasing work load and increasing $\dot{V}_{O_2}$. The difference between the predicted peak heart rate and the observed peak heart rate is called the Heart Rate Reserve or HRR. Failure to achieve the predicted peak heart rate or a wide HRR may be due to cardiac disease or due to medication used to treat cardiovascular disorders such as beta-blockers or calcium-channel blockers. This information in conjunction with 12-lead ECG evidence of ischaemia provides undeniable evidence of primary cardiac dysfunction.

1.6.9 Breathing frequency, B_f

In healthy individuals, breathing frequency is one of the most important respiratory responses to exercise in order to increase oxygen uptake. However, a variety of respiratory disorders including chronic obstructive pulmonary disease or restrictive disorders such as interstitial lung disease can impair this response. Morbidly obese patients may also have additional restrictions on respiratory response due to their body habitus. On the other hand, hyperventilation in an otherwise healthy patient may make interpretation of the results difficult although

the analysis of trends in other parameters such as $P_{ET_{O_2}}$ and PET_{CO_2} aids in the diagnosis of hyperventilation versus true respiratory problems.

1.7 Role of CPET in preoperative assessment

1.7.1 General Surgery

Several studies over the past 2 decades have established the value of cardiopulmonary exercise testing in patients, especially elderly, undergoing major abdominal surgery. Older and co-workers conducted a prospective study of 187 patients over the age of 60 undergoing major abdominal surgery. All patients underwent a symptom-limited exercise test on a cycle ergometer with real-time 12-lead ECG monitoring. The average $\dot{V}_{O_2}$ across all patients was 12.4 ml/min/kg. There were a total of 11 deaths related to cardiovascular causes (5.9%) and 3 deaths due to non-cardiovascular causes. They reported that 10 out of the 11 deaths due to cardiovascular causes occurred in patients with $\dot{V}_{O_2}AT < 11$ml/kg/min (n=55) while only one patient in the group with $\dot{V}_{O_2}AT \geq 11$ml/kg/min (n=132) died of cardiovascular complications (18% vs 0.8%, $p < 0.001$). Eight out of the 10 patients in the low $\dot{V}_{O_2}$AT group who died also had evidence of myocardial ischaemia ($p < 0.01$) [Older et al. 1993].

In a later, larger prospective study of 548 patients who underwent major abdominal surgery including colorectal and abdominal aneurysm surgery, they used a risk stratification system that combined $\dot{V}_{O_2}AT < 11$ml/kg/min, $\dot{V}_E/\dot{V}_{CO_2} > 35$ and evidence of myocardial ischaemia during exercise. High risk patients ($\dot{V}_{O_2}AT < 11$ml/kg/min, n=153) were admitted to intensive care after surgery and had a mortality due to cardiovascular causes of 4.6%. Moderate risk group ($\dot{V}_{O_2}AT > 11$ml/kg/min and either $\dot{V}_E/\dot{V}_{CO_2} > 35$ or evidence of myocardial ischaemia, n=115) was managed in the high dependency unit after surgery and had a cardiovascular mortality of 1.7%. Low risk patients (with none of the risk

factors mentioned above, n=280) were managed on the general surgical ward with no cardiovascular mortality [Older et al. 1999]. Subsequent literature reviews by Older and co-workers have emphasised the value of cardiopulmonary exercise testing in risk assessment as well as optimising perioperative care in the high-risk surgical patient [Older et al. 2000; Older et al. 2004; Older et al. 2005].

These findings have since been replicated in several other studies although the threshold value of $\dot{V}_{O_2}$AT as well as the inclusion of other CPET parameters to attribute risk differ in these studies. Hightower and co-workers studied 32 patients over the age of 18 undergoing a variety of major elective abdominal surgery. In this heterogeneous cohort, they reported that the percent predicted anaerobic threshold achieved $< 75\%$, heart rate at the anaerobic threshold and the heart rate response from rest to anaerobic threshold were all independently associated with postoperative morbidity. While it is difficult to extrapolate results from this small heterogeneous cohort to the general surgical population, it would appear that other cardiopulmonary exercise test parameters may have a role in predicting risk in these patients [Hightower et al. 2010].

Snowden and co-workers reported in a study of 171 patients of who 123 underwent surgery, that $\dot{V}_{O_2}AT < 10.1$ ml/kg/min was associated with not only cardiovascular complications but also with other complications including pulmonary, renal, gastrointestinal, infective and haematological complications. One of the strengths of this study was the fact that clinicians were blinded to the results of preoperative cardiopulmonary exercise testing, thus avoiding management bias. They also included other cardiopulmonary exercise test parameters such as $\dot{V}_{O_2}$Peak and $\dot{V}_E/\dot{V}_{CO_2}$ at the anaerobic threshold in addition to $\dot{V}_{O_2}$AT in their analysis and showed that $\dot{V}_{O_2}$AT was more predictive of postoperative morbidity than POSSUM derived morbidity, cardiac risk scoring index or a validated activity questionnaire. However, this study also included a heterogeneous cohort of diseases including vascular, pancreatic and hepatobiliary disorders and sarcomas [Snowden et al. 2010].

In a study of 847 patients undergoing elective abdominal surgery for colorectal disease, bladder or renal cancer, Wilson and co-workers found that $\dot{V}_{O_2}AT < 11$ ml/kg/min in the absence of documented cardiac risk factors was associated with a relative risk of mortality of 10.0 (95% CI 1.7-61.9) [Wilson et al. 2010]. This emphasises the value of cardiopulmonary exercise testing in diagnosing sub-clinical or previously undiagnosed (and untreated) cardiovascular and respiratory disease. Moreover, 90-day survival was also better in patients with better aerobic capacity ($\dot{V}_{O_2}AT > 11$ ml/kg/min and $\dot{V}_E/\dot{V}_{CO_2} < 34$) and in patients without ischaemic heart disease. This appears to suggest that aerobic capacity influenced not only postoperative outcomes but also medium-term survival after patients left hospital.

1.7.2 Oesophago-gastric and bariatric surgery

In a retrospective study involving 91 patients who underwent curative oesophagectomy with 3-field lymphadenectomy via a right thoracotomy for squamous cell carcinoma of the thoracic oesophagus between 1991 and 1995, Nagamatsu and co-workers reported that $\dot{V}_{O_2}max/m^2 < 800$ml/min/m^2 predicted cardiopulmonary complications [Nagamatsu et al. 2001]. They also reported that $\dot{V}_{O_2}AT/m^2$ and routine spirometry did not predict cardiopulmonary complications. They recommended that in patients with $\dot{V}_{O_2}.max/m^2 < 800$ml/min/m^2, surgical treatment be modified either into a 2-stage procedure or a trans-hiatal procedure avoiding a thoracotomy where possible.

Cardiopulmonary exercise testing has also been useful in predicting short-term complications after bariatric surgery. McCullough and co-workers defined a composite primary outcome measure that included myocardial infarction, unstable angina, deep vein thrombosis, pulmonary embolism, renal failure, stroke and death and applied this in a cohort of 109 consecutive patients who underwent Roux-en-Y gastric bypass surgery. This composite adverse outcome was more likely in patients with high BMI (>45) and low $\dot{V}_{O_2}$Peak (<15.9 ml/kg/min). Patients in whom both these risk factors were absent did not develop postoperative complications.

They also observed a significant negative relationship between BMI and $\dot{V}_{O_2}$ ($p<0.0001$) and age($p<0.0001$). Poor aerobic capacity was also associated with the presence of diabetes and hypertension suggesting further evidence of the metabolic cost of obesity in these patients [McCullough 2006].

However, Forshaw and co-workers reported that cardiopulmonary exercise testing was of limited use in predicting complications after oesophagectomy [Forshaw et al. 2008]. They studied 78 patients undergoing either trans-hiatal (n=39) or trans-thoracic (n=39) oesophagectomy. They evaluated several thresholds for both $\dot{V}_{O_2}$Peak and $\dot{V}_{O_2}$AT and found no useful correlation with cardiopulmonary complications, non-cardiopulmonary complications, length of stay in critical care or in hospital. While $\dot{V}_{O_2}$Peak was significantly lower in patients who developed postoperative cardiopulmonary complications, receiver-operator characteristics (ROC) analysis did not identify a clinically useful threshold that would stratify patients into different risk groups. Post-oesophagectomy complications such as anastomotic leak or sepsis often happen within the thorax and are not necessarily due to cardiopulmonary dysfunction. They postulated that this may have reduced the predictive ability of preoperative cardiopulmonary exercise testing. Older and Hall, the pioneers of cardiopulmonary exercise testing in surgical patients, also raise this issue in their letter to the authors of the above study [Hall et al. 2009].

1.7.3 Vascular surgery

The earliest report of the application of cardiopulmonary exercise test in elective abdominal aortic aneurysm surgery was by Nugent and co-workers in 1998. They reported on cardiopulmonary exercise testing using a treadmill in 36 patients undergoing elective abdominal aortic aneurysm surgery. They found no difference in the $\dot{V}_{O_2}$Peak in patients who developed complications versus those who did not (18.6 vs 2.8 ml/kg/min, $p>0.05$). However, they reported that in the 4 patients who were denied surgery as they were deemed medically unfit, $\dot{V}_{O_2}$Peak was less than 20 ml/kg/min. However, this threshold did not discriminate patients who

developed complications and the authors concluded that cardiopulmonary exercise testing should not be used on its own to guide clinical management of these patients [Nugent et al. 1998].

However, cardiopulmonary exercise testing has been reported to predict 2-year survival in patients undergoing elective aortic aneurysm surgery. Carlisle and Swart reported that a Revised Cardiac Risk Index (RCRI) score > 1 in combination with a $\dot{V}_E/\dot{V}_{CO_2} > 42$ was associated with a 2-year survival rate of 55% while the 2-year survival rate was 97% if neither risk factor was present. $\dot{V}_{O_2}$AT was not a predictor of survival in multi-variate analysis in this study [Carlisle et al. 2007].

While studies have reported that repeated cardiopulmonary exercise testing provides reproducible results in patients with abdominal aortic aneurysm and preoperative exercise regimens are safe and effective at increasing aerobic capacity in patients awaiting surgery, there is no published literature on the association between cardiopulmonary exercise testing and postoperative complications in patients undergoing vascular surgery. There are several papers post 2010.

1.7.4 Liver transplantation

Peak $\dot{V}_{O_2} < 60\%$ predicted and $\dot{V}_{O_2}AT < 50\%$ predicted have been reported to be associated with increased 100-day mortality in patients undergoing liver transplantation. In patients with cirrhosis awaiting hepatic transplantation, reduced aerobic capacity may not only be due to primary cardiorespiratory insufficiency but may also be due to the secondary effects of hepatic dysfunction itself. These include cirrhotic cardiomyopathy, hepatopulmonary syndrome and decreased peripheral oxygen utilisation due to cirrhotic myopathy [Epstein et al. 2004]. This is further supported by the fact that patients who undergo liver transplantation have been shown to have improved aerobic capacity a year after surgery [Iscar et al. 2009]. However, there is very little other evidence of the application of cardiopulmonary exercise testing in patients undergoing major

hepato-pancreato-biliary surgery or liver transplantation.

1.7.5 Thoracic surgery

The role of cardiopulmonary exercise testing in patient undergoing non-cardiac thoracic surgery has been well established for over a decade. In a recent meta-analysis of 14 studies, Benzo and co-workers reported on 955 patients who underwent cardiopulmonary exercise tests as part of their preoperative work-up before lung resection for cancer. $\dot{V}_{O_2}$Max (ml/kg/min), $\dot{V}_{O_2}$Max (% predicted), maximum exercise load achieved (Watts) and FEV1 (% predicted) were all significantly higher in patients who recovered with no postoperative complications. They also found that the mean $\dot{V}_{O_2}$Max in patients who did not develop complications was approximately 20 ml/kg/min and the mean $\dot{V}_{O_2}$Max in patients who developed complications was 15 ml/kg/min across all studies. This would suggest that cardiopulmonary exercise testing can offer clinically useful thresholds across different populations that can be used to risk stratify patients [Benzo et al. 2007].

The 2^{nd} edition of the American College of Chest Physicians' Evidence-Based Clinical Practice Guidelines for the 'Physiologic evaluation of the patient with lung cancer being considered for resectional surgery' recommends that patients with a low $\dot{V}_{O_2}$Max (<10 ml/kg/min) or with low $\dot{V}_{O_2}$Max (<15 ml/kg/min) associated with other risk factors on spirometry and cardiopulmonary exercise testing should be counselled about non-operative treatment options and non-standard surgery as the risk of perioperative death and cardiopulmonary complications was very high. The 1C grading of this recommendation not only represents the observational nature of most of the studies it is based on but also that such observational evidence is sufficiently consistent [Benzo et al. 2007] to make a strong recommendation [Colice et al. 2007].

1.8 Systemic inflammation and outcome

The host inflammatory response to cancer, comorbidity and surgical trauma has been known to influence both short-term and long-term outcomes after major cancer surgery [McMillan et al. 2001; Read et al. 2004; Roxburgh et al. 2010]. Moreover, postoperative complications have been reported to be associated with poorer oncologic outcomes and cancer-specific survival in patients undergoing potentially curative surgery for cancer [McArdle et al. 2005]. The complex interactions between pro-inflammatory cytokines and anti-inflammatory cytokines at different phases during the perioperative period further impact upon the incidence of complications as well as survival.

1.8.1 Measuring systemic inflammation

Numerous tests are available to not only measure systemic inflammation in general but also to quantify the various components of the inflammatory response. The most commonly employed measures in the clinical setting are the serum levels of C-reactive protein (CRP)and the differential leucocyte count.

One of the earliest reports on the use of CRP to predict cancer-specific survival was by McMillan and co-workers in 1995 when they reported that an elevated CRP 4 months after curative resection for colorectal cancer was associated with earlier recurrence [McMillan et al. 1995]. The modified Glasgow Prognostic Score (mGPS) [Elahi et al. 2004] is based on a combination of C-reactive protein and serum albumin and is outlined in Table 1.7. Since its introduction, mGPS has been validated in over a hundred studies looking at several thousand patients with a wide-range of cancers and an increasing score is associated with poorer long-term survival in patients with operable as well as inoperable cancers.

TABLE 1.7: The modified Glasgow Prognostic Score

mGPS	CRP (mg/l)	Albumin (g/l)
0	≤ 10	≥ 35
1	> 10	≥ 35
2	> 10	< 35

1.8.2 Inflammation and long-term survival

Elevated preoperative systemic inflammation is associated with poorer survival in patients undergoing potentially curative surgery for pancreatic cancer [Jamieson et al. 2005; Clark et al. 2007; Bhatti et al. 2010] as well as in patients with advanced pancreatic cancer [Glen et al. 2006]. Patients with pancreatic ductal adenocarcinoma undergoing potentially curative resection survived for a median of 21.5 months if their CRP was $\leq$ 10 mg/dl a month after their surgery but only 8.4 months if their CRP remained persistently elevated over 10 mg/dl approximately a month after their operation [Jamieson et al. 2005].

Similar findings have been reported in cancers involving other organs using both the modified Glasgow Prognostic Score and other scores such as the neutrophil-lymphocyte ratio (NLR). The modified Glasgow Prognostic Score was associated with survival independent of tumour stage in patients with colorectal [McMillan et al. 2007; Leitch et al. 2007], breast [Al Murri et al. 2006; Al Murri et al. 2007], lung [Forrest et al. 2004], oesophago-gastric [Crumley et al. 2006], bladder [Hilmy et al. 2006] and prostate [McArdle et al. 2006] cancer.

1.8.3 Inflammation and postoperative complications

Abnormalities of systemic inflammatory processes present as a continuum that starts in the preoperative phase possibly as a consequence of underlying comorbid illnesses, presence of cancer, an abnormality of the immune system or due to a combination of all of these factors. Surgical trauma in such 'primed' patients

results in a cascade of events that trigger several inflammatory pathways that have now shown to have a direct impact not only on the incidence of postoperative complications but also on cancer recurrence and long-term survival.

1.8.3.1 Preoperative systemic inflammation

Elevated levels of interleukin-6, α-1 antitrypsin and CRP and decreased levels of albumin and prealbumin before surgery have been reported to be associated with a more exaggerated postoperative systemic inflammatory response and infectious complications after major abdominal surgery [Haupt et al. 1997].

Preoperative systemic inflammation has been reported to be associated with infectious complications in patients undergoing potentially curative surgery for colorectal cancer [Moyes et al. 2009]. In a study of 455 patients, Moyes and co-workers reported that an elevated preoperative modified Glasgow Prognostic Score (1.7) was associated with increased incidence of infectious complications in patients undergoing elective as well emergency colorectal cancer surgery. They postulated that several mechanisms may play a role including dysregulation of cell-mediated immunity, impaired T-lymphocyte response, disorders in the complement pathway and possibly due to loss of lean tissue and protein as a consequence of systemic inflammation. Preoperative mGPS was also associated with increased incidence of postoperative complications in patients undergoing oesophageal resection for cancer [Vashist et al. 2010].

1.8.3.2 Postoperative systemic inflammation

An exaggerated and persistent systemic inflammatory response in the early postoperative period is associated with an increased incidence of complications. One of the earliest studies comparing several 'acute-phase proteins' and their role in predicting postoperative complications reported that in patients who developed surgical inflammatory complications, CRP remained significantly elevated after the

third postoperative day [Fischer et al. 1976]. But, other acute-phase proteins such as ceruloplasmin and α-1 antitrypsin where not useful in monitoring the postoperative course.

Further studies have established the value of monitoring trends in serum CRP levels in predicting complications after both elective and emergency surgery [Mustard et al. 1987].

In a study of 383 patients undergoing elective rectal cancer surgery with primary anastomosis, Welsch and co-workers reported that persistently raised CRP level over 140 mg/L after the third/fourth postoperative day was associated with anastomotic leak [Welsch et al. 2007]. They also reported in a separate study of 688 patients undergoing pancreatic resection with pancreatico-jejunostomy for neoplastic disease or chronic pancreatitis, that persistently elevated CRP greater than 140 mg/L on the fourth postoperative day was associated with increased incidence of complications.

Similar findings have been reported after elective colorectal surgery [Ortega-Deballon et al. 2010; Woeste et al. 2010], oesophago-gastric surgery [Dutta et al. 2011], spinal surgery [Meyer et al. 1995; Mok et al. 2008], neurosurgery [Al-Jabi et al. 2010], simultaneous pancreas-kidney transplantation [Wullstein et al. 2004], stem-cell transplantation [McNeer et al. 2010] and paediatric surgery[Laporta Baez et al. 2011].

While CRP level between the third and fifth postoperative day has been reported to be most predictive of complications, the clinical signs do not become apparent until later in the postoperative course, often after the fifth day. This has led some authors to postulate that elevated CRP may in fact be due to an abnormally modulated postoperative inflammatory response resulting in an initial exaggerated systemic inflammatory response syndrome (SIRS) followed by a compensatory anti-inflammatory response syndrome (CARS).

1.8.3.3 Compensatory anti-inflammatory response

The compensatory anti-inflammatory response syndrome (CARS) is characterised by several features including reduction in lymphocyte numbers by apoptosis, decreased responsiveness of monocytes to cytokines, reduced number of human leukocyte antigen presenting receptors on monocytes, expression of cytokines that suppress Tumour Necrosis Factor (TNF) and clonal anergy.

In their seminal work on the role of SIRS and CARS in the pathogenesis of sepsis and organ dysfunction, Bone and co-workers described a state of *'immunologic dissonance'* where a *'pre-primed'* immune system may result in an inappropriate, out-of-balance massive pro-inflammatory response which is followed by a proportionately large compensatory anti-inflammatory response that leaves the patient immunosuppressed and prone to further organ dysfunction, infections and death [Bone et al. 1997; Bone 1996]. It is very likely that similar mechanisms are involved in surgical patients except that the initial stressor in this case is surgical trauma rather than a bacterial infection as in sepsis.

This form of *'immunoparalysis'* was first described in patients after major trauma with tissue damage [Abraham et al. 1985; Bandyopadhyay et al. 2007] or after haemorrhage on its own without associated tissue trauma [Stephan et al. 1987]. In a detailed review of the mechanisms underlying the compensatory anti-inflammatory response syndrome, Ward and co-workers describe SIRS and CARS to be mirror images suggesting that a disproportionately high SIRS is followed by a period of immunosuppression that leaves the patient prone to further complications [Ward et al. 2008].

Patients who developed infectious complications after major cancer surgery had higher levels of interleukin-10 (IL-10), an anti-inflammatory cytokine and marker of the compensatory anti-inflammatory process [Mokart et al. 2002]. Major surgery and the associated surgical trauma is associated with elevated levels of IL-10 which in turn is associated with increase in lymphocyte apoptosis [Delogu et al. 2001],

reduced monocyte expression of HLA-DR antigens [Klava et al. 1997] and a blunted response to endotoxins [Ogata et al. 2000; Kawasaki et al. 2001]. , all considered to be key features of a compensatory anti-inflammatory response syndrome.

Yamaguchi and co-workers compared the levels of pro- and anti-inflammatory cytokines in patients undergoing cholecystectomy versus patients undergoing trans-thoracic oesophagectomy. They reported that the initial inflammatory phase was followed by an immunosuppressive phase that started around the seventh postoperative day in patients undergoing oesophagectomy. However, patient who underwent an open cholecystectomy did not experience this immunosuppressive phase, leading them to postulate that the degree of immunosuppression was directly proportional to the initial pro-inflammatory process. This in turn was related to the greater degree of surgical stress and tissue trauma that occurs with a trans-thoracic oesophagectomy. They also reported that in a randomised cohort that received an infusion of lymphokine-activated natural killer cells immediately after oesophagectomy, there was a trend towards fewer infectious complications [Yamaguchi et al. 2006].

1.8.4 Postoperative complications and long-term survival

There has been increasing evidence that postoperative complications not only have an impact on the short-term outcomes but also on long-term survival after major cancer surgery. A recent meta-analysis of 21 studies including 21,902 patients found that anastomotic leakage was associated with earlier local recurrence after rectal cancer surgery, a trend towards early local recurrence in other colonic cancer surgery and a significant reduction in overall survival [Mirnezami et al. 2011]. The reviewers suggested that several mechanisms may be involved in early recurrence including local spillage of cancer cells from within the bowel lumen. However, the role of the local inflammatory processes that occur as a consequence of anastomotic leakage may play a more important role. This inflammatory process with the attendant milieu of pro-inflammatory cytokines and angiogenic factors

may provide a fertile ground for tumour seeding and proliferation.

McArdle and co-workers reported in their study of 2235 patients undergoing colorectal cancer surgery that anastomotic leakage was associated with early local recurrence and reduced survival. They suggested that the 'double-hit' of surgery followed by anastomotic leak may result in an inflammatory response that is greater and more protracted and that this may explain the poorer cancer outcomes in these patients [McArdle et al. 2005].

In a study of 207 patients undergoing surgery for Duke's B colorectal cancer, Katoh and co-workers reported that anastomotic leakage and persistently elevated CRP two weeks after surgery were independent risk factors for systemic recurrence, further emphasising the important role of inflammation in cancer recurrence as a consequence of complications [Katoh et al. 2011]. Wound infections and intra-abdominal infections have also been associated with poorer survival in colorectal cancer patients [Nespoli et al. 2006]. Similar findings have been reported after curative surgery for advanced gastric cancer with patients who develop an anastomotic leak surviving for 30.5 months while patients who did not have a leak survived for a median of 96.2 months ($p<0.001$) [Yoo et al. 2011].

Patients who develop severe postoperative complications after pancreaticoduodenectomy for cancer had significantly shortened survival in a study involving 428 patients (16.5 vs. 12.4 months, $p=0.002$) and this was independent of other recognised risk factors such as tumour grade and lymph node status [Kamphues et al. 2012]. Similar finding were reported by Raut and co-workers in their study of 360 patients who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma [Raut et al. 2007]. and by Kang and co-workers in their report on 103 patients undergoing R0 resections for cancer of the pancreatic head [Kang et al. 2009].

These reports in conjunction with the studies on preoperative inflammation, sepsis, SIRS and CARS emphasise the important role of perioperative systemic inflammation as a causative factor in postoperative complications and the impact

of the 'second-hit' of postoperative complications on long-term survival after curative cancer surgery.

1.9 The jaundiced patient

Obstructive jaundice is the most common presenting symptom in patients with pancreatic cancer involving the head of the pancreas and the periampullary region due to the anatomical location of the distal bile duct. Obstructive jaundice is known to have a wide range of effects on multiple organ systems including the cardiovascular system, immune system, coagulation cascade, as well as hepatic function.

Until recently, major surgery in jaundiced patients has been considered to be more prone to adverse postoperative events. While this concept has been recently challenged, surgeons remain wary of operating on the severely jaundiced patient. In fact, pancreaticoduodenectomy was initially described by Whipple as a two-stage procedure where the first stage involved a biliary bypass aimed at relieving obstructive jaundice before the second stage of resection was carried out [Whipple et al. 1935].

1.9.1 Impact of jaundice on cardiovascular physiology

The detrimental effects of jaundice on the heart and the circulatory system has been recognised for over 150 years now. King and co-workers reported that the intravenous injection of bile caused bradycardia, hypotension and eventually death in dogs [King et al. 1909]. The concept of a *'jaundiced heart'* was fist put forth by Green and co-workers in 1986 [Green et al. 1986]. They performed choledocho-caval anastomoses in 5 dogs and studied cardiac function before and 2 weeks after this procedure. They reported that 'cholemia' was associated with impaired left ventricular function and blunted response to sympathomimetic

agents. Similar findings have been reported by other authors in animal studies [Binah et al. 1985; Bomzon et al. 1986].

The role of atrial natriuretic peptide (ANP) has also been investigated. Obstructive jaundice was associated with increased levels of ANP as a result of increased cardiac endocrine activity in bile duct ligated rabbits [Pereira et al. 1994]. Similar findings have been reported in humans as well [Gallardo et al. 1998; Martínez-Ródenas et al. 1998].

Moreover, relief of obstructive jaundice is associated with improvement in endocrine markers of fluid homeostasis as well as cardiac function [Padillo et al. 2001b; Gallardo et al. 1998]. Padillo and co-workers reported that there was a negative correlation between serum bilirubin levels and left ventricular systolic work and this was associated with elevated ANP and BNP (brain natriuretic peptide) levels. However, both ANP and BNP levels decreased after biliary drainage and there was a significant improvement in cardiac output, cardiac index, systolic volume and left ventricular systolic work [Padillo et al. 2001b].

More recently, TNFα levels have been reported to mediate cardiac dysfunction in animal studies and treatment with an anti-TNFα agent restored myocardial contractility [Yang et al. 2010]. Obstructive jaundice was also associated with systemic hypotension and there is increasing evidence that some of this may be mediated by bile acid receptors on the vascular tree [Green et al. 1995; Lefebvre et al. 2009]. Bile acids can cause vasodilation by decreasing arterial tone and this may partly explain some of the haemodynamic adverse events that occur after surgery in jaundiced patients.

1.9.2 Impact of jaundice on renal function

Several studies have reported that obstructive jaundice is associated with significant abnormalities in fluid homeostasis. Obstructive jaundice is associated with reduction in the interstitial volume as well as the circulating plasma volume

[Sitges-Serra et al. 1992; Padillo et al. 1999]. In a study of 63 patients with obstructive jaundice, Padillo and co-workers reported that severity of jaundice, age of patient and reduced urinary sodium excretion were independently related to postoperative renal dysfunction. They also reported that these variables were related to abnormalities in the levels of hormones responsible for sodium and water homeostasis including atrial natriuretic peptide [Padillo et al. 2005a]. Endotoxemia consequent to lack of bile salts in the gut has also been postulated as a possible mechanism for renal dysfunction in patients with severe jaundice [Bailey 1976]. Jaundice is one of the leading causes of acute renal failure in tertiary-care hospitals [Liano et al. 1996].

While expansion of the intravascular volume and avoiding dehydration by the judicious use of intravenous fluids has been recommended in avoiding renal dysfunction in jaundiced patients [Parks et al. 1994], others have reported that relief of obstructive jaundice by restoring bile flow improves renal function independent of fluid therapy [Padillo et al. 2005b]. Perioperative fluid management, avoidance of hypotension and sepsis control is important in the prevention of renal failure in jaundiced patients.

1.9.3 Impact of jaundice on the immune system

Obstructive jaundice is associated with a wide range of deleterious effects on the immune system. The absence of bile in the gut increases the proliferation of gram negative bacteria. The absence of bile in the gut of bile duct ligated mice was associated with intestinal bacterial overgrowth and bacterial translocation [Deitch et al. 1990].

This in association with increased bacterial translocation, increased gut mucosal permeability and reduced endotoxin elimination by Kuppfer cells within the liver can predispose the jaundiced patient to septic complications [Nehéz et al. 2002]. Intestinal permeability is normalised within a few weeks of restoring biliary

drainage.

Increased serum bilirubin and bile salts directly affect lymphocyte function as well as the response to pro-inflammatory cytokines [Scott-Conner et al. 1994]. Bile salts in higher than normal concentrations also induce apoptosis in hepatocytes. Biliary obstruction is also associated with significant alterations in hepatic macro and micro-circulation. This in turn can affect the phagocyte clearing function of the liver. Obstructive jaundice is also associated with abnormal cytokine homeostasis predisposing the patient to impaired wound healing, sepsis and increased risk of peri-operative mortality. For instance, concentrations of TNF-α and IL-6 are significantly elevated in jaundiced patients while the concentrations of IL-1 and IL-2 are decreased [Padillo et al. 2001a].

However, unlike in animal models, relief of obstructive jaundice by endoscopic biliary drainage is not associated with an improvement in immune function. On the contrary, it results in colonisation of the biliary tree by gut bacteria in nearly all instances of biliary stenting [Kimmings et al. 2000].

1.9.4 Role of preoperative biliary drainage

The increased incidence of adverse events after surgery in patients with obstructive jaundice resulted in routine preoperative biliary drainage becoming the standard practice in patients undergoing major pancreatic surgery. Moreover, while significant improvements in perioperative care has resulted in reduction in postoperative mortality, morbidity rates have remained high. Obstructive jaundice has provided a potential target for preoperative optimisation in an attempt to improve postoperative outcomes.

Early observational studies of small cohorts of patients challenged this paradigm reporting that surgery in jaundiced patients was not associated with greater risk and in fact preoperative biliary drainage increased hospitalisation costs [Snellen et al. 1985; Bakkevold et al. 1993a; Pitt et al. 1985]. Hatfield and co-workers

reported in one of the earliest randomised controlled trial comparing pancreaticoduodenectomy with or without preoperative biliary drainage in 57 patients that there was no difference in postoperative complications or mortality but increased biliary drainage associated complications [Hatfield et al. 1982].

Similar findings have been reported by other authors as well [Lai et al. 1994; Lai et al. 1994; Jagannath et al. 2005]. However, some authors have recommended that expandable metal stents were associated with fewer stent related complications than plastic stents and may be considered in jaundiced patients where surgery is delayed for other reasons [Wasan et al. 2005; Mullen et al. 2005].

A recent randomised controlled trial of 202 patients reported that there was no significant difference in post-operative morbidity (47% vs 37%, p=0.14), mortality or length of stay between the group that underwent preoperative biliary drainage and the group that underwent early surgery [Gaag et al. 2010]. There was a high incidence of procedure related complications in the drainage group (46%). The high incidence of procedure related complications, the use of plastic stents, the 25% failure to drain at first attempt and exclusion of patients with serum bilirubin $>$ 250 μmol/L were significant limitations of the study. However, the study does show that early surgery in the jaundiced patient with serum bilirubin $<$ 250 μmol/L is safe and not associated with increased morbidity or mortality as was once feared.

Mezhir and co-workers also reported a high (23%) stent related complication rate in their retrospective study of 340 patients where 96% of 201 patients in the biliary drainage group had plastic stents placed. However, they also reported a greater incidence of wound infections (7% vs 20%, p=0.01) and intra-abdominal abscesses (3% vs 12%, p=0.03) in patients who underwent biliary drainage [Mezhir et al. 2009].

The paucity of good quality evidence on the role of preoperative biliary drainage before pancreatic resection [Wang et al. 2008] and the limitations in our understanding of the complex pathophysiological effects of jaundice on multiple organ systems has resulted in persistent wide variation in the perioperative

management of jaundiced patients across different centres.

The historical indication was biliary drainage was to minimise the haemodynamic and renal adverse effects of obstructive jaundice. The above mentioned studies show that surgery in the jaundiced patient is safe and feasible. However, the effect of obstructive jaundice on cardiopulmonary exercise testing in patients with pancreatic disease has not been reported previously. Chapter 3 is an investigation into the relationship between obstructive jaundice and preoperative cardiopulmonary exercise testing.

1.10 Body composition, obesity and outcomes

1.10.1 Body mass index

The Body Mass Index (BMI) is a measure of a person's weight relative to their height and corresponds well with their body composition, especially with the proportion that is body fat. It is the most widely accepted measure of body composition, especially of body fat in spite of criticisms that it may not apply to all populations.

BMI was first devised by Adolphe Quetelet and was formerly known as the Quetelet index [Eknoyan 2008]. Quetelet was a Belgian sociologist and mathematician who played a major role in the application of statistical methods to the social sciences. In his attempts to describe the characteristics of 'normal man', Quetelet found that weight increased nearly as the square of the height except at times of growth spurts in the new born and during puberty [Quetelet et al. 1842]. The calculation of body mass index is simple and as follows:

$$Body\ Mass\ Index = \frac{Weight\ in\ Kilograms}{(Height\ in\ Metres)^2} \tag{1.7}$$

The World Health Organisation uses thresholds to categorise adult populations based on body mass index. These thresholds are independent of age, gender and race. However, there has been increasing criticism of these thresholds and the World Health Organisation is undertaking a further review to assess the validity of these thresholds in different populations. For instance, there is increasing evidence in Asians, the risk of diabetes and cardiovascular disease is greater at BMI levels lower than the current WHO cut-off for being overweight. Nonetheless, the thresholds shown in Table 1.8 are currently in universal use and have been used in this thesis.

Table 1.8: The WHO classification of Body Mass Index

BMI	Category
Below 18.5	Underweight
18.5 – 24.9	Normal range
25.0 – 29.9	Overweight or Pre-obesity
30.0 - 34.9	Obesity class 1
35.0 - 39.9	Obesity class 2
Above 40	Obesity class 3

Obesity is an increasing problem in all developed nations with the proportion of obese patients undergoing surgery increasing every year. Among the European Member States, the proportion of adults considered overweight or obese varied in 2008 between 37.0% and 56.7% for women and 51.0% and 69.3% for men. The United Kingdom had the highest proportion of obese women (23.9%) and the second highest proportion of obese men (22.1%). A greater proportion of men than women were obese and there was a marked increase in BMI with increasing age. There was also an inverse relationship between education level and incidence of obesity [WHO 2000].

Obesity, especially morbid obesity, is associated with a wide range of secondary disease states such as ischaemic heart disease, diabetes mellitus, hypertension and increased incidence of cancers.

Obesity presents unique problems in surgical patients for several reasons. Surgery and anaesthesia in the morbidly obese patients can be technically challenging. The comorbidities associated with morbid obesity require evaluation and management in the perioperative period. Postoperative physiotherapy and mobilisation require particular attention in the morbidly obese patients.

1.10.2 Obesity and postoperative complications

The impact of obesity on the rate of postoperative complications remains controversial. It has been a commonly held belief that obese patients had greater incidence of complications. Some of the adverse outcomes such as wound complications and respiratory dysfunction where considered to be the direct result of the increased body mass index while other complications where related to the associated comorbidities such as cardiovascular disease, obstructive sleep apnoea or diabetes mellitus.

Several studies have reported increased incidence of postoperative complications in obese patients after cardiac, transplant, urologic and gynaecological surgery [Prem et al. 1965; Holley et al. 1990; Fasol et al. 1992; Gruberg et al. 2002; Lee et al. 2004]. Visceral obesity rather than body mass index has been reported to be associated with greater incidence of wound complications, overall complication rate and prolonged hospital stay in patients undergoing laparascopic sigmoid colectomy for cancer [Tsujinaka et al. 2008].

However, in a prospective, multi-institutional, risk-adjusted cohort study of 2258 patients including 699 patients who underwent pancreatectomy for cancer, Mullen and co-workers reported that obesity on its own was not a predictor of major postoperative complications or mortality. However, obesity was an independent predictor of minor complications including wound infections. However, they noted that underweight patients had a five-fold increased risk of postoperative mortality [Mullen et al. 2008].

Dindo and co-workers studied the impact of obesity on postoperative outcomes in a prospective study of 6336 patients undergoing elective general surgery. They reported that obesity was not an independent risk factor for morbidity or mortality. There was no difference in the median operating time, blood transfusions or length of hospital stay between obese and non-obese patients. The type and severity of complications were similar between obese and non-obese patients [Dindo et al. 2003]. In a more recent prospective, multi-institutional, risk-adjusted cohort study of 118,707 patients undergoing non-bariatric general surgery, Mullen and co-workers reported that the risk of mortality was lowest in the overweight (BMI 25 - 30) and moderately obese (BMI 30 - 35) patients and highest in the underweight and morbidly obese patients. This appears to confirm the existence of an 'obesity paradox' in surgical patients [Mullen et al. 2009].

In a study of 356 consecutive patients undergoing pancreaticoduodenectomy at the Memorial Sloan-Kettering Cancer Center between 2000 and 2005, House and co-workers used preoperative cross-sectional imaging of the abdomen (computer tomography and/or magnetic resonance imaging) to measure a variety of indices of body composition including abdominal wall fat thickness, hip girdle fat thickness, retro-renal visceral fat and pancreatic duct diameter [House et al. 2008]. The incidence of wound infection was greater in obese patients with the risk increasing linearly with BMI. But, BMI was not associated with any other complications. They also reported that the thickness of retro-renal fat, a surrogate for visceral adipose tissue, was a significant risk factor for pancreatic fistula as well as wound infection. However, there was no correlation between complications and abdominal wall thickness or hip girdle fat.

The importance of visceral fat in the incidence and severity of postoperative complications is further emphasised by the finding that excess visceral fat is associated with the the occurrence of pancreatic fistula after radical total gastrectomy for gastric cancer. Benns and co-workers reported greater blood loss and increased incidence and severity of postoperative complications in obese patients undergoing surgery compared to non-obese patients. However, there was

no difference in operative time or length of stay in hospital [Benns et al. 2009].

On the contrary, other authors have reported that obesity is not associated with increased complications after pancreatic surgery. Khan and co-workers reported that while obesity was associated with increased incidence of intra-operative bleeding, there was no increase in complications [Khan et al. 2010]. Length of stay in hospital, overall morbidity and in-hospital mortality were not affected by BMI after pancreaticoduodenectomy [Tsai et al. 2010] while neither BMI nor intra-abdominal visceral fat affected postoperative outcomes in another study of patients undergoing pancreaticoduodenectomy [Balentine et al. 2011].

In a recent meta-analysis of 17 studies, including some of those discussed above, Ramsey and co-workers reported that BMI was not associated with length of hospital stay, in-hospital mortality or survival after pancreaticoduodenectomy for cancer. Obesity was associated with postoperative pancreatic fistula. However, the authors concluded that with aggressive perioperative care, postoperative morbidity in obese patients could be mitigated. They also noted several limitations to making meaningful comparisons between studies due to the lack of clear definitions for complications after pancreaticoduodenectomy [Ramsey et al. 2011].

1.10.3 Obesity and cancer survival

The effect of obesity and adipose tissue content on cancer-specific survival in patients with pancreatic cancer is not entirely clear. In a study involving 586 patients who underwent pancreaticoduodenectomy for pancreatic adenocarcinoma, Khan and co-workers reported that obesity was not associated with overall or disease-free survival [Khan et al. 2010]. These are similar to the findings reported by Benns and co-workers who found no difference in overall survival in 306 patients undergoing resections for pancreatic adenocarcinoma [Benns et al. 2009]. Obesity during early adulthood is associated with increased risk of pancreatic cancer while obesity at an older age is associated with reduced overall survival in both resected

and unresected patients [Li et al. 2009]. Morbidly obese patients (BMI > 35) were found to be at 12-fold increased risk of lymph node metastases and associated decreased survival [Fleming et al. 2009].

Tsai and co-workers reported that while obese patients had similar tumour characteristics to non-obese patients and comparable perioperative outcomes, long-term survival was better in obese subjects [Tsai et al. 2010]. This study of 795 patients undergoing potentially curative surgery for pancreatic adenocarcinoma at the Johns Hopkins Medical Institutions in the United States is in contrast to other similar studies. The role of obesity on long-term survival after pancreaticoduodenectomy for pancreatic cancer is less clear with more recent studies suggesting that there was no link between body mass index and survival [Dandona et al. 2011; Benns et al. 2009].

While sarcopenia or loss of skeletal muscle mass is associated with poor outcome in patients with pancreatic cancer, the association between adipose tissue (especially, visceral fat) and long-term outcomes is less clear. Sarcopenic-obesity where concurrent sarcopenia and high fat mass are present is associated with significantly worse survival when compared to sarcopenia or high adiposity on their own [Tan et al. 2009]. It is clear that body mass index on its own is a poor predictor of outcome and body composition changes over time play a more important role in determining cancer survival. While obesity appears to have a protective role in a wide range of chronic disease states [Kalantar-Zadeh et al. 2007; Amundson et al. 2010; Myers et al. 2011], sarcopenic-obesity has a negative impact on survival [Tan et al. 2009].

1.10.4 Measuring body composition

While it is possible to estimate the amount of most tissue types, the ones that are of clinical interest and are related to surgical and cancer outcomes are adipose tissue and skeletal muscle. Numerous methods have been described for estimation

of both absolute and proportional amount of these tissues with varying degrees of complexity and accuracy. Some of the simpler methods include measurement of subcutaneous fat using calipers or bioelectrical impedance, estimation of skeletal muscle from mid-arm circumference or creatinine height ratio. Such methods are valuable to public health and epidemiological studies of malnutrition.

The gold-standard method for assessment of body composition is Dual Energy X-ray Absorptiometry (DEXA) [Haarbo et al. 1991]. While primarily designed for assessment of bone mineral density, DEXA scans have been adapted to measure fat, muscle and water content of subjects accurately and are used widely both in research and clinical settings. Other techniques such as whole body water or air displacement plethysmography are relatively cumbersome for routine clinical use.

More recently, cross-sectional imaging including computed tomography (CT) and magnetic resonance imaging (MRI) have become widely available. Nearly all patients with gastrointestinal cancer undergo either CT or MRI or both before commencing treatment. Accurate measurements of subcutaneous adipose tissue, visceral adipose tissue and skeletal muscle can be made relatively easy either from the entire series of images or estimates can be made from measurements made at certain predetermined anatomical levels. Both specialised software or readily available generic image analysis tools have been used to make these measurements. The proportion of the total cross-sectional area that is made of adipose tissue or skeletal muscle at the level of the 3^{rd} or the 4^{th} lumbar vertebra is commonly used as a surrogate for total body measurements. Thickness of retro-renal visceral fat at the level of the renal vein has also been reported to be usable as a surrogate for total visceral adiposity. Studies have also reported on the association between intra-pancreatic fat content and postoperative complications.

1.11 Aims of the thesis

The overall aim of the thesis was to examine the inter-relationships between preoperative clinico-pathological characteristics including cardiopulmonary exercise physiology, obstructive jaundice, body composition and preoperative systemic inflammation and post-operative complications and the post-surgical systemic inflammatory response in patients undergoing pancreaticoduodenectomy.

More specifically the aims of the thesis were:

To evaluate the clinical utility of preoperative cardiopulmonary exercise testing in predicting postoperative adverse events after pancreaticoduodenectomy.

To examine the patient factors that are related to cardiopulmonary exercise physiology with particular attention to the effect of obstructive jaundice and body composition on aerobic capacity in patients undergoing pancreaticoduodenectomy.

To examine the value of serial daily postoperative markers of systemic inflammatory response like white cell count, albumin and C-reactive protein concentrations in the prediction of post-operative complications after pancreaticoduodenectomy.

To examine the effect of preoperative systemic inflammation and poor aerobic capacity on the magnitude of the post-operative systemic inflammatory response after pancreaticoduodenectomy.

Chapter 2

An investigation into the role of preoperative cardiopulmonary exercise testing in predicting adverse postoperative events after major pancreatic surgery.

2.1 Introduction

Pancreatic cancer is the tenth most common cancer in the UK but the fifth most common cause of cancer death with only 21% surviving beyond the first year and 3% surviving beyond 5 years [CancerResearchUK 2011]. The majority of patients (80-85%) with pancreatic cancer present with inoperable disease [CancerResearchUK 2011; Sener et al. 1999]. In patients with resectable disease, surgery [Sener et al. 1999; Sohn et al. 2000; Geer et al. 1993] followed by adjuvant chemotherapy in selected patients [Neoptolemos et al. 2004; Neoptolemos et al. 2009] remains the primary modality of cure.

The decision to operate on these patients depends not only on preoperative tumour stage but also on patient factors [Bilimoria et al. 2007; Sandroussi et al. 2010]. Patient factors, in particular those that affect fitness, are also important in determining short term outcome in those that do undergo potentially curative surgery [Mann et al. 2010; Mayo et al. 2012]. However, major pancreatic surgery is associated with significant morbidity and mortality and patients who have postoperative complications are less likely to get adjuvant therapy [Teh et al. 2009].

There have been a number of attempts to objectively define patient fitness and its relationship with postoperative outcome. Copeland and co-workers (1991) reported that the Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) criteria, in particular the POSSUM physiology score (PPS) could be used to quantify the risk of postoperative morbidity and mortality [Copeland et al. 1991]. However, the role of POSSUM in predicting postoperative outcome after surgery for pancreatic cancer is not entirely clear [Castro et al. 2009; Khan et al. 2003; Kocher et al. 2005; Pratt et al. 2008b; Tamijmarane et al. 2008]. The physiological component of POSSUM as well as other similar risk scoring systems such as E-PASS (Estimation of Physiologic Ability and Surgical Stress)[Haga et al. 1999] are calculated based on known comorbidities, clinically evident abnormalities in patient physiology or blood tests.

More recently, there has been some evidence that the presence of an ongoing systemic inflammatory response before surgery is associated with the development of postoperative complications in patients undergoing surgery for colorectal cancer [Moyes et al. 2009], oesophageal cancer [Vashist et al. 2010] as well as pancreatic cancer [Knight et al. 2010].

Older and co-workers (1993) reported that cardiopulmonary exercise testing (CPET) was an objective evaluation of the response of the cardiovascular and respiratory systems to an increase in oxygen demand during exercise and was useful in predicting perioperative morbidity and mortality in patients undergoing major abdominal surgery [Older et al. 1993].

2.1.1 Aim

The aim of the present study was to evaluate the role of various measures of patient physiological fitness including cardiopulmonary exercise testing in predicting postoperative length of stay, major postoperative adverse events including operative mortality and fitness to undergo adjuvant therapy when indicated after pancreaticoduodenectomy.

2.2 Patients and Methods

2.2.1 Patients

Patients who underwent pancreaticoduodenectomy or total pancreatectomy for pancreatic head lesions between August 2008, when cardiopulmonary exercise testing was first used for fitness assessment at our hospital, and January 2012 were considered for this retrospective study. Patients who had not undergone cardiopulmonary exercise testing as part of their preoperative assessment and patients who underwent cardiopulmonary exercise testing but did not undergo surgery were excluded.

2.2.2 Preoperative data

Data on patient demographics, comorbidity including cardiovascular and respiratory disease, preoperative blood tests, chest x-ray and cardiopulmonary exercise tests were collected from prospectively maintained databases (march 2009 - January 2012) and case note review (August 2008 - March 2009). Data was also collected for patients who did not undergo cardiopulmonary exercise testing to allow comparison with the study group. The POSSUM Physiology Score was calculated based on 11 physiological parameters (cardiac disease including hypertension, ischaemic heart disease and heart failure, respiratory disease causing breathlessness on exertion and COPD, ECG changes, pulse rate, blood pressure, haemoglobin, white cell count, serum sodium, serum potassium, serum urea and Glasgow Coma Scale) as described previously.

2.2.3 Cardiopulmonary exercise test

Cardiopulmonary exercise tests were performed in the Department of Respiratory Medicine at the Glasgow Royal Infirmary using the ZAN-600 CPET suite (nSpire

Health, Longmont, CO 80501, USA). An electrically-braked cycle ergometer was used to perform a symptom-limited, incremental work-load test preceded by a 3-minute rest period. The test was stopped at maximum exercise tolerance, significant ischaemic changes on ECG or for other safety reasons. The $\dot{V}_{O_2}$AT was calculated using the V-slope [Beaver et al. 1986; Sue et al. 1988] and ventilatory equivalents [Sue et al. 1988] methods. Low $\dot{V}_{O_2}$AT was defined as oxygen consumption less than 10 ml/kg/min based on work by Snowden and co-workers [Snowden et al. 2010] who reported that $\dot{V}_{O_2}$AT less than 10.1 ml/kg/min was associated with an increase in postoperative complications after major abdominal surgery. A detailed description of the cardiopulmonary exercise testing methodology and calculation of $\dot{V}_{O_2}$AT is in Sections 1.5.2 and 1.5.3.

2.2.4 Perioperative care

The decision to operate was based on overall preoperative evaluation of the patient's comorbid conditions and performance status and not exclusively on the result of cardiopulmonary exercise testing. Whilst the results of cardiopulmonary exercise tests were available to the clinicians before surgery, no specific changes were made to perioperative management based exclusively on these results. These results were used in conjunction with other established forms of preoperative evaluation for risk assessment and perioperative care. All patients were routinely admitted to the surgical high dependency unit unless intra-operative events or postoperative complications required admission to the intensive care unit. Patients were discharged after resolution of organ dysfunction and/or sepsis and when nutrition, analgesia and mobilisation were adequately established to the clinician's and patient's satisfaction.

