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Identifying the limitations of cardiopulmonary exercise testing prior to oesophagectomy using a pooled analysis of individual patient data

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ABSTRACT

Background: Preoperative cardiopulmonary exercise testing (CPET) provides an objective assessment of aerobic fitness in patients undergoing surgery. Whilst peak oxygen uptake during exercise ($\dot{V}O2peak$) and anaerobic threshold (AT) have demonstrated a moderate correlation with the development of complications following oesophagectomy, no clinically useful threshold values have been defined. By pooling patient level data from existing studies, we aimed to define optimal thresholds for preoperative CPET parameters to predict patients at high-risk of postoperative complications.

Methods: Studies reporting on the relationship between preoperative CPET variables and post-oesophagectomy complications were determined from a comprehensive literature search. Patient-level data were obtained from six contributing centres for pooled-analyses. Outcomes of interest included cardiopulmonary and non-cardiopulmonary complications, unplanned ICU readmission, 90-day and 12-month all-cause mortality. Receiver operating characteristic (ROC) curves and logistic regression models estimated the predictive value of CPET parameters for each individual outcome of interest.

Results: This analysis comprised of 621 patients who underwent CPET prior to oesophagectomy during the period from January 2004 to March 2017. For both AT and $\dot{V}O_2$peak, none of the ROC curves achieved an area under the curve value higher than 0.66 for the outcomes of interest.

Conclusion: The discriminatory ability of CPET for determining high-risk patients was found to be poor in patients undergoing an oesophagectomy. CPET may only carry an adjunct role to clinical decision making.

Key words: Oesophagectomy, Oesophagus, Cancer, Risk assessment

INTRODUCTION

Oesophageal cancer is the seventh most common malignancy in the world, with an annual incidence of 572,000 cases (1). It carries a poor prognosis and is therefore responsible for approximately 1 in every 20 cancer deaths (1). Surgical resection is an integral component of curative management, but despite modern advancements in perioperative care, oesophagectomy is still associated with significant postoperative morbidity (2, 3).

The most recent data from the *Esophageal Complications Consensus Group* reported an overall complication rate of 59%, and 30-day and 90-day mortality rates of 2.4% and 4.5%, respectively (3). Oesophagectomy is a highly invasive, multi-cavity surgical procedure involving substantial anatomical and physiological changes to a patient's gastrointestinal system, as well as having an ongoing impact on their physical, nutritional and psychological functioning (4). Furthermore, single-lung ventilation is routinely adopted during the thoracic phase of the operation and this is associated with a considerable risk of pulmonary complications in the early postoperative period (5). The emergence of neoadjuvant chemotherapy and chemoradiotherapy as part of the standard treatment pathway is another factor reported to increase the risk of postoperative morbidity and, in addition, diminish a patients' fitness and ability to withstand complications (6).

Given the associated morbidity of multimodal therapy in this patient cohort, there would be significant value in predictive tools that can identify high-risk surgical patients. Accurate risk stratification allows preoperative optimisation, targeted allocation of healthcare resources, and aids the process of shared decision-making for patient and surgeon (7, 8). Various prognostic scoring systems have been adopted to determine potential complications after major surgery, but most of these tools are based on a subjective assessment of comorbidities and functional status, with inadequate discriminative ability (9).

Cardiopulmonary exercise testing (CPET) delivers a comprehensive evaluation of aerobic fitness through measuring cardiopulmonary function under the stress of exercise; simulating the physiological demands of major surgery (7, 10). Typically performed on a cycle ergometer, the test involves an incremental increase of workload to achieve maximal exertion. Gas exchange is measured using a sealed face-mask allowing estimation of oxygen uptake during maximal intensity exercise ($\dot{V}O_2$peak/max) and anaerobic threshold (AT), defined as the physiological point at which anaerobic metabolism exceeds aerobic metabolism (11). The successful implementation of CPET into clinical practice in the United Kingdom is evident from its rapid expansion over the last decade, with now approximately 30,000 tests being conducted annually in surgical patients (12). Several systematic reviews have reported the efficacy of preoperative CPET in risk stratification for predicting adverse postoperative outcomes across multiple surgical disciplines (13-18). Our own recent metanalysis, investigating the prognostic value of CPET in oesophagectomy patients, found it to be a useful predictor of adverse postoperative events (19). Both CPET-derived variables, $\dot{V}O_2$peak and AT, demonstrated a moderate inverse correlation with unplanned intensive care unit (ICU) admissions and mortality at 12 months, whereas $\dot{V}O_2$peak alone moderately inversely correlated with cardiopulmonary complications. A major limitation in the application of CPET is that clinically useful predictive threshold values for $\dot{V}O_2$peak and AT could not be estimated, warranting this research to help guide the management of patients undergoing oesophagectomy.

