FULL/LONG TITLE OF THE STUDY

EFFECTIVENESS OF PRE-OPERATIVE CARDIOPULMONARY EXERCISE TESTING IN PREDICTING POST-OPERATIVE MORBIDITY AND MORTALITY AFTER PANCREATODUODENECTOMY – A RETROSPECTIVE COHORT STUDY

SHORT STUDY TITLE / ACRONYM

THE ROLE OF PRE-OPERATIVE CPET IN PANCREATODUODENECTOMY

RESEARCH REFERENCE NUMBERS

IRAS Number: 284565

SPONSORS Number: NONE

FUNDERS Number: NONE

Document submitted to HRA/IRAS Date: 11-12-2020

Amendments:

Document amended on 21-09-2023 for submission to Clinicaltrials.gov

Document amended again on **28-09-2023** for submission to Clinicaltrials.gov

STUDY SUMMARY

Study Title	EFFECTIVENESS OF PRE-OPERATIVE CARDIOPULMONARY EXERCISE TESTING IN PREDICTING POST-OPERATIVE MORBIDITY AND MORTALITY AFTER PANCREATODUODENECTOMY – A RETROSPECTIVE COHORT STUDY
Internal ref. no. (or short title)	THE ROLE OF PRE-OPERATIVE CPET IN PANCREATODUODENECTOMY
Study Design	RETROSPECTIVE ANALYSIS OF PROSPECTIVELY MAINTAINED DATABASE
Study Participants	PARTICIPANTS WHO HAVE UNDERGONE PANCREATIC RESECTIONS FROM APRIL 2016 TO MARCH 2020
Planned Size of Sample (if applicable)	Approximately 140
Follow up duration (if applicable)	90 DAYS
Planned Study Period	1 YEAR
Research Question/Aim(s)	To assess the usefulness and effectiveness of pre-operative CPET in predicting morbidity and mortality after pancreatoduodenectomy

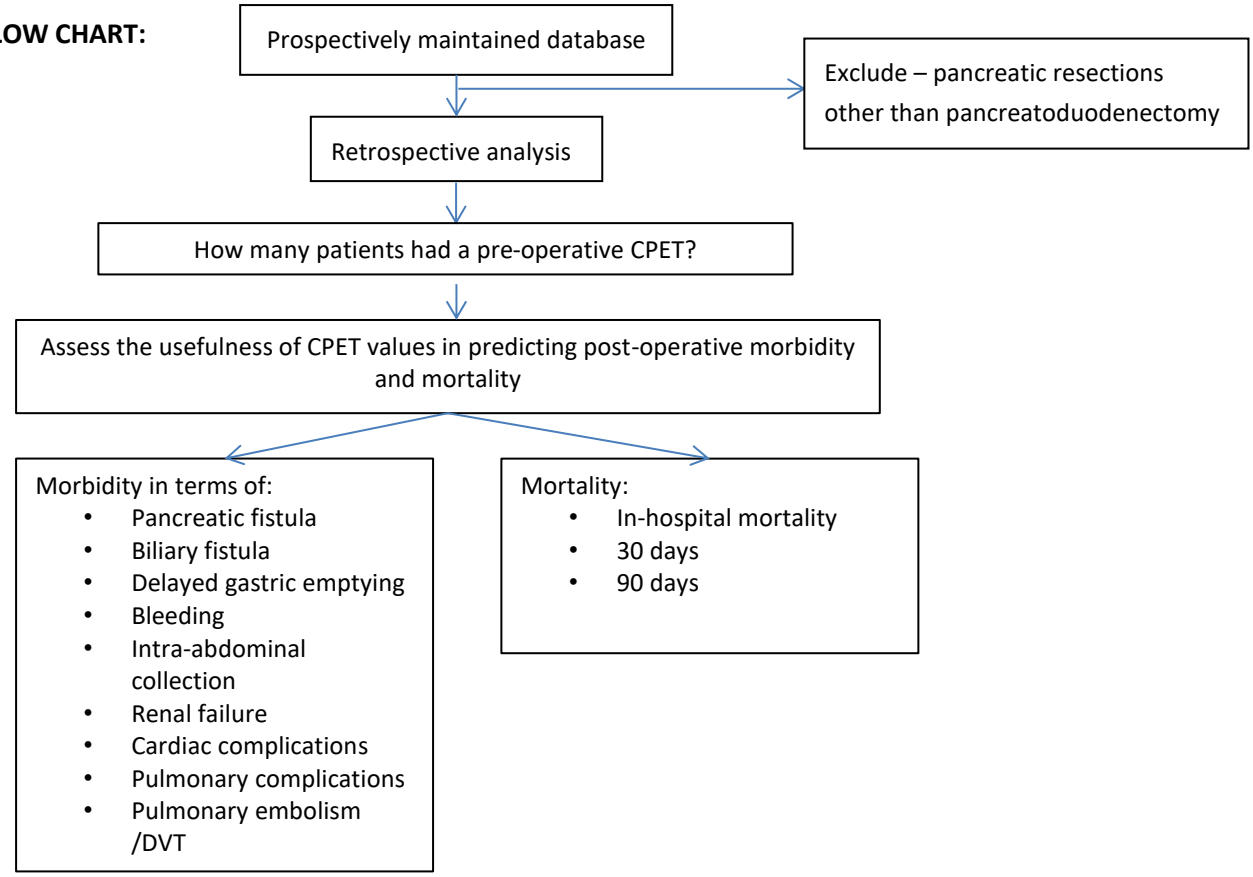
FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN BY**
ROYAL BLACKBURN HOSPITAL, EAST LANCASHIRE HOSPITALS NHS TRUST HASLINGDEN ROAD, BLACKBURN, BB2 3HH CONTACT NUMBER: 01254 263555	NON FINANCIAL SUPPORT