2.2.5 Outcome measures

Postoperative adverse events were recorded using internationally recognised definitions. The International Study Group for Pancreatic Surgery (ISGPS) definitions were used to classify pancreatic fistulae [Bassi et al. 2005a] and post-operative haemorrhage [Wente et al. 2007]. The Clavien-Dindo (CD) classification [Clavien et al. 2009; Dindo et al. 2004] was used to grade other complications and CD grades III-V were considered major. Multiple admissions to critical care as well as re-operations were recorded. Operative mortality was defined as postoperative death in-hospital regardless of duration of stay or occurring within 30 days of the surgery. All complications were discussed at a weekly multidisciplinary meeting attended by three pancreatic surgeons and a radiologist with a specialist interest in pancreatic diseases and recorded in a prospective database.

Primary outcome measures were length of stay in hospital, major postoperative adverse events including operative mortality and fitness to undergo adjuvant therapy when indicated. Secondary outcome measures included cumulative length of stay in critical care and number of critical care admissions.

2.2.6 Statistics

Grouping of the variables was carried out using standard or previously published thresholds. In the absence of such thresholds, the variables were treated as continuous variables and analysed using non-parametric statistical methods. Cox proportional hazards regression analysis was used to study the relationship between preoperative risk factors and length of hospital stay. Chi-square test was used to examine the relationship between complications and $\dot{V}_{O_2}$AT as a categorical variable. Univariate binary logistic regression analysis with calculation of hazard ratios (HR) and 95% confidence intervals was used to explore the association between perioperative clinico-pathological factors and receipt of

adjuvant therapy. Multivariate binary logistic regression analysis was performed on all variables showing a significant association on univariate analysis. Backward stepwise regression was used starting with a saturated model and variables with P-value$>$ 0.1 were excluded at each step until no more variables could be excluded. SPSS software (Version 17.0; SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

2.3 Results

2.3.1 Clinico-pathological characteristics

One hundred and twenty-nine patients had undergone pancreaticoduodenectomy (n=127), sub-total pancreatectomy (n=1) or total pancreatectomy (n=1) during the study period. Sub-total and total pancreatectomy were performed in patients scheduled for a pancreaticoduodenectomy but were found to have pancreatic remnants either too friable or too atrophic during the operation to perform an anastomosis. Of these, 100 patients (pancreaticoduodenectomy - 98, sub-total/total pancreatectomy - 2) had undergone cardiopulmonary exercise testing as part of their preoperative assessment and were included in the study. Pathological examination of the resected specimen showed pancreatic ductal adenocarcinoma (n=37), ampullary adenocarcinoma (n=18), cholangiocarcinoma (n=17), duodenal adenocarcinoma (n=6), intra-ductal papillary mucinous neoplasia (n=4), neuroendocrine tumours (n=7), other neoplasia (n=6) or chronic pancreatitis (n=5).

Twenty-nine patients did not undergo cardiopulmonary exercise testing due to reasons including subjective assessment of fitness, resource constraints and logistics. Table 2.1 shows the clinico-pathological characteristics of patients included in the study compared to the excluded patients. The median age in the study cohort was higher than in the excluded cohort (66 vs. 54 years, p=0.001). However, there was no difference in gender, body mass index, preoperative biliary drainage, jaundice at the time of surgery, modified Glasgow Prognostic Score, POSSUM physiology score, preoperative blood tests including haemoglobin and liver function tests and length of critical care/hospital stay. The overall postoperative mortality during the study period was 5.4% (7/129) with all deaths occurring in the study cohort (p=0.144).

The median $\dot{V}_{O_2}$AT was 10.3 ml/kg/min (inter-quartile range, IQR 8.8 - 11.6). The $\dot{V}_{O_2}$AT was less than 10 ml/kg/min in 49 patients. The distribution of $\dot{V}_{O_2}$AT

TABLE 2.1: Clinico-pathological characteristics of patients undergoing pancreatic resections during the study period.

	All Patients n = 129	Excluded n = 29	Included n = 100	*p*
Age (years)				
≤ 65	71 (55%)	24	47	0.001
> 65	58 (45%)	5	53	
Sex				
Male	77 (60%)	17	60	0.894
Female	52 (40%)	12	40	
Body mass index (kg/m^2)				
≤ 25	53 (44%)	8	45	0.817
> 25	66 (56%)	11	55	
Preoperative Biliary Drainage				
No	68 (59%)	12	56	0.154
Yes	48 (41%)	4	44	
modified Glasgow Prognostic Score (mGPS)				
0	76 (59%)	13	63	0.279
1	11 (9%)	5	6	
2	41 (32.0%)	10	31	
Haemoglobin (g/dl)				
≥ 12	80 (64%)	18	62	0.353
< 12	45 (36%)	7	38	
POSSUM Physiology Score				
11-14	61 (51%)	12	50	0.701
> 14	59 (49%)	10	50	
Serum Bilirubin (μmol/L)				
≤ 35	70 (55%)	12	58	0.156
> 35	58 (45%)	16	42	
Operation Type				
Pancreatico-duodenectomy	127 (98%)	29	98	0.045
(Sub-)Total Pancreatectomy	2 (2%)	0	2	
Operative mortality	7 (5%)	0	7	0.144
Postoperative stay (days)	17 (13-27)	20 (13-30)	17 (13-26)	0.518
Critical care stay (days)	7 (6-12)	7 (6-14)	7 (6-12)	0.448

Values are median (inter-quartile range), *p* using Mann-Whitney U test or number of patients (percentage), *p* using Chi-square test.

across the study cohort is shown in Figure 2.1.

2.3.2 Anaerobic threshold vs. complications

The relationship between $\dot{V}_{O_2}$AT and major postoperative adverse events including mortality is shown in Table 2.2. Patients with $\dot{V}_{O_2}$AT less than 10 ml/kg/min had significantly greater incidence of postoperative pancreatic fistula (35.4% vs.16%, p=0.028) as well as major intra-abdominal abscesses (Clavien-Dindo Grade III - V, 22.4% vs.7.8%, p=0.042). While there was an association between low $\dot{V}_{O_2}$AT and grade of pancreatic fistula, this was not statistically significant (p=0.091). There was no association between low $\dot{V}_{O_2}$AT and cardiopulmonary complications or postoperative mortality. Major cardiopulmonary complications occurred more often in patients with major intra-abdominal adverse events including major intra-abdominal abscesses or Grade B and C pancreatic fistulae or haemorrhage than in patients who did not have these complications (5/31,16.1% vs. 2/69,2.9%, p=0.017). Postoperative mortality was not associated with $\dot{V}_{O_2}$AT (HR 0.77, 95% CI 0.16-3.61, p 0.737) or the POSSUM Physiology Score (HR 0.39, 95% CI 0.07-2.12, p 0.277). Postoperative mortality was associated with postoperative pancreatic fistula (n=5), post-pancreatectomy haemorrhage (n=3), major intra-abdominal sepsis (n=6) and major cardiorespiratory complications (n=4) with 6 patients requiring radiological or operative intervention.

2.3.3 Anaerobic threshold vs. length of stay

The median length of postoperative stay was 17 days (IQR 13 - 26). The median cumulative length of stay in critical care was 7 days (IQR 6 - 12). Twenty-six patients were admitted to critical care more than once. The relationship between preoperative clinico-pathological characteristics and length of postoperative stay in patients who were discharged from hospital (n=93) is shown in Table 2.3. On univariate analysis, age over 65 years (p=0.072) and low $\dot{V}_{O_2}$AT (p=0.010) were

TABLE 2.2: The relationship between anaerobic threshold and complications in patients undergoing major pancreatic surgery.

Complications		$\dot{V}_{O_2}$AT ≥10	$\dot{V}_{O_2}$AT < 10	
	n	n	n	*p*
Cardiac complications				
Grade 0 - II	99	51	48	0.308
Grade III - V	1	0	1	
Respiratory complications				
Grade 0 - II	93	48	45	0.657
Grade III - V	7	3	4	
Intra-abdominal abscess				
Grade 0 - II	85	47	38	0.042
Grade III - V	15	4	11	
Pancreatic Fistula (Total/Sub-total pancreatectomies excluded)				
No	73	42	31	0.028
Yes	25	8	17	
Pancreatic Fistula (ISGPS Classification)				
No	73	42	31	0.091
Grade A	9	3	6	
Grade B	8	1	7	
Grade C	8	4	4	
Post-Pancreatectomy Haemorrhage (ISGPS Classification)				
No	84	41	43	0.207
Grade A	4	2	2	
Grade B	4	2	2	
Grade C	8	6	2	
Admissions to critical care				
1	74	38	36	0.906
>1	26	13	13	
Reoperation				
No	89	47	42	0.306
Yes	11	4	7	
Operative mortality				
No	93	47	46	0.737
Yes	7	4	3	

p - Chi-square test

associated with prolonged postoperative stay. On multivariate Cox proportional hazards regression analysis, $\dot{V}_{O_2}$AT less than 10 ml/kg/min (hazard ratio 1.74, 95% confidence intervals 1.14-2.65, p=0.010) was the only significant factor associated with prolonged postoperative stay. A Kaplan-Meier plot for the probability of remaining in hospital over time for patients with low or normal $\dot{V}_{O_2}$AT is shown in Figure 2.2. Patients with a low $\dot{V}_{O_2}$AT stayed a median 6 days longer in hospital (14 versus 20 days, Mann-Whitney Test p=0.001). There was no significant association between any of the preoperative factors including $\dot{V}_{O_2}$AT and length of critical care stay or number of critical care admissions.

2.3.4 Anaerobic threshold vs. receipt of adjuvant therapy

The relationship between clinico-pathological patient factors and receipt of adjuvant therapy is shown in Table 2.4. Fifty-five patients were included in the analysis. Patients were excluded if chemotherapy was not indicated (n=28, ampullary carcinoma=8, neuroendocrine tumours=7, IPMN=4, other neoplasia=5, chronic pancreatitis=4), in the event of operative mortality (n=7), if chemotherapy was offered but declined by the patient (n=4), or where they had not been seen by an oncologist yet (n=6). On binary logistic regression analysis, $\dot{V}_{O_2}$AT less than 10 ml/kg/min was the only preoperative factor that was associated with with non-receipt of adjuvant therapy (HR 6.30, 95% CI 1.25-31.75, p=0.026).

TABLE 2.3: The relationship between clinico-pathological factors and postoperative stay in patients (excluding operative mortality) undergoing major pancreatic surgery (n=93): Cox regression analysis

Variable	n	HR	95% CI	p	HR	95% CI	p
Age (years)							
≤ 65	44						
> 65	49	1.47	0.97-2.24	0.072	1.48	0.97-2.25	0.068
Sex							
Male	56						
Female	37	1.32	0.86-2.03	0.199			
Body mass index (kg/m^2)							
≤ 25	42						
> 25	51	0.87	0.58-1.32	0.512			
Smoking							
No	56						
Yes	37	1.26	0.82-1.94	0.294			
POSSUM Physiology Score							
≤ 14	45						
> 14	48	1.28	0.85-1.95	0.24			
Preoperative Biliary Drainage							
No	53						
Yes	40	1.08	0.71-1.65	0.724			
Serum Bilirubin (μmol/L)							
≤ 35	54						
> 35	39	1.26	0.83-1.92	0.277			
modified Glasgow Prognostic Score (mGPS)							
0	59						
1	5	1.22	0.78-1.92	0.387			
2	29	1.87	0.71-4.88	0.204			
Haemoglobin (g/dl)							
≥ 12	57						
< 12	36	1.19	0.78-1.81	0.422			
$\dot{V}_{O_2}$AT (ml/kg/min)							
≥ 10	47						
< 10	46	1.74	1.14-2.64	0.01	1.74	1.14-2.65	0.01
$\dot{V}_{O_2}$AT (ml/kg/min)							
≥ 11	33						
< 11	60	1.44	0.94-2.22	0.097			0.395

TABLE 2.4: The relationship between clinico-pathological characteristics and receipt of adjuvant therapy in patients undergoing major pancreatic surgery (n = 55) - Binary logistic regression

Variable	n = 55	HR	95% CI	*p*
Age (years)				
≤ 65	25			
> 65	30	2.63	0.71-9.74	0.149
Sex				
Male	31			
Female	24	2.08	0.61-7.13	0.242
BMI (kg/m^2)				
≤ 25	25			
> 25	30	0.78	0.23-2.64	0.693
Smoking				
No	35			
Yes	20	0.96	0.27-3.41	0.953
POSSUM Physiology Score				
≤ 14	25			
> 14	30	1.63	0.46-5.73	0.447
Preoperative Biliary Drainage				
No	27			
Yes	28	0.95	0.28-3.21	0.937
Serum Bilirubin (μmol/L)				
≤ 35	27			
> 35	28	2.08	0.60-7.30	0.251
modified Glasgow Prognostic Score (mGPS)				
0	32			
1	2	0	0	
2	21	1.2	0.35-4.15	0.773
Haemoglobin (g/dl)				
≥ 12	31			
< 12	24	0.96	0.28-3.26	0.946
Anaerobic Threshold (ml/kg/min)				
≥ 10	23			
< 10	32	6.3	1.25-31.75	0.026
Anaerobic Threshold (ml/kg/min)				
≥ 11	16			
< 11	39	3.11	0.61-15.88	0.172

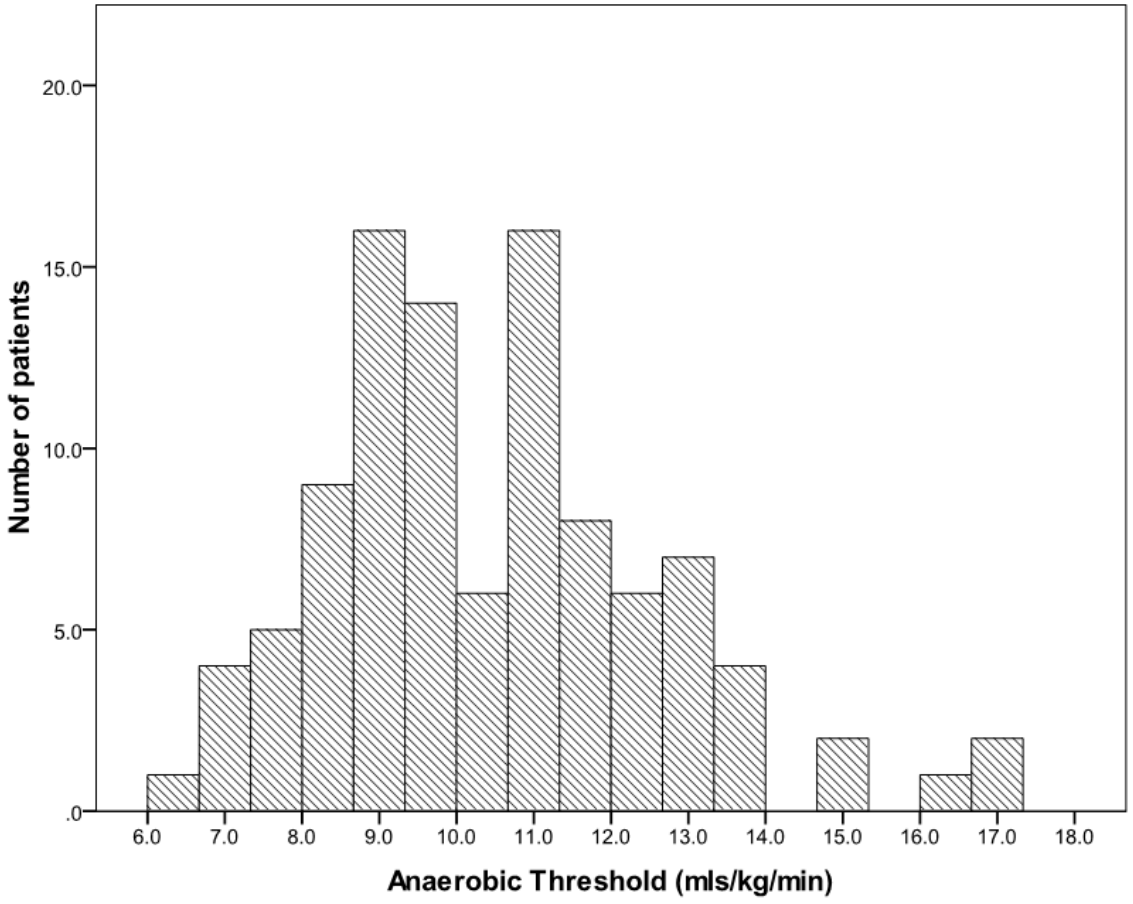
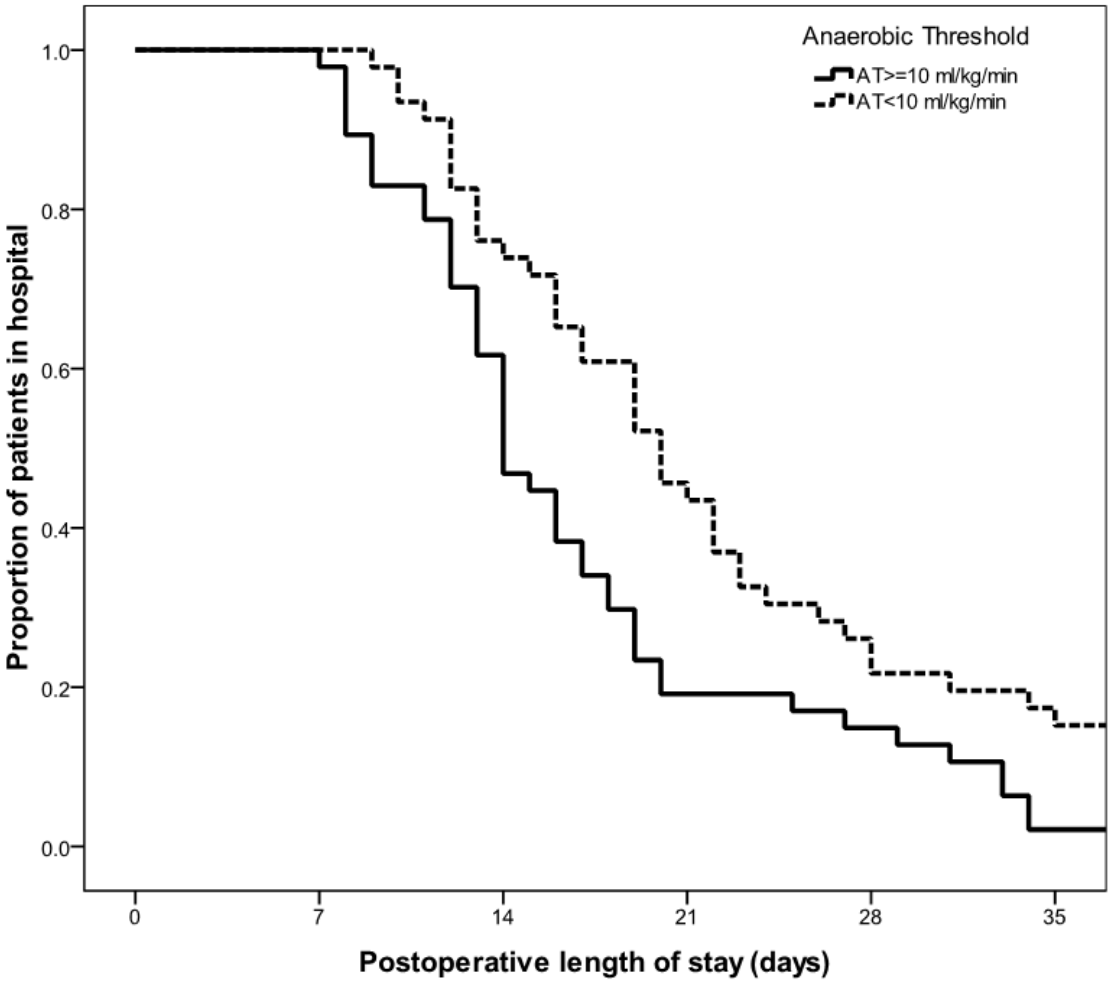


FIGURE 2.1: Distribution of $\dot{V}_{O_2}$AT across the study population.



Number of patients remaining in hospital						
Postoperative Day	0	7	14	21	28	35
AT≥10 ml/kg/min	46	46	22	9	7	1
AT<10 ml/kg/min	45	45	34	20	11	7

FIGURE 2.2: Kaplan-Meier Plot of postoperative length of stay in patients with $\dot{V}_{O_2}$AT >= 10 ml/kg/min versus < 10 ml/kg/min.

2.4 Discussion

The results of the present study show that a low $\dot{V}_{O_2}$AT is associated with prolonged postoperative stay in hospital, postoperative pancreatic fistula and intra-abdominal abscesses in patients undergoing major resections for pancreatic head lesions. The results of this study also show that patients with low $\dot{V}_{O_2}$AT are less likely to receive adjuvant therapy.

Patients with a low $\dot{V}_{O_2}$AT stayed longer in hospital after their operation. While length of stay in hospital is influenced by multiple factors including postoperative complications, it would appear that patients with a low $\dot{V}_{O_2}$AT take longer to recover from the physiological stress placed by major pancreatic surgery and its sequelae.

The incidence of pancreatic fistula was greater in patients with a low $\dot{V}_{O_2}$AT. This association needs further evaluation taking into consideration other well-recognised risk factors for pancreatic fistula such as pancreatic texture, pancreatic duct size and intra-operative blood loss [Braga et al. 2011; Pratt et al. 2008b; Winter et al. 2006]. It is possible that local or operative factors may be compounded by poor oxygen delivery and organ perfusion as measured by cardiopulmonary exercise testing. There was a non-significant trend towards clinically relevant pancreatic fistulae (ISGPS Grades B and C) as well as a significant association with major intra-abdominal abscesses (Clavien-Dindo Grades 3-5 i.e., requiring intervention, associated with organ dysfunction requiring intensive care or resulting in mortality). This would suggest that complications in patients with low $\dot{V}_{O_2}$AT are more likely to be severe than in patients with normal $\dot{V}_{O_2}$AT. However, there was no difference in mortality between patients with normal or low $\dot{V}_{O_2}$AT, indicating that multiple factors including preoperative patient fitness, local and operative factors, systemic inflammatory response, number of complications as well as perioperative critical care all play a role.

The results of this study also show that patients with a low $\dot{V}_{O_2}$AT were less likely

to receive adjuvant therapy. Adjuvant therapy in patients undergoing pancreatic resections for cancer has been shown in multiple randomised trials to improve survival significantly [Neoptolemos et al. 2004; Neoptolemos et al. 2009] While postoperative mortality after pancreatic surgery has steadily improved over the years with major improvements in the quality of surgical and critical care over the past decade [Winter et al. 2006] even in elderly patients [Makary et al. 2006], postoperative morbidity remains high [Mann et al. 2010]. The results of this study show that poor preoperative fitness is not only associated with a protracted protracted postoperative course with complications but also with non-receipt of adjuvant therapy.

In the present study, $\dot{V}_{O_2}$AT was less than 10 ml/kg/min in 49% of patients and less than 11 ml/kg/min in 64% of patients. The proportion of patients with $\dot{V}_{O_2}$AT less than 11 ml/kg/min in this study was much greater than reported in studies involving patients undergoing oesophageal surgery (16%),[Forshaw et al. 2008] liver transplantation (39%)[Epstein et al. 2004] or other major abdominal surgery (29%)[Older et al. 1993] and may indicate the poor preoperative fitness levels of patients undergoing major pancreatic surgery at our unit.

While several studies have shown that low $\dot{V}_{O_2}$AT and/or low $\dot{V}_{O_2}$peak are associated with postoperative complications or prolonged hospital stay following major abdominal surgery as well as non-abdominal surgery,[Older et al. 1993; Epstein et al. 2004; McCullough 2006; Nagamatsu et al. 2001; Older et al. 1999; Older et al. 2004] others have disputed this [Forshaw et al. 2008; Clayton et al. 2011; Hightower et al. 2010].

Older and co-workers reported in 1993 that low $\dot{V}_{O_2}$AT less than 11 ml/kg/min was associated with a significantly higher risk of postoperative mortality from cardiovascular causes in a series of 187 elderly patients undergoing major abdominal surgery [Older et al. 1993]. However, Snowden and co-workers [Snowden et al. 2010] reported that patients with an $\dot{V}_{O_2}$AT less than 10.1 ml/kg/min had significantly greater cardiopulmonary complications as well as

non-cardiopulmonary and infectious complications while Forshaw and co-workers [Forshaw et al. 2008] reported that using a cut-off of 11 ml/kg/min for the $\dot{V}_{O_2}$AT did not predict postoperative adverse events less after oesophagectomy.

The lack of association between low $\dot{V}_{O_2}$AT and cardiopulmonary complications in this study may have been due to two reasons. Major cardiopulmonary complications occurred more often in association with major intra-abdominal adverse events which are determined largely by pancreatic morphology and local anatomy [Braga et al. 2011]. Moreover, the stringent fitness criteria for undergoing pancreaticoduodenectomy may have excluded patients with known co-morbid cardiorespiratory diseases such as severe chronic obstructive pulmonary disease or cardiac failure.

The results of this study are consistent with the findings by Ausania and co-workers [Ausania et al. 2012b] who reported increased incidence of pancreatic fistula and prolonged postoperative stay in patients with $\dot{V}_{O_2}$AT less than 10.1 ml/kg/min. However, this study did not report the association between $\dot{V}_{O_2}$AT and receipt of adjuvant therapy.

The physiological demands placed on a patient undergoing major pancreatic surgery are significant, both during and after the operation. It is not entirely surprising therefore, that conventional parameters of patient fitness like the POSSUM Physiology Score or the modified Glasgow Prognostic Score are limited in their ability to distinguish patients based on their performance under physiological stress. Cardiopulmonary exercise testing overcomes this disadvantage by replicating some of the physiological burden major pancreatic surgery places on the functional capacity of the patient's cardiovascular and respiratory systems.

This functional capacity of patients to withstand the physiological burden of major surgery can be improved by the process of 'prehabilitation' [Topp et al. 2002]. It has been suggested that prehabilitation not only improves aerobic capacity [Jones et al. 2007] but may also improve postoperative recovery [Mayo et al. 2011; Pehlivan et al. 2011]. The results of this study show that impaired aerobic capacity

is associated with postoperative adverse events. Therefore, it would appear that prehabilitation using interventions such as exercise and nutrition, by improving physiological fitness, may have a role in improving postoperative outcomes after major pancreatic surgery and may improve the proportion of patients receiving adjuvant therapy.

Further work needs to be carried out to study the value of cardiopulmonary exercise testing in predicting postoperative complications in conjunction with previously established factors such as pancreatic morphology and operative factors before it can be used on its own to select or exclude patients for pancreaticoduodenectomy. Cardiopulmonary exercise testing would play an important role not only in identifying patients who will benefit from prehabilitation, but also in the objective measurement of the effects of such interventions on aerobic capacity as well as in identifying high risk patients who may not be able to complete oncological treatment. Prehabilitation and optimised perioperative care may allow a greater proportion of high risk patients to progress to oncological treatment after surgery.

Chapter 3

An investigation into the relationship between cardiopulmonary exercise testing, preoperative pathophysiology and obstructive jaundice in patients undergoing pancreaticoduodenectomy.

3.1 Introduction

Patients with tumours involving the pancreatic head or the periampullary region often present with inoperable disease. In the minority of patients with operable disease, resectional surgery in the form of a pancreaticoduodenectomy remains the main modality of treatment and only chance of a potential cure. However, major pancreatic surgery is associated with significant morbidity and mortality and is only undertaken in specialist centres. Patient selection, preoperative optimisation, good surgical technique and improvements in postoperative care have all contributed to a reduction in mortality [Winter et al. 2006] but morbidity remains high [Mann et al. 2010]. While several technical strategies have been described in recent years to minimise morbidity, these strategies are not necessarily based on a better understanding of the physiological basis of postoperative complications in these patients.

The close anatomical relationship between the distal bile duct, distal pancreatic duct, head of the pancreas and the duodenum is responsible for obstructive jaundice being the most common presenting symptom in patients with tumours affecting this region. Distal bile duct strictures also occur in a proportion of patients with severe chronic pancreatitis involving the pancreatic head. In such patients, it may be impossible to distinguish inflammation from malignant disease on preoperative imaging and a proportion of these patients will require a pancreaticoduodenectomy [Abraham et al. 2003]. The perioperative management of the patient with obstructive jaundice is complex and management algorithms are still evolving [Wang et al. 2008].

Obstructive jaundice has been shown to be associated with abnormal cardiovascular physiology in several animal and human studies. Surgery in the jaundiced patient has been reported to be associated with adverse postoperative haemodynamic events and renal dysfunction [Pain et al. 1985; Green et al. 1995]. The association between jaundice and cardiovascular physiology was reported over a hundred years ago by King and co-workers who found that injection of porcine

bile pigment into dogs resulted in bradycardia, hypotension and eventually death [King et al. 1909]. Green and co-workers (1986) described the effects of 'cholemia' in dogs that were subjected to choledochocaval anastomosis. The resultant myocardial depression was described by them as the 'jaundiced heart' [Green et al. 1986] and was associated with poor myocardial response to inotropic stimulation in dogs [Binah et al. 1985; Bomzon et al. 1986] as well as humans [Lumlertgul et al. 1991].

As a result, preoperative biliary drainage (PBD) used to be advocated routinely before subjecting a patient to pancreaticoduodenectomy with the intention of reducing postoperative morbidity. A recent multi-center, randomised trial found that PBD was associated with increased incidence of complications after pancreaticoduodenectomy [Gaag et al. 2010]. However, this trial excluded patients with a bilirubin levels greater than 250 μmol/l from the study. A Cochrane meta-analysis of 6 studies including 520 patients also concluded that pre-operative biliary drainage was associated with increased incidence of complications and should not be used routinely in patients scheduled to undergo pancreaticoduodenectomy [Fang et al. 2012].

3.1.1 Aim

The results presented in Chapter 2 demonstrated that poor performance at cardiopulmonary exercise testing (CPET) was associated with adverse outcomes after pancreaticoduodenectomy with an increased incidence of POPF and prolonged hospital stay. Obstructive jaundice was present in a large proportion of these patients but not associated with prolonged hospitalisation (Table 2.3). The aim of the present study was to evaluate the relationship between cardiopulmonary exercise testing, obstructive jaundice (especially severe obstructive jaundice with serum bilirubin > 250 μmol/l) and preoperative pathophysiology in patients undergoing pancreaticoduodenectomy.

3.2 Patients and methods

3.2.1 Patients

Patients who underwent classical or pylorus-preserving pancreaticoduodenectomy for periampullary lesions (both benign and malignant) between August 2008 and December 2012 and had undergone cardiopulmonary exercise testing as part of their preoperative assessment at the West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow were included in the study. Established criteria for resectability in patients with malignant disease were used as outlined in Section 1.2.1. Segmental or wedge resection of the portal vein or superior mesenteric vein was carried out if the lesion was otherwise resectable.

3.2.2 Preoperative data

Patient demographics, preoperative clinico-pathological characteristics including cardiorespiratory comorbidity, results of preoperative blood tests, chest x-ray, ECG and cardiopulmonary exercise tests were collected from prospectively held databases. The POSSUM Physiology Score was calculated based on 11 physiological parameters (cardiac disease, respiratory disease, ECG changes, pulse rate, blood pressure, haemoglobin, white cell count, serum sodium, serum potassium, serum urea and Glasgow Coma Scale) and was used as an objective score of comorbidity (Table 1.4 on p18). Cardiovascular comorbidity was defined as a score of 2 or more for either the cardiac disease or ECG component of the POSSUM score. Respiratory comorbidity was defined as a score or 2 or more for the respiratory disease component of the POSSUM score.

3.2.3 Obstructive jaundice

Serum bilirubin levels and liver function tests were measured in all patients on the day before surgery. Obstructive jaundice was defined as serum bilirubin > 35 μmol/litre and severe obstructive jaundice was defined as serum bilirubin > 250 μmol/litre. These thresholds were chosen as a recent randomised controlled trial that demonstrated increased complications in patients who underwent PBD excluded patients with serum bilirubin > 250 μmol/litre from the study [Gaag et al. 2010]. The present study aimed to evaluate preoperative pathophysiology in this particular group of patients with 'severe obstructive jaundice'. Due to referral practices at the time of this study, a proportion of patients underwent preoperative biliary interventions and drainage before referral to the West of Scotland Pancreatic Unit. Data regarding biliary intervention and stenting was collected where feasible.

3.2.4 Cardiopulmonary exercise test

Cardiopulmonary exercise tests were performed in the Department of Respiratory Medicine at the Glasgow Royal Infirmary using the ZAN-600 CPET suite (nSpire Health, Longmont, CO 80501, USA). All patients underwent standard pulmonary function tests and spirometry prior to cardiopulmonary exercise testing. A cycle ergometer was used to perform a symptom-limited, incremental work-load test preceded by a 3-minute rest period. The test was stopped when patients achieved their maximum exercise tolerance, when significant ischaemic changes occurred on ECG or for other safety reasons. Peak oxygen consumption achieved at this stage was defined as $\dot{V}_{O_2}$Peak. The $\dot{V}_{O_2}$AT was calculated using the V-slope [Beaver et al. 1986; Sue et al. 1988] and ventilatory equivalents ["ATS/ACCP Statement on Cardiopulmonary Exercise Testing" 2003] methods. $\dot{V}_{O_2}$AT less than 10 ml/kg/min was considered to be low based on previous work by us (Chapter 2) as well as Ausania and co-workers [Ausania et al. 2012b] which has shown increased incidence of complications in patients with $\dot{V}_{O_2}$AT below this threshold. Oxygen

consumption at peak exercise ($\dot{V}_{O_2}$Peak) was dichotomised using a cut-off of 16 ml/kg/min. Cardiopulmonary exercise testing methodology and calculation of $\dot{V}_{O_2}$AT is described in detail in Sections 1.5.2 and 1.5.3. The cardiopulmonary exercise testing parameters described in this study are explained in detail in Section 1.6 on p28 and in published literature [Balady et al. 2010].

3.2.5 Statistics

Grouping of the variables was carried out using standard or previously published thresholds. In the absence of such thresholds, the variables were treated as continuous variables. Non-parametric tests were used to analyse the association between categorical and continuous variables while Chi-square tests were used to analyse the association between categorical variables. Univariate and multivariate binary logistic regression analysis was used to study the relationship between preoperative patient characteristics and $\dot{V}_{O_2}$AT / $\dot{V}_{O_2}$Peak. Scatter-plots were used for visual representation of the relationship between serum bilirubin and $\dot{V}_{O_2}$.

The level of significance was set at $p < 0.05$. SPSS software (Version 17.0; SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

3.3 Results

3.3.1 Clinico-pathological characteristics

One-hundred and thirty eight patients underwent pancreaticoduodenectomy with preoperative cardiopulmonary exercise testing during the study period. Over half of the patients were male (n=93, 67%). Approximately half the number of patients were over the age of 65 (n=68, 49%) and overweight or obese (n=69, 50%). Cardiovascular comorbidity was present in 58 patients (42%) and respiratory comorbidity was present in 12 patients (9%). Fifty patients (36%) had a history of cigarette smoking. The POSSUM Physiology Score was greater than 14 in 61 patients (44%). Obstructive jaundice (serum bilirubin 35-250 μmol/l) was present in 32 (23%) patients while severe obstructive jaundice (serum bilirubin $>$ 250 μmol/l) was present in 19 (14%) patients.

The baseline demographic and clinical characteristics of non-jaundiced and jaundiced patients are shown in Table 3.1. A greater proportion of jaundiced patients were females (p=0.028) and smokers (p=0.038) compared to the non-jaundiced cohort. Elevated POSSUM Physiology Score (p=0.004) and malignancy (p$<$0.001) were significantly associated with the presence of jaundice. However, there was no statistically significant difference in age, body mass index, cardiovascular comorbidity, respiratory comorbidity or PBD between the non-jaundiced and jaundiced patients.

3.3.2 Obstructive jaundice vs. preoperative blood tests

The relationship between obstructive jaundice and preoperative blood tests is shown in Table 3.2. Obstructive jaundice was associated with the presence of a systemic inflammatory response as characterised by raised serum C-reactive protein levels and decrease in serum albumin levels (p$<$0.001). The degree of systemic inflammation was proportionate to the severity of jaundice. Non-jaundiced

patients had a median CRP of 3.6 mg/l (inter-quartile range 0.3 - 89) and serum albumin of 37 g/l (IQR 18 - 46) while patients with severe obstructive jaundice had a median CRP of 13 (IQR 1.7 - 51) and a median serum albumin of 25 g/l (IQR 18 - 33). Obstructive jaundice was also associated with electrolyte abnormalities including serum sodium, serum potassium and serum chloride levels. Jaundiced patients were more likely to be anaemic ($p<0.001$) with lower haematocrit ($p<0.001$) and lower mean corpuscular volume ($p=0.001$). However, there was no significant difference in the preoperative renal function, prothrombin time and white cell count between jaundiced and non-jaundiced patients.

3.3.3 Obstructive jaundice vs. pulmonary function tests

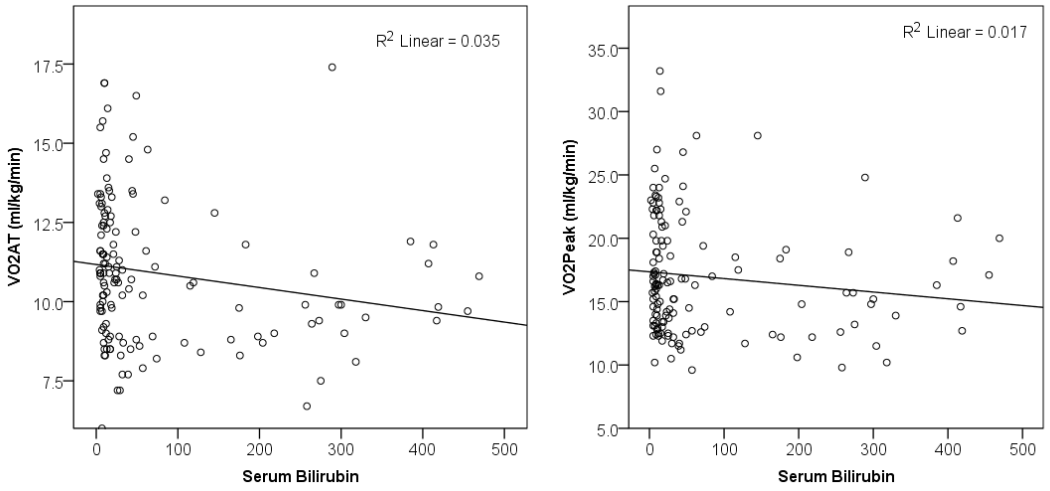
Pulmonary function tests including forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and their derived parameters (predicted FEV1, FEV1/FVC, predicted FEV1/FVC) were compared between jaundiced and non-jaundiced patients. There was a trend towards lower forced vital capacity with increasing severity of jaundice but this did not reach statistical significance ($p=0.092$). There was no association between the other pulmonary function tests and jaundice (Table 3.3).

3.3.4 Obstructive jaundice vs. CPET

Cardiopulmonary exercise test parameters measured at the anaerobic threshold and at peak exercise were compared between jaundiced and non-jaundiced patients using the Kruskal-Wallis test. Obstructive jaundice was associated with lower tidal volume ($p=0.017$), lower absolute $\dot{V}_{O_2}$ ($p=0.003$), lower corrected $\dot{V}_{O_2}$ ($p=0.029$), lower oxygen pulse ($p=0.037$) and lower respiratory rate ($p=0.022$) at the anaerobic threshold. At peak exercise, jaundice was associated with lower tidal volume ($p=0.028$), lower absolute $\dot{V}_{O_2}$Peak ($p=0.007$), lower absolute $\dot{V}_{CO_2}$ ($p=0.016$) and lower end-tidal O_2 or PET_{O_2} ($p=0.026$). However, as shown in

Tables 3.4 and 3.5, several of these associations were not linear with a trend towards poorer results between non-jaundiced and mildly jaundiced patients and better values in the severely jaundiced cohort.

Scatter-plot analysis comparing serum bilirubin versus $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak as continuous variables is depicted in Figure 3.1. This shows that the relationship between serum bilirubin and $\dot{V}_{O_2}$AT is weak with a ρ^2 value of 0.035 Pearson's ρ = - 0.187, p = 0.028. There was no correlation between serum bilirubin and $\dot{V}_{O_2}$Peak (Pearson's ρ = - 0.132, ρ^2 = 0.017, p = 0.123)



(A) $\dot{V}_{O_2}$AT versus serum bilirubin (B) $\dot{V}_{O_2}$Peak versus serum bilirubin

FIGURE 3.1: Scatter-plot analysis comparing serum bilirubin versus $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak.

The relationship between serum bilirubin and $\dot{V}_{O_2}$AT was weak (Pearson's ρ = - 0.187, ρ^2 = 0.035, p = 0.028). There was no correlation between serum bilirubin and $\dot{V}_{O_2}$Peak (Pearson's ρ = - 0.132, ρ^2 = 0.017, p = 0.123)

3.3.5 Preoperative factors related to CPET

Binary logistic regression analysis was undertaken to assess preoperative clinico-pathological patient factors associated with a low $\dot{V}_{O_2}$AT and low $\dot{V}_{O_2}$Peak. On univariate analysis, female sex (HR 2.74, 95% CI 1.30-5.74, p=0.008), body mass index > 25 (HR 3.09, 95% CI 1.51-6.32, p=0.002), presence of malignancy (HR 3.59, 95% CI 1.36-9.43, p=0.010), POSSUM Physiology Score > 14 (HR 2.06,

95% CI 1.02-4.17, p= 0.044), serum bilirubin > 250 μmol/l (HR 5.66, 95% CI 1.87-17.16, p=0.002), haemoglobin < 12 g/dl (HR 2.74, 95% CI 1.30-5.74, p=0.008) and serum C-reactive protein > 10 mg/l (HR 2.18, 95% CI 1.06-4.51, p=0.035) were associated with $\dot{V}_{O_2}$AT < 10 ml/kg/min. Age, cardiovascular and respiratory comorbidity, PBD, mild jaundice and serum albumin were not significantly related to a low $\dot{V}_{O_2}$AT.

The statistically significant independent variables with p<0.05 were entered into a backward step-wise regression model with $\dot{V}_{O_2}$AT < 10 ml/kg/min as a categorical, binomial, dependent variable. Female sex (HR 3.75, 95% CI 1.57-8.95 p<0.005), body mass index > 25 (HR 3.65, 95% CI 1.61-8.26, p<0.005), malignancy (HR 4.02, 95% CI 1.33-12.16, p<0.05) and C-reactive protein > 10 mg/l (HR 2.98, 95% CI 1.29-6.86, p<0.05) were independently related to low $\dot{V}_{O_2}$AT. Obstructive jaundice was not related to low $\dot{V}_{O_2}$AT on multivariate analysis. (Table 3.6)

Binary logistic regression analysis of the relationship between patient factors and low $\dot{V}_{O_2}$Peak (< 16 ml/kg/min) is shown in Table 3.7. On both univariate and multivariate analysis, female sex, body mass index > 25 and haemoglobin < 12 g/dl were significantly associated with a low $\dot{V}_{O_2}$Peak.

TABLE 3.1: The relationship between obstructive jaundice and preoperative patient characteristics in patients undergoing pancreaticoduodenectomy.

	Preoperative Serum Bilirubin (μmol/L)				
n = 138	≤ 17	18-35	35-250	> 250	p
Age ($\leq$65/>65 years)	32/33	13/9	16/16	9/10	0.935
Sex (Male/Female)	48/17	14/8	22/10	9/10	0.028
BMI (Normal/Overweight)	30/35	12/10	20/12	7/12	0.82
Smoking (No / Yes)	48/17	12/10	18/14	10/9	0.038
PPS ($\leq$14/>14)	39/22	16/5	9/23	8/11	0.004
Cardiac disease (No/Yes)	35/28	13/9	17/15	13/6	0.539
Respiratory disease (No/Yes)	57/6	20/2	29/3	18/1	0.664
Biliary Stent (No/Yes)	29/20	3/12	6/17	18/0	0.201
Cancer (No/Yes)	26/39	3/19	3/29	0/19	<0.001

p - Chi-square test

Obstructive jaundice was more common in females, smokers, patients with elevated POSSUM Physiology Score (PPS) and in patients with cancer. BMI - Body Mass Index, PPS - POSSUM Physiology Score

TABLE 3.2: The relationship between obstructive jaundice and preoperative biochemical parameters in patients undergoing pancreaticoduodenectomy.

	Preoperative Serum Bilirubin (μmol/L)				
n = 138	$\leq$ 17	18-35	35-250	> 250	p
Haemoglobin (g/dl)	13.0 (12.1-14.1)	13.2 (12.5-14.2)	11.9 (11.1-12.4)	11.7 (11.3-12.5)	<0.001
White cell count (x 10^9/l)	7.6 (6.5-9.2)	7.6 (6.4-9.5)	8.2 (6.7-9.4)	7.0 (6.2-9.2)	0.591
Prothrombin time (seconds)	11 (10-12)	11 (11-12)	11 (11-12)	11 (11-12)	0.618
Serum Urea (mmol/l)	5.0 (4.3-6.1)	5.2 (4.0-5.6)	5.5 (4.5-6.6)	4.5 (2.3-5.3)	0.093
Serum Creatinine (μmol/l)	71 (64-80)	75 (62-94)	71 (62-80)	65 (53-72)	0.221
Serum Sodium (mmol/l)	138 (136-140)	138 (136-139)	138 (135-140)	135 (130-137)	0.001
Serum Potassium (mmol/l)	4.1 (3.9-4.5)	4.3 (4.1-4.5)	4.1 (3.75-4.25)	3.8 (3.6-4)	<0.001
Aspartate transaminase (IU/l)	21 (17-30)	29 (27-48)	68.5 (33-144)	92.5 (70-116)	<0.001
Alanine transaminase (IU/l)	25 (16-41)	31 (24-73)	86.5 (50-157.5)	95 (53-149)	<0.001
Gamma-glutamyl transferase (IU/l)	81 (35-267)	111 (56-402)	263 (107-947)	495 (150-951)	<0.001
Alkaline phosphatase (IU/l)	110 (80-149)	150 (115-292)	233 (174-698.5)	372 (272-551)	<0.001
C-reactive protein (mg/l)	3.6 (1.8-9.5)	4.3 (2.4-8)	6.9 (3.6-33.5)	13 (8.3-20)	<0.001
Albumin (g/l)	37 (34-39)	36 (33-38)	31 (28-33)	25 (23-28)	<0.001

Values are median (inter-quartile range); p - Kruskal-Wallis test

Obstructive jaundice was associated with several abnormalities in preoperative blood test including low haemoglobin, abnormal electrolytes, deranged liver enzymes as well elevated C-reactive protein and hypoalbuminemia. Severity of inflammation as measured by CRP and albumin was directly related to severity of jaundice.

TABLE 3.3: The relationship between obstructive jaundice and pulmonary function tests in patients undergoing pancreaticoduodenectomy.

	Preoperative Serum Bilirubin (μmol/L)				
Pulmonary Function Test	≤ 17	18-35	35-250	> 250	p
FVC (litres)	4.09 (3.49-4.69)	3.76 (3.38-4.59)	3.76 (3.16-4.05)	3.35 (2.85-4.38)	0.092
FEV1 (litres)	2.95 (2.39-3.51)	2.90 (2.12-3.34)	2.68 (2.37-3.07)	2.72 (2.2-3.28)	0.556
Predicted FEV1 (%)	105.0 (91-116)	98.50 (87-114)	103.0 (95-111.5)	101.0 (94-116)	0.761
FEV1/FVC	72.0 (65-77)	73.0 (65-78)	75.50 (70.5-79.5)	78.0 (70-82)	0.115
Predicted FEV1/FVC (%)	94.0 (87-102)	96.0 (86-100)	99.0 (93-103)	102.0 (88-108)	0.107

Values are median (inter-quartile range); p - Kruskal-Wallis test

Pulmonary function tests performed immediately prior to cardiopulmonary exercise testing were compared between the non-jaundiced, jaundiced and severely jaundiced patients (Total n = 138). This did not show any relationship between obstructive jaundice and preoperative pulmonary function tests. FVC - Forced Vital Capacity, FEV1 - Forced Expiratory Volume in 1 second.

TABLE 3.4: The relationship between obstructive jaundice and cardiopulmonary exercise test parameters at the anaerobic threshold in patients undergoing pancreaticoduodenectomy.

	Preoperative Serum Bilirubin (μmol/L)				
Anaerobic Threshold	≤ 17	18-35	35-250	> 250	p
Load (Watts)	44.3 (32.5-60.0)	33.5 (27.5-51.0)	41.0 (31.0-56.0)	38.3 (30.5-48.0)	0.313
Min. Ventilation (l/min)	25.0 (20.4-30.5)	23.0 (20.5-29.0)	23.0 (19.0-28.0)	22.0 (18.5-25.0)	0.107
Tidal Volume (litres)	1.26 (1.06-1.52)	1.09 (0.83-1.39)	1.06 (0.94-1.44)	1.08 (0.82-1.26)	0.017
$\dot{V}_{O_2}$ (litres/min)	0.85 (0.71-1.00)	0.73 (0.62-0.81)	0.72 (0.58-0.86)	0.70 (0.58-0.82)	0.003
$\dot{V}_{O_2}$/kg (ml/kg/min)	11.1 (9.8-12.8)	10.6 (8.9-11.4)	9.9 (8.5-12.7)	9.6 (9.3-10.8)	0.029
$\dot{V}_E/\dot{V}_{O_2}$	28.5 (25.5-30.1)	29.4 (26.7-31.3)	28.3 (27.0-34.7)	27.8 (24.6-31.9)	0.510
$\dot{V}_{CO_2}$ (litres/min)	0.82 (0.66-1.0)	0.71 (0.58-0.93)	0.75 (0.58-0.90)	0.69 (0.52-0.79)	0.032
$\dot{V}_E/\dot{V}_{CO_2}$	28.9 (27.2-30.7)	28.9 (28.1-30.7)	30.6 (26.3-33.1)	30.4 (27.9-32.2)	0.449
RER	0.96 (0.9-1.03)	0.99 (0.89-1.04)	0.98 (0.94-1.07)	0.93 (0.91-1.04)	0.478
PET_{O2} (mmHg)	110.0 (104.3-112.6)	113.0 (109.0-115.0)	111.0 (106.0-117.0)	111.0 (105.0-114.5)	0.078
PET_{CO2} (mmHg)	36.8 (34.8-39.0)	36.0 (34.0-37.5)	34.0 (32.0-39.0)	35.0 (32.0-39.0)	0.204
O_2Pulse (ml/beat)	8.0 (7.0-9.0)	7.0 (5.0-9.0)	7.5 (5.0-9.0)	6.7 (5.0-8.0)	0.037
Heart rate (/min)	108 (96-122)	107 (90-118)	101 (89-118)	112 (96-125)	0.393
Respiratory Rate (/min)	19 (17-21)	22 (20-27)	21 (18-24)	19 (18-23)	0.022

Values are median (inter-quartile range); p - Kruskal-Wallis test

At anaerobic threshold, obstructive jaundice was compared to multiple CPET parameters. There were several statistically significant but non-linear relationships between preoperative serum bilirubin and CPET parameters. $\dot{V}_{O_2}$ - Oxygen consumption, $\dot{V}_{CO_2}$ - Exhaled CO_2, PETO_2/CO_2 - Partial pressure of end-tidal O_2/CO_2, O_2Pulse - Oxygen pulse.