The aim of this study, by pooling patient level data, was to derive optimal cut-off points for AT and $\dot{V}O_2$peak in patients undergoing oesophagectomy that are predictive of postoperative complications, unplanned ICU readmissions, and mortality.

METHODS

Study Design: This study is a pooled analysis of individual patient data derived from articles identified in a recently published meta-analysis (19).

Study Selection: The review of the literature was conducted as previously described (19). Articles were identified which were published prior to October 2019, with outcomes relevant to the association between preoperative CPET variables, AT and $\dot{V}O_2$peak, and postoperative outcomes following oesophagectomy. CINAHL, Cochrane Library, EMBASE, MEDLINE, PubMed and Scopus databases were investigated for the following key search terms: “Cardiopulmonary exercise testing”, “CPEX”, “CPET”, “Anaerobic threshold”, “$\dot{V}O_2$peak”, “Esophagectomy” and “Oesophagectomy”, including a manual search of references of relevant published articles. Two authors were involved in the screening and selection of articles. Inclusion criteria was the availability of raw data of subjects undergoing CPET prior to an oesophagectomy, with the measurement of postoperative outcomes of interest. Critical appraisal was assessed by two authors based on the Quality in Prognosis Studies (QUIPS) tool (20).

Data Extraction: Seven eligible studies were identified from the meta-analysis, and authors were contacted to obtain an original data set to facilitate a pooled analysis. Individual patient-level data extraction was conducted by the lead investigator. Recorded parameters included study design, patient characteristics, method of CPET, type of surgery, AT, $\dot{V}O_2$peak, as well as the presence or absence of any outcomes of interest – cardiopulmonary complications, non-cardiopulmonary complications, unplanned ICU readmissions as well as mortality at 30 days, 90 days, and 12 months postoperatively. Data was cross-checked against the corresponding publication. Approval was previously obtained from the associated research ethics committee as part of each study’s original research, and anonymised data was obtained to perform this analysis, in line with the recommendation of the General Data Protection Regulation.

Statistical Analysis: Receiver operating characteristic (ROC) curves estimated a threshold for AT and $\dot{V}O_2$peak for each individual outcome of interest. Logistic regression models were fitted with each outcome of interest for AT and $\dot{V}O_2$peak to create a ROC curve. Threshold measures were determined based on the optimal sensitivity and specificity pair for the model using the Youden index (*J*). Patients were analysed together as a combined cohort, and then further analysed in subgroups depending on whether CPET was performed at diagnosis prior to undergoing any treatment, or whether CPET was performed immediately prior to surgery corresponding with a post-neoadjuvant treatment assessment. To account for the effects of intragroup correlation models were fitted with a variance-covariance matrix accounting for clustering by study. Data are presented as mean values and standard deviation, unless otherwise stated. To account for the effects of intragroup correlation, models were fitted with a variance-covariance matrix accounting for clustering by study. All calculations were performed using Stata 15.1 (Stata Corporation, College Station, TX).

RESULTS

Description of Studies

Corresponding authors of five of the eligible seven studies were able to provide individual patient-level data (21-25). All five papers reported on the CPET variables AT and $\dot{V}O_2$peak, and their role as a risk assessment tool in patients undergoing oesophagectomy. Two of the articles were prospective observational cohort studies (24, 25), and three were retrospective cohort studies (21-23). CPET was performed with a stationary cycle ergometer in all studies and involved a graded exercise protocol until the patient's maximum tolerated level was reached. The value for AT was determined using the V-slope method in four studies (21-24), while one study adopted a combination of the V-slope method, ventilatory equivalents and end-tidal graphs to determine its placement (25). One study defined $\dot{V}O_2$peak as the average value recorded in the final 30 seconds of the test (22); three studies defined $\dot{V}O_2$peak as the maximum value during the total exercise process (23-25); and one study did not specifically detail how this value was attained (21). All studies reported AT and $\dot{V}O_2$peak in standard units of mL/kg/min. CPET was undertaken preoperatively in all studies; three of them performed the test prior to commencing neoadjuvant therapy (21, 23, 24) and two studies performed the test after the completion of neoadjuvant therapy (22, 25). All studies reported attempting CPET as a routine risk assessment in every patient, rather than being used a selective tool for patients with high or uncertain surgical risk. The analysis presented is this article is based on data from those that underwent surgery, excluding patients who were deemed unfit for an oesophagectomy. The five studies used a variety of classifications for defining complications, including the Common Terminology Criteria for Adverse Events (21, 23), Clavien-Dindo classification (22), and Accordion score (24). Based on the QUIPS assessment, all studies were determined to be of good quality as reported in the previously cited meta-analysis (19).