ROLE OF STUDY SPONSOR AND FUNDER:

Non-financial support for the study.

STUDY FLOW CHART:



STUDY PROTOCOL

1 BACKGROUND:

Pancreatic resections, particularly Pancreatoduodenectomy, for tumors in the pancreas head, is considered the standard modality of management for pancreatic and periampullary tumors. The morbidity and mortality associated with the procedure, has improved in the recent times, but it still remains high. Post-operative pancreatic fistula, in particular, has an incidence ranging from 20-25%[1]. The operability of the tumour not only depends on the initial staging of the tumour, but also on physiological status of the patient, fitness, pre-existing comorbidities and age. The use of cardiopulmonary Exercise Testing (CPET), in assessing physiological status of the patient has been in discussion, in the past two decades. The efficacy and use of CPET as a guide for pre-operative optimisation of the patient undergoing major abdominal surgeries, has been proven[2]. Levett D Z H et al. in 2017, provided Level 1 evidence, supporting the same and also drew guidelines for the clinicians for indications and interpretation of CPET for perioperative participants[2].

Chandrabalan V V et al. in 2013, conducted a retrospective study, which showed that CPET is useful to predict occurrence of post-operative pancreatic fistula, intra-abdominal abscess and post-operative length of hospital stay[3]. Junejo MA et al. in 2014, by a prospective study showed that, CPET can be used as an adjunct to predict post-operative outcomes in pancreatoduodenectomy. This study showed that raised VE/VCO2 in CPET could predict early post-operative death[4].