TABLE 3.5: The relationship between obstructive jaundice and cardiopulmonary exercise test parameters at peak exercise in patients undergoing pancreaticoduodenectomy.

	Preoperative Serum Bilirubin (μmol/L)				
Peak Exercise	≤ 17	18-35	35-250	> 250	p
Load (Watts)	94.0 (76.5-114.5)	87.5 (56.0-107.0)	73.0 (58.0-108.0)	85.0 (66.0-101.0)	0.066
Min. Ventilation (l/min)	53.5 (46.0-69.0)	46.5 (34.0-62.0)	46.0 (38.0-63.0)	48.0 (37.0-67.0)	0.088
Tidal Volume (litres)	1.95 (1.6-2.41)	1.64 (1.46-1.98)	1.62 (1.35-2.19)	1.86 (1.18-2.21)	0.028
$\dot{V}_{O_2}$ (litres/min)	1.33 (1.09-1.57)	1.14 (0.90-1.32)	1.08 (0.85-1.5)	1.11 (0.89-1.38)	0.007
$\dot{V}_{O_2}$/kg (ml/kg/min)	17.2 (14.45-22.0)	14.7 (13.5-17.3)	15.1 (12.7-19.9)	15.7 (13.3-19.2)	0.056
$\dot{V}_E/\dot{V}_{O_2}$	40.5 (36.2-46.8)	43.1 (37.3-46.5)	41.9 (38.9-47.4)	46.7 (42.1-55.2)	0.073
$\dot{V}_{CO_2}$ (litres/min)	1.67 (1.37-2.01)	1.32 (1.02-1.84)	1.29 (1.04-1.88)	1.47 (1.03-1.76)	0.016
$\dot{V}_E/\dot{V}_{CO_2}$	31.9 (29.5-34.9)	32.1 (29.4-36.4)	33.1 (30.2-37.8)	37.4 (30.9-40.8)	0.110
RER	1.28 (1.20-1.42)	1.27 (1.20-1.42)	1.28 (1.22-1.36)	1.36 (1.25-1.42)	0.675
PET_{O2} (mmHg)	121 (118.5-125)	122 (120-126)	122 (120-125)	126 (123-128)	0.026
PET_{CO2} (mmHg)	35 (32.5-38)	35 (32-38)	34 (30-38)	33 (29-36)	0.283
O_2Pulse (ml/beat)	11.9 (9.11-14)	10.0 (8.0-12.0)	11.0 (9.61-13.93)	11.65 (8.26-13.94)	0.132
Heart rate (/min)	140 (125-158)	140 (129-152)	129 (114-144)	134 (128-158)	0.158
Respiratory Rate (/min)	30 (26-34)	32 (28-35)	30 (26-34)	31 (28-36)	0.512
Exercise Duration (minutes)	8.2 (6.2-10.4)	6.9 (5.5-9.2)	6.6 (4.8-9.0)	8.2 (5.2-9.7)	0.164

Values are median (inter-quartile range); p - Kruskal-Wallis test

At peak exercise, there were several statistically significant but non-linear relationships between obstructive jaundice and CPET parameters. However, total exercise duration, exercise load achieved and $\dot{V}_{O_2}$Peak (ml/kg/min) were not different between the non-jaundiced, jaundiced and severely jaundiced groups. $\dot{V}_{O_2}$ - Oxygen consumption, $\dot{V}_{CO_2}$ - Exhaled CO_2, PETO_2/CO_2 - Partial pressure of end-tidal O_2/CO_2, O_2Pulse - Oxygen pulse.

TABLE 3.6: The relationship between clinico-pathological characteristics and low $\dot{V}_{O_2}$AT (< 10 ml/kg/min) in patients undergoing pancreaticoduodenectomy: Univariate and multivariate binary logistic regression analysis

Variable		n	HR	95% CI	p	HR	95% CI	p
Age (years)	≤ 65	70						
	> 65	68	1.19	0.60-2.35	0.628			
Sex	Male	95						
	Female	43	2.74	1.30-5.74	0.008	3.75	1.57-8.95	0.003
Body Mass Index (kg/m^2)	≤ 25	69						
	> 25	69	3.09	1.51-6.32	0.002	3.65	1.61-8.26	0.002
Smoking	No	88						
	Yes	50	1.38	0.68-2.79	0.378			
Cardiovascular disease	No	78						
	Yes	58	0.82	0.41-1.64	0.569			
Respiratory disease	No	124						
	Yes	12	2.37	0.71-7.91	0.159			
Cancer	No	32						
	Yes	106	3.59	1.36-9.43	0.010	4.02	1.33-12.16	0.014
POSSUM Physiology Score	≤ 14	72						
	> 14	61	2.06	1.02-4.17	0.044			0.164
Biliary stent	No	56						
	Yes	49	0.69	0.32-1.50	0.347			
Bilirubin (μmol/l)	≤ 17	65						
	18-35	22	1.49	0.54-4.16	0.444			0.911
	36-250	32	2.30	0.95-5.56	0.064			0.537
	> 250	19	5.66	1.87-17.16	0.002			0.443
Haemoglobin (g/dl)	≥ 12	95						
	< 12	43	2.74	1.30-5.74	0.008			0.214
C-reactive protein (mg/l)	≤ 10	90						
	> 10	46	2.18	1.06-4.51	0.035	2.98	1.29-6.86	0.010
Albumin (g/l)	≥ 35	65						
	< 35	73	1.53	0.76-3.05	0.231			

Impaired oxygen consumption at the anaerobic threshold ($\dot{V}_{O_2}$AT < 10 ml/kg/min) was independently associated with female sex, body mass index > 25 kg/m^2, presence of cancer and raised preoperative C-reactive protein (CRP) level (> 10mg/l).

TABLE 3.7: The relationship between clinico-pathological characteristics and low $\dot{V}_{O_2}$Peak (< 16 ml/kg/min) in patients undergoing pancreaticoduodenectomy: Univariate and multivariate binary logistic regression analysis

Variable		n	HR	95% CI	p	HR	95% CI	p
Age (years)	≤ 65	70						
	> 65	68	1.50	0.77-2.94	0.237			
Sex	Male	95						
	Female	43	7.44	3.18-17.4	<0.001	7.57	3.09-18.5	<0.001
Body Mass Index (kg/m^2)	≤ 25	69						
	> 25	69	2.02	1.03-3.99	0.042	2.57	1.18-5.63	0.018
Smoking	No	88						
	Yes	50	1.90	0.94-3.85	0.073			
Cardiovascular disease	No	78						
	Yes	58	1.68	0.85-3.33	0.139			
Respiratory disease	No	124						
	Yes	12	2.35	0.67-8.21	0.181			
Cancer	No	32						
	Yes	106	2.06	0.90-4.69	0.085			
POSSUM Physiology Score	≤ 14	72						
	> 14	61	1.76	0.89-3.51	0.107			
Preop Biliary Drainage	No	56						
	Yes	49	0.91	0.42-1.97	0.814			
Bilirubin (μmol/l)	≤ 17	65						
	18-35	22	2.31	0.86-6.19	0.096			
	36-250	32	1.60	0.68-3.76	0.281			
	> 250	19	2.74	0.95-7.90	0.062			
Haemoglobin (g/dl)	≥ 12	95						
	< 12	43	2.80	1.32-5.93	0.007	2.43	1.05-5.63	0.038
C-reactive protein (mg/l)	≤ 10	90						
	> 10	46	1.42	0.69-2.90	0.333			
Albumin (g/l)	≥ 35	65						
	< 35	73	1.28	0.65-2.49	0.476			

Oxygen consumption at peak exercise ($\dot{V}_{O_2}$Peak) < 16 ml/kg/min was independently associated with female sex, body mass index > 25 kg/m^2, presence of cancer and raised preoperative C-reactive protein (CRP) level (> 10 mg/l).

3.4 Discussion

The results of the present study demonstrate that obstructive jaundice, even when severe, is not an independent risk factor for poor preoperative cardiopulmonary exercise physiology in patients undergoing pancreaticoduodenectomy. The results also demonstrate that obstructive jaundice is associated with elevated preoperative systemic inflammation with the severity of systemic inflammation related to the severity of the jaundice. The results also appear to suggest that there may be multiple other determinants of aerobic capacity including female sex, body mass index, haemoglobin, presence of cancer and systemic inflammation.

The use of CPET in preoperative risk prediction was first made popular over two decades ago by Older and co-workers [Older et al. 1993]. Since then cardiopulmonary exercise testing has been reported to be useful in identifying high risk patients prior to major general [Snowden et al. 2010], pancreatic [Ausania et al. 2012b][Chapter 2 of this thesis], oesophagogastric [Nagamatsu et al. 2001] as well as vascular [Carlisle et al. 2007] surgery. Cardiopulmonary exercise testing is superior to conventional measures of fitness due to the dynamic nature of the test that evaluates the adequacy of oxygen delivery to tissues under physiological stress. However, the factors responsible for poor aerobic capacity in surgical patients have not been adequately studied. The present study aimed to address this in patients undergoing major pancreatic surgery.

Experimental and animal studies have shown that obstructive jaundice was associated with myocardial depression [Green et al. 1986], poor myocardial response to inotropic stimulation [Lumlertgul et al. 1991], impaired sympathetic baroreflex sensitivity [Song et al. 2009] and deranged atrial natriuretic peptide levels [Pereira et al. 1994; Gallardo et al. 1998].

Historically, obstructive jaundice has also been reported to be associated with adverse haemodynamic events in patients undergoing major surgery. Intra-operative blood loss, postoperative hypotension, increased susceptibility to

shock and renal dysfunction were more common in patients with obstructive jaundice [Dixon et al. 1983; Pain et al. 1985; Green et al. 1995]. A recent review noted that bile acids had a complex range of receptor mediated effects on the cardiovascular system [Khurana et al. 2011]. Moreover, some of these effects appear to be partly reversible by biliary drainage as demonstrated by Padillo and co-workers [Padillo et al. 2001b].

These observations led to routine pre-operative biliary drainage being recommended in all jaundiced patients before undertaking major surgery. Pancreaticoduodenectomy was described by Whipple initially as a two-stage operation, with the first stage involving a cholecysto-gastrostomy aimed at relieving biliary obstruction before undertaking the resection at a later second operation [Whipple et al. 1935].

However, several recent studies have reported that PBD is associated with increased incidence of complications and that surgery in the jaundiced patients is safe. Pitt and co-workers in a prospective randomised trial compared outcomes in jaundiced patients undergoing surgery with or without PBD. They reported that PBD was associated with increased cost without any decrease in postoperative complications [Pitt et al. 1985]. A recent meta-analysis [Sewnath et al. 2002] pooled data from 5 randomised controlled trials comparing surgery with PBD versus surgery without drainage. The authors concluded that PBD not only did not improve postoperative complication rates or mortality but resulted in a higher overall complication rate due to the morbidity associated with the procedure itself. These findings have been reproduced in a more recent multicenter, randomised trial [Gaag et al. 2010]. A recent Cochrane Collaboration review of six trials including 520 patients concluded that PBD may be associated with serious adverse events and must not be performed routinely outside trial settings [Wang et al. 2008].

In the present study, obstructive jaundice was not independently related to $\dot{V}_{O_2}$AT or $\dot{V}_{O_2}$Peak. There was only a weak negative correlation between serum bilirubin and $\dot{V}_{O_2}$AT in our cohort. These findings are similar to those of Parker and

co-workers who reported that there was only a weak negative correlation between serum bilirubin and $\dot{V}_{O_2}$Peak (Pearson's ρ -0.21, p=0.02) and no correlation with $\dot{V}_{O_2}$AT (ρ = -0.15, p=NS) in patients undergoing pancreaticoduodenectomy [Parker et al. 2014]. Junejo and co-workers studied oxygen extraction in 9 jaundiced patients during cardiopulmonary exercise test by placing catheters within the femoral vein and reported that oxygen extraction was normal during cardiopulmonary exercise even in the presence of jaundice [Junejo et al. 2014a]

However, jaundice was associated with elevated preoperative systemic inflammation as measured by C-reactive protein levels and serum albumin. Obstructive jaundice is known to be associated with wide ranging abnormalities of both humoral and innate immune systems [Nehéz et al. 2002; Padillo et al. 2001a; Scott-Conner et al. 1994]. It is unclear if this preoperative immune dysfunction continues after surgery as an abnormal postoperative systemic inflammatory response and this is explored further in Chapter 5. However, studies suggest that the immunological abnormalities associated with obstructive jaundice did not improve after biliary drainage [Kimmings et al. 2000].

Elevated preoperative CRP was also independently associated with a low $\dot{V}_{O_2}$AT suggesting that impaired aerobic capacity may be associated with a systemic inflammatory response. This finding is similar to that reported by Sultan and co-workers who found that low $\dot{V}_{O_2}$AT was independently associated with an elevated preoperative neutrophil-lymphocyte ratio in patients undergoing colorectal surgery [Sultan et al. 2014].

The association between low haemoglobin and low $\dot{V}_{O_2}$Peak would appear to be more easily explained since the oxygen carrying capacity of blood depends on haemoglobin concentration. Indeed, the linear relationship between oxygen consumption during exercise and haemoglobin concentration has been shown both in disease states [Agostoni et al. 2010] as well as in healthy volunteers [Dellweg et al. 2008]. This would suggest that maintaining optimal haemoglobin levels in the perioperative period will improve oxygen delivery and perhaps outcome as

well. Excessive intra-operative blood loss has been reported to be associated with postoperative complications [Pratt et al. 2008a] and this may in part be due impaired oxygen delivery at a time of maximal physiological burden.

In the present study, it was of interest that $\dot{V}_{O_2}$, both at anaerobic threshold and at peak exercise, was significantly lower in females as well as in patients with a high body mass index. The basis of this relationship is not clear and may be related to body composition differences between these groups. However, such an association has been previously reported [Horwich et al. 2009]. This may reflect the difficulty in obtaining accurate $\dot{V}_{O_2}$ values in obese patients as a result of the calculations involved rather than due to true cardiopulmonary dysfunction. Other authors have suggested that different thresholds for CPET parameters may have to be considered in obese patients to improve risk-prediction [Donnelly et al. 1990; Hulens et al. 2001]. Presence of cancer was also an independent predictor of low $\dot{V}_{O_2}$AT. Sarcopenia is associated with reduced aerobic capacity [Evans et al. 1993] and is common in pancreatic cancer [Joglekar et al. 2015]. $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak must be interpreted with caution in these patient groups. This is the subject of further study in Chapter 4.

In conclusion, obstructive jaundice, including severe obstructive jaundice did not affect preoperative cardiopulmonary exercise physiology. Therefore, preoperative biliary drainage cannot be expected to improve aerobic capacity in patients undergoing pancreaticoduodenectomy. Both obstructive jaundice and low $\dot{V}_{O_2}$AT were associated with elevated preoperative systemic inflammation and provide further evidence of the role of jaundice and impaired aerobic capacity in immune dysregulation in these patients.

Chapter 4

An investigation into the relationship between cardiopulmonary exercise testing and body composition in patients undergoing pancreaticoduodenectomy.

4.1 Introduction

Major abdominal surgery especially for pancreatic disease is associated with significant morbidity and mortality. Patient selection is as important as identifying surgically treatable pathology in ensuring optimal outcomes [Bilimoria et al. 2007; Sandroussi et al. 2010].

4.1.1 Role of preoperative CPET

Cardiopulmonary exercise testing has become a useful tool in the preoperative evaluation and risk assessment/stratification of patients undergoing major thoracic and abdominal surgery. A number of studies have shown that poor aerobic fitness demonstrated by a low $\dot{V}_{O_2}$AT or low $\dot{V}_{O_2}$Peak or both was associated with increased morbidity and mortality after major surgery including bariatric [McCullough 2006], pancreatic [Ausania et al. 2012b][Chapter 2], liver [Epstein et al. 2004], cardiothoracic [Brunelli 2010; Campione et al. 2010; Torchio et al. 2010] and abdominal aortic aneurysm surgery [Carlisle et al. 2007; Thompson et al. 2011]. It is now routinely used in preoperative assessment to aid in risk assessment and patient selection. Cardiopulmonary exercise tests also help in identifying patients who may benefit from perioperative optimisation and more focussed care before, during and after major pancreatic surgery. Occasionally, patients may be denied surgery if their aerobic fitness as determined by cardiopulmonary exercise testing is felt to be too poor based on currently available evidence.

4.1.2 Factors affecting aerobic fitness

Aerobic fitness, as defined by the ability to perform physical exercise, is dependant on and often limited by the ability of the cardiorespiratory and circulatory systems to supply oxygen to skeletal muscles at times of increased demand as well as remove the main end product of aerobic metabolism, CO_2.

Several factors play an important role in meeting this increased metabolic demand. These include a normal cardiac and respiratory response to exercise and the oxygen carrying capacity of blood primarily determined by haemoglobin levels. Peripherally, an adequate circulatory response to local humoral factors and central autonomic control, capillary density within the skeletal muscle and the ability of skeletal muscle to utilise oxygen, which is in turn determined by mitochondrial mass and function are important factors.

Inadequate or inappropriate response of any of the above mentioned factors will result in overall limitation of oxygen delivery or utilisation and aerobic fitness. Cardiopulmonary exercise testing allows the accurate measurement of most of these factors either directly or indirectly during dynamic exercise. This allows identifying not only limitations in aerobic fitness but also the possible causes for such limitation.

A low $\dot{V}_{O_2}$ has universally been attributed to low aerobic fitness due to an inadequate response of the cardiovascular and respiratory systems. This is often thought to be due to cardiorespiratory disease, overt or sub-clinical. Occasionally, other factors such as anaemia [Agostoni et al. 2010], peripheral vascular disease and rarely, mitochondrial diseases [Fernández et al. 2000] have been identified as contributing to low aerobic capacity.

The most common parameters used to quantify perioperative risk in surgical patients are oxygen consumption at the anaerobic threshold ($\dot{V}_{O_2}$AT) and at peak exercise capacity ($\dot{V}_{O_2}$Peak). Conventionally these have been reported as per weight ratios (ml/kg/min) to allow comparison between patients. However, numerous studies on cardiorespiratory exercise physiology have reported that normalising $\dot{V}_{O_2}$ using total body weight leads to spurious correlation errors unfairly penalising obese subjects [Seltzer 1940; Tanner 1949; Toth et al. 1993; Batterham et al. 1999; Goran et al. 2000; Krachler et al. 2014]

4.1.3 Aims

In chapter 2, we reported that low $\dot{V}_{O_2}$AT in patients undergoing pancreaticoduodenectomy was associated with increased incidence of postoperative pancreatic fistula and prolonged hospital stay. We also reported that patients with a $\dot{V}_{O_2}$AT less than 10 ml/kg/min were less likely to receive postoperative adjuvant chemotherapy. In chapter 3, while examining the relationship between preoperative clinico-pathological characteristics and cardiopulmonary exercise physiology, we observed that a high body mass index was associated with a low $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak independent of all other factors. Moreover, most of our patients did not have overt cardiac or respiratory comorbidity to explain these findings.

We hypothesised at the end of chapter 3 that low $\dot{V}_{O_2}$ values in obese patients may be a result of the calculations involved rather than due to true cardiopulmonary dysfunction. The aim of the present study was to examine the relationship between cardiopulmonary exercise testing and body composition in patients undergoing pancreaticoduodenectomy in an attempt to explain the strong negative correlation between low $\dot{V}_{O_2}$ and body mass index.

4.2 Patients and methods

4.2.1 Patients

Patients scheduled to undergo pancreaticoduodenectomy for malignant or benign disease involving the head of the pancreas and periampullary region between August 2008 and October 2010 were included in this study. All data were recorded in a prospectively maintained database. Data was collected on demographics, preoperative clinico-pathological characteristics including blood tests, body mass index, weight, height and the underlying surgical pathology. Detailed breath-by-breath data on a variety of physiological and gas-exchange parameters measured at cardiopulmonary exercise testing were also collected from a prospectively maintained database. Cardiopulmonary exercise testing methodology is discussed in Section 1.5.2 (page 28)and a description of the parameters measured at cardiopulmonary exercise testing is provided in Section 1.6 (page 28). A complete dataset for one sample patient is shown in Appendix C on page 198.

4.2.2 Calculation of body composition

Computed tomography of the abdomen, performed as part of the routine preoperative staging, was used to calculate body composition based on previously published methods [Bredella et al. 2010; Shen et al. 2004].

The coronal and sagittal reconstructions were used to accurately identify the L3 and L4 vertebrae. The CT window width (W) was set at 400 and the level/centre (C) was set at 40. This allowed tissue between -160 Hounsfield units and +240 Hounsfield units to be represented in grayscale with adequate contrast between tissues of interest. The cross-sectional images at these levels where then exported as grayscale bitmap images. The scale in millimetres was included with every image. A representative image is shown in Fig. 4.1a. The GNU Image Manipulation Program (GIMP), an advanced, free, open-source, raster graphics

editor was used for analysis of all images (www.gimp.org). The use of GIMP to analyse cross-sectional imaging for body composition has been described previously although by using a different technique to what has been employed by us [Anblagan et al. 2013].

The first step involved converting the bitmap images into JPEG images using lossy compression set at 85% to minimise sharp transitions between grey areas of very similar colour values. This allowed more consistent selection of contiguous areas of similar grey shades.

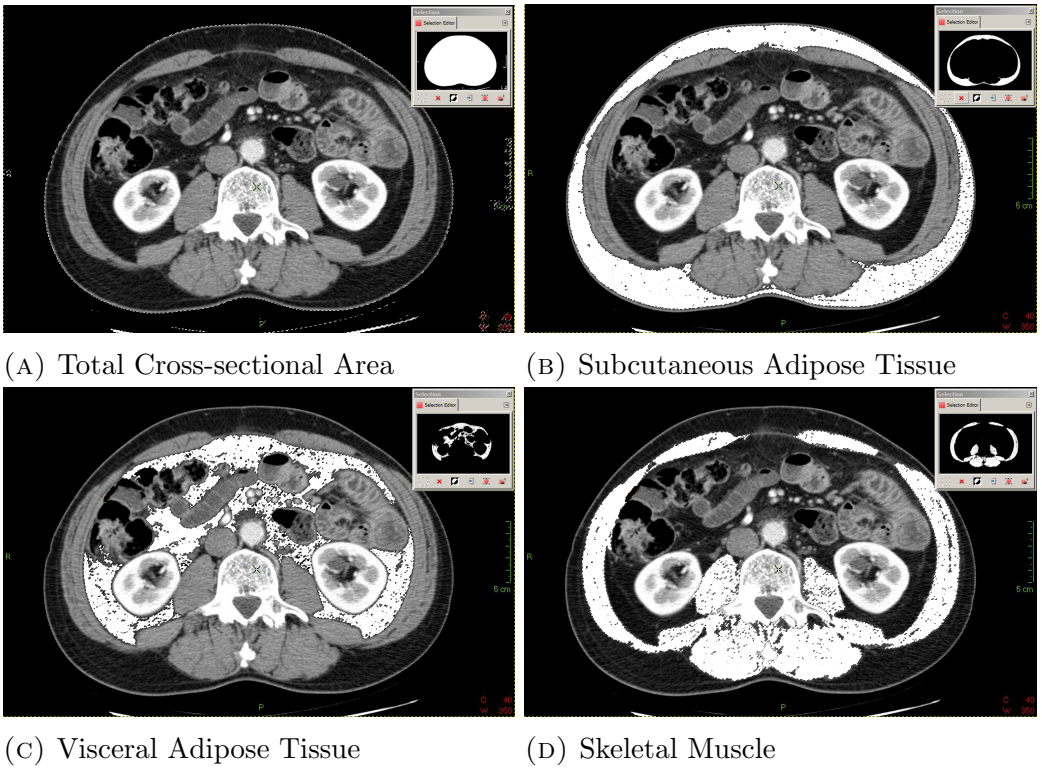
The next step involved standardising the scale of all images by dividing the length of the scale on every image by the number of pixels along the scale. This resulted in a length in millimetres for each pixel in each image. As pixels on a CT image are square, the area of each pixel was calculated as the square of its length.

The Fuzzy Select (Magic Wand) tool was used to select contiguous areas of similar colour while simultaneously confirming visually that the correct anatomical structures had been selected without overspill into adjoining unwanted tissue areas. The number of pixels within the selection was obtained using the 'Histogram' dialog window and entered into a Microsoft Excel spreadsheet. The area was calculated by multiplying the number of pixels by the area of each pixel.

Selecting tissue compartments:

The sequence of steps followed to calculate the area of each tissue compartment is depicted in Fig. 4.1 on page 106. The total cross-sectional area of the abdomen at the level of L3/L4 was calculated by first selecting all the empty space outside the image followed by inverting this selection. This is depicted in Fig. 4.1a. Subcutaneous fat in the image was selected using the Fuzzy Select tool (if necessary by choosing multiple times and removing any unnecessary areas) as depicted in Fig. 4.1b. The same process was repeated for visceral adipose tissue and skeletal muscle as depicted in Fig. 4.1c and Fig. 4.1d respectively. Every selection was visually confirmed for anatomical accuracy by using the layer selection tool to

inspect the selected area as shown in the insets in each of the images.



(A) Total Cross-sectional Area (B) Subcutaneous Adipose Tissue

(C) Visceral Adipose Tissue (D) Skeletal Muscle

FIGURE 4.1: Selection of components of body composition from CT images using GIMP.

The total cross-sectional area was selected by first selecting the empty space outside the image followed by inverting this selection as depicted in (A). The 'Fuzzy Select' tool was then used to select individual body composition components with visual confirmation using the 'layer selection' tool. This is shown in B, C and D. The selected area has been removed for representation purposes. The insets in each image confirm the area selected.

4.2.3 Cardiopulmonary exercise testing

All patients performed cardiopulmonary exercise testing on a cycle ergometer as described in Section 1.5.2. Raw data of all breath-by-breath parameters averaged every 10 seconds was collected for analysis. The first three minutes of the recorded data were during the rest period when the patients were on the exercise bike but did not exercise. The average of each parameter measured between the first and second minute (6 readings) was treated as the rest value. Anaerobic threshold was

identified using previously established methods [Beaver et al. 1986; Sue et al. 1988] and all corresponding parameters at this point were recorded. Peak exercise was identified by the maximum oxygen consumption recorded towards the end of the exercise period and all other parameters recorded at this point were considered as peak exercise values.

In order to distinguish between absolute values and values scaled to total body weight, the terms 'absolute $\dot{V}_{O_2}$' and 'corrected $\dot{V}_{O_2}$' are used throughout this chapter. When $\dot{V}_{O_2}$ has been scaled to an alternate factor, this is stated clearly.

4.2.4 Estimation of lean body mass

Estimated lean body mass (eLBM) was calculated using the Boer formula [Boer 1984] as shown below.

$$Men: \ eLBM = 0.407 \times weight(kg) + 0.267 \times height(cm) - 19.2 \tag{4.1}$$

$$Women: \ eLBM = 0.252 \times weight(kg) + 0.473 \times height(cm) - 48.3 \tag{4.2}$$

4.2.5 Statistics

Comparison between body composition and cardiopulmonary exercise testing parameters was done using Partial correlations controlling for the effect of sex (and/or age). The relationship between body composition and preoperative clinico-pathological characteristics (as categorical variables) was analysed using non-parametric tests. The Mann-Whitney U test was used for variables with two categories while the Kruskal-Wallis test was used for variables with more than two categories. Previously established thresholds were used for categorising continuous variables where applicable. All reported p-values are two-sided. The level of significance was set at $p < 0.05$. SPSS software (Version 22.0; SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

4.3 Results

4.3.1 Body composition and clinico-pathological characteristics

Eighty-two patients (52 male) were included in the study. The clinico-pathological characteristics of the study patients and their relationship to body composition is shown in Table 4.1 on page 109. There were several significant associations between clinico-pathological variables and body composition as shown in this table. Females had a greater area of subcutaneous adipose tissue (223.9 versus 141.6 cm^2, $p<0.001$) but less visceral adipose tissue (79.1 versus 174.9 cm^2, $p<0.001$). However, there was no difference in the total adipose tissue area between men and women (316.6 versus 303.0 cm^2, $p=0.665$). Skeletal muscle area was greater in males than in females (141.3 versus 99.7 cm^2).

There was no association between deprivation as defined by the Scottish Index of Multiple Deprivation (SIMD) and body composition. Hypoalbuminemia was associated with less visceral adipose tissue ($p=0.013$) and less skeletal muscle area that did not reach statistical significance ($p=0.054$). Anaemia (haemoglobin < 12 g/dl) was associated with increased adiposity in the subcutaneous plane and reduced skeletal muscle area.

TABLE 4.1: The relationship between body composition and clinico-pathological characteristics of patients undergoing major pancreatic surgery.

			Subcutaneous fat		Visceral fat		Total fat		Skeletal Muscle	
		n	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
Age (years)	< 65	35	171.4 (115.7)	0.8256	125.3 (95.1)	0.201	297.0 (178.5)	0.309	128.7 (29.4)	0.590
	≥ 65	47	171.9 (119.2)		150.8 (96.9)		322.7 (156.6)		124.1 (31.3)	
Gender	M	52	141.6 (102.4)	<0.001	174.9 (99.1)	<0.001	316.6 (170.8)	0.665	141.3 (26.1)	<0.001
	F	30	223.9 (123.9)		79.1 (51.6)		303.0 (159.3)		99.7 (15.6)	
BMI (kg/m^2)	≤ 25	39	115.1 (54.4)	<0.001	93.2 (76.0)	<0.001	205.9 (97.0)	<0.001	114.6 (26.6)	0.002
	25-30	31	191.6 (86.7)		158.9 (81.9)		350.6 (99.6)		136.0 (30.4)	
	> 30	12	304.6 (196.4)		250.0 (85.5)		554.6 (185.9)		137.6 (30.9)	
SIMD	4-5	23	199.8 (130.9)	0.130	139.5 (94.2)	0.865	339.4 (169.8)	0.345	124.2 (28.7)	0.800
	1-3	59	160.8 (110.4)		140.0 (98.1)		300.8 (164.4)		126.8 (31.2)	
Malignancy	No	10	185.7 (168.3)	0.876	167.1 (148.3)	0.910	352.8 (278.1)	0.955	122.4 (24.0)	0.788
	Yes	72	169.8 (109.5)		136.1 (87.7)		305.9 (145.9)		126.6 (31.3)	
Corr. $\dot{V}_{O_2}$AT	≥ 10	39	132.6 (85.8)	<0.001	124.5 (90.9)	0.171	257.2 (144.3)	0.003	131.5 (33.2)	0.111
(ml/kg/min)	< 10	43	207.2 (130.5)		153.8 (100.2)		361.0 (170.1)		121.2 (27.1)	
Corr. $\dot{V}_{O_2}$Peak	≥ 16	35	125.5 (75.9)	<0.001	123.8 (92.2)	0.170	249.3 (143.0)	0.002	136.9 (31.1)	<0.001
(ml/kg/min)	< 16	47	206.1 (130.4)		151.9 (98.7)		358.1 (167.7)		118.0 (27.5)	
CRP (mg/l)	≤ 10	50	157.4 (96.7)	0.190	146.3 (101.5)	0.635	303.7 (145.2)	0.985	128.7 (33.5)	0.392
	> 10	32	194.1 (141.9)		129.9 (88.6)		324.0 (195.6)		122.0 (24.7)	
Albumin (g/l)	≥ 35	32	162.1 (115.8)	0.300	177.3 (108.1)	0.013	339.4 (179.3)	0.213	134.5 (34.1)	0.054
	< 35	50	177.9 (118.5)		115.9 (80.5)		293.8 (155.8)		120.7 (26.7)	
Haemoglobin (g/dl)	≥ 12	50	148.0 (86.5)	0.031	144.5 (98.5)	0.704	292.5 (145.4)	0.372	133.4 (32.1)	0.005
	< 12	32	208.7 (147.1)		132.8 (94.2)		341.5 (192.2)		114.6 (23.6)	
PPS	≤ 14	41	176.3 (119.7)	0.900	147.0 (98.7)	0.544	323.2 (155.0)	0.347	129.8 (34.5)	0.351
	> 14	41	167.2 (115.5)		132.8 (94.7)		300.0 (177.1)		122.4 (25.5)	
Cardiac	No	43	177.2 (135.9)	0.770	128.3 (102.9)	0.127	305.5 (195.5)	0.208	120.7 (33.0)	0.047
disease	Yes	39	165.7 (93.2)		152.7 (88.4)		318.4 (127.6)		132.0 (26.4)	
Respiratory	No	72	175.2 (120.5)	0.600	143.8 (98.2)	0.321	319.0 (169.3)	0.342	125.8 (30.5)	0.810
disease	Yes	10	146.5 (88.3)		111.8 (81.0)		258.3 (133.3)		128.0 (30.9)	

BMI - Body Mass Index; SIMD - Scottish Index of Multiple Deprivation; PPS - POSSUM Physiology Score

p - Mann-Whitney U test (2 categories), Kruskal-Wallis test (more than 2 categories)

4.3.2 Body composition vs. BMI/sex

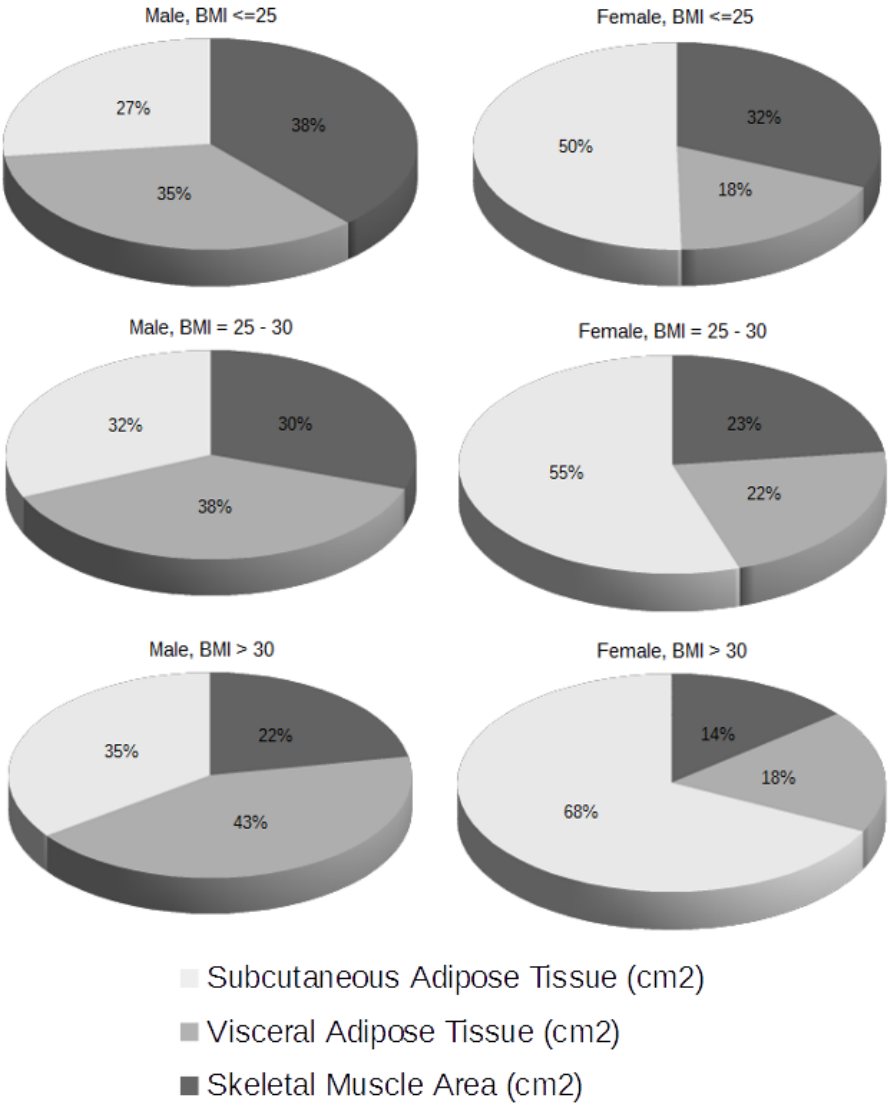


FIGURE 4.2: Differences in body composition according to sex and BMI.

Body composition differed significantly between men and women and with increasing body mass index (BMI). The proportion of skeletal muscle area decreased with increasing BMI in both sexes but there was a larger decrease in women than men. Visceral adipose tissue contributed more to weight in obese men than subcutaneous adipose tissue while the opposite was true in women.

The body composition differences between male and female patients with increasing body mass index is shown in Figure 4.2 on page 110. There were significant differences in the proportion of subcutaneous adipose tissue versus visceral adipose tissue between males and females. Men generally had less

subcutaneous fat but more visceral fat and skeletal muscle areas. However, the proportion of skeletal muscle in both males and females decreased significantly with increasing body mass index.

The proportion of skeletal muscle area decreased from 38% in male patients with normal BMI to 22% in obese males. There was a greater decrease in the proportion of skeletal muscle in females with increasing BMI, with skeletal muscle area decreasing from 32% in females with normal BMI to 14% in obese females. The higher weight in the overweight/obese patients was due to a disproportionate increase in adipose tissue rather than skeletal muscle. Moreover, the distribution of the adipose tissue differed between males and females. Visceral adipose tissue contributed more to weight in obese males (43% VAT vs. 35% SAT) while obese females had a greater proportion of subcutaneous adipose tissue than visceral adipose tissue (18% VAT vs. 68% SAT).

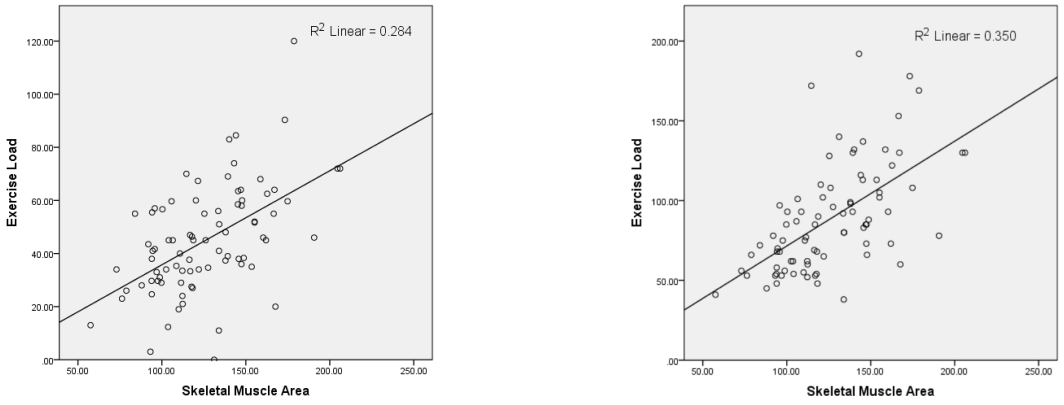
4.3.3 Body composition vs. pulmonary function tests

Partial correlation analysis was performed to study the relationship between pulmonary function tests and body composition. It has been well-established in previous studies that pulmonary function tests are correlated with age and sex and the analysis was therefore adjusted for these two variables. Forced Vital Capacity (FVC, litres), Forced Expiratory Volume in 1 second (FEV1, litres) and the ratio FEV1/FVC (Tiffeneau-Pinelli index,%) were compared against the various components of body composition. Both FVC and FEV1 were positively correlated with skeletal muscle but not with adipose tissue area. FEV1/FVC was not associated with any of the body composition components.

This would indicate that pulmonary function was dependent on skeletal muscle area while FEV1/FVC, a calculated index to quantify restrictive or obstructive lung disease, was not associated with skeletal muscle area. These results are shown in Table 4.2 on page 115.

4.3.4 Body composition vs. exercise load

Exercise loads achieved at anaerobic threshold and at peak exercise capacity were plotted against skeletal muscle area to create scatter-plots(Fig. 4.3 on page 112). Exercise load correlated positively with skeletal muscle area both at anaerobic threshold ($\rho^2 = 0.284, p < 0.001$, Fig. 4.3a) and at peak exercise ($\rho^2 = 0.350, p < 0.001$, Fig. 4.3b). However, no correlation was identified between exercise loads achieved and adipose tissue area either at anaerobic threshold ($\rho^2 = 0.004, p = 0.587$) or peak exercise ($\rho^2 = 0.020, p = 0.206$) as shown in Table 4.2 on page 115.



(A) Anaerobic Threshold (B) Peak Exercise

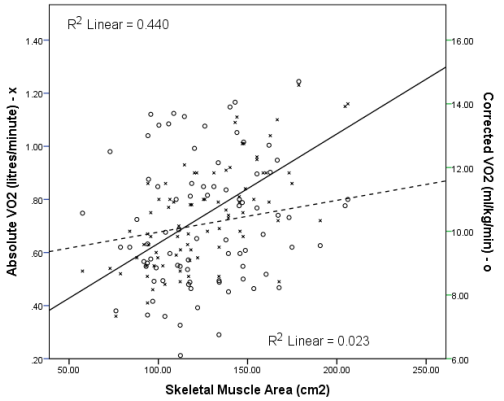
FIGURE 4.3: Correlation between exercise load and skeletal muscle area.

Scatter plots A and B show a positive correlation between exercise load achieved and skeletal muscle area both at anaerobic threshold ($p < 0.001$) and peak exercise ($p < 0.001$) respectively.

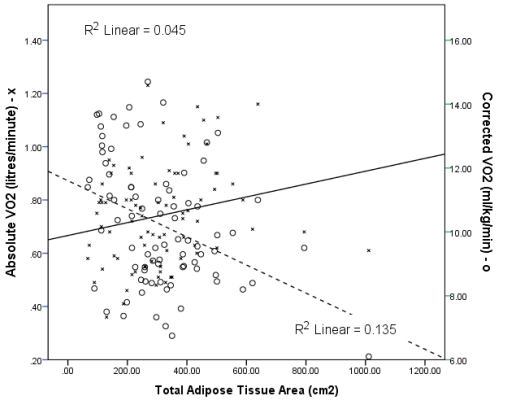
4.3.5 Body composition vs. oxygen consumption

Partial correlations between cardiopulmonary exercise parameters at rest, anaerobic threshold and peak exercise versus body composition were adjusted for sex. Our own findings (Tables 3.6 and 3.7 on pages 94, 95) and the findings of other authors suggest that age is not related to $\dot{V}_{O_2}$AT or $\dot{V}_{O_2}$Peak and therefore no adjustments were made for age. The results of this analysis are shown in Table 4.2 (page 115).

Tidal volume ($\dot{V}_T$, litres) was significantly correlated with skeletal muscle area at all phases of exercise including at rest, anaerobic threshold and peak exercise. There was a statistically significant but weak positive correlation between minute ventilation ($\dot{V}_E$, litres) and skeletal muscle at anaerobic threshold and peak exercise but not at rest. There was no correlation between either of these measures of pulmonary function and adipose tissue area at any phase of exercise.



(A) $\dot{V}_{O_2}$AT vs. Skeletal Muscle



(B) $\dot{V}_{O_2}$AT vs. Total Adipose Tissue

FIGURE 4.4: Correlation between body composition and $\dot{V}_{O_2}$AT before and after correction for total body weight.

The solid line in A shows a positive correlation between absolute $\dot{V}_{O_2}$ and skeletal muscle area ($p < 0.001$) while in B it shows no correlation with total adipose tissue as expected of exercise physiology. However, normalisation of $\dot{V}_{O_2}$ using total body weight results in a 'spurious' negative correlation with total adipose tisue area as depicted by the dotted line in B ($p < 0.001$). This indicates that patients with high body mass index and excess adipose tissue will have low corrected $\dot{V}_{O_2}$, the value that is commonly used in clinical practice.

Absolute $\dot{V}_{O_2}$ (litres/min) had a strong positive correlation with skeletal muscle area at rest ($\rho = 0.353, p = 0.001$), at anaerobic threshold ($\rho = 0.463, p < 0.001$) and at peak exercise ($\rho = 0.375, p = 0.001$). However, this correlation was lost after correction of $\dot{V}_{O_2}$ for total body weight and there was a non-significant change in the direction of correlation to the negative.

Absolute $\dot{V}_{O_2}$ (litres/min) had no correlation with total adipose tissue at rest or at peak exercise and only a weak correlation at anaerobic threshold. However, when corrected for total body weight, there was a strong negative correlation between corrected $\dot{V}_{O_2}$ (ml/kg/min)and total adipose tissue at rest ($\rho = -0.482, p < 0.001$),

anaerobic threshold ($\rho = -0.400, p < 0.001$) and peak exercise ($\rho = -0.374, p = 0.001$).

The loss of physiological relationship between $\dot{V}_{O_2}$ and skeletal muscle after correcting for total body weight is shown in Fig.4.4a and the creation of a spurious relationship with total adipose tissue after correction for total body weight is shown in Fig. 4.4b.

O_2Pulse at the anaerobic threshold and peak exercise was strongly associated with skeletal muscle area with weaker positive correlations with visceral fat and total fat content. There was no correlation between O_2Pulse and subcutaneous adipose tissue at any phase of exercise.

TABLE 4.2: The relationship between body composition and cardiopulmonary exercise testing controlled for sex in patients undergoing major pancreatic surgery.

	Subcut Fat area (cm^2)		Visceral Fat area (cm^2)		Total Fat area (cm^2)		Skeletal muscle (cm^2)	
Variable	ρ	p	ρ	p	ρ	p	ρ	p
Pulmonary Function Tests[a]								
FVC	-0.084	0.461	-0.111	0.332	-0.112	0.325	0.303	0.007
FEV1	-0.050	0.659	0.043	0.704	-0.012	0.919	0.350	0.002
FEV1/FVC	0.0	1.0	0.200	0.077	0.101	0.374	0.003	978
At Rest[b]								
Minute Ventilation	0.117	0.303	0.076	0.504	0.116	0.307	0.136	0.230
Tidal Volume	0.076	0.505	0.130	0.252	0.116	0.305	0.301	0.007
Absolute $\dot{V}_{O_2}$	0.123	0.277	0.163	0.148	0.164	0.145	0.353	0.001
Corrected $\dot{V}_{O_2}$	-0.424	<0.001	-0.396	<0.001	-0.482	<0.001	-0.194	0.085
O_2 Pulse	0.110	0.330	0.134	0.238	0.141	0.212	0.192	0.087
At Anaerobic Threshold[b]								
Exercise Load	0.085	0.454	0.085	0.454	0.105	0.349	0.377	0.001
Minute Ventilation	0.194	0.085	0.127	0.261	0.198	0.076	0.263	0.018
Tidal Volume	0.124	0.274	0.154	0.172	0.170	0.128	0.436	<0.001
Absolute $\dot{V}_{O_2}$	0.191	0.089	0.184	0.103	0.231	0.038	0.463	<0.001
Corrected $\dot{V}_{O_2}$	-0.326	0.003	-0.365	0.001	-0.400	<0.001	-0.078	0.487
O_2 Pulse	0.181	0.108	0.227	0.043	0.242	0.029	0.338	0.002
At Peak Exercise[b]								
Exercise Load	0.029	0.799	-0.025	0.824	0.020	0.859	0.373	0.001
Minute Ventilation	0.080	0.483	0.080	0.483	0.112	0.321	0.242	0.029
Tidal Volume	0.061	0.593	0.153	0.174	0.138	0.219	0.409	<0.001
Absolute $\dot{V}_{O_2}$	0.087	0.444	0.041	0.716	0.093	0.407	0.375	0.001
Corrected $\dot{V}_{O_2}$	-0.295	0.008	-0.365	0.001	-0.374	0.001	-0.027	0.813
O_2 Pulse	0.200	0.075	0.240	0.032	0.261	0.019	0.363	0.001

ρ - Pearson's r adjusted for *a* - age and sex and *b* - sex.

Skeletal muscle area (but not adipose tissue) was positively correlated with FVC and FEV1. Skeletal muscle area also showed positive correlations with CPET parameters that had not been corrected for total body weight as expected during exercise. Exercise load, minute ventilation, tidal volume and O_2Pulse were all positively correlated with skeletal muscle area. However, $\dot{V}_{O_2}$ corrected for total body weight was negatively correlated with adipose tissue area at all phases of exercise suggesting a non-physiological 'spurious' correlation. FVC - Forced Vital Capacity, FEV1 - Forced Expired Volume in 1 second.