Patient Characteristics

The present analysis was performed on 621 patients who underwent CPET prior to oesophagectomy during the period of January 2004 to March 2017, with study characteristics demonstrated in *Table 1*. *Table 2* presents the available data for all studies, including the incidence for relevant outcomes of interest: cardiopulmonary complications (43.4%), non-cardiopulmonary complications (33.3%), unplanned ICU readmissions (12.8%), 30-day mortality (1.5%), 90-day mortality (3.3%), and 12-month mortality (18.1%). The mean CPET-derived variable for these outcomes with respect to each study as well as for the combined cohort are depicted in *Table 3*.

Predictive Value of Preoperative CPET Values

ROC curve analyses are demonstrated in *Table 4*, with the AUC and the cut-off threshold determined by the Youden index, the value at which the sensitivity and specificity trade-off are optimised. There were too few events in the 30-day mortality group to facilitate a ROC curve analysis with respect to this outcome. None of the ROC curves achieved an AUC higher than 0.66, indicating poor discrimination for both AT and $\dot{V}O_2$peak to discriminate patients experiencing any of the four outcomes of interest. Similarly, the Youden index was 0.40 or lower for all ROC curves indicating poor diagnostic performance.

Both AT and $\dot{V}O_2$peak were best at discriminating for patients with 90-day mortality, corresponding to a Youden index of 0.31 and 040, respectively. AT demonstrated an AUC of 0.65, with an optimal cut-off value of 11.1 mL/kg/min. This had a sensitivity of 56.3% and specificity of 75.1%. The AUC value for $\dot{V}O_2$peak was 0.66, with a determined cut-off of 16.3 mL/kg/min. The corresponding sensitivity and specificity of this threshold for predicting 90-day mortality was 58.8% and 81.3%, respectively. The ROC curves for both AT and $\dot{V}O_2$peak for each outcome of interest are presented in *Figure 1*. The accompanying boxplot charts in *Figure 2* estimates that this threshold is not ideal for discriminating between patients who did and did not develop any of the outcomes of interest.

Predictive Value of CPET Depending on Timing of Test

An additional analysis was performed to compare the predictive value of CPET when accounting for the timing of this test around treatment for oesophageal cancer. *Table 5* presents ROC curve analyses for patients that underwent CPET at diagnosis prior to neoadjuvant treatment (n=415), and those that underwent the test immediately prior to surgery (n=247). Unplanned ICU readmissions were excluded from the latter group as this outcome was not measured in any of the patients within this group. 30-day mortality and 90-day mortality were excluded from this analysis as there was insufficient events available in each subgroup with respect to this outcome.

Results were similar to those found for the entire dataset with slightly better discrimination to determine cardiopulmonary complications in the group measured at diagnosis. AT was best at discriminating these complications at diagnosis, corresponding to a Youden index of 0.22. The optimal cut-off value of AT for this outcome was 13.0 mL/kg/min (sensitivity 53.8%; specificity 67.8%). This analysis still demonstrated an unfavourable AUC of 0.63. $\dot{V}O_2$peak demonstrated a low predictive value for cardiopulmonary complication, with an AUC of 0.58. The Youden index was 0.15 and the corresponding optimal cut-off value for $\dot{V}O_2$peak was 17.9 mL/kg/min (sensitivity 61.4%, specificity 56.4%).

DISCUSSION

This collaborative patient-level data analysis aimed to evaluate CPET as a prognostic tool by estimating appropriate clinical thresholds to identify high-risk patients undergoing oesophagectomy. However, while the findings of our earlier metanalysis found CPET variables correlate moderately with adverse postoperative outcomes (19), the present analysis found no evidence to support the use of a single cut-off value for either $\dot{V}O_2$peak or AT.