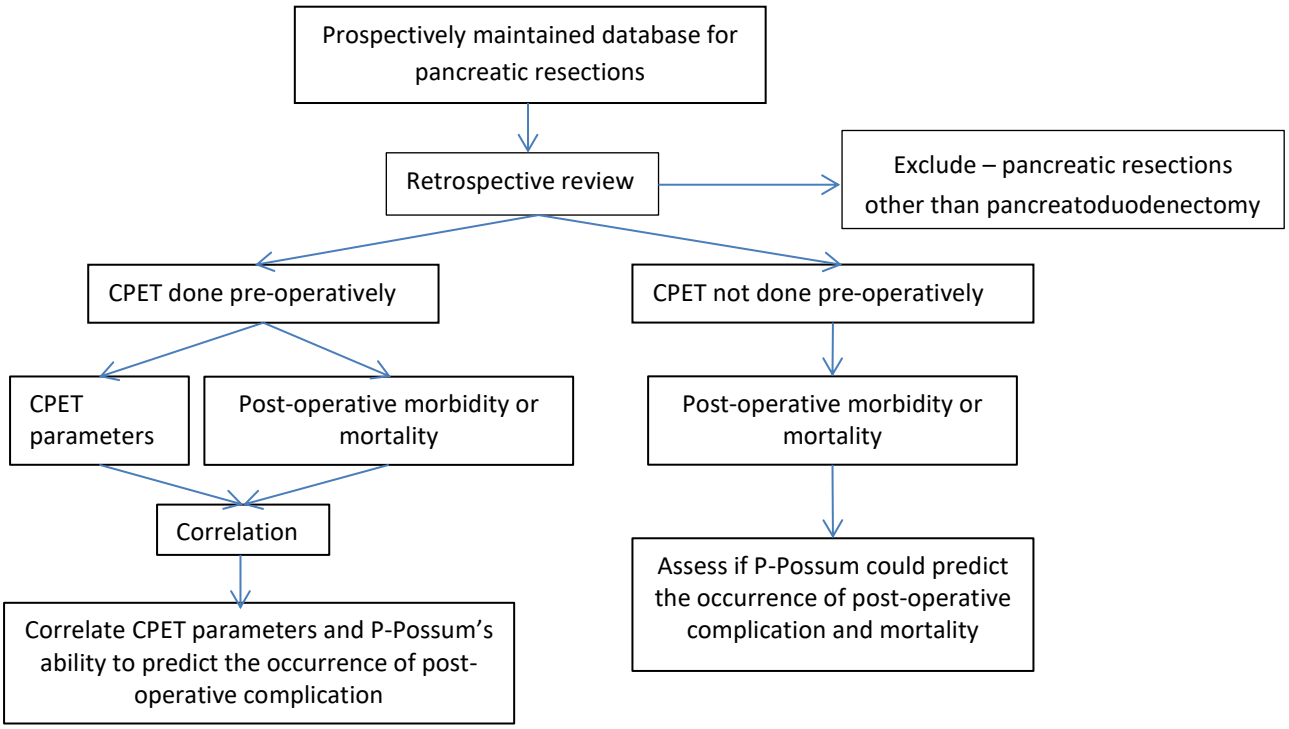
REFERENCES:

1. **Wu J.M., Kuo T.C., Chen H.A., et al. (2019). Randomized trial of oral *versus* enteral feeding for participants with postoperative pancreatic fistula after pancreatoduodenectomy. British Journal of Surgery,106,190–198.**
2. **Levett D Z H, Jack S, Swart M et al. (2018). Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. British Journal of Anaesthesia,120(3):484-500.**
3. **Chandrabalan V V, McMillan D C, Carter R et al. (2013). Pre-operative cardiopulmonary exercise testing predicts adverse post-operative events and non-progression to adjuvant therapy after major pancreatic surgery. HPB,15:899-907.**
4. **Junejo M A, Mason J M, Sheen A J et al. (2014). Cardiopulmonary exercise testing for preoperative risk assessment before pancreaticoduodenectomy for cancer. Annals of Surgical Oncology,21(6):1929-36.**

2 RATIONALE:

With the above mentioned background, we aim to do a retrospective analysis of participants who have undergone pancreatic resections, at our centre. The aim is to assess the ability of physiological parameters assessed by CPET, in predicting post-operative morbidity and mortality. This study also aims at evaluating and analysing a comparator group of participants who did not have CPET and assess their perioperative outcomes, in particular post-operative complications, with those who had CPET.

3 THEORETICAL FRAMEWORK



4 RESEARCH QUESTION/AIM(S)

Objectives: To assess if pre-operative cardiopulmonary exercise testing is useful and effective in predicting at risk participants for post-operative morbidity and mortality, who undergo Whipple's surgery.

DATA ELEMENTS

1. Participant flow

Recruitment Details:

Participants for the study will be identified from a prospectively maintained database, by database search from April 2016 to March 2020, online records, clinical portal and Somerset cancer registry. Duplicates will be removed, cases will be screened.

This is a single centre study, to be done at, Royal Blackburn Hospital, East Lancashire Hospitals NHS trust, a District general Hospital in North of England. The study will be carried out in the department of General and HPB surgery, in liaise with Department of anaesthesia. This is the HPB referral centre for Lancashire and South Cumbria and incorporates participants referred for pancreatic surgery from three hospital trusts (Lancashire Teaching, University Hospital Morecambe Bay and Blackpool Teaching Hospitals).

Arm/Group Information:

The study will have two groups of participants, one who have undergone CPET pre-operatively and the other who have not undergone CPET.

Group 1 – Participants who have undergone CPET as a part of pre-operative assessment as well as P-POSSUM score calculation for predicting post-operative morbidity and mortality.