4.3.6 Scaling oxygen consumption to body composition and other factors

Absolute $\dot{V}_{O_2}$ at the anaerobic threshold was corrected for weight, the square of height, body mass index, skeletal muscle area and estimated lean body mass. Calculation of estimated lean body mass is shown in Section 4.2.4. The resulting values were compared to body composition, height, weight and body mass index using partial correlations controlling for sex (Table 4.3 on page 117). The results from Table 4.2 comparing absolute $\dot{V}_{O_2}$ and corrected $\dot{V}_{O_2}$ at the anaerobic threshold with body composition are reproduced in the first two columns of this table to allow comparison with the new indices.

$\dot{V}_{O_2}$ scaled for skeletal muscle area had no significant correlation with adipose tissue, height, weight or BMI but had a negative correlation with skeletal muscle area. $\dot{V}_{O_2}$ corrected for the square of patient's height had no correlation with adipose tissue but retained a positive correlation with skeletal muscle area as well as a positive correlation with total body weight and BMI.

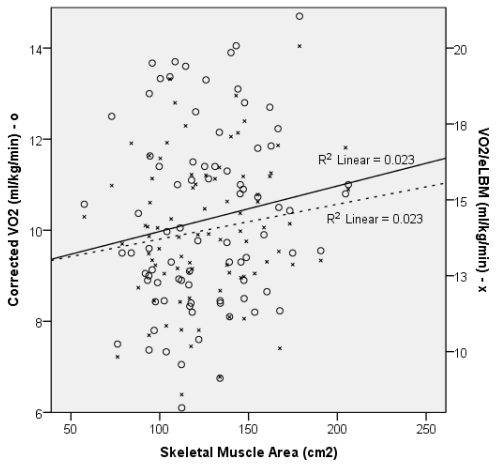
However, when absolute $\dot{V}_{O_2}$ was corrected for lean body mass, there was no correlation with any of the body composition indices or with height, weight or body mass index. The negative correlation between adipose tissue and $\dot{V}_{O_2}$ corrected for total body weight did not occur when $\dot{V}_{O_2}$ was corrected for lean body mass (Fig. 4.5b). Moreover, the correlation with skeletal muscle area remained unchanged regardless of whether $\dot{V}_{O_2}$ was corrected for total body weight or lean body mass (Fig. 4.5a).

TABLE 4.3: The relationship between body composition, body habitus and $\dot{V}_{O_2}$AT scaled using different factors (controlled for sex) in patients undergoing major pancreatic surgery.

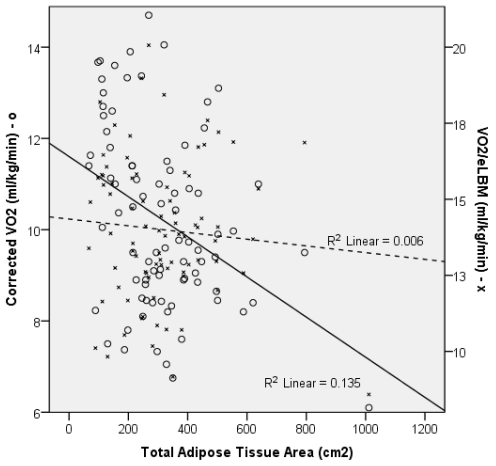
	Absolute $\dot{V}_{O_2}$		$\frac{\dot{V}_{O_2}}{Weight}$		$\frac{\dot{V}_{O_2}}{Height^2}$		$\frac{\dot{V}_{O_2}}{BMI}$		$\frac{\dot{V}_{O_2}}{Skeletal\ Muscle}$		$\frac{\dot{V}_{O_2}}{Lean\ Body\ Mass}$	
Variable	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p	ρ	p
Subcut. fat (cm^2)	0.191	0.089	-0.326	0.003	0.169	0.132	-0.217	0.051	0.018	0.872	-0.041	0.716
Visceral fat (cm^2)	0.184	0.103	-0.365	0.001	0.154	0.168	-0.279	0.012	-0.065	0.563	-0.108	0.339
Total fat (cm^2)	0.231	0.038	-0.400	<0.001	0.191	0.088	-0.286	0.010	-0.021	0.851	-0.082	0.466
Skeletal Muscle (cm^2)	0.463	<0.001	-0.078	0.487	0.329	0.003	0.105	0.353	-0.429	<0.001	0.133	0.237
Height (cm)	0.446	<0.001	0.019	0.870	0.001	0.993	0.475	<0.001	0.105	0.350	0.019	0.865
Weight (kg)	0.545	<0.001	-0.302	0.006	0.358	0.001	-0.043	0.703	0.001	0.995	0.033	0.770
Body Mass Index (kg/m^2)	0.357	0.001	-0.363	0.001	0.425	<0.001	-0.345	0.002	-0.059	0.603	0.035	0.756

ρ - Pearson's partial correlation adjusted for sex.

$\dot{V}_{O_2}$AT normalised using different measures of body habitus (including weight, square of height, body mass index, skeletal muscle area and estimated lean body mass) was compared to body composition as well as weight, height and BMI in an exploratory analysis. Scaling $\dot{V}_{O_2}$AT using estimated lean body mass was the only method studied that did not result in any 'spurious' correlations with body composition or body habitus. This is also depicted in Fig. 4.5 on page 118.



(A) $\dot{V}_{O_2}$AT vs. Skeletal Muscle



(B) $\dot{V}_{O_2}$AT vs. Total Adipose Tissue

FIGURE 4.5: Correlation between body composition and $\dot{V}_{O_2}$AT corrected for total body weight and estimated lean body mass.

Fig. A shows that there is little difference in the relationship between skeletal muscle area and $\dot{V}_{O_2}$ corrected using either total body weight or estimated lean body mass. However, while $\dot{V}_{O_2}$ corrected for total body weight had a 'spurious' negative correlation with total adipose tissue area (solid line in B), this 'spurious' relationship was no longer present when $\dot{V}_{O_2}$ was normalised using estimated lean body mass (dotted line in B).

4.4 Discussion

The results of this study demonstrate that the most important cardiopulmonary exercise test parameters used for preoperative risk evaluation in surgery are influenced significantly by the patient's body composition. Both $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak were significantly affected by patient's body habitus when scaled using total body weight. Furthermore, the results suggest that there may be alternate methods of scaling of $\dot{V}_{O_2}$ that removes the effect of body composition on these parameters. The results also demonstrate the disproportionate decrease in skeletal muscle area with associated increase in adipose tissue with increasing body mass index.

Taken together, these results would suggest that caution should be exercised in interpreting $\dot{V}_{O_2}$ (corrected for total body weight, ml/kg/min) in patients with a raised BMI. Abnormally low values in these patients may not necessarily be due to poor aerobic fitness or lack of cardiopulmonary reserve and may simply be due to current convention used for scaling/representing $\dot{V}_{O_2}$.

4.4.1 Oxygen consumption and body composition

Increased physical activity such as during cardiopulmonary exercise testing or during and after surgery results in greater oxygen consumption ($\dot{V}_{O_2}$). The increased demand for oxygen is primarily due to increased metabolic activity within the exercising skeletal muscle. Therefore, the positive correlation between absolute $\dot{V}_{O_2}$ and skeletal muscle area as has been found here is easily explained by the physiology of aerobic exercise.

However, current convention is to report $\dot{V}_{O_2}$ measured at cardiopulmonary exercise testing according to the following formula:

$$Corrected\ \dot{V}_{O_2}(ml.kg^{-1}.min^{-1}) = \frac{Absolute\ \dot{V}_{O_2}\ (litres.min^{-1}) * 1000}{Total\ body\ weight\ (kg)}$$

In chapter 3, we reported that there was a significant negative correlation between corrected $\dot{V}_{O_2}$ (ml/kg/min) and the patient's body mass index in spite of no observable cardiopulmonary comorbid disease (Tables 3.6 and 3.7). This negative correlation existed both at anaerobic threshold and peak exercise. The results of the present study demonstrate that this negative correlation is consequent to the scaling convention used rather than due to any pathophysiological effect of obesity.

The loss of the strong positive correlation between absolute VO_2 (litres/min) and skeletal muscle area after correcting for total body weight further supports the argument that the corrected value for $\dot{V}_{O_2}$ under-reports aerobic capacity in obese patients. There was no correlation between pulmonary function tests, tidal volume and minute ventilation and adipose tissue area. However, a statistically significant, positive correlation was present between adipose tissue and O_2Pulse at anaerobic threshold as well as peak exercise but not at rest. These findings suggest that adiposity did not contribute to poor cardiopulmonary exercise performance in this cohort of patients.

4.4.2 Comparison with previous studies

Our findings are similar to those reported by several authors previously. The relationship between body size, body composition and aerobic capacity both at rest and during exercise has been studied extensively for over a hundred years.

Seltzer reported in his 1940 study of 34 subjects that individuals who were more 'lateral' than 'linear' had lower oxygen intakes per kilo body weight [Seltzer 1940]. Tanner in his article titled *'Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation'* in the Journal of Applied Physiology in 1947 recognised the dangers of expressing physiological variables as a function of total body mass [Tanner 1949]. In a detailed analysis comparing $\dot{V}_{O_2}$ and body build, he concluded that *'as the index wt./stature increases, O2/wt. must be expected to decrease purely as a result of the method used for representing the data.'*

Batterham and co-workers studied 1314 apparently healthy men employed at the National Aeronautics and Space Administration Johnson Space Center in Houston, Texas [Batterham et al. 1999]. The authors reported that as body mass increased, the proportion composed of fat-free mass decreased. They also found that fat-free mass had a linear relationship with oxygen consumption while total body mass did not. They suggest that ideally estimates of fat-free mass should be used in the representation of oxygen consumption to allow more reliable comparison between subjects. These findings are similar to our results where the proportion of skeletal muscle area decreased significantly as body mass index increased with a greater decrease in females than males. Moreover, the linear relationship between skeletal muscle area and absolute $\dot{V}_{O_2}$ has also been clearly demonstrated in our findings.

We used the Boer formula [Boer 1984] to estimate lean body mass and used this to normalise $\dot{V}_{O_2}$. The resulting value for $\dot{V}_{O_2}$ showed no 'spurious' correlations with body composition, height, total body weight or body mass index. These findings are similar to the recommendations made by Janz and co-workers who studied oxygen consumption and aerobic capacity in adolescents over several years as part of the Muscatine study and reported their findings in 1997 [Janz et al. 1997] and 1998 [Janz et al. 1998]. Aerobic capacity in the form of $\dot{V}_{O_2}$Peak was evaluated annually in 126 children (mean age 10.3 years) for five years. Body composition changes were also tracked over this period. They reported on the changes in body composition that occur over time and the differences in these changes between circum-pubertal boys and girls. They demonstrate significant difficulties in normalising $\dot{V}_{O_2}$ using total body mass and suggested that fat-free mass was the most appropriate variable for normalising $\dot{V}_{O_2}$. They found that $\dot{V}_{O_2}$ normalised using total body mass underestimated aerobic fitness levels of heavier boys and girls. However, this underestimation was greater in girls than in boys.

In a study aimed at determining the optimal method of expressing $\dot{V}_{O_2}$Max, Maciejczyk and co-workers analysed the differing influence of body fat and lean body mass on aerobic performance in two groups of physically fit men categorised based on their body fat percentage [Maciejczyk et al. 2014]. High body mass

regardless of composition was correlated negatively with $\dot{V}_{O_2}$ (ml/kg/min) when it was corrected for total body weight. This penalised otherwise fit men purely based on the proportion of body weight that was contributed by body fat. However, when $\dot{V}_{O_2}$ was corrected for lean body mass, they found that the results were similar between the low body fat and high fat body groups. They, similar to Goran and co-workers [Goran et al. 2000], recommend that $\dot{V}_{O_2}$ be normalised to lean body mass rather than total body weight.

Our results demonstrate that there is no correlation between absolute oxygen consumption at rest or during exercise and the amount of adipose tissue. This further emphasises the fact that adipose tissue is metabolically inactive during exercise although it contributes to increased work load. Therefore, dividing absolute $\dot{V}_{O_2}$ (l/min) by total body weight in overweight/obese subjects whose extra weight is largely due to adipose tissue would result in lower corrected $\dot{V}_{O_2}$ (ml/kg/min) as we have demonstrated here.

Goran and co-workers reported that total body fat did not affect maximal aerobic capacity [Goran et al. 2000]. They reported on $\dot{V}_{O_2}$Max in obese women before and after weight loss. $\dot{V}_{O_2}$Max corrected for total body weight was significantly lower in obese subjects while $\dot{V}_{O_2}$Max corrected for fat-free mass did not change significantly after weight loss. They also reported that the limiting factor in obese patients was not the cardio-respiratory system but the fact that it was more difficult for obese individuals to do the same amount of work as a normal weight person in weight-bearing activities. This is likely due to the extra fat mass in these individuals that did not contribute to aerobic capacity but instead may have increased the exercise load in addition to that set by the investigator during the exercise.

These findings have been replicated by several other authors in different subject groups [Loftin et al. 2001; Lemaitre et al. 2006; Savonen et al. 2012; Krachler et al. 2014]. Several of the above studies also recommended using allometric scaling to avoid the confounding effects of total body weight. However, this has not gained

widespread clinical use.

The conclusion from the above studies would be that oxygen consumption normalised for total body weight unfairly penalises obese patients in the absence of true impairment of cardio-respiratory function. This has significant clinical implications as outlined below.

4.4.3 Clinical implications of spurious correlation

The term *'spurious correlation'* was first introduced by English mathematician and biometrician, Karl Pearson, in 1896. He used the term to describe correlations that occurred as a result of using ratios instead of absolute values rather than because of any actual correlations between the variables being studied [Pearson 1896].

Older and co-workers in their pioneering study in 1993 reported that $\dot{V}_{O_2}$AT < 11 ml/kg/min was associated with increased mortality in elderly patients undergoing major abdominal surgery [Older et al. 1993]. While they did not provide any data on other preoperative or intra-operative factors, they concluded that cardiopulmonary exercise testing was useful in predicting postoperative outcome and that a low $\dot{V}_{O_2}$AT represented cardiac failure. This assertion is repeated in their later work on 548 patients which also showed a clear association between low $\dot{V}_{O_2}$AT (ml/kg/min) and mortality due to cardiovascular causes [Older et al. 1999]. The concepts of *'surgical anaerobic threshold'* and *'postoperative cardiac failure'* were introduced later and were described as the *'inability of the heart to meet the demand of postoperative stress.'*["ATS/ACCP Statement on Cardiopulmonary Exercise Testing" 2003].

Swart and Carlisle also reported that $\dot{V}_{O_2}$AT < 11 ml/kg/min in patients undergoing open colorectal surgery was associated with adverse outcomes [Swart et al. 2012]. However, the proportion of females in the low $\dot{V}_{O_2}$AT group was significantly greater than that in the normal $\dot{V}_{O_2}$AT group (24% vs 51%). The average corrected $\dot{V}_{O_2}$AT in men calculated from the data presented in their paper

was 11.02 ml/kg/min while in women it was 9.81 ml/kg/min.

In a study by Wilson and co-workers which reported that cardiopulmonary exercise testing predicted outcome after major elective intra-abdominal surgery, the proportion of females in the low $\dot{V}_{O_2}$AT group was 51% while it was 28% in the group with normal AT [Wilson et al. 2010]. There was no data presented on body mass index in this study. We reported in Chapter 3 that females were more likely to have a lower $\dot{V}_{O_2}$AT (Table 3.6) and lower $\dot{V}_{O_2}$Peak (Table 3.7). However, all the results in the present study were controlled for the effect of sex.

The 'obesity paradox' would suggest that, in fact, obese patients are not necessarily at an increased risk of postoperative complications. Several authors have reported that obesity was not a risk factor for major complications after pancreaticoduodenectomy [Khan et al. 2010; Tsai et al. 2010; Balentine et al. 2011]. In a large study of 118,707 patients undergoing non-bariatric general surgery, the authors reported that the risk of death was 'paradoxically' low in the overweight and obese group of patients [Mullen et al. 2009]. The results of the present study show that $\dot{V}_{O_2}$ as is currently reported for clinical use will also be low in this very same cohort of patients. This obesity paradox is particularly apparent in patients with heart failure where in spite of a low $\dot{V}_{O_2}$ (corrected for total body weight), obese patients have better survival rates. Horwich and co-workers reported in a study of 2331 patients that body mass index was associated with a low $\dot{V}_{O_2}$Peak (ml/kg/min) independent of all other factors including age, diabetes, cardiac disease, New York Heart Association Class of cardiac failure and race [Horwich et al. 2009].

It is clear from the review presented in Chapter 1 as well as the results presented in Chapter 2, that cardiopulmonary exercise testing is useful in predicting risk after major surgery. Cardiopulmonary exercise testing has become ubiquitous in the preoperative assessment of complex surgical patients. However, the present study demonstrates that cardiopulmonary exercise test parameters in the overweight/obese patient must be interpreted with caution, especially when used

to select patients who may be declined surgery based on these results.

4.4.4 Measuring impact of prehabilitation

Where time to surgery is not critical, prehabilitation has gained an increasingly important role in optimising patients for surgery. Prehabilitation has been defined as the 'process of enhancing functional capacity of the individual to enable him or her to withstand the stressor of inactivity' [Topp et al. 2002]. Jones and co-workers reported an increase in $\dot{V}_{O_2}$Peak by an average 2.4 ml/kg/min when patients were placed on an aerobic exercise regimen before undergoing surgery for lung cancer [Jones et al. 2007]. Kim and co-workers also demonstrated a significant improvement in exercise loads achieved as well as sub-maximal oxygen consumption in patients who undertook a 4-week exercise program before major bowel surgery [Kim et al. 2009b]. Moreover, deterioration in aerobic capacity during prehabilitation was reported to be associated with increased incidence of postoperative complications [Mayo et al. 2011].

However, other authors have not been able to reproduce these findings. Patient compliance and difficulties in trying to modify lifestyle prior to surgery were considered important factors for failure of prehabilitation [Carli et al. 2010; Dronkers et al. 2010].

Cardiopulmonary exercise testing has been reported to be a useful objective measure of the impact of prehabilitation in surgical patients. It was used to demonstrate the decline in $\dot{V}_{O_2}$AT associated with neo-adjuvant chemoradiotherapy in patients with rectal cancer who did not undertake an exercise program. However, $\dot{V}_{O_2}$AT improved in the intervention group who undertook a 6 week exercise program [West et al. 2015].

However, the results presented in this study demonstrate that the success of such prehabilitation programs must not be determined solely by $\dot{V}_{O_2}$ corrected for total body weight. Instead, improvement in the absolute values of $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak

in conjunction with improvement in other parameters that are not affected by body composition such as O_2Pulse, tidal volume [Jones et al. 2007] or maximal exercise load [Kim et al. 2009b] may provide more reliable evidence of improvement in aerobic capacity.

The combination of nutritional assessment and advice, home-based exercise programs and weight loss may help improve aerobic capacity and eventually postoperative outcomes. Such preoperative interventions may also be associated with improvements in body composition with increase in skeletal muscle mass and reduction in adipose tissue. This may result in apparent improvements in cardiopulmonary exercise test parameters that are scaled using total body weight as well as improvements in true aerobic fitness. Further studies are required to validate the findings presented here as well as to identify optimal scaling methods for cardiopulmonary exercise test parameters. This will improve the clinical utility of cardiopulmonary exercise testing in the preoperative risk assessment as well as optimisation of patients undergoing major surgery.

Chapter 5

An investigation into the relationship between preoperative clinico-pathological characteristics and post-operative systemic inflammatory response in patients undergoing pancreaticoduodenectomy.

5.1 Introduction

The perioperative systemic inflammatory response has a significant role in determining short-term and long-term outcomes following potentially curative surgery for a wide variety of cancers. Systemic inflammation both before and after major surgery has been reported to be associated with significant morbidity.

Elevated preoperative systemic inflammation was associated with increased complications after colorectal surgery [Moyes et al. 2009; Kubo et al. 2013], oesophagectomy [Vashist et al. 2010] as well as liver surgery for colorectal metastases [Neal et al. 2011]. The modified Glasgow Prognostic Score in particular, which uses the combination of C-reactive protein and serum albumin, has been reported to be associated with increased incidence of complications [Moyes et al. 2009; Mohri et al. 2014; Vashist et al. 2010]. Elevated preoperative CRP levels have also been reported to be associated with increased incidence of complications including infections and renal dysfunction as well as increased in-hospital mortality after cardiac surgery [Lorenzo et al. 2012; Mezzomo et al. 2011; Kim et al. 2009a; Biancari et al. 2003; Boeken et al. 1998].

Moreover, an elevated postoperative systemic inflammatory response in the first few days after surgery was associated with increased incidence of infective complications after a wide variety of thoraco-abdominal procedures [Singh et al. 2014; Platt et al. 2012; Dutta et al. 2011; Welsch et al. 2008] as well as other types of surgery [McNeer et al. 2010; Laporta Baez et al. 2011]. The magnitude of this postoperative inflammatory response has also been reported to be associated with the severity of the complications [McSorley et al. 2015].

In patients undergoing pancreaticoduodenectomy, preoperative systemic inflammation may be affected by several factors. These include the presence of obstructive jaundice with or without cholangitis, preoperative biliary intervention including endoscopic retrograde cholangio-pancreatography for diagnosis or biliary drainage and in some patients acute or chronic pancreatitis either due to

obstruction of the main pancreatic duct or due to other causes. The effect of this 'priming' of the immune system on postoperative outcomes is poorly understood in this cohort of patients.

Chronic inflammation is also a recognised feature of obesity which is increasingly common in patients undergoing major surgery for pancreatic and other gastro-intestinal cancers. The impact of obesity, especially visceral obesity, on complications after pancreaticoduodenectomy remains controversial with some authors reporting that obesity was associated with increased incidence of complications [House et al. 2008; Ramsey et al. 2011] while others reporting similar outcomes in obese and non-obese patients [Khan et al. 2010; Tsai et al. 2010; Balentine et al. 2011].

More recently, levels of adipocytokines, inflammatory mediators produced exclusively in adipose tissue, have been reported to be associated with postoperative surgical site infections after colorectal [Ortega-Deballon et al. 2013; Matsuda et al. 2009] and gastric cancer surgery [Yamamoto et al. 2013]. Sarcopenia has also been reported to be associated with elevated postoperative systemic inflammation after colorectal surgery [Reisinger et al. 2015]. This emphasises the importance of adipose tissue metabolism and body composition in the preoperative systemic inflammatory status of surgical patients.

To our knowledge, the relationship between the preoperative systemic inflammatory response and the magnitude of the postoperative systemic inflammatory response after pancreaticoduodenectomy has not been examined before. While obstructive jaundice in itself has recently been reported to have no effect on postoperative complications, the impact of preoperative obstructive jaundice on postoperative systemic inflammation has not been previously reported. Moreover, the relationship between comorbidity, body composition and aerobic capacity as measured by cardiopulmonary exercise testing and postoperative systemic inflammation has not been studied.

5.1.1 Aim

The aim of this study was to examine the relationship between patient factors including preoperative systemic inflammation, obstructive jaundice, cardiopulmonary exercise test parameters and body composition and the magnitude of the postoperative systemic inflammation during the first week after a pancreaticoduodenectomy.

5.2 Patients and methods

5.2.1 Patients

Patients who underwent elective pancreaticoduodenectomy between January 2008 and December 2012 at the West of Scotland Pancreatic Unit at the Glasgow Royal Infirmary were included in this study. Patients who underwent only a trial dissection or palliative surgical bypass for unresectable disease during this period were excluded.

5.2.2 Preoperative data

Routine preoperative blood tests including full blood count, liver function tests and serum C-reactive protein were performed in all patients on the day before surgery. These blood tests were also repeated every day for at least the first postoperative week. These results were collected from the hospital laboratory database using an automated MS Access application as outlined in Appendix A.

The modified Glasgow Prognostic Score (mGPS) was calculated as shown in Table 1.7 on page 40 in Chapter 1. Standard thresholds were used to categorise other biochemical parameters. Obstructive jaundice was defined as serum bilirubin >35 μmol/L while severe obstructive jaundice was defined as serum bilirubin >250 μmol/L.

5.2.3 BMI and body composition

Body Mass Index (BMI) was categorised using the World Health Organisation thresholds as shown in Table 1.8 on p 52 in Chapter 1. Only one patient had a BMI less than 18.5 kg/m2 and was excluded from analysis involving BMI. Body composition was calculated in a subset of these patients using preoperative

computed tomography of the abdomen. The methodology used in the calculation of the individual components of body composition including visceral fat, subcutaneous fat and skeletal muscle is described in detail in Section 4.2.2 on page 104. Continuous data were converted into categorical data using tertiles.

5.2.4 Comorbidity and CPET

The Scottish Index of Multiple Deprivation (SIMD) Quintile Scores were calculated from the post-code of the patient's primary residence and dichotomised into two groups with scores of 1-3 and 4-5 respectively. Lower scores indicated greater deprivation. The POSSUM Physiology Score was calculated based on 11 physiological parameters (cardiac disease including hypertension, ischaemic heart disease and heart failure, respiratory disease causing breathlessness on exertion and COPD, ECG changes, pulse rate, blood pressure, haemoglobin, white cell count, serum sodium, serum potassium, serum urea and Glasgow Coma Scale) as described in Table 1.4 on page 18.

In patients who underwent cardiopulmonary exercise testing, $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak were compared against postoperative systemic inflammation. $\dot{V}_{O_2}$AT was dichotomised using a value of 10 ml/kg/min while $\dot{V}_{O_2}$Peak was dichotomised using a value of 16 ml/kg/min. Cardiopulmonary exercise testing methodology has been described in Section 1.5.2 on page 23.

5.2.5 Statistics

Continuous variables are reported as median (inter-quartile range).
Non-parametric tests were used to compare postoperative inflammatory markers (continuous data) with preoperative clinico-pathological characteristics (categorical data). Mann-Whitney U test was used when two categories were present and Kruskal-Wallis test was used when more than two categories were present.

Line-plots were created comparing the trend of inflammatory markers during the first postoperative week with preoperative systemic inflammation, obstructive jaundice and $\dot{V}_{O_2}$AT with error bars representing 95% confidence intervals.

SPSS software (Version 22.0; IBM, USA) was used to perform statistical analysis. Effects were considered significant at $\alpha \leq 0.05$.

5.3 Results

5.3.1 Clinico-pathological characteristics

Pancreaticoduodenectomy was performed in 188 patients (126 male, 67%) during the study period. Preoperative C-reactive protein was elevated in 70 (37.6%) patients while just over half the patients had a low preoperative serum albumin (96, 51.1%). The modified Glasgow Prognostic Score revealed normal preoperative systemic inflammatory status (mGPS = 0) in 116 (62.4%) patients, mild systemic inflammation in 16 (8.6%) and severe inflammation in 54 (29.0%) patients. Obstructive jaundice was present in 44 (23.4%) patients and severe obstructive jaundice was present in 31 (16.5%) patients. BMI data was available in 167 patients. More than half of these patients were overweight or obese with a BMI > 25 in 87 (52.1%) patients. All the variables necessary for calculation of the POSSUM Physiology Score, a composite score of comorbidity and preoperative biochemistry, were available in 180 patients and it was elevated in 87 (48.3%) patients.

The relationship between preoperative clinico-pathological characteristics and postoperative C-reactive protein levels is shown in Tables 5.1 and 5.2.

5.3.2 Preoperative vs. postoperative systemic inflammation

The relationship between preoperative CRP and postoperative systemic inflammation is depicted graphically in Fig. 5.1a and Fig. 5.1b on page 138. The median CRP levels on the day of surgery and the first postoperative day (POD) were significantly higher in patients who had an elevated preoperative CRP. However, this association was not present after the first postoperative day.

Preoperative hypoalbuminemia on the other hand was associated with lower

TABLE 5.1: The relationship between postoperative CRP and preoperative clinico-pathological characteristics in patients undergoing pancreaticoduodenectomy.

Preop. variable		n 188	Postoperative C-Reactive Protein Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
CRP	≤10	116	18 (11-31)*	115 (86-145)*	214 (166-262)	181 (132-245)	142 (85-216)	114 (60-193)	109 (56-175)	103 (55-175)
	>10	70	39 (26-56)	151 (99-186)	211 (158-282)	195 (145-252)	152 (89-231)	114 (61-197)	105 (55-162)	109 (50-172)
Albumin	≥35	92	25 (13-39)	126 (95-157)	220 (165-279)	205 (151-276)*	170 (103-241)*	131 (83-227)*	140 (71-204)*	124 (72-192)*
	<35	96	26 (14-44)	119 (87-166)	204 (161-253)	175 (124-237)	134 (83-209)	101 (47-155)	87 (44-159)	88 (41-151)
mGPS	0	116	18 (11-31)*	115 (86-145)*	214 (166-262)*	181 (132-245)*	142 (85-216)	114 (60-193)*	109 (56-175)	103 (55-175)
	1	16	34 (25-72)	164 (130-185)	279 (196-304)	229 (179-309)	194 (128-281)	164 (112-283)	133 (77-226)	127 (72-226)
	2	54	39 (27-53)	145 (95-186)	200 (152-248)	179 (124-241)	140 (79-216)	102 (58-153)	96 (54-159)	109 (44-154)
NLR	≤5	159	24 (13-38)*	121 (88-161)	218 (165-270)	186 (136-258)	148 (85-226)	115 (60-197)	113 (56-175)	117 (57-176)
	>5	29	43 (19-66)	141 (95-167)	189 (152-232)	160 (124-236)	141 (92-189)	113 (67-144)	89 (54-149)	89 (50-119)
Bilirubin	≤35	113	25 (13-41)	131 (95-165)*	231 (180-275)*	204 (154-273)*	171 (102-237)*	127 (81-218)*	121 (72-192)*	113 (71-175)
	36-250	44	24 (14-43)	124 (100-167)	212 (167-277)	182 (139-239)	136 (90-203)	110 (51-139)	113 (48-163)	103 (44-174)
	>250	31	28 (17-37)	99 (67-128)	165 (116-202)	149 (82-214)	95 (60-166)	59 (37-153)	55 (26-154)	70 (24-158)
BMI	< 25	80	21 (12-42)	121 (88-163)	207 (156-252)	174 (132-242)	134 (86-217)	105 (58-193)	87 (51-175)	92 (50-164)
	25-29.9	64	26 (17-39)	127 (93-164)	220 (187-269)	203 (137-250)	149 (86-201)	115 (62-164)	109 (55-165)	110 (54-170)
	30-34.9	23	34 (12-42)	114 (90-133)	220 (148-270)	205 (152-287)	190 (97-230)	141 (67-222)	142 (55-181)	136 (70-198)
	>35	9	31 (27-44)	167 (116-178)	204 (173-311)	235 (147-293)	210 (91-290)	167 (76-232)	172 (88-207)	162 (148-178)
SIMD	4-5	61	26 (13-45)	128 (98-168)	226 (183-271)	208 (150-274)	171 (108-231)	127 (88-200)	137 (72-205*)	136 (71-220)*
	1-3	126	25 (14-39)	121 (88-161)	207 (148-264)	180 (132-242)	140 (84-215)	105 (57-190)	94 (50-163)	98 (50-158)
$\dot{V}_{O_2}$AT	≥10	77	23 (12-40)*	118 (85-165)	222 (166-264)	186 (132-252)	148 (85-231)	111 (58-193)	106 (54-177)	107 (51-173)
	<10	52	28 (19-41)	121 (96-150)	222 (158-275)	204 (151-262)	175 (123-221)	119 (80-204)	116 (63-174)	113 (66-189)
$\dot{V}_{O_2}$Peak	≥16	65	21 (12-37)*	106 (78-150)*	214 (140-264)	181 (132-235)	150 (85-213)	110 (59-190)	113 (57-181)	115 (51-175)
	<16	65	28 (19-44)	123 (100-161)	234 (173-279)	214 (149-278)	174 (92-237)	119 (63-204)	111 (57-172)	111 (60-180)
Hb	≥12	127	24 (13-38)*	116 (85-161)	214 (165-263)	184 (136-247)	151 (88-214)	111 (59-192)	102 (54-172)	104 (51-174)
	<12	61	28 (18-45)	140 (104-165)	216 (163-279)	186 (124-258)	137 (89-231)	119 (64-197)	119 (63-170)	106 (60-170)
PPS	≤14	93	24 (13-36)	116 (84-161)	205 (144-264)	180 (129-242)	131 (83-210)	107 (55-168)	104 (54-174)	104 (52-174)
	>14	87	26 (14-45)	128 (99-156)	214 (175-262)	198 (136-255)	158 (95-226)	118 (71-193)	114 (58-167)	109 (53-173)

Postoperative CRP levels were related to preoperative systemic inflamation as well as obstructive jaundice. Hypoalbuminemia and obstructive jaundice were associated with lower postoperative CRP levels. * - Statistically significant differences with $p < 0.05$. The corresponding p-values are shown in Table 5.2 on the next page.

TABLE 5.2: The relationship between postoperative C-reactive protein and preoperative clinicopathological characteristics in patients undergoing pancreaticoduodenectomy: p-values only.

Preop.	Postoperative C-Reactive Protein							
Variable	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
CRP	<0.001	<0.001	0.669	0.522	0.741	0.831	0.789	0.834
Albumin	0.445	0.916	0.148	0.045	0.018	0.001	0.002	0.006
mGPS	<0.001	0.001	0.037	0.048	0.084	0.029	0.215	0.347
NLR	0.001	0.310	0.143	0.217	0.490	0.427	0.227	0.111
Bilirubin	0.869	0.009	0.001	0.001	0.003	<0.001	0.005	0.072
BMI	0.181	0.312	0.744	0.376	0.424	0.504	0.556	0.214
SIMD	0.563	0.418	0.121	0.099	0.114	0.051	0.016	0.011
$\dot{V}_{O_2}$AT	0.042	0.749	0.838	0.587	0.330	0.448	0.659	0.389
$\dot{V}_{O_2}$Peak	0.022	0.050	0.122	0.154	0.218	0.537	0.992	0.527
Haemoglobin	0.025	0.078	0.735	0.973	0.905	0.838	0.682	0.987
PPS	0.114	0.192	0.525	0.308	0.127	0.338	0.954	0.919

p - Mann-Whitney U test or Kruskal-Wallis test

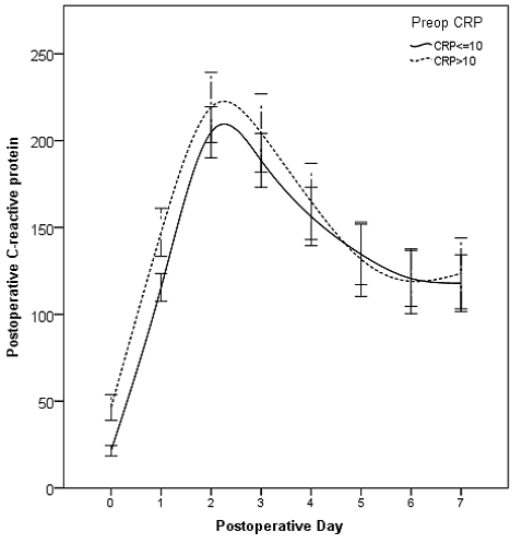
median postoperative CRP levels starting with POD 3. The median difference in postoperative CRP between patients with or without preoperative hypoalbuminemia was 30 g/l on POD 3 ($p<0.045$) and 53 g/l on POD 6 ($p=0.002$) with lower CRP levels in patients with hypoalbuminemia. This relationship is shown in Fig. 5.1b.

The trend in postoperative CRP appeared to differ depending on whether preoperative CRP and albumin were independently deranged. Fig. 5.2 and Table 5.3 on page 139 show the results of this analysis. When both preoperative CRP and preoperative albumin were normal, the trend in postoperative CRP is shown by the solid line (Line 0 in Fig. 5.2). When preoperative CRP was elevated in the presence of a normal preoperative albumin, postoperative CRP levels were significantly elevated and remained elevated during the first postoperative week (Line 1 in Fig. 5.2). However, hypoalbuminemia was associated with lower postoperative CRP levels regardless of whether preoperative CRP was normal (Line 2 in Fig. 5.2) or elevated (Line 3 in Fig. 5.2).

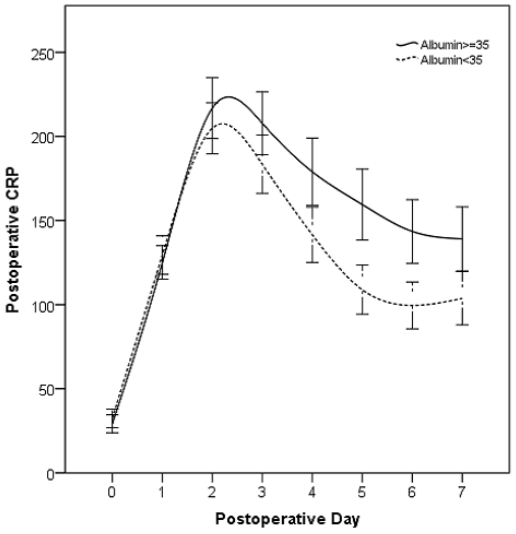
5.3.3 Obstructive jaundice vs. postoperative inflammation

Obstructive jaundice was associated with significant differences in the postoperative systemic inflammatory response. The trends in postoperative CRP were significantly different between the jaundiced and non-jaundiced patients. Obstructive jaundice was associated with a significantly lower peak CRP on POD 2 ($p=0.001$) and this persisted until POD 6 ($p=0.005$, Table 5.1, 5.2). Median postoperative CRP had an inverse relationship with severity of preoperative obstructive jaundice (Fig. 5.1c).

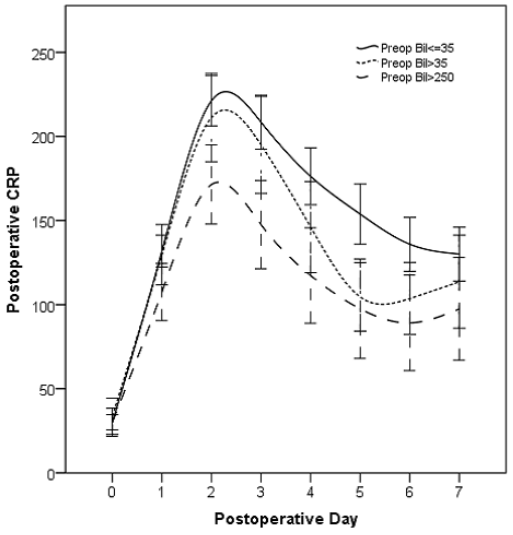
FIGURE 5.1: Relationship between preoperative factors and postoperative CRP in the first week after pancreaticoduodenectomy.



(A) Preop. CRP vs. postop. CRP



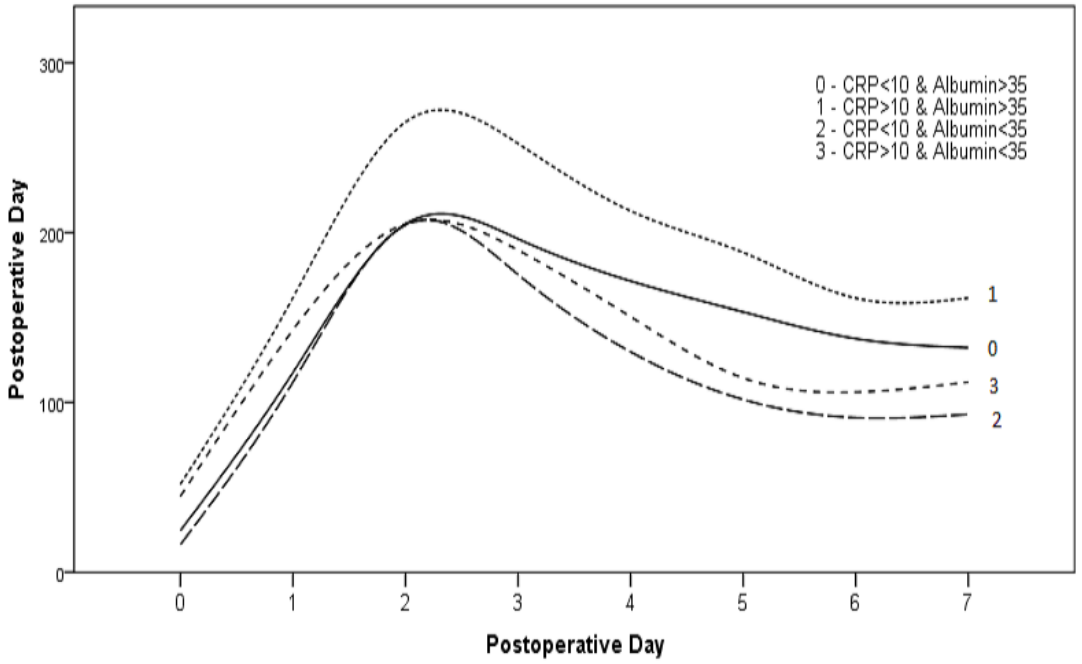
(B) Preop. Albumin vs. postop. CRP



(C) Preop. Bilirubin vs. postop. CRP

Elevated preoperative CRP was associated with a greater postoperative CRP on the first postoperative day. Preoperative hypoalbuminemia was associated with significantly lower postoperative CRP levels during the first postoperative week after pancreaticoduodenectomy. Preoperative obstructive jaundice was also associated with a significantly dampened postoperative systemic inflammatory response.

FIGURE 5.2: Relationship between preoperative CRP and postoperative CRP in the presence or absence of preoperative hypoalbuminemia.



Elevated preoperative CRP in the absence of hypoalbuminemia was associated with an exaggerated postoperative inflammatory response (line 1). However, preoperative hypoalbuminemia resulted in a dampened postoperative inflammatory response regardless of the preoperative CRP (lines 2,3).

TABLE 5.3: The relationship between preoperative CRP and postoperative CRP in the presence or absence of preoperative hypoalbuminemia in patients undergoing pancreaticoduodenectomy.

	Preop Albumin $\geq$ 35 g/l		Preop Albumin $<$ 35 g/l		
	CRP $\leq$ 10 mg/l	CRP $>$ 10 mg/l	CRP $\leq$ 10 mg/l	CRP $>$ 10 mg/l	p
n	74	16	42	54	
Day 0	21 (12-35)	34 (25-72)	14 (10-19)	39 (27-53)	<0.001
Day 1	122 (90-147)	164 (130-185)	110 (84-141)	145 (95-186)	0.002
Day 2	215 (155-268)	279 (196-304)	213 (168-257)	200 (152-248)	0.083
Day 3	198 (136-259)	229 (179-309)	174 (124-235)	179 (124-241)	0.056
Day 4	157 (97-238)	194 (128-281)	132 (83-184)	140 (79-216)	0.046
Day 5	129 (78-222)	164 (112-283)	95 (45-155)	102 (58-153)	0.003
Day 6	136 (66-195)	133 (77-226)	80 (38-167)	96 (54-159)	0.025
Day 7	123 (70-180)	127 (72-226)	76 (27-140)	109 (44-154)	0.037

p - Kruskal-Wallis test

5.3.4 CPET, comorbidity vs. postoperative inflammation

Cardiopulmonary exercise testing was performed in 130 patients. $\dot{V}_{O_2}$AT could not be estimated in one patient. $\dot{V}_{O_2}$AT was less than 10 ml/kg/min in 52 (40%) of patients indicating reduced aerobic capacity in these patients. There was no significant relationship between $\dot{V}_{O_2}$AT, $\dot{V}_{O_2}$Peak and postoperative CRP.

There was no significant, persistent relationship between postoperative CRP and preoperative SIMD score, body mass index, preoperative haemoglobin levels or the POSSUM Physiology score.

5.3.5 Body composition vs. postoperative inflammation

Body composition data was available for 90 patients. Visceral adipose tissue area (cm^2) was divided into tertiles as low (n=30, median 57.1 cm^2, IQR 29.0-62.4), moderate (n=30, median 128.9 cm^2, IQR 119.0-150.8) and high (n=30, median 241.2 cm^2, IQR 221.9-313.1). Subcutaneous adipose tissue area was divided into tertiles as low (n=30, median 94.1 cm^2, IQR 63.2-102.5), moderate (n=30, median 152.5 cm^2, IQR 141.3-175.3) and high (n=30, median 253.9 cm^2, IQR 203.2-290.3). Skeletal muscle area was also divided into tertiles as low (n=30, median 96.7 cm^2, IQR 91.9-102.5), moderate (n=30, median 121.7 cm^2, IQR 116.4-130.9) and high (n=30, median 153.0 cm^2, IQR 145.3-167.6).

The relationship between body composition and postoperative CRP is shown in Table 5.4. Postoperative CRP was not related to any of the components of body composition.

TABLE 5.4: The relationship between postoperative CRP and body composition in patients undergoing pancreaticoduodenectomy.

a. Visceral fat vs. postoperative CRP

	Low	Moderate	High	p
Day 0	22 (13-37)	26 (19-38)	30 (24-43)	0.161
Day 1	122 (89-179)	143 (108-165)	121 (80-161)	0.374
Day 2	189 (155-261)	244 (181-269)	200 (152-245)	0.326
Day 3	165 (104-214)	202 (132-287)	192 (136-248)	0.161
Day 4	113 (69-216)	166 (85-239)	157 (129-210)	0.409
Day 5	87 (45-176)	142 (59-200)	115 (95-168)	0.229
Day 6	75 (40-137)	148 (60-170)	146 (73-172)	0.167
Day 7	86 (31-141)	130 (64-174)	123 (66-175)	0.172

b. Subcutaneous fat vs. postoperative CRP

	Low	Moderate	High	p
Day 0	31 (19-44)	25 (15-33)	25 (18-42)	0.368
Day 1	132 (106-167)	125 (68-168)	120 (99-153)	0.431
Day 2	216 (155-247)	209 (181-278)	226 (157-268)	0.767
Day 3	156 (132-206)	189 (110-273)	217 (149-266)	0.306
Day 4	132 (88-214)	159 (84-232)	157 (108-216)	0.694
Day 5	105 (56-158)	115 (54-199)	121 (80-197)	0.690
Day 6	91 (40-147)	154 (56-170)	145 (76-174)	0.126
Day 7	95 (29-132)	117 (57-175)	136 (86-189)	0.089

c. Skeletal muscle vs. postoperative CRP

	High	Moderate	Low	p
Day 0	27 (18-37)	24 (18-43)	25 (17-44)	0.951
Day 1	108 (78-167)	131 (109-188)	140 (82-156)	0.090
Day 2	210 (155-278)	223 (163-282)	206 (162-245)	0.382
Day 3	203 (149-273)	174 (136-255)	166 (104-241)	0.356
Day 4	163 (117-218)	145 (96-232)	132 (79-180)	0.304
Day 5	138 (80-197)	115 (82-213)	88 (40-163)	0.135
Day 6	156 (84-179)	121 (57-192)	94 (42-147)	0.080
Day 7	130 (77-178)	105 (64-151)	100 (33-165)	0.237

Patients were divided into three equal groups based on each component of body composition and the median CRP during the first postoperative after pancreaticoduodenectomy was compared between these groups using the Kruskal-Wallis test. No relationship was identified between body composition and postoperative CRP levels. Values are median (inter-quartile range) for postoperative CRP (mg/l).

5.4 Discussion

The results of the present study demonstrate that preoperative systemic inflammation is associated with the magnitude of the postoperative systemic inflammatory response in patients undergoing pancreaticoduodenectomy. The results also appear to show that preoperative obstructive jaundice is associated with a dampened systemic inflammatory response as measured by CRP levels. Taken together, these results appear to suggest that the preoperative inflammatory status of the patient plays an important role in modulating postoperative systemic inflammation which may not simply be due to the effect of surgery and its sequelae.

The role of postoperative CRP in predicting complications after surgery has been well established. A recent meta-analysis of six studies involving 1832 patients reported that CRP level less than 135 mg/l on the fourth postoperative day had a high negative predictive value of 89% for infectious complications [Warschkow et al. 2012]. Postoperative CRP has been shown to predict complications after pancreaticoduodenectomy by us (chapter 6) as well as other authors [Welsch et al. 2008; Hiyoshi et al. 2013; Kosaka et al. 2014]. The role of preoperative systemic inflammation as measured by the modified Glasgow Prognostic Score or the neutrophil-lymphocyte ratio has also been reported to be adversely affect long-term survival in patients undergoing potentially curative surgery in over a hundred studies involving a variety of gastrointestinal and non-gastrointestinal cancers.

However, preoperative systemic inflammation as measured by elevated C-reactive protein or an abnormal modified Glasgow Prognostic Score is increasingly recognised as an independent risk factor for postoperative infectious complications [Mohri et al. 2014; Kubo et al. 2013; Moyes et al. 2009].

We hypothesized that preoperative systemic inflammation may adversely affect postoperative immuno-modulation resulting in an abnormal response in patients whose immune systems have been 'primed' before the surgical insult. This may affect the healing processes as well as the patient's ability to clear endotoxins and

may predispose the patient to infective and other complications. The results of the present study appear to support this hypothesis.

In this study, raised preoperative CRP in the absence of hypoalbuminemia was associated with elevated postoperative systemic inflammation. However, preoperative hypoalbuminemia was associated with significantly lower levels of postoperative CRP. These apparently opposite effects of preoperative CRP and albumin on the postoperative systemic inflammatory response is further evidenced by the fact that the effect of elevated preoperative CRP on postoperative inflammation is attenuated by the presence of preoperative hypoalbuminemia. These results appear to suggest when hypoalbuminemia is present as part of preoperative systemic inflammation, not only is the exaggerated postoperative response due to elevated CRP lost but the response appears to be dampened.

The impact of hypoalbuminemia on the acute phase response was noted by Christou and co-workers who performed a delayed type hypersensitivity (DTH) skin test in addition to measuring acute phase markers including CRP, albumin, white cell count, haemoglobin and immunoglobulins in 245 patients prior to undergoing gastrointestinal surgery [Christou et al. 1989]. They noted that hypoalbuminemia and anergy to the DTH skin test were the only variables independently associated with postoperative sepsis-related mortality. Moreover, both low albumin and elevated CRP were significantly associated with cutaneous anergy. Cutaneous anergy is one of the hallmarks of the compensatory anti-inflammatory response syndrome (CARS) [Ward et al. 2008].