CPET is a dynamic integrated test of cardiovascular and respiratory mechanisms that evaluates the patient’s capacity to tolerate the additional metabolic demands and increased oxygen requirements of major oesophageal cancer surgery (26). An AT ≥ 11 mL/kg/min was initially proposed by Older et al. as a discriminator for low risk of cardiovascular death after major abdominal and thoracic surgery (27, 28). Mancini et al. reported a $\dot{V}O_2$peak > 14 mL/kg/min as an indicator that heart failure patients may be safely deferred from cardiac transplantation with a minimal risk of 12-month mortality (29). These historical thresholds have since been implemented to identify high-risk patients across a range of surgical disciplines, including oesophageal surgery. The need for these cut-off values to be re-defined is highlighted by the fact that they were developed from data that is almost forty years old and are not standardised to an oesophagectomy-specific cohort, an important consideration given that the variation of physiological stress provoked is likely to be procedure-dependent (30).

The inability of this analyses to identify optimal CPET cut-off values to assess risk is consistent with earlier research from Moyes et al. and Patel et al. who also found discriminatory ability to be poor in patients undergoing oesophagectomy (23, 31). Moyes et al. postulated that an AT of 9.0 mL/kg/min was a more reliable prognosticator of cardiopulmonary complications (AUC 0.60), with a sensitivity of 74% and specificity of 57% (23). Patel et al determined optimal cut-off points for predicting major morbidity were a $\dot{V}O_2$peak of 17.0 mL/kg/min (AUC 0.66; sensitivity 70%, specificity 53%), and an AT of 10.5 mL/kg/min (AUC.62; sensitivity 60%, specificity of 44%) (31). Given the potential consequences of such a high rate of false-positives and false-negatives, these risk thresholds require further refinement. The suboptimal findings thus far demonstrated in the oesophageal cancer cohorts are in contrast to the previous ROC curve analyses from single-centre studies in which optimal risk thresholds for major procedures were reliably determined for hepatopancreatobiliary surgery (32), colon surgery (33), and rectal surgery (34).

The complex interactions between cardiopulmonary reserve and the physiological demand of surgical stress may partially reconcile the lack of significance from this analysis (33). In addition to CPET-derived variables, a multitude of other factors such as patient demographics, comorbidities, the use of neoadjuvant systemic therapy and intraoperative technical factors are all likely to play significant roles in the incidence of morbidity and mortality (35). This is one of the main factors limiting the accuracy of risk stratification with defined cut-off values. Another criticism of the real-world practice of CPET is the binary approach toward risk assessment (36, 37). Some clinicians have subsequently advocated in favour of adopting a dynamic range of values as a superior method to distinguishing the various stages of surgical risk (37). Looking beyond a single cut-point to encapsulate fitness is also supported by the concept of *critical difference*. This describes the natural biological variation of cardiopulmonary fitness measured around a true homeostatic point at any given moment in time (38, 39). Rose et al. formulated a revised stratification model whereby patients were labelled as indeterminate-fitness, based on the relationship between the critical difference zone and cut-off value for each respective CPET variable (37). Future research endeavours warrant validating this coefficient of variation for each CPET-derived parameter to ensure reliable and reproducible CPET measurements.

While neoadjuvant therapy in patients with resectable oesophageal cancer is the standard of care (40), the associated decline in functional capacity must also be accounted for with CPET (41). Three prior studies have quantified a 9.1-17.3% reduction in AT (mean difference 1.9-2.4 mL/kg/min) and a 12.0-16.3% reduction in $\dot{V}O_2$peak following neoadjuvant chemotherapy specific for oesophageal cancer (42-44). Despite a four-week convalescence period between the completion of systemic treatment and undergoing surgery, this reduction has not been shown to spontaneously improve which may have significant implications on postoperative morbidity (45). This explains the rationale for preoperative exercise interventions to improve fitness and postoperative outcomes in the setting of high-risk surgeries (46-48). Another important consideration in this domain is the lack of standardisation around whether CPET measurements should be undertaken before or after neoadjuvant chemotherapy. The present analysis features three studies that performed CPET prior to neoadjuvant treatment and two studies that performed the test after neoadjuvant treatment. This is a notable drawback to this study, and a major confounder contributing to the lack of significance in this data. While undertaking CPET in patients immediately prior to surgery may provide the most accurate assessment of pre-operative fitness, it is important to consider that this will also result in less time to intervene and optimise patients.