P-POSSUM is a scoring system for general elective and emergency surgeries which takes into account various physiological and operative parameters to calculate risk of morbidity and mortality in terms of percentages.

Group 2 – Participants who have not undergone CPET as a part of pre-operative assessment rather have only P-POSSUM calculated for predicting post-operative morbidity and mortality.

Period of Overall Study:

The study was conducted from February 2021 to March 2022. The database search was conducted and data collated. The study was conducted in one stage over a year.

Participants:

143 participants were recruited for the study during a period of 1 year. Out of 143 participants, 30 participants had undergone CPET as a part of pre-operative assessment.

2. Baseline Characteristics:

Baseline Analysis Population Information:

Data on baseline characteristics included age, sex, comorbidities, Rockwell frailty score, ASA grade, BMI.

Data on study specific characteristics included dates of admission and discharge, diagnosis, details of surgery undergone, details of morbidity using Clavien-Dindo classification and mortality. Details of CPET and its measures as well as P-POSSUM scores were collated.

CPET specific data collected:

1) Exercise induced ST ischaemia- yes/no
2) VO_2 peak: actual and predicted
3) Anaerobic threshold:
4) VE/VCO_2:
5) Pulmonary function test- normal/ obstructive/ restrictive
6) Duration of pedalling bike
7) 30 day predicted risk

3. Outcome Measures:

Primary Outcome measures:

Primary outcome was measured in terms of CPET/P-POSSUM predicted mortality compared to actual 30 day mortality.

- In-hospital mortality
- 30 days
- 90 days

Secondary outcome measures:

Secondary outcome was measured in terms of CPET/ P-POSSUM predicted morbidity compared to actual morbidity (Clavien-Dindo grade 3 and above).

Morbidity in terms of:

- Post-operative pancreatic fistula
- Biliary fistula
- Delayed gastric emptying
- Bleeding
- Intra-abdominal collection
- Renal failure
- Cardiac complications
- Pulmonary complications
- Pulmonary embolism /DVT

The occurrence of morbidity and mortality were measured in terms of numbers and percentages. The calculated risk of morbidity and mortality by CPET and P-POSSUM are in terms of percentages, ranging from 0 to 100%, higher the percentage leading to worse outcome.

Statistical analyses overview:

The baseline characteristics were analysed using percentages and frequencies (mean, median, mode, standard deviation). Chi-square test was used to assess if the two study groups were

comparable. The p-value calculated was considered significant if <0.05 and confidence interval of 95%.

The study specific measures were analysed using parametric and non-parametric tests and binary logistic regression analyses to compare predicted to actual mortality and morbidity, between the participants who have had CPET and those who have not.

Univariate and multivariate analysis were done to assess if CPET measures could be used to predict occurrence of post-operative complications and morbidity.

4. Adverse Event information:

This was a retrospective review of a prospectively maintained database.

No adverse events were overcome during the time of the study

5. Limitations and Caveat:

This was a retrospective review of a prospectively maintained database. The participants who underwent CPET was small compared to participants who did not. A prospective study with a large sample size is required to obtain more reliable results.

6. Certain Agreements:

All PIs are employees of Sponsor.

There is no specified results disclosure agreement between the PIs and sponsor.

7. Results Point of Contact

Name: Miss Meghana Taggarsi (Principal Investigator)

Organization Name: East Lancashire Hospitals NHS Trust

Phone: 07471565288

Email Id: meghana.t87@gmail.com

8. Results of the study

143 participants had Pancreatoduodenectomy during the study period. CPET was performed in 30 participants (21%). The participants' age was 67 ±9 (Mean±SD). Forty participants (28.2%) had developed intra-abdominal collection (Clavien-Dindo III). In the CPET subgroup, Anaerobic Threshold (AT) ≤ 14 on CPET was a risk factor to develop intra-abdominal collection, according to univariate analysis (60% Vs 9%, p-value 0.02) and multivariate analysis (HR 3.5, 95% CI 1.6-657, p-value 0.02). Another significant risk factor was post-operative pancreatic leak (POPF) (40% Vs 22%, p-value 0.04).

By this study we concluded that participants who have Anaerobic Threshold ≤ 14 on CPET, are more likely to develop intra-abdominal collection requiring drainage after Pancreatoduodenectomy. This group of participants will be less likely to start chemotherapy early.