Preoperative hypoalbuminemia has been reported to be a risk factor for postoperative complications independent of both inflammation and nutritional status [Gibbs et al. 1999; Don et al. 2004; Hennessey et al. 2010]. Albumin is a negative acute phase protein and elevated CRP levels are often associated with low serum albumin levels [Margarson et al. 1998]. Hypoalbuminemia in patients scheduled to undergo pancreaticoduodenectomy is likely to be multi-factorial in origin. Systemic inflammation, obstructive jaundice and the associated complex

physiological, biochemical and immunological abnormalities, malnutrition, cancer cachexia, changes in body composition including sarcopenic-obesity may all contribute to low serum albumin levels. Contrary to our findings, hypoalbuminemia and poor preoperative nutritional status were found to be associated with higher postoperative levels of pro-inflammatory cytokines and CRP in surgical patients [Nakamura et al. 1999]. The association of hypoalbuminemia with obstructive jaundice may have influenced our findings.

In patients with pancreatic cancer, malignant obstructive jaundice further complicates the preoperative inflammatory status and the behaviour of the immune system [Nehéz et al. 2002]. We reported in Chapter 3 that obstructive jaundice was associated with elevated preoperative CRP and low serum albumin on the day before surgery with a linear relationship with severity of jaundice (Table 3.2 on page 90). Hypoalbuminemia in jaundiced patients persisted after surgery in the present study. However, the CRP response appears to have reversed in jaundiced patients. While preoperative CRP was elevated in jaundiced patients, CRP levels after surgery were significantly lower in jaundiced patients with an inverse relationship with severity of jaundice.

While preoperative biliary intervention and resolution of jaundice may be offered as an explanation for the priming of the immune system in the non-jaundiced patients, this does not explain the initially low preoperative CRP in these patients. Padillo and co-workers reported that malignant obstructive jaundice was associated with elevated CRP levels which only improved transiently following biliary drainage. CRP returned to pre-drainage levels presumably due to bacterial colonisation of the biliary tree [Padillo et al. 2002; Padillo et al. 2001a]. It would therefore appear that obstructive jaundice adversely affects the ability to mount an adequate postoperative inflammatory response and this may be further compounded by the presence of hypoalbuminemia in these patients.

Immunosuppression and immune dysregulation have been recognised in patients with obstructive jaundice [Scott-Conner et al. 1994]. Our results are similar to

those reported by Mackenzie and Woodhouse who studied the CRP response to bacteraemia in 126 critically ill patients with or without liver dysfunction [Mackenzie et al. 2006]. Liver dysfunction was defined as serum bilirubin > 20 μmol/l and prothrombin time longer than 18 seconds. The CRP response to bacteraemia was significantly lower in patients with liver dysfunction than in those with normal liver function (103 vs. 146 mg/l, p=0.03). These findings have been corroborated by other authors in patients with cirrhosis [Pieri et al. 2014; Janum et al. 2011].

Although CRP on POD 0 was significantly different between patients with a normal $\dot{V}_{O_2}$AT/$\dot{V}_{O_2}$Peak and those with low aerobic capacity, this difference was not present on other days. The lack of association between aerobic capacity, POSSUM Physiology Score and postoperative CRP in this study may have been due to the dominant effect of preoperative systemic inflammation and obstructive jaundice on the postoperative inflammatory response.

Richards and co-workers reported that elevated preoperative systemic inflammation was related to low skeletal muscle index [Richards et al. 2012]. Hassen and co-workers reported that fat-free mass and skeletal muscle were inversely related to the severity of the postoperative inflammatory response following endo-vascular surgery for abdominal aortic aneurysm [Hassen et al. 2007]. Elevated systemic inflammation has been reported to be related to obesity as well as sarcopenia. 'Sarcopenic-obesity' in patients with pancreatic cancer where there is relative loss of skeletal muscle with preservation of adipose tissue puts these patients at particular risk for immune dysfunction [Berg et al. 2005; Reisinger et al. 2015], post-pancreatectomy complications [Joglekar et al. 2015] and shorter long-term survival [Tan et al. 2009; Peng et al. 2012]. However, the present study did not identify any relationship between body composition and postoperative CRP levels. This may have been due to several reasons including the effect of preoperative obstructive jaundice, hypoalbuminemia as well as cancer related inflammation and body composition changes.

5.4.1 Limitations of the study

The results in this study report the relationship between preoperative clinico-pathological factors and postoperative systemic inflammation in patients undergoing pancreaticoduodenectomy. The impact of complications on the systemic inflammatory response was not studied here but has been reported separately in Chapter 6. Moreover, it is not clear how the interaction between the various preoperative factors, especially obstructive jaundice and systemic inflammation affect postoperative inflammation or which variables are independently associated with the postoperative inflammatory response. Postoperative systemic inflammation is likely to be determined by multiple factors including preoperative factors, intra-operative factors including magnitude of the surgical insult, blood loss, anaesthetic factors as well as post-operative complications. Further study of the inter-play between these factors extending from the preoperative period into the early postoperative period will help elucidate the complex interaction between preoperative inflammation, aerobic capacity and obstructive jaundice on postoperative outcomes.

5.4.2 Conclusion

The results presented in this study emphasise the importance of the preoperative inflammatory status of the patient in influencing postoperative systemic inflammation. The results also demonstrate the immunosuppressive effects of obstructive jaundice in patients undergoing pancreaticoduodenectomy.

Chapter 6

An investigation into the relationship between postoperative systemic inflammation and complications after pancreaticoduodenectomy.

6.1 Introduction

Pancreaticoduodenectomy is associated with significant morbidity in spite of advances in patient selection, perioperative care and surgical technique. Early identification of complications can help improve outcomes by better allocation of critical care resources and aggressive early-rescue strategies [Ferraris VA et al. 2014]. Postoperative pancreatic fistula is one of the most dreaded complications after a pancreaticoduodenectomy and can lead to a cascade of other complications including delayed haemorrhage, infected intra-abdominal collections, delayed gastric emptying, prolonged hospitalisation and in some cases, death. The International Study Group for Pancreatic Fistula (ISGPF) have not only defined what constitutes a post-operative pancreatic fistula but have also graded the severity of this complication based on its impact on the management of the patient [Bassi et al. 2005a]. However, these definitions are applied after the event and there are no clear strategies to predict the severity of complications.

Postoperative CRP levels have been shown to predict infective complications after major surgery including colorectal, oesophago-gastric and pancreatic surgery [Mustard et al. 1987; Matthiessen et al. 2008; McNeer et al. 2010; Dutta et al. 2011; MacKay et al. 2011; Murakami et al. 2008; Welsch et al. 2008]. It has been postulated that an unmitigated and exaggerated systemic inflammatory response in the early postoperative period is followed by a compensatory anti-inflammatory response that predisposes the patient to sepsis and impaired healing [Bone et al. 1997; Bone 1996].

However, the mechanisms underlying the pathogenesis of post-operative pancreatic fistula are largely attributed to anatomical factors including soft texture of the pancreas and small pancreatic duct diameter as well as surgical technique with increased intra-operative blood loss and pancreatico-jejunostomy rather than pancreatico-gastrostomy being associated with increased incidence of anastomotic leakage [Pratt et al. 2008a; Xiong et al. 2014]. The association between the early postoperative systemic inflammatory response and the severity of postoperative

pancreatic fistula has not been reported. Moreover, the role postoperative CRP in predicting infective complications when these occur in association with postoperative pancreatic fistula has not been studied either.

6.1.1 Aim

The aim of this study was to investigate the association between trends in postoperative systemic inflammation, postoperative pancreatic fistula and infective complications in patients undergoing pancreaticoduodenectomy.

6.2 Patients and methods

6.2.1 Patients

Patients who underwent elective pancreaticoduodenectomy between January 2008 and December 2012 at the West of Scotland Pancreatic Unit at the Glasgow Royal Infirmary were included in this study. Patients who underwent only a trial dissection or palliative surgical bypass for unresectable disease during this period were excluded.

6.2.2 Perioperative care

All patients were given antibiotic prophylaxis at induction and this was continued for 24 hours after surgery. All patients had general anaesthesia supplemented either with epidural analgesia or spinal diamorphine and patient-controlled opiate analgesia for postoperative pain relief. Octreotide (200μg) was administered subcutaneously three times a day for 5 days in all patients and continued longer in patients diagnosed with a postoperative pancreatic fistula. Patients were routinely admitted to the surgical high dependency unit where a standardised regimen was followed for early mobilisation, chest physiotherapy and early enteral nutrition. All patients had one or two surgical drain(s) placed at the time of surgery which were removed at the clinician's discretion during the postoperative period based on the presence or absence of postoperative pancreatic fistula or other intra-abdominal collections. Further details regarding operative technique and postoperative care are provided in Chapter 1.

6.2.3 Biochemical parameters

Patients had routine measurements of inflammatory markers including C-reactive protein (CRP) from the day before surgery and every day for at least a week after

surgery. These results were collected from the hospital laboratory database using an automated MS Access application as outlined in Appendix A.

6.2.4 Complications and severity grading

All complications were discussed at a weekly morbidity meeting and prospectively recorded in an electronic database. The diagnosis and grading of pancreas-specific complications including postoperative pancreatic fistula (POPF, Section 1.2.4.1) were made according to the International Study Group classifications [Bassi et al. 2005a] as shown in Table 1.1 on page 10. A postoperative pancreatic fistula was defined as drain output of any measurable quantity after the third postoperative day with amylase content greater than three times the upper limit of the normal serum amylase value at our laboratory.

All other complications were graded using the Clavien-Dindo classification system [Clavien et al. 2009; Dindo et al. 2004] as shown in Table 1.3. This allowed grading of the severity of complications based on the magnitude of intervention(s) required to treat them. Postoperative mortality was defined as death within 30-days of surgery or while still in hospital after the operation. Re-intervention in the form of radiological, endoscopic or surgical procedures was recorded prospectively.

6.2.5 Statistics

Continuous data are presented as median (inter-quartile range, IQR) unless otherwise specified. Mann-Whitney U test was used to compare the distribution of postoperative CRP (as a continuous variable) in patients who had a complication and those who did not. Line plots with error bars depicting 95% confidence intervals were used to depict the trends in CRP over time across different patient groups.

Receiver operating characteristic (ROC) analysis [Robertson et al. 1981; Zweig

et al. 1993] was used to identify the optimum thresholds for postoperative CRP for predicting infective complications with a preference for thresholds that had a greater negative predictive value.

Patients were categorised using these thresholds to analyse the relationship between CRP (as a categorical variable) and re-operation, hospital stay, critical care stay, number of critical care admissions as well as postoperative mortality using the Chi-square test.

SPSS software (Version 22.0; IBM, USA) was used to perform statistical analysis. Effects were considered significant at $\alpha \leq 0.05$.

6.3 Results

6.3.1 POPF, infective complications and other outcomes

Pancreaticoduodenectomy was performed in 188 patients (126 male, 67%) during the study period. The median age was 63.5 years (IQR 54 - 70 years). 79 (42%) patients were over the age of 65 years.

Post-operative pancreatic fistula (POPF) as defined by the International Study Group for Pancreatic Fistula (ISGPF) occurred in 62 (33%) patients. Of these patients, 19 (10.1%) had a Grade A POPF, 25 (13.3%) had a Grade B POPF and 18 (9.6%) had a Grade C POPF. Significant infective complications of Clavien-Dindo grade 3 or higher occurred in 84 patients. Infective complications were more common in patients with age >65 years (35.6% vs. 50.0%, p=0.046) and $\dot{V}_{O_2}$AT<10 ml/kg/min (28.8% vs. 52.4%, p=0.006). Sex, body mass index, smoking status, modified Glasgow Prognostic Score, preoperative serum bilirubin and POSSUM physiology score were not associated with infective complications.

Infective complications were also significantly associated with other complications including post-operative pancreatic fistula, post-pancreatectomy haemorrhage as well as length of stay in hospital, critical care stay, number of critical care admissions, re-operation rates and in-hospital mortality (Table 6.2).

TABLE 6.1: The relationship between preoperative clinicopathological characteristics and infective complications in patients undergoing pancreaticoduodenectomy.

		Infective complication		
		CD 0 - 2	CD 3 - 5	p
Age (years)	≤65	67 (64.4%)	42 (50.0%)	0.046
	>65	37 (35.6%)	42 (50.0%)	
Sex	Male	70 (67.3%)	56 (66.7%)	0.926
	Female	34 (32.7%)	28 (33.3%)	
BMI (kg/m^2)	≤25	48 (50.5%)	37 (46.3%)	0.573
	>25	47 (49.5%)	43 (53.8%)	
Smoking	No	53 (62.4%)	44 (59.5%)	0.709
	Yes	32 (37.6%)	30 (40.5%)	
mGPS	0	67 (64.4%)	49 (59.8%)	0.570
	1	7 (6.7%)	9 (11.0%)	
	2	30 (28.8%)	24 (29.3%)	
Bilirubin (μmol/l)	≤35	66 (63.5%)	47 (56.0%)	0.574
	35 - 250	22 (21.2%)	22 (26.2%)	
	>250	16 (15.4%)	15 (17.9%)	
$\dot{V}_{O_2}$AT (ml/kg/min)	≥10	47 (71.2%)	30 (47.6%)	0.006
	<10	19(28.8%)	33 (52.4%)	
PPS	≤14	56 (56.0%)	37 (46.3%)	0.193
	>14	44 (44.0%)	43 (53.8%)	

CD - Clavien-Dindo Grade, BMI - Body Mass Index

mGPS - Modified Glasgow Prognostic Score

PPS - POSSUM Physiology Score

p - Chi-square test

Table 6.2: The relationship between infective complications and other adverse events in patients undergoing pancreaticoduodenectomy.

		Infective complication		
		CD 0 - 2	CD 3 - 5	*p*
POPF	No	85 (81.7%)	41 (48.8%)	<0.001
	Grade A	10 (9.6%)	9 (10.7%)	
	Grade B	7 (6.7%)	18 (21.4%)	
	Grade C	2 (1.9%)	16 (19.0%)	
PPH	No	95 (92.2%)	64 (77.1%)	0.048
	Grade A	2 (1.9%)	2 (2.4%)	
	Grade B	2 (1.9%)	6 (7.2%)	
	Grade C	4 (3.9%)	11 (13.2%)	
Postoperative stay	≤14 days	65 (62.5%)	17 (20.2%)	<0.001
	>14 days	39 (37.5%)	67 (79.8%)	
Critical care stay	≤7 days	84 (80.8%)	34 (40.5%)	<0.001
	>7 days	20 (19.2%)	50 (59.5%)	
Critical care admissions	1	92 (88.5%)	53 (63.1%)	<0.001
	>1	12 (11.5%)	31 (36.9%)	
Reoperation	No	99 (95.2%)	64 (76.2%)	<0.001
	Yes	5 (4.8%)	20 (23.8%)	
In-hospital mortality	No	103 (99.0%)	76 (90.5%)	0.006
	Yes	1 (1.0%)	8 (9.5%)	

POPF - Post-operative pancreatic fistula

PPH - Post-pancreatectomy haemorrhage

p - Chi-square test

6.3.2 Postoperative CRP vs. POPF

Postoperative CRP levels on days 2 through 7 were significantly higher in patients who developed a postoperative pancreatic fistula ($p = 0.002$ for CRP on Day 2 and $p<0.001$ for CRP on Days 3 through 7, Mann-Whitney U test). These results are presented in Table 6.3 and Fig. 6.1 on page 157. Fig. 6.1b shows that CRP in the first postoperative week was not significantly different between postoperative pancreatic fistulae of ISGPF Grade A, B and C.

However, there is no useful clinical application for the association between CRP in the early postoperative period and pancreatic fistula as the diagnosis of POPF is based on the amylase content in surgical drains on the third postoperative day. Moreover, early postoperative CRP did not predict the severity of the pancreatic fistula.

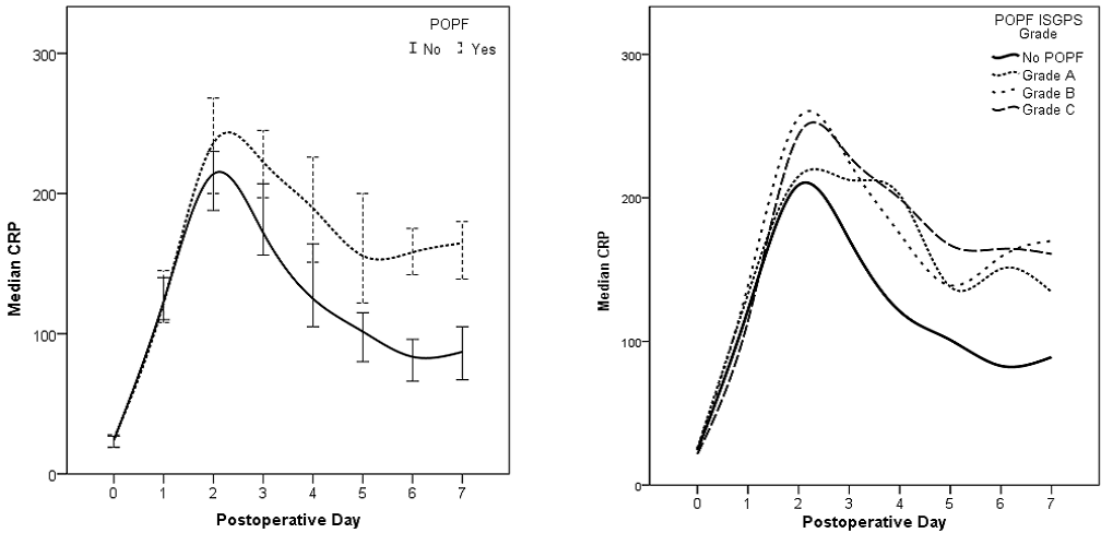
6.3.3 Postoperative CRP vs. infective complications

The median CRP levels on or after postoperative day 3 were significantly higher in patients who developed clinically significant infective complications in the absence of a POPF (Fig. 6.2a). However, there was no such association between CRP and infective complications in patients who developed a POPF (Fig. 6.2b).

For instance, the median CRP on Day 4 in patients who did not develop a POPF and did not have an infective complication was 97 mg/L (IQR 71 - 174) but was 173 mg/L if they had an infective complication. ($p<0.001$). However, in patients who had a POPF, the CRP on day 4 was 214 mg/L (IQR 151 - 250) in the absence of infective complications and 190 mg/L (IQR 137 - 252) in the presence of infective complications. ($p = 0.559$)

Therefore, CRP on or after the third postoperative day appears to be useful in predicting infective complications only in patients who did not develop a POPF and these results are shown in Table 6.4 and Fig. 6.2 on page 158.

FIGURE 6.1: Serum CRP levels in the first week after pancreaticoduodenectomy in patients with postoperative pancreatic fistula (POPF).



(A) POPF Absent vs. Any Grade (B) POPF ISGPF Grades

Median daily CRP levels in the first postoperative week in 188 patients undergoing pancreaticoduodenectomy were compared between patients who developed a postoperative pancreatic fistula (POPF) and those who did not develop a POPF. Figure A shows a significantly raised CRP in the presence of a pancreatic fistula. However, severity of POPF did not affect CRP levels in the first postoperative week as shown in Figure B. Error bars represent 95% confidence interval for the median.

TABLE 6.3: The relationship between CRP during the first postoperative week and post-operative pancreatic fistula (POPF) in patients undergoing pancreaticoduodenectomy.

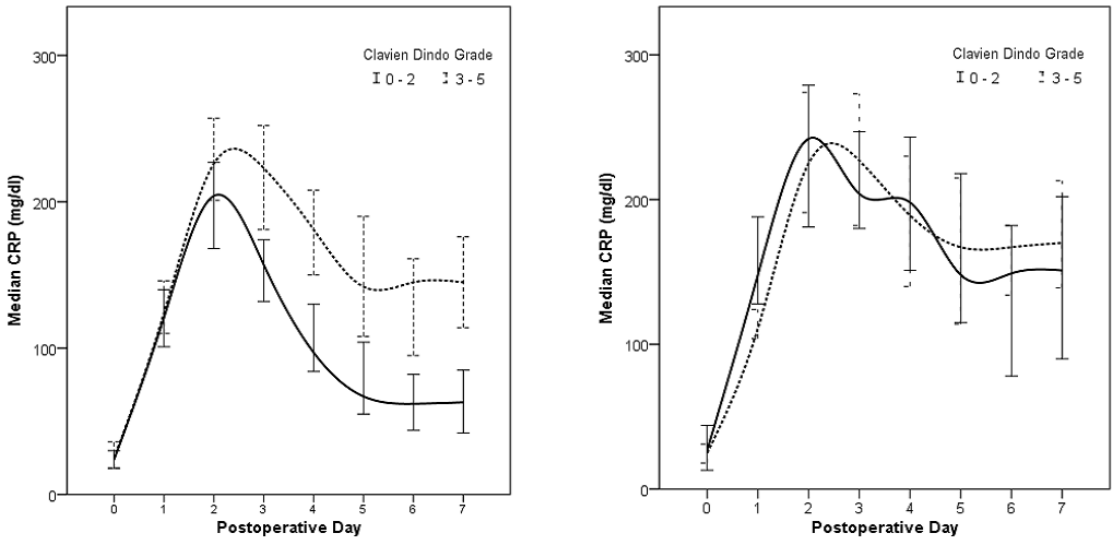
	POPF ISGPS Grades - p			
Postop Day	No vs. Any Grade	No vs. A	A vs. B	B vs. C
0	0.722	0.582	0.849	0.730
1	0.242	0.331	0.740	0.295
2	0.002	0.161	0.222	0.563
3	<0.001	0.022	0.602	0.530
4	<0.001	0.007	0.906	0.834
5	<0.001	0.035	0.611	0.959
6	<0.001	0.012	0.638	0.781
7	<0.001	0.006	0.235	0.356

p - Mann-Whitney U test

ISGPS - International Study Group for Pancreatic Surgery

POPF - Postoperative Pancreatic Fistula

FIGURE 6.2: Relationship between postoperative CRP and clinically significant infective complications in patients without (A) and with (B) POPF.



(A) Patients with **no** POPF (B) Patients with POPF

Median CRP was significantly higher in patients who developed infective complications in the absence of a pancreatic fistula (A). This difference was not seen in the presence of POPF(B). Error bars - 95% confidence interval for the median.

TABLE 6.4: The relationship between postoperative CRP and infective complications grouped by absence/presence of postoperative pancreatic fistula.

Postop Day	POPF Absent Infective Complication			POPF Present Infective Complication		
	No (n=85)	Yes (n=41)	*p*	No (n=19)	Yes (n=43)	*p*
0	24 (12 - 42)	25 (14 - 41)	0.379	27 (13 - 44)	25 (16 - 34)	0.629
1	122 (85 - 156)	123 (87 - 148)	0.667	148 (114 - 176)	116 (94 - 161)	0.038
2	204 (136 - 242)	218 (165 - 262)	0.203	242 (181 - 279)	228 (186 - 296)	0.919
3	157 (105 - 211)	213 (150 - 258)	0.011	206 (180 - 297)	226 (175 - 281)	0.846
4	97 (71 - 174)	173 (118 - 216)	<0.001	214 (151 - 250)	190 (137 - 252)	0.559
5	76 (40 - 129)	122 (87 - 202)	<0.001	140 (115 - 218)	167 (111 - 222)	0.639
6	64 (31 - 133)	121 (87 - 172)	<0.001	148 (78 - 182)	168 (109 - 224)	0.275
7	62 (25 - 106)	141 (90 - 190)	<0.001	158 (90 - 231)	167 (101 - 226)	0.644

Values are median (inter-quartile range; *p* - Mann-Whitney U test)

6.3.4 Receiver operating characteristic (ROC) analysis

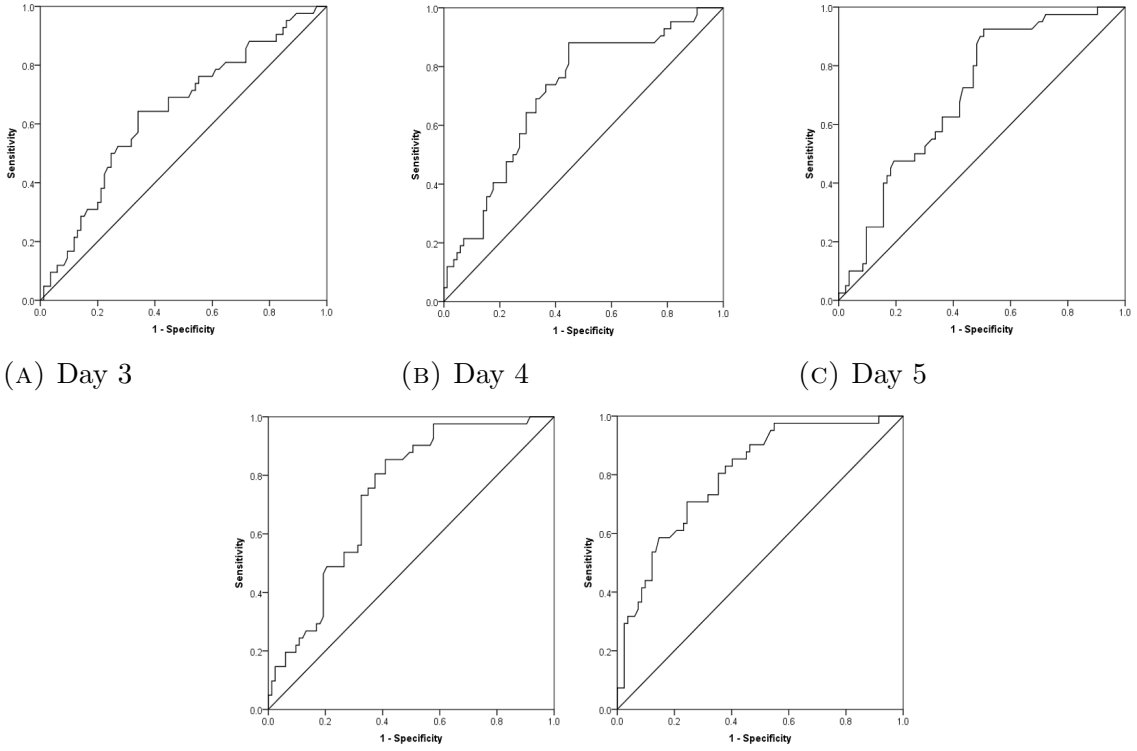
Receiver operating characteristic (ROC) analysis was undertaken to find the optimum threshold for the relationship between CRP and infective complications in patients without POPF. ROC curves were plotted with CRP as a continuous variable and infective complication as a dichotomous outcome variable for postoperative days 3 through 7.

The area under curve (AUC) was significantly higher than 0.5 for CRP on days 3 though 7. The optimum thresholds along with the corresponding sensitivity, specificity, negative predictive value, positive predictive value, 95% confidence intervals (CI) and p-values are shown in Table 6.5 and the corresponding ROC curves are shown in Fig. 6.3 on page 160. The thresholds were identified with a bias towards a higher negative predictive value to allow identification of patients who did not develop an infective complication.

A CRP level of 125 mg/L on the fourth postoperative day had a sensitivity of 74% and specificity of 64% with a negative predictive value of 83% for predicting infective complications (AUC 0.71, 95%CI 0.61 - 0.80, $p<0.001$). The AUC improved to 0.80 on day 7 but only with a modest increase in the negative predictive value to 87%, with corresponding sensitivity, specificity of 65% and 81% respectively (95%CI 0.72 - 0.88, $p<0.001$).

The relationship between CRP on the fourth day and other postoperative events is shown in Table 6.6. There were no deaths in this group of patients who did not have a POPF.

FIGURE 6.3: Receiver operating characteristics analysis of C-reactive protein as a marker of postoperative infective complications.



(A) Day 3 (B) Day 4 (C) Day 5

(D) Day 6 (E) Day 7

In the 126 patients who did not develop a postoperative pancreatic fistula, C-reactive protein levels as early as the third and fourth postoperative days had a high negative predictive value of 0.79 (for Day 3 CRP $\leq$ 178 mg/l) and 0.83 (for Day 4 CRP $\leq$125 mg/l) respectively for the prediction of infective complications.

TABLE 6.5: Receiver operating characteristics analysis of C-reactive protein as a marker of postoperative infective complications in patients who did not develop a POPF

Day	AUC	p	95% CI	CRP	Spec.	Sens.	NPV	PPV
3	0.64	0.011	0.54 - 0.74	178	0.66	0.64	0.79	0.48
4	0.71	<0.001	0.61 - 0.80	125	0.64	0.74	0.83	0.50
5	0.70	<0.001	0.61 - 0.80	107	0.64	0.63	0.78	0.45
6	0.73	<0.001	0.65 - 0.82	92	0.68	0.73	0.84	0.53
7	0.80	<0.001	0.72 - 0.88	87	0.65	0.81	0.87	0.52

AUC - Area under curve, Spec. - Specificity, Sens. - Sensitivity

NPV - Negative Predictive Value, PPV - Positive Predictive Value

TABLE 6.6: The relationship between CRP on Day 4 and other postoperative events in patients with no POPF.

		Day 4 CRP (mg/l)		
		≤125	>125	*p*
Postoperative stay	Days	12 (9 - 16)	15 (13 - 26)	<0.001[a]
(days)	≤14	43 (66.2%)	30 (49.2%)	<0.054[b]
	>14	22 (33.8%)	31 (50.8%)	
Critical care stay	Days	6 (4 - 7)	7 (5 - 10)	0.001[a]
(days)	≤7	57 (87.7%)	38 (62.3%)	0.001[b]
	>7	8 (12.3%)	23 (37.7%)	
Crit. care admissions	1	60 (92.3%)	48 (78.7%)	0.029[b]
	>1	5 (7.7%)	13 (21.3%)	
Reoperation	No	63 (96.9%)	57 (93.4%)	<0.359[b]
	Yes	2 (3.1%)	4 (6.6%)	

a - Mann-Whitney U test; b - Chi-square test

In patients who did not develop a postoperative pancreatic fistula (n=126), CRP ≤ 125 mg/l on the fourth postoperative day was associated with shorter stay in hospital, fewer days in critical care and lower rate of readmission to critical care.

6.4 Discussion

The results of the present study show that the severity of the postoperative systemic inflammatory response as measured by serial serum CRP levels in the first week is associated with postoperative complications after pancreaticoduodenectomy. The results also demonstrate that postoperative CRP trends are more useful in predicting infective complications in patients who did not develop a post-operative pancreatic fistula.

While numerous studies have reported on a variety of methods to predict as well as diagnose POPF, few have reported on the role of CRP in predicting complications other than POPF.

The introduction of the ISGPF definition for POPF has made the diagnosis of this complication simple and uniform [Bassi et al. 2005a]. The rate of POPF before the standardised definition was introduced varied anywhere between 2% and 40%. However, in the post-ISGPF era, the rate of POPF in published literature has remained approximately 25% [Knight et al. 2010]. The sole criterion for the diagnosis of POPF is a drain amylase content on or after the third postoperative day three times the upper limit of normal for serum amylase in the testing laboratory [Bassi et al. 2005a] .

In the present study, while CRP was significantly greater in patients with POPF, this difference did not occur until the second postoperative day and therefore had no further clinical use in the prediction of this complication. The early rise in CRP in patients who developed a POPF is expected as the most common risk factors for POPF are encountered intra-operatively including soft pancreatic texture, small pancreatic duct size and operative blood loss. Soft pancreatic texture has in fact been reported to be associated with elevated CRP levels after pancreaticoduodenectomy [Murakami et al. 2008].

However, the magnitude of increase in CRP during the first postoperative week was not associated with the severity of POPF. This lack of association appears to

suggest that the determinants of the severity of POPF may occur later in the postoperative course and are not related to the magnitude of the initial systemic inflammatory response.

The presumed cascade of events following a POPF involves accumulation of amylase rich fluid in the peritoneal cavity around recently dissected tissues and ligated blood vessels. This can lead to localised collections that can become secondarily infected, result in erosion of blood vessels resulting in post-pancreatectomy haemorrhage, result in delayed gastric emptying or postoperative ileus as well as respiratory complications including sympathetic pleural effusions or pneumonic consolidation. In fact, most large series report a close association between POPF and PPH with the latter often following the former [Choi et al. 2004; Koukoutsis et al. 2006; Tien et al. 2005]. The eventual outcome in patients with POPF is often determined by the cascade of complications associated with the POPF itself. In fact, all deaths in this study were in patients who developed POPF.

However, in patients without a POPF, CRP in the first week after surgery was associated with infective complications and preceded the clinical manifestation of complications. The postoperative course of patients who do not develop a POPF is not dissimilar to that in patients undergoing other major gastrointestinal resectional surgery such as colorectal or oesophago-gastric surgery. The impact of the systemic inflammatory response and the compensatory anti-inflammatory response in these patients is not confounded by the presence of POPF. Our results show that once the absence of POPF is confirmed by normal drain amylase content on the third postoperative day, serum CRP on the next (fourth) postoperative day less than 125 mg/L had a negative predictive value of 83% in excluding an infective complication.

The results of this study are similar to the findings of Welsch and co-workers who analysed 688 patients undergoing a variety of pancreatic resections with pancreaticojejunal anastomosis [Welsch et al. 2008]. They compared 91 patients

who developed an 'inflammatory postoperative complication' with a random subset of 60 consecutive pancreatic resections. They reported that a threshold of 140 mg/L for serum CRP on the fourth postoperative day had the best diagnostic accuracy for the prediction of inflammatory postoperative complications (sensitivity 69.5%, specificity 87.1%, positive predictive value 48.7% for an estimated prevalence of 15%). However, the definitions used for POPF in this study were different from the ISGPF definition and the authors did not report on the predictive ability of CRP in the presence or absence of a POPF. Moreover, Grade A and B POPF were not included in the analysis. Our results clearly demonstrate that early CRP elevation occurs in all grades of POPF with no difference between the different grades.

In the present study, preoperative systemic inflammation as measured by the modified Glasgow Prognostic Score was not associated with infective complications. A preoperative acute phase response has been reported to be associated with an exaggerated postoperative systemic inflammatory response and septic complications [Haupt et al. 1997]. The modified Glasgow Prognostic Score, a validated measure of preoperative systemic inflammation, has also been reported to be associated with postoperative infective complications in patients undergoing curative colorectal resections [Moyes et al. 2009].

The lack of association between the modified Glasgow Prognostic Score and complications in the present study may have been due to the multiple factors that are responsible for preoperative systemic inflammation in these patients including obstructive jaundice, cholangitis, biliary drainage procedures and pancreatitis consequent to intervention or pancreatic duct obstruction by tumours. These findings are similar to those reported by Dutta and co-workers who did not find any relationship between preoperative systemic inflammation and postoperative complications in patients undergoing oesophago-gastric surgery [Dutta et al. 2011].

The temporal association between CRP and infective complications may reflect the sensitivity of CRP as a marker of systemic inflammation. This finding is similar to

one of the earliest reports on the role of serial CRP measurements in predicting septic complications after surgery [Mustard et al. 1987] as well as in several subsequent reports [Matthiessen et al. 2008; Welsch et al. 2008; Dutta et al. 2011]. This study was not designed to look at inflammatory markers later in the postoperative period. However, Mustard and co-workers monitored CRP, white cell count and temperature for 14 days after surgery and found that CRP was the only reliable marker of septic complications [Mustard et al. 1987].

Several mechanisms have been postulated to explain the association between postoperative CRP and complications. The most common explanation is that the CRP rise is consequent to tissue ischaemia, necrosis at the anastomotic site, bacterial translocation from the gut or bacterial infection of wounds. However, our findings and that of other authors show that the difference in CRP occurs very early in the postoperative period before infective complications become clinically manifest.

More recently, the compensatory anti-inflammatory response with the associated immunosuppressive effects has been recognised as a possible factor in predisposing the patient to infective complications and delayed wound healing. Such an anti-inflammatory response is proportional to the initial systemic inflammatory response and therefore patients with an exaggerated inflammatory response in the immediate aftermath of surgery may be at increased risk of developing complications [Ward et al. 2008].

Mokart and co-workers studied trends in inflammatory cytokine levels in the serum of 30 patients undergoing major abdominal surgery for cancer [Mokart et al. 2002]. They reported that the levels of anti-inflammatory cytokines IL-10 and IL-1ra were significantly greater in patients who developed infective complications and were correlated with IL-6 levels on the first postoperative day. T-cell function is also depressed after surgical trauma and the degree of suppression is related to the initial pro-inflammatory response and IL-6 [Faist et al. 1997]. The complex interactions between the pro and anti-inflammatory processes, neurohormonal

factors of the stress response, the role of the blood-gut barrier in bacterial translocation, local factors including tissue ischaemia and damage, the immunological effects of anaesthesia, blood transfusion and hypothermia remain the subject of ongoing research [Buttenschoen et al. 2010].

One of the most important strengths of this study is the separate analysis of infective complications in patients who did not develop a POPF. Other strengths of this study include the homogeneous cohort of patients all of who underwent a pancreaticoduodenectomy, the serial measurements of CRP on every day of the first postoperative week, prospective record of complications and use of the ISGPF definition for POPF. We did not measure levels of other inflammatory cytokines routinely in these patients. Future work should be aimed at characterising the inflammatory cytokine profile after pancreaticoduodenectomy to identify potential targets for immunomodulation in the perioperative period.

In summary, the advent of enhanced recovery protocols in surgery including pancreatic surgery requires the early identification of patients not only at increased risk of complications but also those who are likely to have an uncomplicated course. This allows early identification of patients who are expected to continue on the enhanced recovery pathway and allocation of resources to improve the management of patients who are likely to develop complications. A recent meta-analysis of seven studies including 1427 patients established the value of CRP on the third postoperative day in identifying patients who are safe for early discharge on an enhanced recovery programme [Straatman et al. 2015]. This study shows that CRP on the third postoperative day is associated with infective complications in patients undergoing pancreaticoduodenectomy who do not develop a POPF but not in patients with a POPF.

Chapter 7

Discussion

7.1 Summary

The overall aim of the thesis was to examine the inter-relationships between preoperative clinico-pathological characteristics including cardiopulmonary exercise physiology, obstructive jaundice, body composition and preoperative systemic inflammation and post-operative complications and the post-surgical systemic inflammatory response in patients undergoing pancreaticoduodenectomy.

The present work also examined the factors that affect cardiopulmonary exercise physiology in order to enable a better understanding of the complex pathophysiology in these patients that is a consequence of the interaction of the patient's chronic conditions with the acute derangements brought on by pancreatic disease, including obstructive jaundice.

This was one of the largest studies involving patients who underwent cardiopulmonary exercise testing before undergoing pancreaticoduodenectomy in a tertiary specialist pancreato-biliary unit in the West of Scotland. The results presented here demonstrate the clinical utility of cardiopulmonary exercise testing in major pancreatic surgery in the largest cohort of patients in published literature.

The thesis also examined the effect of obstructive jaundice including severe obstructive jaundice on cardiopulmonary exercise physiology and postoperative systemic inflammation in this cohort. We are not aware of any other published reports on this subject.

This work also demonstrated a novel application of the trends in postoperative CRP in identifying patients at risk of infective complications which is different from the accepted paradigm for the use of postoperative CRP in published literature.

The results presented here provide the foundations for future work on prehabilitation, mitigating perioperative risks and improving outcomes after pancreaticoduodenectomy.

7.2 Clinical utility of CPET

7.2.1 Risk assessment and predicting complications

The results presented in chapter 2 demonstrated that cardiopulmonary exercise testing had a role in identifying high risk patients who were more likely to develop complications, stay longer in hospital and were less likely to receive adjuvant therapy after pancreaticoduodenectomy. These findings have since been replicated by other authors examining the role of cardiopulmonary exercise testing in pancreatic surgery.

Ausania and co-workers evaluated the role of cardiopulmonary exercise testing in 122 patients who underwent a pancreaticoduodenectomy [Ausania et al. 2012b] Low $\dot{V}_{O_2}$AT (<10.1 ml/kg/min) was the only independent predictor of a postoperative pancreatic fistula. The incidence of a postoperative pancreatic fistula was 45% in patients with a low $\dot{V}_{O_2}$AT while it was only 19% in patients with a normal $\dot{V}_{O_2}$AT (p=0.02). The association between $\dot{V}_{O_2}$AT and postoperative pancreatic fistula was independent of pancreatic duct size, body mass index, obstructive jaundice or preoperative biliary drainage. They also reported in a separate study of 50 patients that complication rates were higher in patients with a low $\dot{V}_{O_2}$AT undergoing palliative surgical bypass for advanced pancreatic cancer [Ausania et al. 2012a].

Junejo and co-workers identified elevated $\dot{V}_E/\dot{V}_{CO_2}$ to be an independent predictor of 30-day mortality after pancreaticoduodenectomy in their study that included 64 patients who had undergone cardiopulmonary exercise testing [Junejo et al. 2014b]. However, they also noted that a high $\dot{V}_E/\dot{V}_{CO_2}$ was also associated with poor long-term survival.

The results of our work in chapter 2 as well as that of several others over the past two decades support the use of cardiopulmonary exercise testing as a clinical risk assessment tool in patients undergoing major surgery.

7.2.2 Assessing impact of prehabilitation and neoadjuvant treatment

Our results also suggest that a better understanding of the determinants of aerobic capacity as well as the perioperative systemic inflammatory response will enable clinicians to identify high risk patients and optimise their perioperative care.

In a recent study of 8266 patients undergoing pancreaticoduodenectomy in the United States, Tzeng and co-workers reported that a third (3033) were of borderline fitness as a consequence of advanced age (> 80 years), poor performance status, weight loss > 10%, pulmonary disease, recent myocardial infarction/angina, stroke history, and/or preoperative sepsis. Major complications (31.3 vs. 26.2%) and mortality (4.1 vs. 2.3%) were greater in patients with borderline fitness [Tzeng et al. 2014]. The authors recommended that surgeons identify these patients early, institute interventions to optimise their comorbidities and enrol these patients for prehabilitation.

Neoadjuvant treatments were associated with significant reduction in $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak in patients with rectal cancer [West et al. 2014] and oesphago-gastric cancer [Jack et al. 2014]. West and co-workers used prehabilitation to return aerobic capacity, as measured by cardiopulmonary exercise testing, to baseline levels in patients with locally advanced rectal cancer undergoing neo-adjuvant chemoradiotherapy [West et al. 2015]. Neoadjuvant therapy in borderline resectable pancreatic cancer is the subject of several trials with generally promising results [Evans et al. 2008; Gillen et al. 2010; Golcher et al. 2015; Kim et al. 2013; Sahora et al. 2014].

The impact of neoadjuvant treatment on fitness in patients with pancreatic cancer are likely to be similar or worse to that observed in other cancer patients. Prehabilitation can play an important role in improving outcomes in these patients while cardiopulmonary exercise testing serves as an objective clinical tool to quantify the impact of prehabilitation.

7.2.3 Assessing impact on long-term survival

There is some evidence that cardiopulmonary exercise testing may predict long-term survival after pancreaticoduodenectomy for pancreatic cancer [Junejo et al. 2014b]. Reduced aerobic capacity was also associated with poor survival in patients with lung cancer [Jones et al. 2010] and reduced long-term survival after abdominal aortic aneurysm surgery [Tang et al. 2012; Grant et al. 2015].

While an elevated preoperative systemic inflammatory response was associated with shorter survival in patients with pancreatic cancer, both after potentially curative surgery [Jamieson et al. 2005; Torre et al. 2012] or palliation for advanced disease [Glen et al. 2006], the impact of aerobic capacity on long-term survival in patients with pancreatic cancer is less clear. Some have suggested that comorbidity was associated with shorter survival in patients with pancreatic cancer [Dias-Santos et al. 2015]. However, other authors have reported that the relatively short median survival after pancreatic cancer surgery is not affected by comorbidity whose effects are more long-term [Kos et al. 2014].

Further studies examining the relationship between aerobic capacity measured using objective methods and long-term survival are important. Aerobic capacity is a relatively easy therapeutic target that may have the potential to improve not only short-term but also long-term outcomes.

7.3 Prehabilitation, improving aerobic capacity and mitigating risk

In Chapters 3 and 4 we examined the preoperative patient factors that had an adverse effect on aerobic capacity. A better understanding of the factors that affect $\dot{V}_{O_2}$ may identify potential therapeutic targets or modifiable risk factors that may be used to improve patient fitness and mitigate the risks of surgery. We found that

female sex, high body mass index, anaemia, presence of cancer and elevated CRP were all associated with either a low $\dot{V}_{O_2}$AT or a low $\dot{V}_{O_2}$Peak.

7.3.1 Obstructive jaundice

In our opinion, the most important observation made in chapter 3 was the lack of association between obstructive jaundice and cardiopulmonary function. We are aware of only one other similar study by Junejo and co-workers. They reported that peripheral oxygen extraction was normal during cardiopulmonary exercise in patients with malignant obstructive jaundice [Junejo et al. 2014a]. Preoperative biliary drainage is unlikely to improve aerobic fitness or modify their cardiopulmonary response to exercise/surgery [Parker et al. 2014].

We also demonstrated the immunosuppressive effects of obstructive jaundice on the postoperative systemic inflammatory response in chapter 5. To our knowledge, this is the first detailed study of the postoperative systemic inflammatory response in jaundiced versus non-jaundiced patients undergoing pancreaticoduodenectomy.

In their, appropriately titled paper *'The Quandary of Preresection Biliary Drainage for Pancreatic Cancer'*, the authors discuss the complex physiological effects of obstructive jaundice, its impact on immune function and the differences between findings in animal studies and humans [Tol et al. 2012]. However, they also review recent literature where there appears to be overwhelming evidence that preoperative biliary drainage increases the incidence of postoperative complications, especially infective complications [Gaag et al. 2010; Arkadopoulos et al. 2014; Fujii et al. 2015; Furukawa et al. 2015].

In chapter 2 we reported that obstructive jaundice was not associated with increased incidence of postoperative complications or prolonged hospital stay. Taken together, our results support the emerging view that preoperative biliary drainage should no longer be performed routinely in all patients undergoing a pancreaticoduodenectomy unless specifically indicated such as in cholangitis.

7.3.2 Systemic inflammation

We reported on the preoperative factors affecting postoperative systemic inflammation in chapter 5 and the clinical utility of monitoring trends in the early postoperative systemic inflammatory response in predicting complications in chapter 6.

Preoperative systemic inflammation is increasingly recognised as playing an important role in determining not only long-term outcomes but also short-term outcomes after cancer surgery [Kubo et al. 2013; Mohri et al. 2014; Moyes et al. 2009; Neal et al. 2011; Vashist et al. 2010; Haupt et al. 1997]. While we did not find an association between elevated preoperative systemic inflammation and complications in our cohort of patients, we demonstrated in chapter 5 that preoperative systemic inflammation had a significant impact on the magnitude of the postoperative inflammatory response. This supports the theory that abnormal systemic inflammation is a continuum that starts in the preoperative phase and continues into the postoperative phase.

It would appear that preoperative patient factors affect the postoperative systemic inflammatory response independent of intra-operative factors or postoperative complications. The mechanisms underlying the association between pre- and post-operative systemic inflammation require further study.

7.3.3 Body composition

Overweight and obese patients had significantly lower $\dot{V}_{O_2}$AT and $\dot{V}_{O_2}$Peak in spite of no significant increase in known cardiac or respiratory comorbidities. We present a detailed analysis of the relationship between body composition and preoperative cardiopulmonary exercise testing in chapter 4. This has not been reported before in surgical patients to the best of our knowledge.

The loss of skeletal muscle mass in patients with pancreatic cancer and spurious

correlation with obesity due to correction for total body weight may partly explain the low $\dot{V}_{O_2}$ in these patients. Low aerobic capacity as measured by cardiopulmonary exercise testing must be interpreted with caution in overweight/obese patients and in patients with pancreatic cancer. This is especially true for $\dot{V}_{O_2}$ that has been scaled for total body weight. Further studies must evaluate other parameters such as O_2Pulse or $\dot{V}_E/\dot{V}_{CO_2}$ for their ability to predict postoperative outcomes. The proportion of obese patients undergoing major surgery is increasing. Moreover, sarcopenia and sarcopenic-obesity are recognised as important adverse prognostic features in pancreatic cancer [Tan et al. 2009; Peng et al. 2012] and were associated with increased postoperative complications after pancreaticoduodenectomy [Joglekar et al. 2015; Pausch et al. 2012]. Sarcopenia was also an independent risk factor for an elevated postoperative systemic inflammatory response in patients with colorectal cancer [Reisinger et al. 2015].

Our results suggest that poor performance at cardiopulmonary exercise testing may not necessarily be related to only cardiac or pulmonary function. Body composition appears to affect not only aerobic capacity but also systemic inflammation. Improvements in body composition in cancer patients are achievable through nutritional supplementation [Machado et al. 2015] as well as increased physical activity. Perioperative nutritional supplementation has been reported to be associated with reduced postoperative complications and improved outcomes [Kabata et al. 2015; Zhang et al. 2012].

7.3.4 Anaemia

Measures other than exercise may also improve aerobic capacity. Correction of anaemia was associated with an improvement in $\dot{V}_{O_2}$AT by 0.39 ml/kg/min for every 1 gm/dl improvement in haemoglobin [Wright et al. 2014]. While anaemia did not change the effect of aerobic exercise in improving physical performance, the overall aerobic fitness was significantly lower in anaemic patients than in patients

with normal haemoglobin [Bellotto et al. 2011]. However, perioperative blood transfusion in pancreatic cancer patients was associated with poorer long-term outcomes [Kneuertz et al. 2011; Sutton et al. 2014].

While iron supplementation is associated with correction of anaemia and reduction in the requirement for blood transfusion, the role of preoperative iron supplementation in improving outcomes is unclear. Further randomised controlled trials investigating the short-term and long-term consequences of preoperative iron supplementation in patients undergoing cancer surgery are required before this becomes accepted clinical practice [Beris et al. 2008; Hallet et al. 2014].