As previously stated, the poor sensitivity and specificity from the present oesophagectomy data conflicts with the evidence from other high-risk procedures. This may be due to the proximity of the operating field to the mediastinum, as this has capacity to directly impact the cardiopulmonary system. Certain pulmonary complications may occur secondarily due to the distinct nature of this surgery causing thoracic insult, both from local and technical factors, and are not able to be predicted with CPET (4). Two key risk factors for the development of pulmonary complications include the degree of mediastinal dissection and the technique of an open or minimally invasive approach (49, 50). Although these factors would subsequently limit the value of CPET for predicting adverse events, it may be better served to evaluate patients’ resilience to respond to the physiological insult of complications. Prospective studies should subsequently focus on studying the relationship between CPET and these secondary outcomes such as the incidence of unplanned critical care readmissions, duration of inotropic support, length of stay, and incidence of mortality.

While CPET procedures are standardised (26), there are clinically influential confounding factors between each institution that may have caused inconsistencies between the six studies included in this pooled analysis, and therein contribute to the inability to achieve a definitive threshold. These limitations include the differences in classification of postoperative outcomes, presence or absence of blinding clinicians to CPET data, the specific timing of CPET with respect to surgery as previously described, equipment calibration errors, method of detection of CPET-derived variables, inter-observer reliability with laboratory staff, and surgical technique. As addressed in the associated meta-analysis, there was substantial heterogeneity between contributing centres, a potential reflection of differences in demographics, comorbidities and operative approaches (19). Various other patient-related factors are also thought to influence CPET results, particularly age, gender, body habitus, musculoskeletal disabilities, and physical deconditioning (51, 52). There is also recent evidence to suggest that presence of sarcopaenia and myosteatosis, which are associated with oesophageal cancer (53, 54), may affect cardiopulmonary reserve and subsequently compromise CPET performance (55). It is also important to note that the patients included in this study are those that were deemed fit to undergo curative surgical treatment, which carries a degree of selection bias given the selective sampling. This selection bias is further compounded by the notion that most of this analysis is based on retrospective studies. These confounders are all likely to be controlled from the development of multicentre prospective studies with standardised measurement protocols for undertaking CPET. Another deficiency of this research is that only two CPET parameters were evaluated. There is emerging evidence regarding the prognostic significance of ventilatory efficiency and oxygen uptake efficiency slope (30), however this is beyond the scope of this article.

To overcome the confounding influences of this study, a composite model comprising of CPET parameters with other physiologically important clinical factors may improve the predictive ability of the test (56-58). Given the evidence that gender and height play independent roles in establishing V̇O2peak results (59, 60), ongoing research in this field should involve undertaking a subgroup analysis to discriminate between patients based on these variables. It is still important to acknowledge that a true assessment of fitness is unlikely to be determined by a single metric on CPET alone. This tool should rather be viewed as an adjunct to a thorough medical evaluation. A collaborative model of care led by experienced clinicians that incorporates CPET results is the most appropriate approach to individualising patient's risk. A multidisciplinary team meeting centred around this would ensure a consensus is reached regarding the patient's risk, facilitate communication between treating specialists on this matter, and provide a forum from which pre-operative optimisation strategies may be discussed. The next phase of this research is determining the optimal type and delivery of prehabilitation programs, although there is some evidence favouring aerobic, resistance and inspiratory muscle training (61).

CONCLUSION

This study found insufficient evidence to support the use of a CPET-based single-measure risk stratification system in clinical practice for patients undergoing oesophagectomy. Developing a robust risk prediction tool for oesophageal cancer patients requires further research exploring the accuracy of CPET variables when accounting for other physiological factors as well as the toxicity of neoadjuvant oncological treatments. These tools are not predictive of operative risk or complications, but can be adopted as a clinically useful tool to assist in complex multidisciplinary decision making.

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APPENDIX

Table 1: Study characteristics.

	Forshaw (2008)	**Moyes (2013)**	**Sinclair (2017)**	**Whibley (2018)**	**Lam (2019)**
Sample size	78	64	273	41	206
Study type	Retrospective	Retrospective	Prospective	Prospective	Retrospective
Location	London, UK	Glasgow, UK	Newcastle, UK	London, UK	Norwich, UK
Timing of preoperative CPET	At time of diagnosis	At time of diagnosis	At time of diagnosis	Immediately prior to surgery	Immediately prior to surgery
CPET variables assessed	$\dot{V}O_2$peak, AT	$\dot{V}O_2$peak, AT	$\dot{V}O_2$peak, AT, $\dot{V}E/\dot{V}CO_2$	$\dot{V}O_2$peak, AT	$\dot{V}O_2$peak, AT

Table 2: Descriptive statistics for the six studies and the combined data.