7.3.5 Aerobic exercise

West and co-workers used prehabilitation to return aerobic capacity to baseline levels in patients with locally advanced rectal cancer undergoing neo-adjuvant chemoradiotherapy [West et al. 2015]. Moderate aerobic and resistance exercises and protein supplementation started 4 weeks before surgery was noted to improve postoperative functional exercise capacity in patients undergoing colorectal cancer surgery [Gillis et al. 2014]. Exercise programs as short as 4 weeks in duration have been reported to improve aerobic capacity by upto 10% measured objectively by cardiopulmonary exercise testing. This could potentially move approximately 30% of high risk patients into the low risk category [Dunne et al. 2012].

A recent consensus statement by the 'Exercise Prehabilitation in Colorectal Cancer Delphi Study Group' in the United Kingdom showed agreement between colorectal surgeons that prehabilitation must form an important part of the preparation of elective patients for major surgery [Boereboom et al. 2015]. The surgeons also agreed that improving aerobic capacity is likely to improve outcomes but recommended that further studies were needed before this became established clinical practice.

7.4 Improving outcomes after pancreaticoduodenectomy

7.4.1 Centralisation and Specialisation

One of the biggest factors in improving both short-term and long-term outcomes after cancer surgery has been the centralisation of cancer treatment and the associated specialisation of surgeons.

Birkmeyer and co-workers were the first to report in 1999 that hospital volume was not only related to postoperative mortality and morbidity but also to long-term cancer survival in patients undergoing pancreaticoduodenectomy in the United States [Birkmeyer et al. 1999]. Better overall quality of care, better cancer operations based on oncological principles, better rates of adjuvant therapy may have all contributed to better outcomes in high-volume centres. They also reported in 2003 that operative mortality was inversely related to surgeon volume emphasising the importance of surgical expertise in improving outcomes [Birkmeyer et al. 2003]. Gouma and co-workers reported very similar findings in the Netherlands were morbidity and mortality after pancreaticoduodenectomy were linked to hospital volume [Gouma et al. 2000].

The importance of multi-disciplinary teams in the administration of complex perioperative care in these patients by Ho and Heslin who reported that the overall duration with pancreaticoduodenectomy in a hospital was associated with better postoperative outcomes [Ho et al. 2003]. This finding stresses the importance of organisational processes and allied specialists including anaesthetists, intensivists, diagnostic/interventional radiologists, nurses, physiotherapists and dietitians.

However, in spite of these advances, significant variation in practice remains an obstacle in improving outcomes after pancreaticoduodenectomy for pancreatic cancer [Cyr et al. 2015].

7.4.2 Goal-directed therapy

The results of chapter 2 and the work of Ausania and co-workers [Ausania et al. 2012b] suggest a link between reduced oxygen delivery and increased incidence of pancreatic fistula. We hypothesised that tissue hypoperfusion may have contributed to poor healing of the pancreatico-jejunal anastomosis.

Reyad and co-workers performed a randomised trial of the effect of dobutamine infusion during pancreaticoduodenectomy on splanchnic perfusion, hemodynamics, and overall postoperative outcome [Reyad et al. 2013]. They reported that intra-operative dobutamine use was associated with improved global oxygen delivery as measured by arterial and venous blood gases. Splanchnic perfusion measured by gastric tonometry also improved. It was interesting to note that the incidence of anastomotic leak was 30% in the control group, 15% in the group that received 3μg/kg/min of dobutamine and 5% in the group that received 5μg/kg/min of dobutamine ($p<0.05$). The overall complication rate also decreased from 70% in the control group to 40% and 20% in the dobutamine groups ($p< 0.05$).

However, the benefit of such goal-directed therapy to improve organ perfusion and oxygen delivery in improving postoperative outcomes remains unclear [Grocott et al. 2013; Pearse et al. 2014]. A recent randomised controlled trial evaluated the role of goal-directed therapy in high-risk patients undergoing major elective surgery that targeted individualised oxygen delivery [Ackland et al. 2015]. The study did show that patients whose postoperative oxygen delivery was similar to their preoperative values had fewer complications. However, oxygen delivery was not influenced by goal-directed therapy as any beneficial effect of the intervention was lost with the autonomic nervous system changes that accompanied the increased intravenous fluids and inotropes in the treatment cohort.

However, the results presented in this thesis support the argument for therapeutic interventions aimed at improving oxygen delivery and organ perfusion before the patient reaches the operating room as outlined in section 7.3.

7.4.3 Early recognition and aggressive management of complications

Postoperative complications and the associated systemic inflammatory response are associated with early recurrence and poor-survival after colorectal [Artinyan et al. 2015; McArdle et al. 2005], gastric [Hayashi et al. 2015; Kubota et al. 2014] and pancreatic cancer surgery [Aoyama et al. 2015; Kamphues et al. 2012].

Early recognition and aggressive management of complications is therefore important in mitigating the harmful long-term effects of such adverse events and the associated inflammation. Several recent studies have demonstrated the value of monitoring trends in postoperative CRP levels in predicting complications after pancreaticoduodenectomy [Hiyoshi et al. 2013; Ansorge et al. 2014; Kosaka et al. 2014].

Our approach to interpreting the postoperative systemic inflammatory response has been different from these studies. We demonstrated in chapter 6 that postoperative CRP did not predict the severity of a pancreatic fistula and did not have any clinical utility in the prediction of a POPF (section 6.3.2). However, we demonstrated a clear role for the use of postoperative CRP in predicting infective complications in the absence of a POPF. The combination of a low CRP and absence of POPF reduced the likelihood of any other infective complications and identified patients who may be suitable for early discharge.

'Failure to rescue' after postoperative complications is one of the factors responsible for the discrepancy between morbidity and mortality in low-volume versus high-volume centres. Mortality rates in patients undergoing a variety of complex surgical procedures including pancreatectomy was 2.5 times higher in low-volume centres than high-volume centres [Ghaferi et al. 2009]. However, complication rates were similar between these hospitals. Failure to identify and manage complications aggressively may have resulted in the increased mortality in the low-volume hospitals. In a recent large study involving nearly 2 million

surgical patients, Ferraris VA and co-workers studied the outcome of over two-hundred thousand patients who had complications [Ferraris VA et al. 2014]. They noted that 20% of high-risk patients accounted for 90% of deaths due to postoperative complications. They also reported that a simple risk-score based on preoperative characteristics was able to identify these patients. Early recognition of complications in these high patients and aggressive management will reduce mortality. These findings are supported by other studies involving emergency abdominal surgery [Sheetz et al. 2013] and major trauma [Haas et al. 2011]

The results presented in this thesis not only allow identification of high risk patients before surgery but also help in the early identification of postoperative complications.

7.5 Future directions

The work done in this thesis raises a number of important clinical questions. Further studies on the inter-relationships between aerobic fitness, comorbidity, systemic inflammation at the metabolic level in patients with cancer will allow better understanding of their impact of postoperative outcomes. Objective measurement of aerobic fitness and systemic inflammation will allow for individualised perioperative care that starts at the time of diagnosis and continues in the postoperative period. Further studies will have to focus on improving modifiable risk factors such as $\dot{V}_{O_2}$ starting with community/home-based interventions and continuing with individualised goal-directed therapy during and after surgery. Aggressive protocol-driven early rescue strategies that include identification of high risk patients before surgery, early recognition of complications and multi-disciplinary management may help improve postoperative outcomes and attenuate the adverse effects of complications on long-term survival. This in combination with individualised cancer treatments both in the neo-adjuvant and adjuvant settings will help improve outcomes in patients with pancreatic cancer.

Appendix A

Visual Basic for Applications For Data Collection

The following VBA code was written to facilitate collection of laboratory data from the existing user interface that did not allow easy automation. It forms part of a Microsoft Access database. Some parts of the code has been removed or reformatted to be accommodated within the constraints of this thesis.

The RealLink for Windows (RFW, http://www.nps-reality.com/reallink) application used at Glasgow Royal Infirmary allowed access from VBA via Dynamic Data Exchange. This was used to collect and parse laboratory data for preoperative and postoperative blood tests efficiently and without error.

```
'#########################################################################
'Dynamic Data Exchange with RealLink application
'#########################################################################
Option Compare Database
Function RLChannel() As Long
  Dim AppName As String
  Dim Topic As String
  AppName = "******"
  Topic = "******"
  DDETerminateAll

  On Error GoTo ErrorHandler
  RLChannel = DDEInitiate(AppName, Topic)
  Exit Function
  ErrorHandler:
  MsgBox "Error initiating connection to RealLink   Error ID: " & _
  Err.Description, vbOKOnly, "Error"
End Function
Sub RLSendData(strdata As String, WaitSecs As Integer)
  On Error GoTo ErrorHandler
  Dim starttime As Double
  AppActivate "RealLink   NGTBIO", Wait
  starttime = Timer
  SendKeys strdata, True
  starttime = Timer
  While Timer < starttime + WaitSecs: Wend
  Exit Sub
  ErrorHandler:
'Error gets dealt with by procedure calling this function
End Sub

Function RLGetData(ChannelNum As Long) As String
  On Error GoTo ErrorHandler
  Dim RLItem As String
  RLItem = "Table 0,0,80,24,Comma"
  RLGetData = DDERequest(ChannelNum, RLItem)
  Exit Function
  ErrorHandler:
  MsgBox "Error capturing data from RealLink   : " & _
    Err.Description, vbOKOnly, "Error"
End Function

Sub WaitFor(intSeconds As Integer)
  Dim starttime As Single
  starttime = Timer
  While Timer < starttime + intSeconds: Wend
End Sub
Function ChkLabScreen(strLabScreen As String, _
 strSurname As String, strLab As String) As Integer
  If InStr(1, strLabScreen, strSurname) = 0 Then
    ChkLabScreen = ChkLabScreen + 1
  If InStr(1, strLabScreen, strLab) Then
    ChkLabScreen = ChkLabScreen + 2
End Function
Sub RunRealLink()
'Wait for application to start then wait 5 seconds
```

```
'Shell runs commands asynchronously
'DDEPoke does not work   use windows shell and processID instead
  Dim dReturnValue As Single
  dReturnValue = Shell("C:\RFW\RFW.EXE /LC:\RFW\RFWDDE.DLL NGTBIO",_
   vbMaximizedFocus)
  While dReturnValue < 0: Wend
  Call WaitFor(5)
End Sub
Sub Login(LabNum As String, Username As String, Password As String)
' Login to Biochem/Haem
  Dim strSend As String

  strSend = "***" & vbCr
  Call RLSendData(strSend, 2)

  strSend = LabNum & vbCr
  Call RLSendData(strSend, 2)

  strSend = Username & vbCr
  Call RLSendData(strSend, 1)

  strSend = Password & vbCr
  Call RLSendData(strSend, 1)
End Sub
Sub SearchPatient(Surname As String, HospitalNumber As String, _
 Optional EarliestDate As Date, Optional LatestDate As Date)
'Enter patient information and date range(optional)
  Dim strSend As String
  strSend = ""
  Call RLSendData(strSend, 1)
  strSend = HospitalNumber & vbCr
  Call RLSendData(strSend, 1)
  strSend = Left(Surname, 2) & vbCr
  Call RLSendData(strSend, 1)
  strSend = Format(EarliestDate, "dd.mm.yy") & vbCr
  Call RLSendData(strSend, 0) 'Earliest date to search
  strSend = Format(LatestDate, "dd.mm.yy") & vbCr
  Call RLSendData(strSend, 0) 'Latest date to search
End Sub

'#########################################################
'Parser for results scraped from RealLink screengrab
'#########################################################
Option Compare Database
'Results parsers
Public Sub ParseFBC(strHD As String)
On Error GoTo ErrorHandler
Dim strA() As String 'string to hold rows of data
Dim intRows As Long
Dim intTests As Integer
Dim intPosition As Integer
Dim strTest() As Variant 'name of test eg WBC
Dim strResult(10, 1) As String
'change first dimension if changing number of tests
strTest = Array("WBC", "Hb", "Hct", "MCV", "Plts", _
"NEUT", "LYMPH", "MONO", "EOS", "BASO")
intTests = UBound(strTest)
strA = Split(strHD, vbCr)
intRows = UBound(strA)
Dim tempRow As String
Dim rowdate As Integer
For rowdate = 0 To 10
  tempRow = strA(rowdate)
  If InStr(1, tempRow, "Collected") > 0 Then
   Dim strDateTime() As String
   Dim strDate As String
   Dim strTime As String
   strDateTime = Split(tempRow, "Collected")
   strDateTime = Split(strDateTime(1), ",")
   If InStr(1, strDateTime(1), "*") > 0 Then
```

```
   strDate = Trim(Replace(strDateTime(1), ".", "/"))
   End If
   If UBound(strDateTime) > 2 Then
   strDate = Trim(Replace(strDateTime(1), ".", "/"))
   strTime = Trim(strDateTime(2))
   End If
  End If
Next rowdate
For t = 0 To intTests 'cycle through list of tests   strTest
  For i = 0 To intRows 'cycle through rows   strA
   tempRow = strA(i)
   tempRow = Replace(tempRow, vbCrLf, "")
   tempRow = Replace(tempRow, vbLf, "")
   tempRow = Replace(tempRow, vbCr, "")
   temptest = strTest(t)
   intPosition = InStr(tempRow, temptest)
   If intPosition > 0 Then
    Dim strTemp() As String
    strTemp = Split(tempRow, ",")

    For j = 0 To UBound(strTemp)
    'cycle through values in a single row   strTemp
     If Trim(strTemp(j)) = strTest(t) Then
      strResult(t, 0) = strTest(t)

      If Trim(strTemp(j + 1)) = "+" Or Trim(strTemp(j + 1)) = " " Then
       strResult(t, 1) = Trim(strTemp(j + 2))
      Else
       strResult(t, 1) = Trim(strTemp(j + 1))
      End If
     End If
    Next j
   End If
  Next i
Next t
'Fill in results into form
  Call SaveHaem(strDate, strTime, strResult)
  Exit Sub
  ErrorHandler:
End Sub
Sub ParseCoag(strCoag As String)
  On Error GoTo ErrorHandler
  Dim strA() As String 'string to hold rows of data
  Dim intRows As Long
  Dim intTests As Integer
  Dim intPosition As Integer
  Dim strTest() As Variant 'name of test eg WBC
  Dim strResult(23, 1) As String
  'change first dimension if changing number of tests
  strTest = Array("PT", "PT C Ratio", "APTT", "APTT Ratio", "TCT", "TCT Ratio")
  intTests = UBound(strTest)
  strA = Split(strCoag, vbCr)
  intRows = UBound(strA)
  Dim tempRow As String
  Dim rowdate As Integer
  For rowdate = 0 To 10
   tempRow = strA(rowdate)
   If InStr(1, tempRow, "Collected") > 0 Then
    Dim strDateTime() As String
    Dim strDate As String
    Dim strTime As String
    strDateTime = Split(tempRow, "Collected")
    strDateTime = Split(strDateTime(1), ",")
    If InStr(1, strDateTime(1), "*") > 0 Then
    strDate = Trim(Replace(strDateTime(1), ".", "/"))
    End If
    If UBound(strDateTime) > 2 Then
    strDate = Trim(Replace(strDateTime(1), ".", "/"))
    strTime = Trim(strDateTime(2))
    End If
```

```
   End If
  Next rowdate
  For t = 0 To intTests 'cycle through list of tests   strTest
   For i = 0 To intRows 'cycle through rows   strA
   tempRow = strA(i)
   tempRow = Replace(tempRow, ",+", "")
   tempRow = Replace(tempRow, ", ", "")
   tempRow = Replace(tempRow, "+,", ",")
   tempRow = Replace(tempRow, " ,", ",")
   tempRow = Replace(tempRow, "|", ",")
   temptest = strTest(t)
   intPosition = InStr(tempRow, temptest)
   If intPosition > 0 Then
    Dim strTemp() As String
    strTemp = Split(tempRow, ",")
    For j = 0 To UBound(strTemp)
    'cycle through values in a single row   strTemp
     If Trim(strTemp(j)) = strTest(t) Then
      strResult(t, 0) = strTest(t)
      If Trim(strTemp(j + 1)) = "+" Or Trim(strTemp(j + 1)) = " " _
        Or Trim(strTemp(j + 1)) = "" Then
       strResult(t, 1) = Trim(strTemp(j + 2))
      Else
       strResult(t, 1) = Trim(strTemp(j + 1))
      End If
     End If
    Next j
   End If
    Next i
  Next t
'Fill in results into form
  Call SaveCoag(strDate, strTime, strResult)
  Exit Sub
  ErrorHandler:
End Sub
Sub ParseBio(strBD As String)
  Dim strSurname As String
  Dim strHNum As String
  Dim strA() As String 'string to hold rows of data
  Dim intRows As Long
  Dim intTests As Integer
  Dim intPosition As Integer
  Dim strTest() As Variant 'name of test eg Sodium
  strTest = Array("Sodium", "Potassium", "Urea", "Creat", "eGFR", "Phos",_
   "Mg++", "Chloride", "Bili", "G GT", "A Phos", "ALT", "AST",_
   "T Prot", "Alb", "Globulin", "Glucose", "CRP", "Trop I", _
   "Calcium", "Ad Cal", "Amylase")
  Dim strResult(21, 1) As String
  'change first dimension if changing number of tests
  intTests = UBound(strTest)
  strBD = Replace(strBD, ".Amylase.", "..")
  strBD = Replace(strBD, vbCrLf, "")
  strBD = Replace(strBD, vbLf, "")
  strBD = Replace(strBD, vbCr, "")
  strA = Split(strBD, "|")
  Dim strTempDate As String
  strTempDate = strA(0)
  If InStr(strTempDate, "Collected") Then
   Dim strDateTime() As String
   Dim strDate As String
   Dim strTime As String
   strDateTime = Split(strTempDate, "Collected")
   strDateTime = Split(strDateTime(1), ",")
   strDate = strDateTime(1)
   strDate = Replace(strDate, ".", "/")
   strTime = strDateTime(2)
  End If
  intRows = UBound(strA)
  For t = 0 To intTests 'cycle through list of tests   strTest
   For i = 0 To intRows 'cycle through rows   strA
```

```
   tempRow = strA(i)
   temptest = strTest(t)
   intPosition = InStr(tempRow, temptest)
    If intPosition > 0 Then
     Dim strTemp() As String
     Dim intDots As Integer

    'Routine to remove dots word dots
     intDots = InStr(strA(i), "..")
     If intDots > 0 Then
      strTemp = Split(NoDots(strA(i)), ",")
     Else
      strTemp = Split(strA(i), ",")
     End If
    'End of Routine to remove dots word dots

     For j = 0 To UBound(strTemp)
     'cycle through values in a single row   strTemp
      If Trim(strTemp(j)) = strTest(t) Then
       strResult(t, 0) = strTest(t)

       If Trim(strTemp(j + 1)) = "+" Or Trim(strTemp(j + 1)) = " " Then
        strResult(t, 1) = Trim(strTemp(j + 2))
       Else
        strResult(t, 1) = Trim(strTemp(j + 1))
       End If
      End If
     Next j
    End If
   Next i
  Next t
  'Fill in results into form
   Call SaveBio(strDate, strTime, strResult)
End Sub
Function NoDots(strWithDots As String) As String
  Dim intDotEndPos As Integer
  Dim intDotStartPos As Integer
  Dim intRowLen As Integer
  intDotEndPos = InStrRev(strWithDots, "..")
  'find the first occurrence of .. from the end
  intDotStartPos = InStr(strWithDots, "..")
  'find the first occurrence of .. from the end
  intRowLen = Len(strWithDots)
  'get the total length of the string with dots
'get the substring on the right and left of the dots based on above values
  NoDots = Left(strWithDots, intDotStartPos) & "," & _
  Right(strWithDots, intRowLen   intDotEndPos   1)
'Debug.Print NoDots
End Function

'#########################################################
'Code to save results to respective tables
'#########################################################
Option Compare Database
Sub SaveBio(strDate, strTime, strResult)
Dim tf_B As SubForm
Set tf_B = Forms!frm_Demo!frm_Bloods
'create a new record
tf_B.SetFocus
DoCmd.GoToRecord , , acNewRec
tf_B!CHI = Forms!frm_Demo!CHI
tf_B!Surname = Forms!frm_Demo!Surname
tf_B!Date = strDate
tf_B!Time = strTime
intTests = UBound(strResult, 1)
For i = 0 To intTests
  Select Case strResult(i, 0)
  Case "Potassium"
   tf_B!K = strResult(i, 1)
  Case "Urea"
```

```
   tf_B!Urea = strResult(i, 1)
  Case "Creat"
   tf_B!Creatine = strResult(i, 1)
'Case "eGFR"
  Case "Phos"
   tf_B!PO4 = strResult(i, 1)
  Case "Mg++"
   tf_B!Magnesium = strResult(i, 1)
  Case "Chloride"
   tf_B!Cl = strResult(i, 1)
  Case "Bili"
   tf_B!Bilirubin = strResult(i, 1)
  Case "G GT"
   tf_B!GGT = strResult(i, 1)
  Case "A Phos"
   tf_B!Al_Phos = strResult(i, 1)
  Case "ALT"
   tf_B!ALT = strResult(i, 1)
  Case "AST"
   tf_B!AST = strResult(i, 1)
  Case "T Prot"
   tf_B!Protein = strResult(i, 1)
  Case "Alb"
   tf_B!Albumin = strResult(i, 1)
  Case "Globulin"
   tf_B!Globulin = strResult(i, 1)
  Case "Glucose"
   tf_B!Glucose = strResult(i, 1)
  Case "CRP"
   tf_B!CRP = strResult(i, 1)
  Case "Trop I"
   tf_B!Troponin = strResult(i, 1)
  Case "Calcium"
   tf_B!Ca = strResult(i, 1)
  Case "Ad Cal"
   tf_B!Adj_Ca = strResult(i, 1)
  Case "Amylase"
   tf_B!Amylase = strResult(i, 1)
  Case "Sodium"
   tf_B!Na = strResult(i, 1)
  End Select
  Next i
End Sub
Sub SaveCoag(TestDate As String, TestTime As String, Results() As String)
Dim tf_C As SubForm
Set tf_C = Forms!frm_Demo!frm_Coag
'create a new record
tf_C.SetFocus
DoCmd.GoToRecord , , acNewRec
tf_C!CHI = Forms!frm_Demo!CHI
tf_C!Surname = Forms!frm_Demo!Surname
tf_C!Date = TestDate
If TestTime <> "*" And TestTime <> "NK" Then tf_C!Time = TestTime
intTests = UBound(Results, 1)
For i = 0 To intTests
  Select Case Results(i, 0)
  Case "PT"
   tf_C!PT = Results(i, 1)
  Case "PT C Ratio"
   tf_C![PT C Ratio] = Results(i, 1)
  Case "APTT"
   tf_C!APTT = Results(i, 1)
  Case "APTT Ratio"
   tf_C![APTT Ratio] = Results(i, 1)
  Case "TCT"
   tf_C!TCT = Results(i, 1)
  Case "TCT Ratio"
   tf_C![TCT Ratio] = Results(i, 1)
  End Select
  Next i
```

```
End Sub
Sub SaveHaem(TestDate As String, TestTime As String, Results() As String)
Dim tf_H As SubForm
Set tf_H = Forms!frm_Demo!frm_Haematology
'create a new record
tf_H.SetFocus
DoCmd.GoToRecord , , acNewRec
tf_H!CHI = Forms!frm_Demo!CHI
tf_H!Surname = Forms!frm_Demo!Surname
tf_H!Date = TestDate
If TestTime <> "*" Then tf_H!Time = TestTime
intTests = UBound(Results, 1)
For i = 0 To intTests
'frmHaem.strResult(i, 0) = strResult(i, 1)
  Select Case Results(i, 0)
  Case "WBC"
   tf_H!WBC = Results(i, 1)
  Case "Plts"
   tf_H!Plts = Results(i, 1)
  Case "Hb"
   tf_H!HB = Results(i, 1)
  Case "MCV"
   tf_H!MCV = Results(i, 1)
  Case "MCHC"
   tf_H!MCHC = Results(i, 1)
  Case "RDW"
   tf_H!RDW = Results(i, 1)
  Case "RBC"
   tf_H!RBC = Results(i, 1)
  Case "NEUT"
   tf_H!NEUT = Results(i, 1)
  Case "LYMPH"
   tf_H!LYMPH = Results(i, 1)
  Case "MONO"
   tf_H!MONO = Results(i, 1)
  Case "EOS"
   tf_H!EOS = Results(i, 1)
  Case "BASO"
   tf_H!BASO = Results(i, 1)
  Case "Hct"
   tf_H!Hct = Results(i, 1)
  Case "MCH"
   tf_H!MCH = Results(i, 1)
  Case "MPV"
   tf_H!MPV = Results(i, 1)
  Case "PDW"
   tf_H!PDW = Results(i, 1)
  Case "PCT"
   tf_H!PCT = Results(i, 1)
  End Select
  Next i
End Sub

'############################################################
'User interface functions
'############################################################

Option Compare Database
Private Sub Form_Load()
  Me.RecordSource = "tb_Demo"
End Sub
Private Sub cmbAllPatients_AfterUpdate()
  ' Find the record that matches the control.
  Dim rs As Object
  Set rs = Me.Recordset.Clone
  rs.FindFirst "[IPID] = " & Str(Nz(Me![cmbAllPatients], 0))
  If Not rs.EOF Then Me.Bookmark = rs.Bookmark
End Sub
Private Sub cmbChooseProcedure_AfterUpdate()
  'Filter by operation name
```

```
  Dim strSQL As String
  Dim strFilter As String
  If Me.cmbChooseProcedure = "All" Or IsNull(Me.cmbChooseProcedure) Then
   ' If the combo is Null, use the whole table as the RecordSource.
   Me.RecordSource = "tb_Demo"
  Else
   strFilter = Me.cmbChooseProcedure
   strSQL = "SELECT tb_Demo.* FROM tb_Demo LEFT JOIN tb_Operation ON _
    tb_Demo.IPID = tb_Operation.IPID WHERE ((([tb_Operation]![Primary _
     Procedure]) LIKE '*" & strFilter & "*'))ORDER BY _
      [tb_Operation]![Operation Date];"
   Me.RecordSource = strSQL
  End If
End Sub
Private Sub cmbChooseOpDate_AfterUpdate()
  'Filter by operation DATE
  Dim strSQL As String
  Dim strFilter As Date
  If IsNull(Me.cmbChooseOpDate) Then
   ' If the combo is Null, use the whole table as the RecordSource.
   Me.RecordSource = "tb_Demo"
  Else
   strFilter = CDate(Me.cmbChooseOpDate)
   strSQL = "SELECT tb_Demo.* FROM tb_Demo LEFT JOIN tb_Operation ON _
    tb_Demo.IPID = tb_Operation.IPID WHERE _
    ((([tb_Operation]![Operation Date]) > #" & strFilter & "#))_
    ORDER BY [tb_Operation]![Operation Date];"
   Me.RecordSource = strSQL
  End If
End Sub
Private Sub cmbChooseSpecialty_AfterUpdate()
  'Filter by Specialty
  Dim strSQL As String
  Dim strFilter As String
  strFilter = Me.cmbChooseSpecialty
  If strFilter = "All" Or IsNull(Me.cmbChooseSpecialty) Then
   ' If the combo is Null, use the whole table as the RecordSource.
   Me.RecordSource = "tb_Demo"
  Else
   strSQL = "SELECT tb_Demo.* FROM tb_Demo LEFT JOIN tb_Event_Admission _
   ON tb_Demo.IPID = tb_Event_Admission.IPID WHERE _
    ((([tb_Event_Admission]![Specialty] _
    LIKE '*" & strFilter & "*')));"
   Me.RecordSource = strSQL
  End If
End Sub
Private Sub cmdNewPatient_Click()
  On Error GoTo Err_cmdNewPatient_Click
  DoCmd.DoMenuItem acFormBar, acRecordsMenu, 5, , acMenuVer70
  DoCmd.GoToRecord , , acNewRec
  Exit Sub
  Err_cmdNewPatient_Click:
  MsgBox Err.Description
End Sub
Private Sub listCurrentPatients_AfterUpdate()
  ' Find the record that matches the control.
  Dim rs As Object
  Set rs = Me.Recordset.Clone
  rs.FindFirst "[IPID] = " & Str(Nz(Me![listCurrentPatients], 0))
  If Not rs.EOF Then Me.Bookmark = rs.Bookmark
  Me.frm_Physiology.Form.Refresh
End Sub
Private Sub cmdSendDetails_Click()
  'checked and works
  Dim Surname As String 'Surname from frm_demo
  Dim HospitalNum As String 'Hospital number from frm_demo
  Dim OpDate As Date 'Date of operation from frm_operation
  Dim Edate As Date 'Earliest date of bloods to return
  Dim Ldate As Date 'Latest date of bloods to return
  On Error GoTo ErrorHandler:
```

```
  Surname = Me.Surname
  HospitalNum = Me.HospitalNum
  OpDate = Me.frm_Operation.Form![Operation Date]
  'Set search date range
  Edate = OpDate   10
  Ldate = OpDate + 5
  If Me.chkResuse = 0 Then 'Is Reuse box not checked then start a new RL session
   Call RunRealLink
   Select Case Me.frameChooseLab.Value
    Case 1
     Call Login("3", "******", "******")
    Case 2
     Call Login("2", "******", "******")
   End Select
  End If
  Call SearchPatient(Surname, HospitalNum, Edate, Ldate)
  Exit Sub
  ErrorHandler:
MsgBox "cmdHaem Error" & Err.Description
End Sub
Private Sub cmdImport_Click()
  On Error GoTo ErrorHandler
  Dim intRepeat As Integer
  KillSwitch = False
  If CInt(Me.txtAutoRepeat) > 0 Then
   intRepeat = CInt(Me.txtAutoRepeat)
  Else
   intRepeat = 1
  End If
  If Me.chkAutoUpdate.Value =  1 Then
   For i = 1 To intRepeat
    Call ImportData
    Me.Refresh
    Call cmdLater_Click
    If KillSwitch = True Then Exit Sub
   Next
  End If
  ErrorHandler:
  Exit Sub
End Sub
Private Sub ImportData()
  Dim LabChannel As Long
  LabChannel = RLChannel
  'Grab screen text from existing RL window
  Dim strResultScreen As String
  Call WaitFor(3)
  If LabChannel > 0 Then
   strResultScreen = RLGetData(LabChannel)
  Else
   MsgBox "RealLink connection could not be established", vbOKOnly,_
    "Connection Error"
   Exit Sub
  End If
  'Send to either FBC/Coag parser
  If InStr(1, strResultScreen, "Press Esc") Then KillSwitch = True
  If InStr(1, strResultScreen, "..FBC..") Then
   Call ParseFBC(strResultScreen)
  End If
  If InStr(1, strResultScreen, "..C/Screen..") Then
   Call ParseCoag(strResultScreen)
  End If
  If InStr(1, strResultScreen, "Biochem") Then
   Call ParseBio(strResultScreen)
  End If
  'Terminate all DDE connections
DDETerminate LabChannel
End Sub
Private Sub cmdEarlier_Click()
  Dim strTemp As String
  strTemp = "E" & vbCr
```

```
  Call RLSendData(strTemp, 0)
End Sub
Private Sub cmdLater_Click()
  Dim strTemp As String
  strTemp = "L" & vbCr
  Call RLSendData(strTemp, 0)
End Sub
Private Sub tb_ABG_ALL_subform_Enter()
  Me.Refresh
End Sub
Private Sub tgDemoDupes_Click()
  Select Case Me.tgDemoDupes.Value
   Case  1
    Me.tgDemoDupes.SetFocus
    Me.tgDemoDupes.Caption = "DemoDupes ON"
    Me.RecordSource = "qs_DemoDupes"
   Case 0
    Me.tgDemoDupes.SetFocus
    Me.tgDemoDupes.Caption = "DemoDupes OFF"
    Me.RecordSource = "tb_Demo"
  End Select
End Sub
Private Sub cmdRefresh_Click()
  On Error GoTo Err_cmdRefresh_Click
  DoCmd.DoMenuItem acFormBar, acRecordsMenu, 5, , acMenuVer70
  Exit_cmdRefresh_Click:
  Exit Sub
  Err_cmdRefresh_Click:
  MsgBox Err.Description
  Resume Exit_cmdRefresh_Click
End Sub

'############################################################
'VBA code to import CPET results into database
'############################################################
Option Compare Database
Private Sub cmdImport_Click()
  Dim strEmptyline As String
  On Error Resume Next
  Dim strResult As String
  Dim strResult2 As String
  Dim strTemp() As String
  Dim channel As Long
  channel = TermChannel
  strResult = TermGetData(channel)
  If strResult = "" Then Exit Sub
  strResult = Replace(strResult, "qq", "")
  'strTemp = Split(strResult, "COMMENT SCREEN")
  ' strResult = strTemp(1)
  'strResult = strTemp(0)
  strTemp = Split(strResult, vbCrLf)
  For j = 0 To UBound(strTemp)
  If Trim(strTemp(j)) <> "" Then
   Me.txtFull.SetFocus
   Me.txtFull.Value = Me.txtFull.Value & Trim(strTemp(j)) & vbCrLf
  'Debug.Print Trim(strTemp(j))
  End If
  Next j
  Me.Application.DDEPoke channel, "qvt_term_item", "1"
  WaitFor (1)
  DDETerminateAll
End Sub
Function TermGetData(ChannelNum As Long) As String
  On Error GoTo ErrorHandler
  Dim RLItem As String
  RLItem = "Table 0,0,80,24,Comma"
  TermGetData = DDERequest(ChannelNum, RLItem)
  Exit Function
  ErrorHandler:
  MsgBox "Error capturing data from RealLink   : " & _
```

```
  Err.Description, vbOKOnly, "Error"
End Function
Function TermChannel() As Long
  Dim AppName As String
  Dim Topic As String
  AppName = "qvt_term"
  Topic = "Respiratory"
  DDETerminateAll
  On Error GoTo ErrorHandler
  TermChannel = DDEInitiate(AppName, Topic)
  Exit Function
  ErrorHandler:
  MsgBox "Error initiating connection to Term   Error ID: " & _
  Err.Description, vbOKOnly, "Error"
End Function
Sub TermSendData(strdata As String, WaitSecs As Integer)
  On Error GoTo ErrorHandler
  Dim starttime As Double
  AppActivate "RealLink   NGTBIO", Wait
  SendKeys strdata, True
  starttime = Timer
  While Timer < starttime + WaitSecs: Wend
  Exit Sub
  ErrorHandler:
'Error gets dealt with by procedure calling this function
End Sub
Private Sub cmdSendPatient_Click()
  Dim channel As Long
  Dim strName As String
  strName = "ret" & vbCr & "7" & Me.Parent!Surname & " " _
   & Me.Parent!Forename & vbCr
  channel = TermChannel
  Me.Application.DDEPoke channel, "qvt_term_item", strName
  DDETerminateAll
End Sub
```

Appendix B

Visual Basic for Applications For CPET Analysis

The following VBA code was written to facilitate detailed analysis of large volumes of raw CPET data that would not have been otherwise available from the final report generated for clinical use. This allowed analysis of all parameters measured at rest, anaerobic threshold and peak exercise rather than just $\dot{V}_{O_2}$.

```
Option Explicit
Sub RenameSortSheets()
   Dim ws As Worksheet
   Dim strName() As String
   For Each ws In Worksheets
     If ws.Range("$B$1").Value="" Then
       Exit Sub
     End If
     If ws.Name <> "aaa_main" Then
       strName=Split(CStr(ws.Range("$B$1").Value), "(")
       ws.Name=LCase(strName(0))
       ws.Activate
       ws.Range("B4").Select
       ActiveWindow.FreezePanes=True
     End If
   Next ws
   Dim N As Integer
   Dim M As Integer
   Dim FirstWSToSort As Integer
   Dim LastWSToSort As Integer
   Dim SortDescending As Boolean
   SortDescending=False
   If ActiveWindow.SelectedSheets.Count=1 Then
     'Change the 1 to the worksheet you want sorted first
     FirstWSToSort=1
     LastWSToSort=Worksheets.Count
    Else
     With ActiveWindow.SelectedSheets
       For N=2 To .Count
         If .Item(N - 1).Index <> .Item(N).Index - 1 Then
           MsgBox "You cannot sort non-adjacent sheets"
           Exit Sub
         End If
       Next N
       FirstWSToSort=.Item(1).Index
       LastWSToSort=.Item(.Count).Index
     End With
   End If
   For M=FirstWSToSort To LastWSToSort
     For N=M To LastWSToSort
       If SortDescending=True Then
         If UCase(Worksheets(N).Name) > UCase(Worksheets(M).Name) Then
           Worksheets(N).Move Before:=Worksheets(M)
         End If
       Else
         If UCase(Worksheets(N).Name) < UCase(Worksheets(M).Name) Then
           Worksheets(N).Move Before:=Worksheets(M)
         End If
       End If
     Next N
   Next M
   Dim x As Integer
   x=2
   Sheets("aaa_main").Range("A:A").Clear
   Sheets("aaa_main").Cells(1, 1)="SheetName"
   For Each ws In Worksheets
     Sheets("aaa_main").Cells(x, 1)=ws.Name
     x=x + 1
   Next ws
End Sub
Sub GotoSheet()
  If ActiveWindow.ActiveSheet.Name="aaa_main" Then
    Dim selName As String
    selName=ActiveWindow.ActiveCell.Value
```

```
    Worksheets(selName).Activate
  Else
    Worksheets("aaa_main").Activate
  End If
End Sub
Sub VCO2VO2()
  Dim ws As Worksheet
  For Each ws In Worksheets
    Dim x As Integer
    x=4
    While ws.Cells(x, 2) > 0
      If ws.Cells(x, 9) <> "-" And ws.Cells(x, 6) <> "-" Then
        ws.Cells(x, 22)=CDbl(ws.Cells(x, 9)) / CDbl(ws.Cells(x, 6))
      End If
      x=x + 1
    Wend
  Next ws
End Sub
Sub ClearColumn()
  Dim ws As Worksheet
  For Each ws In Worksheets
    ws.Range("AD9")=ws.Range("A1")
    ws.Range("A1").Clear
  Next ws
End Sub
Sub DeleteAllCharts()
  Dim ws As Worksheet
  Dim chart As ChartObject
  For Each ws In Worksheets
    For Each chart In ws.ChartObjects
      chart.Delete
    Next chart
  Next ws
End Sub
Sub AddRCValues()
  Dim x As Integer
  For x=3 To 88
    Sheets(Sheets("aaa_main").Cells(x, 1).Value).Range("AD8")=_
      Sheets("aaa_main").Cells(x, 27).Value
    Sheets(Sheets("aaa_main").Cells(x, 1).Value).Range("AD9")=_
      Sheets("aaa_main").Cells(x, 28).Value
  Next x
End Sub
Sub CopyLineForSPSS()
  Dim rng As Range
  Dim selrow As Integer
  Dim selrng As String
  selrow=ActiveWindow.ActiveCell.Row
  selrng="AF" & CStr(selrow) & ":BX" & CStr(selrow)
  Range(selrng).Select
  Selection.Copy
End Sub

%---------------------------------
Sub ValuesAT()
  Dim r As Integer
  r=3 - Selection.Cells(1, 1).Row
  ActiveSheet.Range("X29")=Selection.Cells(r, 1)
  ActiveSheet.Range("Y29")=Selection.Cells(r, 3)
  ActiveSheet.Range("Z29")=Selection.Cells(r, 4)'VE
  ActiveSheet.Range("AA29")=Selection.Cells(r, 5)'VT
  ActiveSheet.Range("AB29")=Selection.Cells(r, 6)'VO2
  ActiveSheet.Range("AC29")=Selection.Cells(r, 7)'VO2/KG
  ActiveSheet.Range("AD29")=Selection.Cells(r, 8)'VE/VO2
  ActiveSheet.Range("AE29")=Selection.Cells(r, 9)'VCO2
  ActiveSheet.Range("AF29")=Selection.Cells(r, 10)'VE/VCO2
  ActiveSheet.Range("AG29")=Selection.Cells(r, 11)'RER
  ActiveSheet.Range("AH29")=Selection.Cells(r, 12)'PETO2
  ActiveSheet.Range("AI29")=Selection.Cells(r, 13)'PETCO2
  ActiveSheet.Range("AJ29")=Selection.Cells(r, 14)'O2PULSE
```

```
  ActiveSheet.Range("AK29")=Selection.Cells(r, 15)'HR
  ActiveSheet.Range("AL29")=Selection.Cells(r, 16)'Bf

  ActiveSheet.Range("W30")="AT"
  ActiveSheet.Range("X30")=WorksheetFunction.Average(Selection.Columns(1))'TIME
  ActiveSheet.Range("Y30")=WorksheetFunction.Average(Selection.Columns(3))'LOAD
  ActiveSheet.Range("Z30")=WorksheetFunction.Average(Selection.Columns(4))'VE
  ActiveSheet.Range("AA30")=WorksheetFunction.Average(Selection.Columns(5))'VT
  ActiveSheet.Range("AB30")=WorksheetFunction.Average(Selection.Columns(6))'VO2
  ActiveSheet.Range("AC30")=WorksheetFunction.Average(Selection.Columns(7))'VO2/KG
  ActiveSheet.Range("AD30")=WorksheetFunction.Average(Selection.Columns(8))'VE/VO2
  ActiveSheet.Range("AE30")=WorksheetFunction.Average(Selection.Columns(9))'VCO2
  ActiveSheet.Range("AF30")=WorksheetFunction.Average(Selection.Columns(10))'VE/VCO2
  ActiveSheet.Range("AG30")=WorksheetFunction.Average(Selection.Columns(11))'RER
  ActiveSheet.Range("AH30")=WorksheetFunction.Average(Selection.Columns(12))'PETO2
  ActiveSheet.Range("AI30")=WorksheetFunction.Average(Selection.Columns(13))'PETCO2
  ActiveSheet.Range("AJ30")=WorksheetFunction.Average(Selection.Columns(14))'O2PULSE
  ActiveSheet.Range("AK30")=WorksheetFunction.Average(Selection.Columns(15))'HR
  ActiveSheet.Range("AL30")=WorksheetFunction.Average(Selection.Columns(16))'Bf
End Sub

Sub ValuesPeak()
  ActiveSheet.Range("W31")="Peak"
  ActiveSheet.Range("X31")=WorksheetFunction.Average(Selection.Columns(1))'TIME
  ActiveSheet.Range("Y31")=WorksheetFunction.Max(Selection.Columns(3))'LOAD
  ActiveSheet.Range("Z31")=WorksheetFunction.Max(Selection.Columns(4))'VE
  ActiveSheet.Range("AA31")=WorksheetFunction.Max(Selection.Columns(5))'VT
  ActiveSheet.Range("AB31")=WorksheetFunction.Max(Selection.Columns(6))'VO2
  ActiveSheet.Range("AC31")=WorksheetFunction.Max(Selection.Columns(7))'VO2/KG
  ActiveSheet.Range("AD31")=WorksheetFunction.Max(Selection.Columns(8))'VE/VO2
  ActiveSheet.Range("AE31")=WorksheetFunction.Max(Selection.Columns(9))'VCO2
  ActiveSheet.Range("AF31")=WorksheetFunction.Max(Selection.Columns(10))'VE/VCO2
  ActiveSheet.Range("AG31")=WorksheetFunction.Max(Selection.Columns(11))'RER
  ActiveSheet.Range("AH31")=WorksheetFunction.Max(Selection.Columns(12))'PETO2
  ActiveSheet.Range("AI31")=WorksheetFunction.Max(Selection.Columns(13))'PETCO2
  ActiveSheet.Range("AJ31")=WorksheetFunction.Max(Selection.Columns(14))'O2PULSE
  ActiveSheet.Range("AK31")=WorksheetFunction.Max(Selection.Columns(15))'HR
  ActiveSheet.Range("AL31")=WorksheetFunction.Max(Selection.Columns(16))'Bf
End Sub

Sub ValuesOther()
  ActiveSheet.Range("W32")="Other"
  ActiveSheet.Range("X32")=WorksheetFunction.Average(Selection.Columns(1))'TIME
  ActiveSheet.Range("Y32")=WorksheetFunction.Average(Selection.Columns(3))'LOAD
  ActiveSheet.Range("Z32")=WorksheetFunction.Average(Selection.Columns(4))'VE
  ActiveSheet.Range("AA32")=WorksheetFunction.Average(Selection.Columns(5))'VT
  ActiveSheet.Range("AB32")=WorksheetFunction.Average(Selection.Columns(6))'VO2
  ActiveSheet.Range("AC32")=WorksheetFunction.Average(Selection.Columns(7))'VO2/KG
  ActiveSheet.Range("AD32")=WorksheetFunction.Average(Selection.Columns(8))'VE/VO2
  ActiveSheet.Range("AE32")=WorksheetFunction.Average(Selection.Columns(9))'VCO2
  ActiveSheet.Range("AF32")=WorksheetFunction.Average(Selection.Columns(10))'VE/VCO2
  ActiveSheet.Range("AG32")=WorksheetFunction.Average(Selection.Columns(11))'RER
  ActiveSheet.Range("AH32")=WorksheetFunction.Average(Selection.Columns(12))'PETO2
  ActiveSheet.Range("AI32")=WorksheetFunction.Average(Selection.Columns(13))'PETCO2
  ActiveSheet.Range("AJ32")=WorksheetFunction.Average(Selection.Columns(14))'O2PULSE
  ActiveSheet.Range("AK32")=WorksheetFunction.Average(Selection.Columns(15))'HR
  ActiveSheet.Range("AL32")=WorksheetFunction.Average(Selection.Columns(16))'Bf
End Sub

Sub AutomatePeakOtherValues()
  Dim ws As Worksheet
  Dim topRow As Integer
  Dim bottomRow As Integer
  For Each ws In Worksheets
    If ws.Name <> "aaa_main" Then
      ws.Activate
      'Fill other values
      Dim rng As Range
      Dim fdrng As Range
      Set rng=ws.Range("C:C")
```

```
      Set fdrng=rng.Find(30, LookIn:=xlValues)
      If Not fdrng Is Nothing Then
        topRow=fdrng(0, 1).Row
        bottomRow=fdrng(2, 0).Row
        Set rng=ws.Range(topRow & ":" & bottomRow)
        rng.Select
        Call ValuesOther
      End If

      'Fill peak values
      Dim maxVO2
      maxVO2=WorksheetFunction.Max(ws.Range("G:G"))
      Set rng=ws.Range("G:G")
      Set fdrng=rng.Find(maxVO2)
        If Not fdrng Is Nothing Then
          topRow=fdrng(-1, 1).Row
          bottomRow=fdrng(3, 0).Row
        If ws.Range("W31").Value="" Then
          Set rng=ws.Range(topRow & ":" & bottomRow)
          rng.Select
          Call ValuesPeak
        End If
      End If

    End If
  Next ws
End Sub

Sub ChartResize()
  Range("Y35").Select
  ActiveSheet.ChartObjects("Chart 1").Activate
  ActiveChart.Axes(xlCategory).Select
  ActiveChart.ChartArea.Select
  ActiveSheet.Shapes("Chart 1").ScaleWidth 0.5, msoFalse, _
  msoScaleFromBottomRight
  ActiveSheet.Shapes("Chart 1").IncrementLeft 102#
  ActiveSheet.Shapes("Chart 1").IncrementTop 253.5
End Sub

Sub VECharts()
  Dim ws As Worksheet
  For Each ws In Worksheets
    With ws.ChartObjects.Add _
      (Left:=800, Top:=725, Width:=400, Height:=225)
      .chart.ChartType=xlLine
      .chart.SetSourceData Source:=ws.Range("A:A,H:H,J:J") _
      , PlotBy:=xlColumns

      .chart.HasAxis(xlCategory, xlPrimary)=True
      .chart.HasAxis(xlValue, xlPrimary)=True

      .chart.Axes(xlCategory, xlPrimary).CategoryType=xlAutomatic
    End With
  Next ws
End Sub

Sub CopyCPETParametersFromSheetsToMain()
  Dim x As Integer
  For x=3 To 99
    Dim sheetname As String
    Sheets("aaa_main").Activate
    sheetname=ActiveSheet.Cells(x, 1)
    ActiveSheet.Cells(x, 32).Select
    Sheets(sheetname).Select
    Range("X30:AL30").Select
    Selection.Copy
    Sheets("aaa_main").Select
    ActiveSheet.Paste

    ActiveSheet.Cells(x, 47).Select
```

```
    Sheets(sheetname).Select
    Range("X31:AL31").Select
    Selection.Copy
    Sheets("aaa_main").Select
    ActiveSheet.Paste

    ActiveSheet.Cells(x, 62).Select
    Sheets(sheetname).Select
    Range("X32:AL32").Select
    Selection.Copy
    Sheets("aaa_main").Select
    ActiveSheet.Paste
  Next x

End Sub

Sub CopyVEVO2VEVCO2FromSheetsToMain()
  Dim x As Integer
  For x=3 To 99
    Dim sheetname As String
    Sheets("aaa_main").Activate
    sheetname=ActiveSheet.Cells(x, 1)
    ActiveSheet.Cells(x, 79).Select
    Sheets(sheetname).Select
    Range("Y22").Select
    Selection.Copy
    Sheets("aaa_main").Select
    ActiveSheet.Paste

    ActiveSheet.Cells(x, 80).Select
    Sheets(sheetname).Select
    Range("Y23").Select
    Selection.Copy
    Sheets("aaa_main").Select
    ActiveSheet.Paste
  Next x

End Sub

Sub FindStartEndTimeofExercise()
  Dim x As Integer
  Dim y As Integer
  Dim starttime As String
  Dim endtime As String
  Dim sheetname As String
  For x=3 To 99
    Sheets("aaa_main").Activate
    sheetname=ActiveSheet.Cells(x, 1)
    Sheets(sheetname).Select
    y=15
    While ActiveSheet.Cells(y, 3)="-"
      y=y + 1
    Wend
    starttime=ActiveSheet.Cells(y, 1)
    y=y + 5
    While ActiveSheet.Cells(y, 3) > "0"
      y=y + 1
    Wend
    endtime=ActiveSheet.Cells(y - 1, 1)
    Sheets("aaa_main").Activate
    ActiveSheet.Cells(x, 77)=starttime
    ActiveSheet.Cells(x, 78)=endtime
  Next x
End Sub
```

Appendix C

Breath-by-breath CPET sample data

FIGURE C.1: Breath-by-breath sample data with values averaged every 10 seconds - Part 1.

Time min:sec	%peakVO$_2$	Load W	VE l/min	Vt l	VO$_2$ l/min	VO$_2$/kg ml/(kg*min)	VE/VO$_2$ l/l	VCO$_2$ l/min	VE/VCO$_2$ l/l	RER	PETO$_2$ mmHg	PETCO$_2$ mmHg	O$_2$Puls ml/beat	HR beats/min	Bf 1/min	Vd/Vt %	O2sat %
00:10	20	-	13	0.74	0.39	4.6	31.3	0.38	31.9	0.98	111	34	5	75	18	34	97
00:20	18	-	12	0.71	0.35	4.2	30.6	0.34	31.3	0.98	110	34	5	74	16	33	97
00:30	18	-	12	0.78	0.37	4.4	29.7	0.36	30.7	0.97	109	35	5	73	15	33	97
00:40	20	-	12	0.77	0.36	4.4	30.4	0.36	30.9	0.98	110	35	5	73	16	33	97
00:50	17	-	12	0.82	0.35	4.2	31.8	0.36	31.3	1.02	111	34	5	73	15	33	97
01:00	18	-	12	0.84	0.34	4.1	33.2	0.35	32	1.04	113	34	5	74	14	34	97
01:10	17	-	11	0.73	0.29	3.5	34.9	0.31	33.3	1.05	114	33	4	75	15	35	98
01:20	13	-	12	0.71	0.29	3.5	38.3	0.31	36.2	1.06	117	31	4	75	17	35	98
01:30	25	-	14	1.03	0.34	4.1	39.5	0.38	35.9	1.1	119	30	5	73	14	33	98
01:40	12	-	14	1.2	0.36	4.3	36.2	0.4	31.9	1.14	119	31	5	74	11	27	98
01:50	15	-	10	0.95	0.28	3.3	35.7	0.31	31.3	1.14	117	33	4	76	11	30	98
02:00	16	-	10	0.81	0.25	3	37.6	0.28	33.4	1.12	117	33	3	76	13	34	98
02:10	9	-	11	0.76	0.29	3.4	35.6	0.31	32.9	1.08	115	33	4	76	15	34	98
02:20	15	-	12	0.57	0.28	3.4	38.5	0.29	36.9	1.04	116	32	4	78	21	38	97
02:30	22	-	15	0.6	0.41	4.9	33.8	0.4	34.5	0.98	113	33	5	84	25	36	97
02:40	28	-	20	0.75	0.55	6.5	33.1	0.55	32.9	1.01	114	34	6	86	26	34	97
02:50	25	-	19	0.73	0.5	5.9	35.9	0.53	33.7	1.06	117	33	6	88	26	35	97
03:00	27	-	20	1	0.51	6	36.7	0.56	33.2	1.11	117	33	6	87	20	34	98
03:10	22	-	18	0.87	0.43	5.2	38.3	0.49	33.9	1.13	117	33	5	86	21	36	98
03:20	24	-	18	0.82	0.47	5.6	35.1	0.51	32.1	1.09	116	34	5	86	22	34	98
03:30	24	-	17	0.95	0.49	5.8	33.6	0.53	30.6	1.1	115	35	6	87	18	32	98
03:40	27	-	18	0.95	0.49	5.8	34.1	0.53	31.1	1.1	115	35	6	86	19	33	98
03:50	25	-	17	0.94	0.47	5.7	34.2	0.52	31.4	1.09	115	35	6	86	18	33	98
04:00	21	-	16	0.73	0.42	5	35.4	0.45	33	1.07	116	33	5	85	22	35	98
04:10	25	4	18	0.7	0.48	5.7	35.4	0.51	33.3	1.06	116	33	6	85	26	34	98
04:20	21	6	17	0.68	0.44	5.3	34.9	0.46	33.3	1.05	115	34	5	86	25	36	98
04:30	29	9	19	0.92	0.53	6.4	33.7	0.57	31.6	1.07	114	34	6	86	21	33	98
04:40	25	13	19	0.91	0.5	6	35.3	0.56	31.7	1.11	116	34	6	87	21	33	98
04:50	25	16	19	0.94	0.5	6	35.2	0.56	31.8	1.11	115	34	6	88	21	34	98
05:00	35	20	20	1.17	0.5	5.9	38.5	0.56	34.3	1.12	116	34	6	88	17	37	98
05:10	18	23	18	0.98	0.44	5.2	38.9	0.49	34.6	1.12	116	34	5	88	19	37	98
05:20	24	26	16	0.74	0.46	5.5	33.2	0.48	31.6	1.05	113	35	5	89	22	34	98
05:30	26	29	17	0.73	0.52	6.2	30.3	0.5	31.2	0.97	111	35	6	92	23	34	98
05:40	31	32	17	0.82	0.58	6.9	27.9	0.54	29.8	0.94	109	36	6	92	21	32	98
05:50	31	36	18	1	0.63	7.5	27.5	0.59	29.2	0.94	109	36	7	91	19	30	97
06:00	35	40	21	0.98	0.66	7.9	29.8	0.64	30.8	0.97	111	35	7	91	21	32	97
06:10	33	43	21	0.88	0.66	7.9	30.1	0.64	31.1	0.97	111	35	7	92	24	33	98
06:20	37	45	21	1.05	0.69	8.3	29.3	0.67	30.2	0.97	110	36	8	91	20	33	98
06:30	34	49	21	0.96	0.7	8.4	28.5	0.68	29.6	0.96	109	36	8	92	22	32	98
06:40	41	53	23	1.08	0.78	9.4	27.4	0.75	28.5	0.96	108	37	8	92	21	30	98
06:50	42	56	23	1.07	0.8	9.5	27.8	0.77	28.8	0.96	109	37	9	93	22	31	98
07:00	40	59	25	1.25	0.8	9.6	29.5	0.79	30	0.98	110	36	8	94	20	33	97

FIGURE C.2: Breath-by-breath sample data with values averaged every 10 seconds - Part 2.

07:10	39	63	24	1.27	0.75	9	29.9	0.75	29.9	1	110	37	8	94	19	33	97
07:20	40	67	23	0.96	0.78	9.4	28.1	0.76	28.8	0.98	109	37	8	93	24	31	98
07:30	44	70	25	1.11	0.85	10.2	27.5	0.82	28.4	0.97	109	37	9	95	22	31	97
07:40	47	73	25	1.22	0.9	10.8	26.6	0.88	27.4	0.97	108	38	9	97	21	29	97
07:50	46	76	25	1.15	0.88	10.5	27.3	0.86	28	0.97	107	38	9	98	22	32	97
08:00	35	80	24	1.3	0.86	10.3	26.6	0.84	27.4	0.97	106	39	9	100	18	31	97
08:10	56	83	28	1.27	1.01	12	26.4	0.97	27.4	0.97	107	39	10	102	22	30	97
08:20	54	86	31	1.46	1.04	12.5	28.5	1.06	28.1	1.01	109	38	10	103	21	31	97
08:30	52	90	31	1.44	1.02	12.2	28.9	1.07	27.5	1.05	110	39	10	103	22	30	97
08:40	50	93	32	1.58	0.99	11.9	31.4	1.06	29.3	1.07	111	38	10	104	21	33	97
08:50	49	96	30	1.16	0.95	11.4	29.8	1.01	28.2	1.06	111	38	9	105	26	32	98
09:00	56	100	32	1.34	1.09	13	28.2	1.14	26.9	1.05	109	39	10	105	24	30	98
09:10	57	103	33	1.54	1.12	13.3	28.8	1.18	27.2	1.06	110	39	10	107	22	30	97
09:20	63	107	35	1.69	1.14	13.7	29.5	1.24	27.2	1.08	110	39	11	108	21	30	98
09:30	56	109	35	1.5	1.14	13.6	29.7	1.24	27.3	1.09	111	39	11	108	23	30	98
09:40	64	112	36	1.73	1.17	13.9	29.7	1.28	26.9	1.1	111	39	11	110	21	29	98
09:50	55	116	35	1.56	1.14	13.6	29.3	1.24	26.8	1.09	110	40	10	111	22	30	98
10:00	64	120	36	1.64	1.23	14.7	28.7	1.34	26.2	1.09	110	40	11	112	22	29	97
10:10	72	123	43	1.94	1.39	16.5	30.4	1.56	27	1.13	111	39	12	113	22	28	97
10:20	67	126	43	1.65	1.32	15.8	31.4	1.54	26.9	1.17	113	38	12	114	26	28	97
10:30	72	130	42	1.65	1.38	16.5	29.4	1.58	25.7	1.15	112	39	12	116	26	26	98
10:40	68	133	42	1.85	1.35	16.2	30.3	1.57	26.2	1.16	112	39	11	118	23	27	98
10:50	68	136	39	2.08	1.31	15.6	29.3	1.49	25.6	1.14	110	40	11	120	19	26	98
11:00	77	140	44	1.99	1.49	17.8	28.7	1.69	25.3	1.13	111	40	12	120	22	24	98
11:10	79	142	48	1.85	1.53	18.3	30.8	1.81	26	1.18	113	38	13	121	26	25	97
11:20	75	147	47	2.06	1.47	17.6	31	1.75	25.9	1.19	113	39	12	125	23	25	97
11:30	77	150	47	1.96	1.52	18.1	30.2	1.75	26.1	1.15	112	40	12	127	24	26	98
11:40	81	153	51	1.92	1.59	19	31.3	1.9	26.3	1.19	114	38	12	128	27	24	97
11:50	83	156	54	2.02	1.59	18.9	32.9	1.95	26.8	1.23	116	38	12	130	27	24	97
12:00	90	159	61	2.56	1.78	21.2	33.8	2.22	27	1.25	116	37	14	132	24	22	97
12:10	104	163	71	2.65	2	23.8	34.9	2.57	27.1	1.29	119	35	15	134	27	18	97
12:20	98	166	75	2.36	1.95	23.3	37.6	2.55	28.7	1.31	121	34	14	136	32	21	97
12:30	95	169	74	2.13	1.85	22.1	39.3	2.46	29.5	1.33	122	33	13	138	35	23	98
12:40	91	172	73	2.16	1.77	21.2	39.9	2.36	30	1.33	121	34	13	139	34	25	97
12:50	89	-	72	2.15	1.71	20.4	41	2.32	30.1	1.36	122	33	12	140	33	24	98
13:00	81	-	71	2.05	1.58	18.9	43.9	2.23	31.1	1.41	124	32	11	138	35	25	98
13:10	68	-	55	1.91	1.29	15.5	40.9	1.88	28.2	1.45	123	34	10	136	29	20	98
13:20	72	-	56	2.11	1.45	17.3	37.7	2.05	26.6	1.41	122	36	11	130	27	19	98
13:30	65	-	65	1.89	1.28	15.3	49.5	1.97	32.1	1.54	127	31	10	125	34	26	97
13:40	46	-	46	1.69	0.95	11.4	46.6	1.5	29.6	1.57	126	32	8	119	27	23	95
13:50	49	-	50	1.51	0.89	10.6	54.6	1.42	34.1	1.6	128	28	8	117	33	25	96
14:00	36	-	48	1.53	0.74	8.8	63.1	1.24	37.5	1.68	129	29	6	115	32	33	96
14:10	40	-	43	1.22	0.78	9.4	53	1.25	33.3	1.59	127	31	7	110	35	29	97
14:20	39	-	43	1.15	0.77	9.2	52.4	1.18	34.2	1.53	127	30	7	107	37	31	97
14:30	36	-	39	1.14	0.71	8.4	52.6	1.07	34.7	1.52	127	30	7	105	34	31	98
14:40	34	-	39	0.99	0.67	8	54.5	1.02	35.7	1.52	127	29	6	104	39	32	97

Bibliography

Abraham, E. and Y. H. Chang (1985). "The effects of hemorrhage on mitogen-induced lymphocyte proliferation". In: *Circulatory Shock* 15.2, pp. 141–149. ISSN: 0092-6213.

Abraham, S. C. et al. (2003). "Pancreaticoduodenectomy (Whipple resections) in patients without malignancy - Are they all 'chronic pancreatitis'?" In: *American Journal of Surgical Pathology* 27.1. WOS:000180144000012, pp. 110–120. ISSN: 0147-5185. DOI: 10.1097/00000478-200301000-00012.

Ackland, Gareth L et al. (2015). "Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial". In: *The Lancet Respiratory Medicine* 3.1, pp. 33–41. ISSN: 2213-2600. DOI: 10.1016/S2213-2600(14)70205-X.

Agostoni, Piergiuseppe et al. (2010). "Relationship of resting hemoglobin concentration to peak oxygen uptake in heart failure patients". In: *Am J Hematol* 85.6. 00019, pp. 414–7.

Al Murri, A. M. et al. (2006). "Evaluation of an inflammation-based prognostic score (GPS) in patients with metastatic breast cancer." In: *British journal of cancer* 94.2, pp. 227–230. DOI: 10.1038/sj.bjc.6602922.

Al Murri, A. M. et al. (2007). "Evaluation of the relationship between the systemic inflammatory response and cancer-specific survival in patients with primary operable breast cancer." In: *British journal of cancer* 96.6, pp. 891–895. DOI: 10.1038/sj.bjc.6603682.

Aloia, Thomas A. et al. (2007). "Delayed recovery after pancreaticoduodenectomy: a major factor impairing the delivery of adjuvant therapy?" In: *Journal of the American College of Surgeons* 204.3, pp. 347–355. ISSN: 1072-7515. DOI: 10.1016/j.jamcollsurg.2006.12.011.

Amundson, Dennis E., Svetolik Djurkovic, and Gregory N. Matwiyoff (2010). "The obesity paradox". In: *Critical Care Clinics* 26.4, pp. 583–596. ISSN: 1557-8232. DOI: 10.1016/j.ccc.2010.06.004.

Anblagan, D. et al. (2013). "Measurement of fetal fat in utero in normal and diabetic pregnancies using magnetic resonance imaging". In: *Ultrasound in Obstetrics & Gynecology* 42.3, pp. 335–340. ISSN: 1469-0705. DOI: 10.1002/uog.12382.

Ansorge, C. et al. (2014). "Diagnostic value of abdominal drainage in individual risk assessment of pancreatic fistula following pancreaticoduodenectomy". In:

The British Journal of Surgery 101.2, pp. 100–108. ISSN: 1365-2168. DOI: 10.1002/bjs.9362.

Aoyama, Toru et al. (2015). "Impact of Postoperative Complications on Survival and Recurrence in Pancreatic Cancer". In: *Anticancer Research* 35.4. 00000, pp. 2401–2409. ISSN: 0250-7005, 1791-7530.

Arkadopoulos, Nikolaos et al. (2014). "Preoperative biliary drainage of severely jaundiced patients increases morbidity of pancreaticoduodenectomy: results of a case-control study". In: *World Journal of Surgery* 38.11, pp. 2967–2972. ISSN: 1432-2323. DOI: 10.1007/s00268-014-2669-x.

Artinyan, Avo et al. (2015). "Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients". In: *Annals of Surgery* 261.3, pp. 497–505. ISSN: 1528-1140. DOI: 10.1097/SLA.0000000000000854.

"ATS/ACCP Statement on Cardiopulmonary Exercise Testing" (2003). In: *American Journal of Respiratory and Critical Care Medicine* 167.2, pp. 211–277. ISSN: 1073-449X, 1535-4970. DOI: 10.1164/rccm.167.2.211.

Ausania, F. et al. (2012a). "Double bypass for inoperable pancreatic malignancy at laparotomy: postoperative complications and long-term outcome". In: *Annals of the Royal College of Surgeons of England* 94.8, pp. 563–568. ISSN: 1478-7083. DOI: 10.1308/003588412X13373405386934.

Ausania, F et al. (2012b). "Effects of low cardiopulmonary reserve on pancreatic leak following pancreaticoduodenectomy". In: *Br J Surg* 99.9, pp. 1290–4.

Bailey, M. E. (1976). "Endotoxin, bile salts and renal function in obstructive jaundice". In: *British Journal of Surgery* 63.10, pp. 774–778. ISSN: 1365-2168. DOI: 10.1002/bjs.1800631011.

Bakkevold, K E and B Kambestad (1993a). "Morbidity and mortality after radical and palliative pancreatic cancer surgery. Risk factors influencing the short-term results". In: *Ann Surg* 217.4, pp. 356–68.

Bakkevold, K. E. et al. (1993b). "Adjuvant combination chemotherapy (AMF) following radical resection of carcinoma of the pancreas and papilla of Vater–results of a controlled, prospective, randomised multicentre study". In: *European Journal of Cancer (Oxford, England: 1990)* 29A.5. 00367, pp. 698–703. ISSN: 0959-8049.

Balady, G. J. et al. (2010). "Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association". In: *Circulation* 122.2, pp. 191–225. ISSN: 0009-7322, 1524-4539. DOI: 10.1161/CIR.0b013e3181e52e69.

Balentine, Courtney J. et al. (2011). "Obesity does not increase complications following pancreatic surgery". In: *The Journal of Surgical Research* 170.2. 00011, pp. 220–225. ISSN: 1095-8673. DOI: 10.1016/j.jss.2011.03.048.

Balladur, P et al. (1996). "Bleeding of the pancreatic stump following pancreatoduodenectomy for cancer". In: *Hepatogastroenterology* 43.7. 00000, pp. 268–70.

Bandyopadhyay, Gautam et al. (2007). "Negative signaling contributes to T-cell anergy in trauma patients". In: *Critical Care Medicine* 35.3, pp. 794–801. ISSN: 0090-3493. DOI: 10.1097/01.CCM.0000256847.61085.A5.

Bassi, Claudio et al. (2005a). "Postoperative pancreatic fistula: an international study group (ISGPF) definition". In: 138. 02498.

Bassi, Claudio et al. (2005b). "Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study". In: *Annals of Surgery* 242.6. 00339, 767–771, discussion 771–773. ISSN: 0003-4932.

Bassi, Claudio et al. (2010). "Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial". In: *Annals of Surgery* 252.2. 00189, pp. 207–214. ISSN: 1528-1140. DOI: 10.1097/SLA.0b013e3181e61e88.

Batterham, A. M. et al. (1999). "Modeling the influence of body size on V(O2) peak: effects of model choice and body composition". In: *Journal of Applied Physiology (Bethesda, Md.: 1985)* 87.4, pp. 1317–1325. ISSN: 8750-7587.

Beaver, W. L., K. Wasserman, and B. J. Whipp (1986). "A new method for detecting anaerobic threshold by gas exchange". In: *Journal of Applied Physiology* 60.6, pp. 2020–2027. ISSN: 8750-7587, 1522-1601.

Bellotto, Fabio et al. (2011). "Anemia does not preclude increments in cardiac performance during a short period of intensive, exercise-based cardiac rehabilitation". In: *European Journal of Cardiovascular Prevention & Rehabilitation* 18.2. WOS:000289895800002, pp. 150–157. ISSN: 1741-8267. DOI: 10.1177/1741826710389372.

Benns, Matthew et al. (2009). "The impact of obesity on outcomes following pancreatectomy for malignancy". In: *Annals of Surgical Oncology* 16.9, pp. 2565–2569. ISSN: 1534-4681. DOI: 10.1245/s10434-009-0573-7.

Benzo, Roberto et al. (2007). "Complications of lung resection and exercise capacity: A meta-analysis". In: *Respiratory Medicine* 101.8, pp. 1790–1797. ISSN: 09546111. DOI: 10.1016/j.rmed.2007.02.012.

Berg, Anders H. and Philipp E. Scherer (2005). "Adipose Tissue, Inflammation, and Cardiovascular Disease". In: *Circulation Research* 96.9, pp. 939–949. ISSN: 0009-7330, 1524-4571. DOI: 10.1161/01.RES.0000163635.62927.34.

Beris, P. et al. (2008). "Perioperative anaemia management: consensus statement on the role of intravenous iron". In: *British Journal of Anaesthesia* 100.5. WOS:000254955000004, pp. 599–604. ISSN: 0007-0912. DOI: 10.1093/bja/aen054.

Berrington de Gonzalez, A., S. Sweetland, and E. Spencer (2003). "A meta-analysis of obesity and the risk of pancreatic cancer". In: *British Journal of Cancer* 89.3. 00267, pp. 519–523. ISSN: 0007-0920. DOI: 10.1038/sj.bjc.6601140.

Bhatti, Imran et al. (2010). "Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio". In: *The American Journal of Surgery* 200.2, pp. 197–203. ISSN: 0002-9610. DOI: 10.1016/j.amjsurg.2009.08.041.

Biancari, Fausto et al. (2003). "Preoperative C-reactive protein and outcome after coronary artery bypass surgery". In: *The Annals of Thoracic Surgery* 76.6, pp. 2007–2012. ISSN: 0003-4975. DOI: 10.1016/S0003-4975(03)01067-1.

Bilimoria, Karl Y et al. (2007). "National failure to operate on early stage pancreatic cancer". In: *Ann Surg* 246.2, pp. 173–80.

Binah, O et al. (1985). "Obstructive jaundice blunts myocardial contractile response to isoprenaline in the dog: a clue to the susceptibility of jaundiced patients to shock?" In: *Clin Sci (Lond)* 69.6, pp. 647–53.

Birkmeyer, John D. et al. (1999). "Relationship between hospital volume and late survival after pancreaticoduodenectomy". In: *Surgery* 126.2, pp. 178–183.

Birkmeyer, John D. et al. (2003). "Surgeon Volume and Operative Mortality in the United States". In: *New England Journal of Medicine* 349.22. 00000, pp. 2117–2127. ISSN: 0028-4793. DOI: 10.1056/NEJMsa035205.

Boeken, U. et al. (1998). "Increased preoperative C-reactive protein (CRP)-values without signs of an infection and complicated course after cardiopulmonary bypass (CPB)-operations". In: *European Journal of Cardio-Thoracic Surgery: Official Journal of the European Association for Cardio-Thoracic Surgery* 13.5. 00000, pp. 541–545. ISSN: 1010-7940.

Boer, P. (1984). "Estimated lean body mass as an index for normalization of body fluid volumes in humans". In: *The American Journal of Physiology* 247.4, F632–636. ISSN: 0002-9513.

Boereboom, C. L. et al. (2015). "Forming a consensus opinion on exercise prehabilitation in elderly colorectal cancer patients: a Delphi study". In: *Techniques in Coloproctology* 19.6, pp. 347–354. ISSN: 1128-045X. DOI: 10.1007/s10151-015-1317-2.

Bomzon, A et al. (1986). "Systemic hypotension and decreased pressor response in dogs with chronic bile duct ligation". In: *Hepatology* 6.4, pp. 595–600.

Bone, Roger C. (1996). "Immunologic Dissonance: A Continuing Evolution in Our Understanding of the Systemic Inflammatory Response Syndrome (SIRS) and the Multiple Organ Dysfunction Syndrome (MODS)". In: *Annals of Internal Medicine* 125.8. 01103, pp. 680–687. ISSN: 0003-4819. DOI: 10.7326/0003-4819-125-8-199610150-00009.

Bone, Roger C., Charles J. Grodzin, and Robert A. Balk (1997). "Sepsis: a new hypothesis for pathogenesis of the disease process". In: *CHEST Journal* 112.1, pp. 235–243.

Bower, Matthew et al. (2011). "Irreversible electroporation of the pancreas: definitive local therapy without systemic effects". In: *Journal of Surgical Oncology* 104.1, pp. 22–28. ISSN: 1096-9098. DOI: 10.1002/jso.21899.

Braga, Marco et al. (2011). "A prognostic score to predict major complications after pancreaticoduodenectomy". In: *Ann Surg* 254.5, 702–7, discussion 707–8.

Bredella, Miriam A. et al. (2010). "Comparison of DXA and CT in the Assessment of Body Composition in Premenopausal Women With Obesity and Anorexia Nervosa". In: *Obesity (Silver Spring, Md.)* 18.11, pp. 2227–2233. ISSN: 1930-7381. DOI: 10.1038/oby.2010.5.

Brunelli, Alessandro (2010). "Risk assessment for pulmonary resection". In: *Semin Thorac Cardiovasc Surg* 22.1. 00000, pp. 2–13.

Buttenschoen, Klaus, Kamran Fathimani, and Daniela Carli Buttenschoen (2010). "Effect of major abdominal surgery on the host immune response to infection".

In: *Current Opinion in Infectious Diseases* 23.3. 00020, pp. 259–267. ISSN: 1473-6527. DOI: 10.1097/QCO.0b013e32833939cb.

Campione, Andrea et al. (2010). "Oxygen pulse as a predictor of cardiopulmonary events in lung resection". In: *Asian Cardiovasc Thorac Ann* 18.2, pp. 147–52.

CancerResearchUK (2011). *Cancer Stats report - Pancreatic Cancer, Cancer Research UK*.

Carli, F. et al. (2010). "Randomized clinical trial of prehabilitation in colorectal surgery". In: *British Journal of Surgery* 97.8, pp. 1187–1197. ISSN: 00071323. DOI: 10.1002/bjs.7102.

Carlisle, J. and M. Swart (2007). "Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing". In: *The British Journal of Surgery* 94.8, pp. 966–969. ISSN: 0007-1323. DOI: 10.1002/bjs.5734.

Castro, S M M de et al. (2009). "Evaluation of POSSUM for patients undergoing pancreatoduodenectomy". In: *World J Surg* 33.7, pp. 1481–7.

Choi, Seong Ho et al. (2004). "Delayed hemorrhage after pancreaticoduodenectomy". In: *J Am Coll Surg* 199.2, pp. 186–91.

Christou, N V et al. (1989). "Estimating mortality risk in preoperative patients using immunologic, nutritional, and acute-phase response variables." In: *Annals of Surgery* 210.1, pp. 69–77. ISSN: 0003-4932.

Clark, E.J. et al. (2007). "Preoperative lymphocyte count as a prognostic factor in resected pancreatic ductal adenocarcinoma". In: *HPB : The Official Journal of the International Hepato Pancreato Biliary Association* 9.6, pp. 456–460. ISSN: 1365-182X. DOI: 10.1080/13651820701774891.

Clavien, Pierre A. et al. (2009). "The Clavien-Dindo Classification of Surgical Complications: Five-Year Experience". In: *Annals of Surgery* 250.2, pp. 187–196. ISSN: 0003-4932. DOI: 10.1097/SLA.0b013e3181b13ca2.

Clayton, R A et al. (2011). "Cardiopulmonary exercise testing and length of stay in patients undergoing major surgery". In: *Anaesthesia* 66.5. No association with LOS, pp. 393–4.

Colice, Gene L. et al. (2007). "Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines". In: *CHEST Journal* 132.3, 161S–177S.

Conlon, K. C. et al. (2001). "Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection". In: *Annals of Surgery* 234.4. 00363, 487–493, discussion 493–494. ISSN: 0003-4932.

Copeland, G P, D Jones, and M Walters (1991). "POSSUM: a scoring system for surgical audit". In: *Br J Surg* 78.3, pp. 355–60.

Copeland, G P et al. (1993). "Comparative vascular audit using the POSSUM scoring system". In: *Ann R Coll Surg Engl* 75.3, pp. 175–7.

Copeland, G P et al. (1995). "Risk-adjusted analysis of surgeon performance: a 1-year study". In: *Br J Surg* 82.3, pp. 408–11.

Crumley, A. B. C. et al. (2006). "An elevated C-reactive protein concentration, prior to surgery, predicts poor cancer-specific survival in patients undergoing resection for gastro-oesophageal cancer." In: *British journal of cancer* 94.11, pp. 1568–1571. DOI: 10.1038/sj.bjc.6603150.

Cyr, David P. et al. (2015). "Canadian practice patterns for pancreaticoduodenectomy". In: *Canadian Journal of Surgery* 58.2, pp. 121–127. ISSN: 0008-428X. DOI: 10.1503/cjs.011714.

Dandona, Monica et al. (2011). "Influence of obesity and other risk factors on survival outcomes in patients undergoing pancreaticoduodenectomy for pancreatic cancer". In: *Pancreas* 40.6, pp. 931–937. ISSN: 1536-4828. DOI: 10.1097/MPA.0b013e318215a9b1.

Deitch, E. A. et al. (1990). "Obstructive jaundice promotes bacterial translocation from the gut". In: *American Journal of Surgery* 159.1. 00000, pp. 79–84. ISSN: 0002-9610.

Dellweg, D et al. (2008). "Cardiopulmonary exercise testing before and after blood donation". In: *Pneumologie* 62.6, pp. 372–7.

Delogu, G. et al. (2001). "Interleukin-10 and apoptotic death of circulating lymphocytes in surgical/anesthesia trauma". In: *The Journal of Trauma* 51.1, pp. 92–97. ISSN: 0022-5282.

DeOliveira, Michelle L et al. (2006). "Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy". In: *Ann Surg* 244.6. 00000, 931–7, discussion 937–9.

Dias-Santos, Daniela et al. (2015). "The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer". In: *Surgery* 157.5, pp. 881–887. ISSN: 0039-6060. DOI: 10.1016/j.surg.2014.12.006.

Diener, M. K. et al. (2008). "Pancreaticoduodenectomy (classic Whipple) versus pylorus-preserving pancreaticoduodenectomy (pp Whipple) for surgical treatment of periampullary and pancreatic carcinoma". In: *The Cochrane Database of Systematic Reviews* 2. 00072, p. CD006053. ISSN: 1469-493X. DOI: 10.1002/14651858.CD006053.pub2.

Dindo, Daniel, Nicolas Demartines, and Pierre-Alain Clavien (2004). "Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey". In: *Ann Surg* 240.2, pp. 205–13.

Dindo, Daniel et al. (2003). "Obesity in general elective surgery". In: *The Lancet* 361.9374. 00000, pp. 2032–2035.

Dixon, J M et al. (1983). "Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients". In: *Gut* 24.9, pp. 845–52.

Don, Burl R. and George Kaysen (2004). "POOR NUTRITIONAL STATUS AND INFLAMMATION: Serum Albumin: Relationship to Inflammation and Nutrition". In: *Seminars in Dialysis* 17.6, pp. 432–437. ISSN: 1525-139X. DOI: 10.1111/j.0894-0959.2004.17603.x.

Donnelly, J E et al. (1990). "Criteria to verify attainment of maximal exercise tolerance test with obese females". In: *Diabetes research and clinical practice* 10 Suppl 1, S283–286. ISSN: 0168-8227.

Dronkers, J. J. et al. (2010). "Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study". In: *Clinical Rehabilitation* 24.7, pp. 614–622. ISSN: 0269-2155, 1477-0873. DOI: 10.1177/0269215509358941.

Dunne, D. et al. (2012). "PMO-029 Prehabilitation program for liver surgery". In: *Gut* 61 (Suppl 2), A85–A85. ISSN: , 1468-3288. DOI: 10.1136/gutjnl-2012-302514b.29.

Dutta, Sumanta et al. (2011). "Persistent elevation of C-reactive protein following esophagogastric cancer resection as a predictor of postoperative surgical site infectious complications." In: *World journal of surgery* 35.5, pp. 1017–1025. DOI: 10.1007/s00268-011-1002-1.

Eknoyan, Garabed (2008). "Adolphe Quetelet (1796–1874)—the average man and indices of obesity". In: *Nephrology Dialysis Transplantation* 23.1. 00000, pp. 47–51. ISSN: 0931-0509, 1460-2385. DOI: 10.1093/ndt/gfm517.

Elahi, Maqsood M. et al. (2004). "Score based on hypoalbuminemia and elevated C-reactive protein predicts survival in patients with advanced gastrointestinal cancer." In: *Nutrition and cancer* 48.2, pp. 171–173. DOI: 10.1207/s15327914nc4802_6.

Emick, Dawn M et al. (2006). "Hospital readmission after pancreaticoduodenectomy". In: *J Gastrointest Surg* 10.9, 1243–52, discussion 1252–3.

Epstein, Scott K et al. (2004). "Aerobic capacity is associated with 100-day outcome after hepatic transplantation". In: *Liver Transpl* 10.3, pp. 418–24.

Evans, Douglas B. et al. (2008). "Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head". In: *Journal of Clinical Oncology* 26.21. WOS:000258050500008, pp. 3496–3502. ISSN: 0732-183X. DOI: 10.1200/JCO.2007.15.8634.

Evans, William J. and Wayne W. Campbell (1993). "Sarcopenia and Age-Related Changes in Body Composition and Functional Capacity". In: *The Journal of Nutrition* 123.2, pp. 465–468. ISSN: 0022-3166, 1541-6100.

Faist, Eugen, Matthias Wichmann, and Caroline Kim (1997). "Immunosuppression and immunomodulation in surgical patients". In: *Current Opinion in Critical Care* 3.4, pp. 293–298. ISSN: 1070-5295.

Fang, Yuan et al. (2012). "Pre-operative biliary drainage for obstructive jaundice". In: *The Cochrane Database of Systematic Reviews* 9, p. CD005444. ISSN: 1469-493X. DOI: 10.1002/14651858.CD005444.pub3.

Fasol, R. et al. (1992). "The influence of obesity on perioperative morbidity: retrospective study of 502 aortocoronary bypass operations". In: *The Thoracic and Cardiovascular Surgeon* 40.3, pp. 126–129. ISSN: 0171-6425. DOI: 10.1055/s-2007-1020129.

Fernández, J et al. (2000). "The use of cardiopulmonary exercise test in patients with mitochondrial myopathies". In: *Med Clin (Barc)* 114.4, pp. 121–7.

Ferraris VA et al. (2014). "Identification of patients with postoperative complications who are at risk for failure to rescue". In: *JAMA Surgery* 149.11, pp. 1103–1108. ISSN: 2168-6254. DOI: 10.1001/jamasurg.2014.1338.

Fischer, C. L. et al. (1976). "Quantitation of "acute-phase proteins" postoperatively. Value in detection and monitoring of complications". In: *American Journal of Clinical Pathology* 66.5, pp. 840–846. ISSN: 0002-9173.

Fleming, Jason B. et al. (2009). "Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma". In: *Archives of*

Surgery (Chicago, Ill.: 1960) 144.3, pp. 216–221. ISSN: 1538-3644. DOI: 10.1001/archsurg.2008.580.

Forrest, L. M. et al. (2004). "Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer." In: *British journal of cancer* 90.9, pp. 1704–1706. DOI: 10.1038/sj.bjc.6601789.

Forshaw, Matthew J. et al. (2008). "Is Cardiopulmonary Exercise Testing a Useful Test Before Esophagectomy?" In: *The Annals of Thoracic Surgery* 85.1, pp. 294–299. ISSN: 00034975. DOI: 10.1016/j.athoracsur.2007.05.062.

Fuhrman, G. M. et al. (1996). "Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group". In: *Annals of Surgery* 223.2, pp. 154–162. ISSN: 0003-4932.

Fujii, Tsutomu et al. (2015). "Preoperative internal biliary drainage increases the risk of bile juice infection and pancreatic fistula after pancreatoduodenectomy: a prospective observational study". In: *Pancreas* 44.3, pp. 465–470. ISSN: 1536-4828. DOI: 10.1097/MPA.0000000000000265.

Furukawa, Kenei et al. (2015). "Negative Impact of Preoperative Endoscopic Biliary Drainage on Prognosis of Pancreatic Ductal Adenocarcinoma After Pancreaticoduodenectomy". In: *Anticancer Research* 35.9, pp. 5079–5083. ISSN: 1791-7530.

Gaag, Niels A van der et al. (2010). "Preoperative biliary drainage for cancer of the head of the pancreas". In: *N Engl J Med* 362.2. BD increases complications, pp. 129–37.

Gallardo, J M et al. (1998). "Increased plasma levels of atrial natriuretic peptide and endocrine markers of volume depletion in patients with obstructive jaundice". In: *Br J Surg* 85.1, pp. 28–31.

Geer, R J and M F Brennan (1993). "Prognostic indicators for survival after resection of pancreatic adenocarcinoma". In: *Am J Surg* 165.1. Cited 474, 68–72, discussion 72–3.

Ghaferi, Amir A., John D. Birkmeyer, and Justin B. Dimick (2009). "Complications, Failure to Rescue, and Mortality With Major Inpatient Surgery in Medicare Patients". In: *Annals of Surgery* 250.6. 00000 WOS:000272313700027, pp. 1029–1034. ISSN: 0003-4932. DOI: 10.1097/SLA.0b013e3181bef697.

Gibbs, J. et al. (1999). "Preoperative serum albumin level as a predictor of operative mortality and morbidity - Results from the national VA surgical risk study". In: *Archives of Surgery* 134.1. WOS:000078053500009, pp. 36–42. ISSN: 0004-0010. DOI: 10.1001/archsurg.134.1.36.

Gillen, Sonja et al. (2010). "Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages". In: *PLoS medicine* 7.4. 00476, e1000267. ISSN: 1549-1676. DOI: 10.1371/journal.pmed.1000267.

Gillis, Chelsia et al. (2014). "Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer". In:

Anesthesiology 121.5, pp. 937–947. ISSN: 1528-1175. DOI: 10.1097/ALN.0000000000000393.

Glen, Paul et al. (2006). "Evaluation of an inflammation-based prognostic score in patients with inoperable pancreatic cancer." In: *Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.]* 6.5. 00000, pp. 450–453. DOI: 10.1159/000094562.

Golcher, Henriette et al. (2015). "Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer". In: *Strahlentherapie Und Onkologie* 191, pp. 7–16. ISSN: 0179-7158. DOI: 10.1007/s00066-014-0737-7.

Goran, M. et al. (2000). "Total body fat does not influence maximal aerobic capacity". In: *International Journal of Obesity* 24.7. WOS:000088025500005, pp. 841–848. ISSN: 0307-0565. DOI: 10.1038/sj.ijo.0801241.

Gouma, Dirk J. et al. (2000). "Rates of Complications and Death After Pancreaticoduodenectomy: Risk Factors and the Impact of Hospital Volume". In: *Annals of Surgery* 232.6, pp. 786–795. ISSN: 0003-4932.

Grant, S. W. et al. (2015). "Cardiopulmonary exercise testing and survival after elective abdominal aortic aneurysm repair". In: *British Journal of Anaesthesia* 114.3, pp. 430–436. ISSN: 0007-0912, 1471-6771. DOI: 10.1093/bja/aeu383.

Green, J and O S Better (1995). "Systemic hypotension and renal failure in obstructive jaundice-mechanistic and therapeutic aspects". In: *J Am Soc Nephrol* 5.11. 00000, pp. 1853–71.

Green, J et al. (1986). "The "jaundiced heart": a possible explanation for postoperative shock in obstructive jaundice". In: *Surgery* 100.1. cited 54, pp. 14–20.

Grocott, M. P. W. et al. (2013). "Perioperative increase in global blood flow to explicit defined goals and outcomes after surgery: a Cochrane Systematic Review". In: *British Journal of Anaesthesia* 111.4, pp. 535–548. ISSN: 1471-6771. DOI: 10.1093/bja/aet155.

Gruberg, Luis et al. (2002). "The impact of obesity on the short-term andlong-term outcomes after percutaneous coronary intervention: the obesity paradox?" In: *Journal of the American College of Cardiology* 39.4. 00349, pp. 578–584. ISSN: 0735-1097. DOI: 10.1016/S0735-1097(01)01802-2.

Haarbo, J. et al. (1991). "Validation of body composition by dual energy X-ray absorptiometry (DEXA)". In: *Clinical Physiology* 11.4, pp. 331–341. ISSN: 1365-2281. DOI: 10.1111/j.1475-097X.1991.tb00662.x.

Haas, Barbara et al. (2011). "Prevention of complications and successful rescue of patients with serious complications: characteristics of high-performing trauma centers". In: *Journal of Trauma-Injury Infection* 70.3. 00010, pp. 575–582. DOI: 10.1097/TA.0b013e31820e75a9.

Haga, Y, S Ikei, and M Ogawa (1999). "Estimation of Physiologic Ability and Surgical Stress (E-PASS) as a new prediction scoring system for postoperative morbidity and mortality following elective gastrointestinal surgery". In: *Surg Today* 29.3, pp. 219–25.

Hall, A and P Older (2009). "Cardiopulmonary exercise testing accurately predicts risk of major surgery including esophageal resection: letter 1". In: *Ann Thorac Surg* 87.2, 670–1, author reply 671–2.

Hallet, Julie et al. (2014). "The Impact of Perioperative Iron on the Use of Red Blood Cell Transfusions in Gastrointestinal Surgery: A Systematic Review and Meta-Analysis". In: *Transfusion Medicine Reviews* 28.4. WOS:000345059300004, pp. 205–211. ISSN: 0887-7963. DOI: 10.1016/j.tmrv.2014.05.004.

Halloran, C M et al. (2002). "Complications of pancreatic cancer resection". In: *Dig Surg* 19.2. 00168, pp. 138–46.

Hashimoto, Daisuke et al. (2010). "Is an estimation of physiologic ability and surgical stress able to predict operative morbidity after pancreaticoduodenectomy?" In: *J Hepatobiliary Pancreat Sci* 17.2. 00022, pp. 132–8.

Hassen, T. A. et al. (2007). "Preoperative Nutritional Status Predicts the Severity of the Systemic Inflammatory Response Syndrome (SIRS) Following Major Vascular Surgery". In: *European Journal of Vascular and Endovascular Surgery* 33.6, pp. 696–702. ISSN: 1078-5884. DOI: 10.1016/j.ejvs.2006.12.006.

Hatfield, A R et al. (1982). "Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial". In: *Lancet* 2.8304. Cochrane review paper, pp. 896–9.

Haupt, W. et al. (1997). "Association between preoperative acute phase response and postoperative complications". In: *The European Journal of Surgery = Acta Chirurgica* 163.1, pp. 39–44. ISSN: 1102-4151.

Hayashi, Tsutomu et al. (2015). "Impact of infectious complications on gastric cancer recurrence". In: *Gastric Cancer: Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association* 18.2, pp. 368–374. ISSN: 1436-3291. DOI: 10.1007/s10120-014-0361-3.

Hennessey, Derek B. et al. (2010). "Preoperative Hypoalbuminemia is an Independent Risk Factor for the Development of Surgical Site Infection Following Gastrointestinal Surgery: A Multi-Institutional Study". In: *Annals of Surgery* 252.2, pp. 325–329. ISSN: 0003-4932. DOI: 10.1097/SLA.0b013e3181e9819a.

Hightower, C E et al. (2010). "A pilot study evaluating predictors of postoperative outcomes after major abdominal surgery: physiological capacity compared with the ASA physical status classification system". In: *Br J Anaesth.*

Hill, A. V., C. N. H. Long, and H. Lupton (1924). "Muscular Exercise, Lactic Acid, and the Supply and Utilisation of Oxygen". In: *Proceedings of the Royal Society of London B: Biological Sciences* 97.681. 00591, pp. 84–138. ISSN: 0962-8452, 1471-2954. DOI: 10.1098/rspb.1924.0045.

Hilmy, M. et al. (2006). "The relationship between the systemic inflammatory response, tumour proliferative activity, T-lymphocytic infiltration and COX-2 expression and survival in patients with transitional cell carcinoma of the urinary bladder." In: *British journal of cancer* 95.9, pp. 1234–1238. DOI: 10.1038/sj.bjc.6603415.

Hiyoshi, Masahide et al. (2013). "Usefulness of drain amylase, serum C-reactive protein levels and body temperature to predict postoperative pancreatic fistula

after pancreaticoduodenectomy". In: *World Journal of Surgery* 37.10, pp. 2436–2442. ISSN: 1432-2323. DOI: 10.1007/s00268-013-2149-8.

Ho, V. and M. J. Heslin (2003). "Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy". In: *Annals of Surgery* 237.4. 00000 WOS:000185834400012, pp. 509–514. ISSN: 0003-4932. DOI: 10.1097/00000658-200304000-00012.

Holley, J. L. et al. (1990). "Obesity as a risk factor following cadaveric renal transplantation". In: *Transplantation* 49.2, pp. 387–389. ISSN: 0041-1337.

Horwich, Tamara B. et al. (2009). "The relationship between body mass index and cardiopulmonary exercise testing in chronic systolic heart failure". In: *American Heart Journal* 158.4, S31–S36. ISSN: 00028703. DOI: 10.1016/j.ahj.2009.07.016.

House, Michael G. et al. (2008). "Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 12.2, pp. 270–278. ISSN: 1091-255X. DOI: 10.1007/s11605-007-0421-7.

Hulens, M et al. (2001). "Exercise capacity in lean versus obese women". In: *Scandinavian journal of medicine & science in sports* 11.5, pp. 305–309. ISSN: 0905-7188.

Iodice, Simona et al. (2008). "Tobacco and the risk of pancreatic cancer: a review and meta-analysis". In: *Langenbeck's Archives of Surgery / Deutsche Gesellschaft Für Chirurgie* 393.4. 00267, pp. 535–545. ISSN: 1435-2451. DOI: 10.1007/s00423-007-0266-2.

Iscar, M. et al. (2009). "Functional Capacity Before and After Liver Transplantation". In: *Transplantation Proceedings* 41.3, pp. 1014–1015. ISSN: 00411345. DOI: 10.1016/j.transproceed.2009.02.013.

Al-Jabi, Yasser and Amr El-Shawarby (2010). "Value of C-reactive protein after neurosurgery: a prospective study". In: *British Journal of Neurosurgery* 24.6, pp. 653–659. ISSN: 1360-046X. DOI: 10.3109/02688697.2010.500408.

Jack, S. et al. (2014). "The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery". In: *European Journal of Surgical Oncology (EJSO)* 40.10, pp. 1313–1320. ISSN: 0748-7983. DOI: 10.1016/j.ejso.2014.03.010.

Jagannath, P et al. (2005). "Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy". In: *Br J Surg* 92.3, pp. 356–61.

Jamieson, N. B. et al. (2005). "Systemic inflammatory response predicts outcome in patients undergoing resection for ductal adenocarcinoma head of pancreas." In: *British journal of cancer* 92.1. 00000, pp. 21–23. DOI: 10.1038/sj.bjc.6602305.

Janum, Sine H. et al. (2011). "C-reactive protein level as a predictor of mortality in liver disease patients with bacteremia". In: *Scandinavian Journal of Gastroenterology* 46.12, pp. 1478–1483. ISSN: 0036-5521, 1502-7708. DOI: 10.3109/00365521.2011.615855.

Janz, Kathleen F. and Larry T. Mahoney (1997). "Three-Year Follow-up of Changes in Aerobic Fitness during Puberty: The Muscatine Study". In: *Research*

Quarterly for Exercise and Sport 68.1, pp. 1–9. ISSN: 0270-1367, 2168-3824. DOI: 10.1080/02701367.1997.10608861.

Janz, KATHLEEN F. et al. (1998). "Longitudinal analysis of scaling VO2 for differences in body size during puberty: the Muscatine Study." In: *Medicine and science in sports and exercise* 30.9, pp. 1436–1444.

Jiao, Li et al. (2009). "Alcohol use and risk of pancreatic cancer: the NIH-AARP Diet and Health Study". In: *American Journal of Epidemiology* 169.9. 00054, pp. 1043–1051. ISSN: 1476-6256. DOI: 10.1093/aje/kwp034.

Joglekar, Savita et al. (2015). "Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma". In: *Journal of Surgical Oncology* 111.6, pp. 771–775. ISSN: 1096-9098. DOI: 10.1002/jso.23862.

Jones, Lee W et al. (2007). "Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions". In: *Cancer* 110.3, pp. 590–8.

Jones, Lee W et al. (2010). "Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer". In: *Cancer*.

Junejo, M. A., A. K. Siriwardena, and M. J. Parker (2014a). "Peripheral oxygen extraction in patients with malignant obstructive jaundice". In: *Anaesthesia* 69.1, pp. 32–36. ISSN: 1365-2044. DOI: 10.1111/anae.12478.

Junejo, M. A. et al. (2014b). "Cardiopulmonary Exercise Testing for Preoperative Risk Assessment before Pancreaticoduodenectomy for Cancer". In: *Annals of Surgical Oncology* 21.6, pp. 1929–1936. ISSN: 1068-9265, 1534-4681. DOI: 10.1245/s10434-014-3493-0.

Kabata, Paweł et al. (2015). "Preoperative nutritional support in cancer patients with no clinical signs of malnutrition—prospective randomized controlled trial". In: *Supportive Care in Cancer* 23. 00005, pp. 365–370. ISSN: 0941-4355. DOI: 10.1007/s00520-014-2363-4.

Kalantar-Zadeh, Kamyar et al. (2007). "Risk factor paradox in wasting diseases". In: *Current Opinion in Clinical Nutrition and Metabolic Care* 10.4, pp. 433–442. ISSN: 1363-1950. DOI: 10.1097/MCO.0b013e3281a30594.

Kamath, Anil et al. (2009). "Rationale for an Intraperitoneal Gemcitabine Chemotherapy Treatment for Patients with Resected Pancreatic Cancer". In: *Recent Patents on Anti-Cancer Drug Discovery* 4.2. WOS:000267049800008, pp. 174–179. ISSN: 1574-8928.

Kamphues, Carsten et al. (2012). "Postoperative complications deteriorate long-term outcome in pancreatic cancer patients". In: *Annals of Surgical Oncology* 19.3. 00000, pp. 856–863. ISSN: 1534-4681. DOI: 10.1245/s10434-011-2041-4.

Kang, Chang Moo et al. (2009). "Detrimental effect of postoperative complications on oncologic efficacy of R0 pancreatectomy in ductal adenocarcinoma of the pancreas". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 13.5. 00015, pp. 907–914. ISSN: 1873-4626. DOI: 10.1007/s11605-009-0823-9.

Katoh, Hiroshi et al. (2011). "Anastomotic leakage contributes to the risk for systemic recurrence in stage II colorectal cancer". In: *Journal of Gastrointestinal*

Surgery: Official Journal of the Society for Surgery of the Alimentary Tract 15.1, pp. 120–129. ISSN: 1873-4626. DOI: 10.1007/s11605-010-1379-4.

KATZ LN et al. (1934). "A "metabolic exercise tolerance test" for patients with cardiac disease: A feasible method for using the excess oxygen consumption and the recovery time of exercise as criteria of the cardiac status". In: *Archives of Internal Medicine* 53.5, pp. 710–723. ISSN: 0730-188X. DOI: 10.1001/archinte.1934.00160110079008.

Kausch, W (1912). "Das carcinom der papilla duodeni und seine radikale Entfeinung". In: *Beitr Z Clin Chir* 78, pp. 439–486.

Kawai, Manabu et al. (2006). "Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients". In: *Annals of Surgery* 244.1. 00239, pp. 1–7. ISSN: 0003-4932. DOI: 10.1097/01.sla.0000218077.14035.a6.

Kawasaki, T. et al. (2001). "Surgical stress induces endotoxin hyporesponsiveness and an early decrease of monocyte mCD14 and HLA-DR expression during surgery". In: *Anesthesia and Analgesia* 92.5, pp. 1322–1326. ISSN: 0003-2999.

Khan, Abdaal W et al. (2003). "Evaluation of the POSSUM scoring system for comparative audit in pancreatic surgery". In: *Dig Surg* 20.6, pp. 539–45.

Khan, Saboor et al. (2010). "Does body mass index/morbid obesity influence outcome in patients who undergo pancreatoduodenectomy for pancreatic adenocarcinoma?" In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 14.11, pp. 1820–1825. ISSN: 1873-4626. DOI: 10.1007/s11605-010-1285-9.

Khurana, Sandeep, Jean-Pierre Raufman, and Thomas L Pallone (2011). "Bile acids regulate cardiovascular function". In: *Clin Transl Sci* 4.3, pp. 210–8.

Kim, Dae Hee et al. (2009a). "Predictive Value of C-Reactive Protein for Major Postoperative Complications Following Off-Pump Coronary Artery Bypass Surgery". In: *Circulation Journal* 73.5, pp. 872–877. DOI: 10.1253/circj.CJ-08-1010.

Kim, Do Jun et al. (2009b). "Responsive Measures to Prehabilitation in Patients Undergoing Bowel Resection Surgery". In: *The Tohoku Journal of Experimental Medicine* 217.2, pp. 109–115. DOI: 10.1620/tjem.217.109.

Kim, Edward J. et al. (2013). "A Multi-Institutional Phase II Study of Neoadjuvant Gemcitabine and Oxaliplatin with Radiation Therapy in Patients with Pancreatic Cancer". In: *Cancer* 119.15, pp. 2692–2700. ISSN: 0008-543X. DOI: 10.1002/cncr.28117.

Kimmings, A. N. et al. (2000). "Endotoxin, cytokines, and endotoxin binding proteins in obstructive jaundice and after preoperative biliary drainage". In: *Gut* 46.5, pp. 725–731. ISSN: , 1468-3288. DOI: 10.1136/gut.46.5.725.

King, J H and H A Stewart (1909). "Effect of the injection of bile on the circulation". In: *J Exp Med* 11.5, pp. 673–85.

Klava, A. et al. (1997). "Interleukin-10. A role in the development of postoperative immunosuppression". In: *Archives of Surgery (Chicago, Ill.: 1960)* 132.4, pp. 425–429. ISSN: 0004-0010.

Knaus, W. A. et al. (1985). "APACHE II: a severity of disease classification system". In: *Critical Care Medicine* 13.10. 13383, pp. 818–829. ISSN: 0090-3493.

Kneuertz, Peter J. et al. (2011). "Effects of Perioperative Red Blood Cell Transfusion on Disease Recurrence and Survival After Pancreaticoduodenectomy for Ductal Adenocarcinoma". In: *Annals of Surgical Oncology* 18.5. WOS:000289564600020, pp. 1327–1334. ISSN: 1068-9265. DOI: 10.1245/s10434-010-1476-3.

Knight, B C et al. (2010). "Evaluation of surgical outcome scores according to ISGPS definitions in patients undergoing pancreatic resection". In: *Dig Surg* 27.5, pp. 367–74.

Kocher, Hemant M et al. (2005). "Risk-adjustment in hepatobiliary pancreatic surgery". In: *World J Gastroenterol* 11.16, pp. 2450–5.

Kollmar, O. et al. (2008). "Prophylactic octreotide and delayed gastric emptying after pancreaticoduodenectomy: results of a prospective randomized double-blinded placebo-controlled trial". In: *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 34.8. 00050, pp. 868–875. ISSN: 1532-2157. DOI: 10.1016/j.ejso.2008.01.014.

Kos, F. Tugba et al. (2014). "Evaluation of the effect of comorbidity on survival in pancreatic cancer by using "Charlson Comorbidity Index" and "Cumulative Illness Rating Scale"". In: *Wiener Klinische Wochenschrift* 126.1, pp. 36–41. ISSN: 1613-7671. DOI: 10.1007/s00508-013-0453-9.

Kosaka, Hisashi et al. (2014). "Multivariate logistic regression analysis for prediction of clinically relevant pancreatic fistula in the early phase after pancreaticoduodenectomy". In: *Journal of Hepato-Biliary-Pancreatic Sciences* 21.2. 00000, pp. 128–133. ISSN: 1868-6982. DOI: 10.1002/jhbp.11.

Koukoutsis, I et al. (2006). "Haemorrhage following pancreaticoduodenectomy: risk factors and the importance of sentinel bleed". In: *Dig Surg* 23.4, pp. 224–8.

Krachler, Benno et al. (2014). "Cardiopulmonary fitness is a function of lean mass, not total body weight: The DR's EXTRA study". In: *European Journal of Preventive Cardiology*, p. 2047487314557962. ISSN: 2047-4873, 2047-4881. DOI: 10.1177/2047487314557962.

Kubo, Toru et al. (2013). "Elevated preoperative C-reactive protein levels are a risk factor for the development of postoperative infectious complications following elective colorectal surgery". In: *Langenbeck's Archives of Surgery* 398.7, pp. 965–971. ISSN: 1435-2443, 1435-2451. DOI: 10.1007/s00423-013-1107-0.

Kubota, Takeshi et al. (2014). "Prognostic significance of complications after curative surgery for gastric cancer". In: *Annals of Surgical Oncology* 21.3. 00023, pp. 891–898. ISSN: 1534-4681. DOI: 10.1245/s10434-013-3384-9.

Lai, E C et al. (1994). "Preoperative endoscopic drainage for malignant obstructive jaundice". In: *Br J Surg* 81.8. Cochrane review paper, pp. 1195–8.

Laporta Baez, Yolanda et al. (2011). "C-reactive protein in the diagnosis of postoperative infection in pediatric patients: a prospective observational study of 103 patients". In: *Journal of Pediatric Surgery* 46.9, pp. 1726–1731. ISSN: 1531-5037. DOI: 10.1016/j.jpedsurg.2011.03.014.

Larsson, Susanna C., Nicola Orsini, and Alicja Wolk (2007). "Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies". In:

International Journal of Cancer 120.9. 00221, pp. 1993–1998. ISSN: 0020-7136. DOI: 10.1002/ijc.22535.

Lee, Cheryl T. et al. (2004). "Impact of body mass index on radical cystectomy". In: *The Journal of Urology* 172.4, pp. 1281–1285. ISSN: 0022-5347.

Lefebvre, Philippe et al. (2009). "Role of Bile Acids and Bile Acid Receptors in Metabolic Regulation". In: *Physiological Reviews* 89.1, pp. 147–191. ISSN: 0031-9333, 1522-1210. DOI: 10.1152/physrev.00010.2008.

Leitch, E. F. et al. (2007). "Comparison of the prognostic value of selected markers of the systemic inflammatory response in patients with colorectal cancer." In: *British journal of cancer* 97.9, pp. 1266–1270. DOI: 10.1038/sj.bjc.6604027.

Lemaitre, J et al. (2006). "Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training in chronic heart failure". In: *European Journal of Heart Failure* 8.3, pp. 243–248. ISSN: 13889842. DOI: 10.1016/j.ejheart.2005.07.011.

Li, Donghui et al. (2004). "Pancreatic cancer". In: *The Lancet* 363.9414. 02452, pp. 1049–1057. ISSN: 0140-6736. DOI: 10.1016/S0140-6736(04)15841-8.

Li, Donghui et al. (2009). "Body mass index and risk, age of onset, and survival in patients with pancreatic cancer". In: *JAMA* 301.24, pp. 2553–2562. ISSN: 1538-3598. DOI: 10.1001/jama.2009.886.

Liano, F. et al. (1996). "Epidemiology of acute renal failure: A prospective, multicenter, community-based study". In: *Kidney International* 50.3. WOS:A1996VD76600011, pp. 811–818. ISSN: 0085-2538. DOI: 10.1038/ki.1996.380.

Lin, John W. et al. (2004). "Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 8.8, pp. 951–959. ISSN: 1091-255X. DOI: 10.1016/j.gassur.2004.09.044.

Loftin, Mark et al. (2001). "Scaling Vo2 Peak in Obese and Non-obese Girls". In: *Obesity Research* 9.5, pp. 290–296. ISSN: 1550-8528. DOI: 10.1038/oby.2001.36.

Lorenzo, Andrea De, Felipe Pittella, and Antonio Rocha (2012). "Increased Preoperative C-Reactive Protein Levels Are Associated with Inhospital Death After Coronary Artery Bypass Surgery". In: *Inflammation* 35.3, pp. 1179–1183. ISSN: 0360-3997, 1573-2576. DOI: 10.1007/s10753-011-9426-1.

Lowy, A. M. et al. (1997). "Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease". In: *Annals of Surgery* 226.5. 00350, pp. 632–641. ISSN: 0003-4932.

Lumlertgul, D et al. (1991). "The jaundiced heart: evidence of blunted response to positive inotropic stimulation". In: *Ren Fail* 13.1, pp. 15–22.

Machado, Júlia Figueiredo et al. (2015). "Whey and soy protein supplements changes body composition in patients with Crohn's disease undergoing azathioprine and anti-TNF-alpha therapy". In: *Nutrición Hospitalaria* 31.4, pp. 1603–1610. ISSN: 1699-5198. DOI: 10.3305/nh.2015.31.4.8362.

Maciejczyk, Marcin et al. (2014). "The Influence of Increased Body Fat or Lean Body Mass on Aerobic Performance". In: *PLoS ONE* 9.4. Ed. by Marià Alemany, e95797. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0095797.

MacKay, G. J., R. G. Molloy, and P. J. O'Dwyer (2011). "C-reactive protein as a predictor of postoperative infective complications following elective colorectal resection: CRP predicting infective complications". In: *Colorectal Disease* 13.5, pp. 583–587. ISSN: 14628910. DOI: 10.1111/j.1463-1318.2010.02236.x.

Mackenzie, Iain and Joe Woodhouse (2006). "C-reactive protein concentrations during bacteraemia: a comparison between patients with and without liver dysfunction". In: *Intensive Care Medicine* 32.9, pp. 1344–1351. ISSN: 0342-4642, 1432-1238. DOI: 10.1007/s00134-006-0251-1.

Maisonneuve, Patrick and Albert B. Lowenfels (2010). "Epidemiology of Pancreatic Cancer: An Update". In: *Digestive Diseases* 28.4. 00137, pp. 645–656. ISSN: 1421-9875, 0257-2753. DOI: 10.1159/000320068.

Makary, Martin A et al. (2006). "Pancreaticoduodenectomy in the very elderly". In: *J Gastrointest Surg* 10.3, pp. 347–56.

Mallinson, C. N. et al. (1980). "Chemotherapy in pancreatic cancer: results of a controlled, prospective, randomised, multicentre trial". In: *British Medical Journal* 281.6255. 00231, pp. 1589–1591. ISSN: 0007-1447.

Mann, Chris D et al. (2010). "A review of factors predicting perioperative death and early outcome in hepatopancreaticobiliary cancer surgery". In: *HPB (Oxford)* 12.6. 00000, pp. 380–8.

Margarson, M. P. and N. Soni (1998). "Serum albumin: touchstone or totem?" In: *Anaesthesia* 53.8, pp. 789–803. ISSN: 1365-2044. DOI: 10.1046/j.1365-2044.1998.00438.x.

Martínez-Ródenas, F et al. (1998). "Circulating bile is the main factor responsible for atrial natriuretic peptide release in experimental obstructive jaundice". In: *Br J Surg* 85.4, pp. 480–4.

Matsuda, Akihisa et al. (2009). "Preoperative Plasma Adiponectin Level Is a Risk Factor for Postoperative Infection Following Colorectal Cancer Surgery". In: *Journal of Surgical Research* 157.2, pp. 227–234. ISSN: 0022-4804. DOI: 10.1016/j.jss.2008.09.007.

Matthiessen, P. et al. (2008). "Increase of serum C-reactive protein is an early indicator of subsequent symptomatic anastomotic leakage after anterior resection". In: *Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland* 10.1, pp. 75–80. ISSN: 1463-1318. DOI: 10.1111/j.1463-1318.2007.01300.x.

Mayo, Nancy E et al. (2011). "Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery". In: *Surgery* 150.3, pp. 505–14.

Mayo, Skye C. et al. (2012). "Management of Patients with Pancreatic Adenocarcinoma: National Trends in Patient Selection, Operative Management, and Use of Adjuvant Therapy". In: *Journal of the American College of Surgeons* 214.1, pp. 33–45. ISSN: 10727515. DOI: 10.1016/j.jamcollsurg.2011.09.022.

McArdle, C. S., D. C. McMillan, and D. J. Hole (2005). "Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer". In: *British Journal of Surgery* 92.9, pp. 1150–1154. ISSN: 1365-2168. DOI: 10.1002/bjs.5054.

McArdle, Peter A. et al. (2006). "Systemic inflammatory response, prostate-specific antigen and survival in patients with metastatic prostate cancer." In: *Urologia internationalis* 77.2, pp. 127–129. DOI: 10.1159/000093905.

McCullough, P. A. (2006). "Cardiorespiratory Fitness and Short-term Complications After Bariatric Surgery". In: *Chest* 130.2, pp. 517–525. ISSN: 0012-3692. DOI: 10.1378/chest.130.2.517.

McKay, A. et al. (2006). "Meta-analysis of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy". In: *The British Journal of Surgery* 93.8. 00201, pp. 929–936. ISSN: 0007-1323. DOI: 10.1002/bjs.5407.

McMillan, D. C. et al. (1995). "A prospective study of tumor recurrence and the acute-phase response after apparently curative colorectal cancer surgery." In: *American journal of surgery* 170.4, pp. 319–322.

McMillan, D. C. et al. (2001). "Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer." In: *Nutrition and cancer* 41.1, pp. 64–69. DOI: 10.1080/01635581.2001.9680613.

McMillan, Donald C. et al. (2007). "Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer." In: *International journal of colorectal disease* 22.8, pp. 881–886. DOI: 10.1007/s00384-006-0259-6.

McNeer, Jennifer L. et al. (2010). "Early elevation of C-reactive protein correlates with severe infection and nonrelapse mortality in children undergoing allogeneic stem cell transplantation". In: *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation* 16.3, pp. 350–357. ISSN: 1523-6536. DOI: 10.1016/j.bbmt.2009.10.036.

McSorley, Stephen T. et al. (2015). "Postoperative C-reactive protein measurement predicts the severity of complications following surgery for colorectal cancer." In: *International journal of colorectal disease*. DOI: 10.1007/s00384-015-2229-3.

Merchant, Nipun B. et al. (2009). "Adjuvant chemoradiation therapy for pancreatic adenocarcinoma: who really benefits?" In: *Journal of the American College of Surgeons* 208.5, 829–838, discussion 838–841. ISSN: 1879-1190. DOI: 10.1016/j.jamcollsurg.2008.12.020.

Meyer, B. et al. (1995). "The C-reactive protein for detection of early infections after lumbar microdiscectomy". In: *Acta Neurochirurgica* 136.3, pp. 145–150. ISSN: 0001-6268.

Mezhir, James J et al. (2009). "A matched case-control study of preoperative biliary drainage in patients with pancreatic adenocarcinoma: routine drainage is not justified". In: *J Gastrointest Surg* 13.12, pp. 2163–9.

Mezzomo, Agda et al. (2011). "Preoperative C-reactive protein predicts respiratory infection after coronary artery bypass graft surgery". In: *Arquivos Brasileiros de Cardiologia* 97.5, pp. 365–371. ISSN: 0066-782X. DOI: 10.1590/S0066-782X2011005000092.

Mirnezami, Alexander et al. (2011). "Increased Local Recurrence and Reduced Survival From Colorectal Cancer Following Anastomotic Leak: Systematic

Review and Meta-Analysis". In: *Annals of Surgery* 253.5. 00000, pp. 890–899. ISSN: 0003-4932. DOI: 10.1097/SLA.0b013e3182128929.

Mohri, Yasuhiko et al. (2014). "Correlation between preoperative systemic inflammation and postoperative infection in patients with gastrointestinal cancer: a multicenter study". In: *Surgery Today* 44.5, pp. 859–867. ISSN: 1436-2813. DOI: 10.1007/s00595-013-0622-5.

Mok, James M. et al. (2008). "Use of C-reactive protein after spinal surgery: comparison with erythrocyte sedimentation rate as predictor of early postoperative infectious complications". In: *Spine* 33.4, pp. 415–421. ISSN: 1528-1159. DOI: 10.1097/BRS.0b013e318163f9ee.

Mokart, D. et al. (2002). "Early postoperative compensatory anti-inflammatory response syndrome is associated with septic complications after major surgical trauma in patients with cancer". In: *British Journal of Surgery* 89.11, pp. 1450–1456. ISSN: 1365-2168. DOI: 10.1046/j.1365-2168.2002.02218.x.

Montorsi, M. et al. (1995). "Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: a prospective, controlled, randomized clinical trial". In: *Surgery* 117.1. 00275, pp. 26–31. ISSN: 0039-6060.

Moyes, L. H. et al. (2009). "Preoperative systemic inflammation predicts postoperative infectious complications in patients undergoing curative resection for colorectal cancer". In: *British Journal of Cancer* 100.8. 00000, pp. 1236–1239. ISSN: 0007-0920. DOI: 10.1038/sj.bjc.6604997.

Mullen, John T., Donald W. Moorman, and Daniel L. Davenport (2009). "The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery". In: *Annals of Surgery* 250.1. 00000, pp. 166–172. ISSN: 1528-1140. DOI: 10.1097/SLA.0b013e3181ad8935.

Mullen, John T et al. (2005). "Pancreaticoduodenectomy after placement of endobiliary metal stents". In: *J Gastrointest Surg* 9.8, 1094–104, discussion 1104–5.

Mullen, John T. et al. (2008). "Impact of Body Mass Index on Perioperative Outcomes in Patients Undergoing Major Intra-abdominal Cancer Surgery". In: *Annals of Surgical Oncology* 15.8, pp. 2164–2172. ISSN: 1068-9265, 1534-4681. DOI: 10.1245/s10434-008-9990-2.

Murakami, Yoshiaki et al. (2008). "A soft pancreatic remnant is associated with increased drain fluid pancreatic amylase and serum CRP levels following pancreatoduodenectomy". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 12.1, pp. 51–56. ISSN: 1091-255X. DOI: 10.1007/s11605-007-0340-7.

Mustard, R. A. et al. (1987). "C-reactive protein levels predict postoperative septic complications". In: *Archives of Surgery (Chicago, Ill.: 1960)* 122.1. 00000, pp. 69–73. ISSN: 0004-0010.

Myers, Jonathan et al. (2011). "The obesity paradox and weight loss". In: *The American Journal of Medicine* 124.10, pp. 924–930. ISSN: 1555-7162. DOI: 10.1016/j.amjmed.2011.04.018.

Nagamatsu, Y et al. (2001). "Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with

squamous cell carcinoma of the thoracic esophagus". In: *J Thorac Cardiovasc Surg* 121.6. 00071, pp. 1064–8.

Naimark, Arnold, Karlman Wasserman, and Malcolm B. McIlroy (1964). "Continuous measurement of ventilatory exchange ratio during exercise". In: *Journal of Applied Physiology* 19.4, pp. 644–652. ISSN: 8750-7587, 1522-1601.

Nakamura, Kazuo et al. (1999). "Influence of preoperative nutritional state on inflammatory response after surgery". In: *Nutrition* 15.11, pp. 834–841. ISSN: 0899-9007. DOI: 10.1016/S0899-9007(99)00176-8.

Nakatsuka, A. et al. (2000). "Octreotide inhibits pancreatic exocrine secretion and prevents pancreatoenterostomy leakage". In: *International Surgery* 85.2. 00021, pp. 124–129. ISSN: 0020-8868.

Neal, Christopher P et al. (2011). "Preoperative systemic inflammation and infectious complications after resection of colorectal liver metastases". In: *Arch Surg* 146.4, pp. 471–8.

Nehéz, László and Roland Andersson (2002). "Compromise of Immune Function in Obstructive Jaundice". In: *European Journal of Surgery* 168.6, pp. 315–328. ISSN: 11024151. DOI: 10.1080/11024150260284815.

Neoptolemos, J P et al. (2001). "Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial". In: *Lancet* 358.9293, pp. 1576–85.

Neoptolemos, J P et al. (2009). "Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials". In: *Br J Cancer* 100.2, pp. 246–50.

Neoptolemos, John P et al. (2004). "A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer". In: *N Engl J Med* 350.12, pp. 1200–10.

Neoptolemos, John P et al. (2010). "Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial". In: *JAMA* 304.10, pp. 1073–81.

Nespoli, Angelo et al. (2006). "Impact of postoperative infections on survival in colon cancer patients". In: *Surgical Infections* 7 Suppl 2, S41–43. ISSN: 1096-2964. DOI: 10.1089/sur.2006.7.s2-41.

Nugent, A. M. et al. (1998). "Cardiopulmonary exercise testing in the pre-operative assessment of patients for repair of abdominal aortic aneurysm". In: *Irish Journal of Medical Science* 167.4, pp. 238–241. ISSN: 0021-1265.

Oettle, Helmut et al. (2007). "Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial". In: *JAMA* 297.3, pp. 267–277. ISSN: 1538-3598. DOI: 10.1001/jama.297.3.267.

Ogata, M. et al. (2000). "Role of interleukin-10 on hyporesponsiveness of endotoxin during surgery". In: *Critical Care Medicine* 28.9, pp. 3166–3170. ISSN: 0090-3493.

Older, P, A Hall, and R Hader (1999). "Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly". In: *Chest* 116.2, pp. 355–62.

Older, Paul and Adrian Hall (2004). "Clinical review: how to identify high-risk surgical patients". In: *Crit Care* 8.5. 00067, pp. 369–72.

Older, Paul and Adrian Hall (2005). "Preoperative evaluation of cardiac risk". In: *Br J Hosp Med (Lond)* 66.8. 00000, pp. 452–7.

Older, P et al. (1993). "Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing". In: *Chest* 104.3, pp. 701–4.

Older, P et al. (2000). "Preoperative cardiopulmonary risk assessment by cardiopulmonary exercise testing". In: *Crit Care Resusc* 2.3, pp. 198–208.

Ortega-Deballon, Pablo et al. (2010). "C-reactive protein is an early predictor of septic complications after elective colorectal surgery". In: *World J Surg* 34.4, pp. 808–14.

Ortega-Deballon, Pablo et al. (2013). "Preoperative adipocytokines as a predictor of surgical infection after colorectal surgery: a prospective survey". In: *International Journal of Colorectal Disease* 29.1, pp. 23–29. ISSN: 0179-1958, 1432-1262. DOI: 10.1007/s00384-013-1782-x.

Padillo, F. J. et al. (2001a). "Cytokines and acute-phase response markers derangements in patients with obstructive jaundice". In: *Hepato-Gastroenterology* 48.38. 00024 WOS:000168303500019, pp. 378–381. ISSN: 0172-6390.

Padillo, F. J. et al. (2005a). "Multivariate analysis of factors associated with renal dysfunction in patients with obstructive jaundice". In: *British Journal of Surgery* 92.11. 00000, pp. 1388–1392. ISSN: 0007-1323, 1365-2168. DOI: 10.1002/bjs.5091.

Padillo, F. J. et al. (2005b). "Randomized clinical trial of the effect of intravenous fluid administration on hormonal and renal dysfunction in patients with obstructive jaundice undergoing endoscopic drainage". In: *British Journal of Surgery* 92.1, pp. 39–43. ISSN: 00071323. DOI: 10.1002/bjs.4790.

Padillo, Francisco J. et al. (1999). "Preoperative Assessment of Body Fluid Disturbances in Patients with Obstructive Jaundice". In: *World Journal of Surgery* 23.7, pp. 681–687. ISSN: 0364-2313, 1432-2323. DOI: 10.1007/PL00012368.

Padillo, Francisco J. et al. (2002). "Effect of internal biliary drainage on plasma levels of endotoxin, cytokines, and C-reactive protein in patients with obstructive jaundice". In: *World Journal of Surgery* 26.11, pp. 1328–1332. ISSN: 0364-2313, 1432-2323. DOI: 10.1007/s00268-002-6232-9.

Padillo, Javier et al. (2001b). "Improved cardiac function in patients with obstructive jaundice after internal biliary drainage: hemodynamic and hormonal assessment". In: *Annals of surgery* 234.5, p. 652.

Pain, J A, C J Cahill, and M E Bailey (1985). "Perioperative complications in obstructive jaundice: therapeutic considerations". In: *Br J Surg* 72.12, pp. 942–5.

Parker, M., A. Bryan, and A. Siriwardena (2014). "Serum bilirubin and cardiopulmonary exercise parameters in patients presenting for elective pancreato-duodenectomy". In: *British Journal of Anaesthesia* 113.2. WOS:000340017500062, pp. 331–332. ISSN: 0007-0912.

Parks, R W et al. (1994). "Prospective study of postoperative renal function in obstructive jaundice and the effect of perioperative dopamine". In: *Br J Surg* 81.3, pp. 437–9.

Pausch, Thomas et al. (2012). "Cachexia but not obesity worsens the postoperative outcome after pancreatoduodenectomy in pancreatic cancer". In:

Surgery. Topics in Pancreatic Surgery: A Festschrift Honoring Andrew L. Warshaw 152.3, S81–S88. ISSN: 0039-6060. DOI: 10.1016/j.surg.2012.05.028.

Pearse, Rupert M. et al. (2014). "Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review". In: *JAMA* 311.21, pp. 2181–2190. ISSN: 1538-3598. DOI: 10.1001/jama.2014.5305.

Pearson, Karl (1896). "Mathematical Contributions to the Theory of Evolution.–On a Form of Spurious Correlation Which May Arise When Indices Are Used in the Measurement of Organs". In: *Proceedings of the Royal Society of London* 60.359. 00000, pp. 489–498. ISSN: 0370-1662, DOI: 10.1098/rspl.1896.0076.

Pehlivan, Esra et al. (2011). "The effects of preoperative short-term intense physical therapy in lung cancer patients: a randomized controlled trial". In: *Ann Thorac Cardiovasc Surg* 17.5, pp. 461–8.

Peng, Peter et al. (2012). "Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 16.8, pp. 1478–1486. ISSN: 1873-4626. DOI: 10.1007/s11605-012-1923-5.

Pereira, J A et al. (1994). "Increased cardiac endocrine activity after common bile duct ligation in the rabbit. Atrial endocrine cells in obstructive jaundice". In: *Ann Surg* 219.1, pp. 73–8.

Pieri, Giulia, Banwari Agarwal, and Andrew K. Burroughs (2014). "C-reactive protein and bacterial infection in cirrhosis". In: *Annals of Gastroenterology : Quarterly Publication of the Hellenic Society of Gastroenterology* 27.2, pp. 113–120. ISSN: 1108-7471.

Pitt, H A et al. (1985). "Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost?" In: *Ann Surg* 201.5. Cochrane review paper, pp. 545–53.

Platt, Jonathan J. et al. (2012). "C-reactive Protein as a Predictor of Postoperative Infective Complications after Curative Resection in Patients with Colorectal Cancer". In: *Annals of Surgical Oncology* 19.13, pp. 4168–4177. ISSN: 1068-9265, 1534-4681. DOI: 10.1245/s10434-012-2498-9.

Pratt, Wande B, Mark P Callery, and Charles M Jr Vollmer (2008a). "Risk prediction for development of pancreatic fistula using the ISGPF classification scheme". In: *World J Surg* 32.3, pp. 419–28.

Pratt, Wande et al. (2008b). "POSSUM accurately predicts morbidity for pancreatic resection". In: *Surgery* 143.1, pp. 8–19.

Prem, K. A., N. Mensheha, and J. L. Mckelvey (1965). "OPERATIVE TREATMENT OF ADENOCARCINOMA OF THE ENDOMETRIUM IN OBESE WOMEN". In: *American Journal of Obstetrics and Gynecology* 92. 00000, pp. 16–22. ISSN: 0002-9378.

Quetelet, Lambert Adolphe Jacques and T. Smibert (1842). *A Treatise on Man and the Development of His Faculties*. Cambridge University Press. 145 pp. ISBN: 978-1-108-06442-2.

Raimondi, Sara, Patrick Maisonneuve, and Albert B. Lowenfels (2009). "Epidemiology of pancreatic cancer: an overview". In: *Nature Reviews.*

Gastroenterology & Hepatology 6.12. 00337, pp. 699–708. ISSN: 1759-5053. DOI: 10.1038/nrgastro.2009.177.

Raimondi, Sara et al. (2007). "Early onset pancreatic cancer: evidence of a major role for smoking and genetic factors". In: *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 16.9. 00059, pp. 1894–1897. ISSN: 1055-9965. DOI: 10.1158/1055-9965.EPI-07-0341.

Ramsey, Andrew M. and Robert C. Martin (2011). "Body mass index and outcomes from pancreatic resection: a review and meta-analysis". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 15.9, pp. 1633–1642. ISSN: 1873-4626. DOI: 10.1007/s11605-011-1502-1.

Raut, Chandrajit P. et al. (2007). "Impact of Resection Status on Pattern of Failure and Survival After Pancreaticoduodenectomy for Pancreatic Adenocarcinoma". In: *Annals of Surgery* 246.1, pp. 52–60. ISSN: 0003-4932. DOI: 10.1097/01.sla.0000259391.84304.2b.

Read, William L. et al. (2004). "Differential Prognostic Impact of Comorbidity". In: *Journal of Clinical Oncology* 22.15, pp. 3099–3103. ISSN: 0732-183X, 1527-7755. DOI: 10.1200/JCO.2004.08.040.

Reisinger, Kostan W. et al. (2015). "Sarcopenia is associated with an increased inflammatory response to surgery in colorectal cancer". In: *Clinical Nutrition (Edinburgh, Scotland)*. 00000. ISSN: 1532-1983. DOI: 10.1016/j.clnu.2015.07.005.

Reyad, Amal Rashad et al. (2013). "Effect of intraoperative dobutamine on splanchnic tissue perfusion and outcome after Whipple surgery". In: *Journal of Critical Care* 28.4, 531.e7–531.e15. ISSN: 0883-9441. DOI: 10.1016/j.jcrc.2013.02.017.

Richards, C. H. et al. (2010). "The relationship between patient physiology, the systemic inflammatory response and survival in patients undergoing curative resection of colorectal cancer." In: *British journal of cancer* 103.9, pp. 1356–1361. DOI: 10.1038/sj.bjc.6605919.

Richards, Colin H. et al. (2012). "The relationships between body composition and the systemic inflammatory response in patients with primary operable colorectal cancer." In: *PloS one* 7.8. DOI: 10.1371/journal.pone.0041883.

Robertson, E. A. and M. H. Zweig (1981). "Use of receiver operating characteristic curves to evaluate the clinical performance of analytical systems." In: *Clinical Chemistry* 27.9. 00148, pp. 1569–1574. ISSN: 0009-9147, 1530-8561.

Rohrmann, Sabine et al. (2009). "Ethanol intake and the risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC)". In: *Cancer causes & control: CCC* 20.5. 00041, pp. 785–794. ISSN: 1573-7225. DOI: 10.1007/s10552-008-9293-8.

Roxburgh, C. S. D. et al. (2010). "Relationship Between Preoperative Comorbidity, Systemic Inflammatory Response, and Survival in Patients Undergoing Curative Resection for Colorectal Cancer". In: *Annals of Surgical Oncology* 18.4, pp. 997–1005. ISSN: 1068-9265, 1534-4681. DOI: 10.1245/s10434-010-1410-8.

Russ, Andrew J. et al. (2009). "Impact of Selection Bias on the Utilization of Adjuvant Therapy for Pancreas Adenocarcinoma". In: *Annals of Surgical Oncology* 17.2, pp. 371–376. ISSN: 1068-9265, 1534-4681. DOI: 10.1245/s10434-009-0759-z.

Sahora, Klaus et al. (2014). "A phase II trial of two durations of Bevacizumab added to neoadjuvant gemcitabine for borderline and locally advanced pancreatic cancer". In: *Anticancer Research* 34.5, pp. 2377–2384. ISSN: 1791-7530.

Sandroussi, Charbel et al. (2010). "Sociodemographics and Comorbidities Influence Decisions to Undergo Pancreatic Resection for Neoplastic Lesions". In: *Journal of Gastrointestinal Surgery* 14.9, pp. 1401–1408. ISSN: 1091-255X, 1873-4626. DOI: 10.1007/s11605-010-1255-2.

Savonen, K. et al. (2012). "The current standard measure of cardiorespiratory fitness introduces confounding by body mass: the DR's EXTRA study". In: *International Journal of Obesity (2005)* 36.8, pp. 1135–1140. ISSN: 1476-5497. DOI: 10.1038/ijo.2011.212.

Scott-Conner, Carol E. H. and James B. Grogan (1994). "The Pathophysiology of Biliary Obstruction and Its Effect on Phagocytic and Immune Function". In: *Journal of Surgical Research* 57.2, pp. 316–336. ISSN: 0022-4804. DOI: 10.1006/jsre.1994.1151.

Seltzer, Carl C. (1940). "BODY BUILD AND OXYGEN METABOLISM AT REST AND DURING EXERCISE". In: *American Journal of Physiology – Legacy Content* 129.1, pp. 1–13. ISSN: 0002-9513.

Sener, Stephen F. et al. (1999). "Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database". In: *Journal of the American College of Surgeons* 189.1, pp. 1–7.

Sewnath, Miguel E et al. (2002). "A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice". In: *Ann Surg* 236.1, pp. 17–27.

Sheetz, Kyle H. et al. (2013). "Improving Mortality Following Emergency Surgery in Older Patients Requires Focus on Complication Rescue". In: *Annals of surgery* 258.4. 00000, pp. 614–618. ISSN: 0003-4932. DOI: 10.1097/SLA.0b013e3182a5021d.

Shen, Wei et al. (2004). "Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image". In: *Journal of Applied Physiology (Bethesda, Md.: 1985)* 97.6. 00000, pp. 2333–2338. ISSN: 8750-7587. DOI: 10.1152/japplphysiol.00744.2004.

Singh, P. P. et al. (2014). "Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery". In: *The British Journal of Surgery* 101.4, pp. 339–346. ISSN: 1365-2168. DOI: 10.1002/bjs.9354.

Sitges-Serra, A et al. (1992). "Body water compartments in patients with obstructive jaundice". In: *Br J Surg* 79.6. 00042, pp. 553–6.

Snellen, J P et al. (1985). "The influence of preoperative jaundice, biliary drainage and age on postoperative morbidity and mortality after pancreatoduodenectomy and total pancreatectomy". In: *Neth J Surg* 37.3, pp. 83–6.

Snowden, Chris P. et al. (2010). "Submaximal Cardiopulmonary Exercise Testing Predicts Complications and Hospital Length of Stay in Patients Undergoing Major Elective Surgery:" in: *Annals of Surgery* 251.3. 00105, pp. 535–541. ISSN: 0003-4932. DOI: 10.1097/SLA.0b013e3181cf811d.

Sohn, Taylor A. et al. (2000). "Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators". In: *Journal of Gastrointestinal Surgery* 4.6. 00000, pp. 567–579.

Song, Jian-Gang et al. (2009). "Baroreflex sensitivity is impaired in patients with obstructive jaundice". In: *Anesthesiology* 111.3, pp. 561–5.

Spitz, F. R. et al. (1997). "Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas". In: *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 15.3, pp. 928–937. ISSN: 0732-183X.

Starr, Isaac M. D., Robert L. M. D. Mayock, and Mahjorie G. Battles (1945). "Convalescence from Surgical Procedures II. Studies of Various Physiological Responses to a Mild Exercise Test". In: *Journal of the Medical Sciences* 210.6, pp. 713–725. ISSN: 0002-9629.

Stephan, R. N. et al. (1987). "Hemorrhage without tissue trauma produces immunosuppression and enhances susceptibility to sepsis". In: *Archives of Surgery (Chicago, Ill.: 1960)* 122.1, pp. 62–68. ISSN: 0004-0010.

Straatman, Jennifer et al. (2015). "Predictive Value of C-Reactive Protein for Major Complications after Major Abdominal Surgery: A Systematic Review and Pooled-Analysis". In: *PLoS ONE* 10.7. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0132995.

Sue, D Y et al. (1988). "Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination". In: *Chest* 94.5. 00311, pp. 931–8.

Sultan, Pervez et al. (2014). "Cardiopulmonary Exercise Capacity and Preoperative Markers of Inflammation". In: *Mediators of Inflammation* 2014. ISSN: 0962-9351. DOI: 10.1155/2014/727451.

Sutton, Frank C., James A. Britton, and James G. Carr (1940). "Estimation of cardiopulmonary functional capacity by means of oxygen debt studies". In: *American Heart Journal* 20.4, pp. 423–442. ISSN: 0002-8703. DOI: 10.1016/S0002-8703(40)90876-6.

Sutton, Jeffrey M. et al. (2014). "Perioperative blood transfusion is associated with decreased survival in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma: a multi-institutional study". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 18.9, pp. 1575–1587. ISSN: 1873-4626. DOI: 10.1007/s11605-014-2567-4.

Swart, M. and J. B. Carlisle (2012). "Case-controlled study of critical care or surgical ward care after elective open colorectal surgery". In: *British Journal of Surgery* 99.2. 00000, pp. 295–299. ISSN: 00071323. DOI: 10.1002/bjs.7789.

Tamijmarane, Appou et al. (2008). "Application of Portsmouth modification of physiological and operative severity scoring system for enumeration of morbidity

and mortality (P-POSSUM) in pancreatic surgery". In: *World J Surg Oncol* 6, p. 39.

Tan, Benjamin H. L. et al. (2009). "Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer". In: *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 15.22, pp. 6973–6979. ISSN: 1078-0432. DOI: 10.1158/1078-0432.CCR-09-1525.

Tang, T. Y., P. D. Hayes, and J. R. Boyle (2012). "Cardiopulmonary exercise testing provides a predictive tool for early and late outcomes in abdominal aortic aneurysm patients". In: *Annals of the Royal College of Surgeons of England* 94.5, p. 373. ISSN: 1478-7083. DOI: 10.1308/003588412X13171221591493.

Tanner, J. M. (1949). "Fallacy of Per-Weight and Per-Surface Area Standards, and Their Relation to Spurious Correlation". In: *Journal of Applied Physiology* 2.1, pp. 1–15. ISSN: 8750-7587, 1522-1601.

Teh, Swee H. et al. (2009). "Patient and hospital characteristics on the variance of perioperative outcomes for pancreatic resection in the United States: a plea for outcome-based and not volume-based referral guidelines". In: *Archives of surgery* 144.8, p. 713.

Thompson, A. R. et al. (2011). "Cardiopulmonary exercise testing provides a predictive tool for early and late outcomes in abdominal aortic aneurysm patients". In: *Annals of the Royal College of Surgeons of England* 93.6, pp. 474–481. ISSN: 1478-7083. DOI: 10.1308/003588411X587235.

Tien, Yu-Wen et al. (2005). "Risk factors of massive bleeding related to pancreatic leak after pancreaticoduodenectomy". In: *J Am Coll Surg* 201.4, pp. 554–9.

Tol, Johanna A. M. G. et al. (2012). "The Quandary of Preresection Biliary Drainage for Pancreatic Cancer". In: *Cancer Journal* 18.6. WOS:000311833400010, pp. 550–554. ISSN: 1528-9117. DOI: 10.1097/PPO.0b013e31827568b6.

Topp, Robert et al. (2002). "The effect of bed rest and potential of prehabilitation on patients in the intensive care unit". In: *AACN Advanced Critical Care* 13.2, pp. 263–276.

Torchio, Roberto et al. (2010). "Exercise ventilatory inefficiency and mortality in patients with chronic obstructive pulmonary disease undergoing surgery for non-small-cell lung cancer". In: *Eur J Cardiothorac Surg* 38.1, pp. 14–9.

Torre, Marco La et al. (2012). "The Glasgow Prognostic Score as a Predictor of Survival in Patients with Potentially Resectable Pancreatic Adenocarcinoma". In: *Annals of Surgical Oncology* 19.9. 00038, pp. 2917–2923. ISSN: 1068-9265, 1534-4681. DOI: 10.1245/s10434-012-2348-9.

Toth, Mj et al. (1993). "Examination of Data Normalization Procedures for Expressing Peak V-Center-Dot-O2 Data". In: *Journal of Applied Physiology* 75.5. WOS:A1993MG96000051, pp. 2288–2292. ISSN: 8750-7587.

Tran, Khe T. C. et al. (2004). "Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors". In: *Annals of Surgery* 240.5. 00381, pp. 738–745. ISSN: 0003-4932.

Tsai, Susan et al. (2010). "Impact of obesity on perioperative outcomes and survival following pancreaticoduodenectomy for pancreatic cancer: a large

single-institution study". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 14.7, pp. 1143–1150. ISSN: 1873-4626. DOI: 10.1007/s11605-010-1201-3.

Tsujinaka, Shingo et al. (2008). "Visceral Obesity Predicts Surgical Outcomes after Laparoscopic Colectomy for Sigmoid Colon Cancer:" in: *Diseases of the Colon & Rectum* 51.12, pp. 1757–1767. ISSN: 0012-3706. DOI: 10.1007/s10350-008-9395-0.

Tzeng, Ching-Wei D. et al. (2014). "Morbidity and mortality after pancreaticoduodenectomy in patients with borderline resectable type C clinical classification". In: *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract* 18.1, 146–155, discussion 155–156. ISSN: 1873-4626. DOI: 10.1007/s11605-013-2371-6.

Vashist, Yogesh K et al. (2010). "Glasgow Prognostic Score is a Predictor of Perioperative and Long-term Outcome in Patients with only Surgically Treated Esophageal Cancer". In: *Ann Surg Oncol*. 00000.

Wang, Qin et al. (2008). "Preoperative biliary drainage for obstructive jaundice". In: *The Cochrane Database of Systematic Reviews* 3. 00096, p. CD005444. ISSN: 1469-493X. DOI: 10.1002/14651858.CD005444.pub2.

Ward, Nicholas S., Brian Casserly, and Alfred Ayala (2008). "The Compensatory Anti-inflammatory Response syndrome (CARS) in Critically ill patients". In: *Clinics in chest medicine* 29.4, pp. 617–viii. ISSN: 0272-5231. DOI: 10.1016/j.ccm.2008.06.010.

Warschkow, Rene et al. (2012). "Safe and early discharge after colorectal surgery due to C-reactive protein: a diagnostic meta-analysis of 1832 patients". In: *Annals of Surgery* 256.2, pp. 245–250. ISSN: 1528-1140. DOI: 10.1097/SLA.0b013e31825b60f0.

Wasan, Sanjeev M et al. (2005). "Use of expandable metallic biliary stents in resectable pancreatic cancer". In: *Am J Gastroenterol* 100.9, pp. 2056–61.

Wasserma.k et al. (1973). "Anaerobic Threshold and Respiratory Gas-Exchange During Exercise". In: *Journal of Applied Physiology* 35.2. WOS:A1973Q489000011, pp. 236–243. ISSN: 8750-7587.

Wasserman, K. (1967). "Lactate and related acid base and blood gas changes during constant load and graded exercise." In: *Canadian Medical Association Journal* 96.12, pp. 775–783. ISSN: 0008-4409.

Wasserman, K. and M. B. Mcilroy (1964). "DETECTING THE THRESHOLD OF ANAEROBIC METABOLISM IN CARDIAC PATIENTS DURING EXERCISE". In: *The American Journal of Cardiology* 14, pp. 844–852. ISSN: 0002-9149.

Weitz, Jürgen et al. (2010). "The "Artery First" Approach for Resection of Pancreatic Head Cancer". In: *Journal of the American College of Surgeons* 210.2, e1–e4. ISSN: 1072-7515. DOI: 10.1016/j.jamcollsurg.2009.10.019.

Welsch, Thilo et al. (2008). "Persisting elevation of C-reactive protein after pancreatic resections can indicate developing inflammatory complications". In: *Surgery* 143.1, pp. 20–28. ISSN: 0039-6060. DOI: 10.1016/j.surg.2007.06.010.

Welsch, T. et al. (2007). "C-reactive protein as early predictor for infectious postoperative complications in rectal surgery". In: *International Journal of*

Colorectal Disease 22.12, pp. 1499–1507. ISSN: 0179-1958, 1432-1262. DOI: 10.1007/s00384-007-0354-3.

Wente, Moritz N. et al. (2007). "Postpancreatectomy hemorrhage (PPH)–An International Study Group of Pancreatic Surgery (ISGPS) definition". In: *Surgery* 142.1, pp. 20–25. ISSN: 00396060. DOI: 10.1016/j.surg.2007.02.001.

West, M. A. et al. (2014). "The effects of neoadjuvant chemoradiotherapy on physical fitness and morbidity in rectal cancer surgery patients". In: *European Journal of Surgical Oncology (EJSO)* 40.11, pp. 1421–1428. ISSN: 0748-7983. DOI: 10.1016/j.ejso.2014.03.021.

West, M. A. et al. (2015). "Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study". In: *British Journal of Anaesthesia* 114.2, pp. 244–251. ISSN: 0007-0912, 1471-6771. DOI: 10.1093/bja/aeu318.

Whipple, Allen O. (1941). "The rationale of radical surgery for cancer of the pancreas and ampullary region". In: *Annals of Surgery* 114.4. 00000, pp. 612–615. ISSN: 0003-4932.

– (1950). "Radical Surgery in the Treatment of Cancer". In: *Annals of Surgery* 131.6, pp. 812–818. ISSN: 0003-4932.

Whipple, Allen O., William Barclay Parsons, and Clinton R. Mullins (1935). "Treatment of Carcinoma of Ampulla of Vater". In: *Annals of Surgery* 102.4, pp. 763–779. ISSN: 0003-4932.

WHO (2000). *Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894.*

Wilson, R. J. T. et al. (2010). "Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery". In: *British Journal of Anaesthesia* 105.3, pp. 297–303. ISSN: 0007-0912, 1471-6771. DOI: 10.1093/bja/aeq128.

Winter, Jordan M et al. (2006). "1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience". In: *J Gastrointest Surg* 10.9. 00876, 1199–210, discussion 1210–1.

Winter, Jordan M et al. (2007). "Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy". In: *J Am Coll Surg* 204.5, 1029–36, discussion 1037–8.

Woeste, Guido et al. (2010). "Increased serum levels of C-reactive protein precede anastomotic leakage in colorectal surgery". In: *World J Surg* 34.1, pp. 140–6.

Wright, S. E. et al. (2014). "Cardiopulmonary exercise testing before and after blood transfusion: a prospective clinical study". In: *British Journal of Anaesthesia* 113.1, pp. 91–96. ISSN: 0007-0912, 1471-6771. DOI: 10.1093/bja/aeu050.

Wullstein, C. et al. (2004). "High levels of C-reactive protein after simultaneous pancreas-kidney transplantation predict pancreas graft-related complications and graft survival:" in: *Transplantation* 77.1, pp. 60–64. ISSN: 0041-1337. DOI: 10.1097/01.TP.0000100683.92689.27.

Xiong, J. J. et al. (2014). "Meta-analysis of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy". In: *British Journal of Surgery* 101.10, pp. 1196–1208. ISSN: 1365-2168. DOI: 10.1002/bjs.9553.

Yamaguchi, Yoshiyuki et al. (2006). "Postoperative immunosuppression cascade and immunotherapy using lymphokine-activated killer cells for patients with esophageal cancer: possible application for compensatory anti-inflammatory response syndrome". In: *Oncology Reports* 15.4, pp. 895–901. ISSN: 1021-335X.

Yamamoto, Hiroshi et al. (2013). "Association between Reduction of Plasma Adiponectin Levels and Risk of Bacterial Infection after Gastric Cancer Surgery". In: *PLoS ONE* 8.3. 00000. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0056129.

Yang, Ying-Ying et al. (2010). "Mechanisms of TNFalpha-induced cardiac dysfunction in cholestatic bile duct-ligated mice: interaction between TNFalpha and endocannabinoids". In: *J Hepatol* 53.2, pp. 298–306.

Yeo, C. J. et al. (1995). "A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy". In: *Annals of Surgery* 222.4. 00798, 580–588, discussion 588–592. ISSN: 0003-4932.

Yeo, C J et al. (1997). "Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes". In: *Ann Surg* 226.3. 01784, 248–57, discussion 257–60.

Yeo, C. J. et al. (2000). "Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial". In: *Annals of Surgery* 232.3. 00489, pp. 419–429. ISSN: 0003-4932.

Yoo, Han Mo et al. (2011). "Negative impact of leakage on survival of patients undergoing curative resection for advanced gastric cancer". In: *Journal of Surgical Oncology* 104.7. 00000, pp. 734–740. ISSN: 1096-9098. DOI: 10.1002/jso.22045.

Zhang, Yan et al. (2012). "Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials". In: *Surgical Oncology* 21.2, e87–95. ISSN: 1879-3320. DOI: 10.1016/j.suronc.2012.01.002.

Zweig, M. H. and G. Campbell (1993). "Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine." In: *Clinical Chemistry* 39.4. 00000, pp. 561–577. ISSN: 0009-9147, 1530-8561.