	Forshaw (2008)	**Moyes (2013)**	**Sinclair (2017)**	**Whibley (2018)**	**Lam (2019)**	**Combined (n = 662)**	**CPET at diagnosis (n = 415)**	**CPET prior to surgery (n = 247)**
Sex *n(%)*								
Male	64 (82.1)	52 (81.3)	202 (74.0)	-	159 (77.2)	466 (76.8)	318 (76.6)	159 (77.2)
Age *mean (SD)*	64.7 (8.7)	63.2 (8.4)	65.1 (9.3)	60.4 (8.7)	67.1 (9.0)	65.2 (9.1)	64.7 (9.0)	66.0 (9.2)
BMI *mean (SD)*	26.4 (5.0)	27.3 (4.8)	26.7 (5.1)	-	27.3 (5.3)	26.9 (5.0)	26.7 (5.0)	27.4 (4.9)
AT *mean (SD)*	13.9 (2.9)	10.9 (3.2)	14.9 (4.3)	11.7 (2.1)	12.4 (2.8)*	13.3 (3.8)	14.0 (4.2)	12.3 (2.7)
$\dot{V}O_2$Peak *mean (SD)*	20.5 (5.0)	16.3 (5.7)	19.4 (5.1)	18.2 (3.1)	21.2 (4.4)	19.7 (5.0)	19.1 (5.3)	20.7 (4.4)
Cardiopulmonary complications *n(%)*	33 (42.3)	36 (56.3)	109 (39.9)	30 (73.2)	80 (38.8)	288 (43.5)	178 (42.9)	110 (44.5)
Non-cardiopulmonary complications *n(%)*	19 (24.4)	-	109 (39.9)	12 (29.3)	59 (28.6)	199 (33.3)	128 (36.5)	71 (28.7)
Unplanned ICU readmissions *n(%)*	13 (16.7)	-	32 (11.7)	-	-	45 (12.8)	45 (12.8)	-
Mortality *n(%)*								
30 Day	-	-	4 (1.5)	1 (2.4)	0 (0.0)	5 (1.0)	4 (1.5)	1 (0.4)
90 Day	-	-	9 (3.3)	2 (4.9)	6 (2.9)	17 (3.3)	9 (3.3)	8 (3.2)
12 Months	-	-	57 (20.9)	8 (19.5)	29 (14.1)	94 (18.1)	57 (20.9)	37 (15.0)

**AT is only available for n=201 patients in the study by Lam et al.*

Table 3: Mean and standard deviation for AT and $\dot{V}O_2$peak by outcome status for each study and the combined cohort.

	<u>Cardiopulmonary Complications</u>			
	Yes		**No**	
	AT	**$\dot{V}O_2$Peak**	**AT**	**$\dot{V}0_2$Peak**
Forshaw	13.2 (3.1)	19.1 (5.1)	14.4 (2.6)	21.4 (4.8)
Moyes	10.9 (2.9)	16.4 (5.7)	10.8 (3.5)	16.0 (5.7)
Sinclair	13.8 (3.9)	18.0 (4.6)	15.6 (4.5)	20.3 (5.1)
Whibley	11.4 (2.1)	17.6 (3.1)	12.6 (1.8)	20.0 (2.6)
Lam	12.6 (2.9)	21.8 (5.0)	12.2 (2.8)	20.8 (10.1)
Combined	12.7 (3.4)	19.0 (5.2)	13.8 (4.0)	20.3 (4.8)
	<u>Non-Cardiopulmonary Complications</u>			
	Yes		**No**	
	AT	**$\dot{V}O_2$Peak**	**AT**	**$\dot{V}0_2$Peak**
Forshaw	14.1 (3.0)	20.7 (4.3)	13.9 (2.9)	20.4 (5.2)
Sinclair	15.0 (5.0)	19.6 (5.7)	14.9 (3.9)	19.3 (4.6)
Whibley	12.4 (1.7)	19.2 (2.7)	11.4 (2.1)	17.7 (3.2)
Lam	12.6 (3.1)	21.2 (4.4)	12.3 (2.7)	21.2 (4.4)
Combined	14.0 (4.2)	20.2 (5.1)	13.5 (3.4)	20.1 (4.7)
	<u>Unplanned ICU Readmissions</u>			
	Yes		**No**	
	AT	**$\dot{V}O_2$Peak**	**AT**	**$\dot{V}0_2$Peak**
Forshaw	12.6 (3.2)	18.9 (5.1)	14.2 (2.8)	20.8 (5.0)
Sinclair	13.9 (3.5)	18.4 (4.8)	15.1 (4.4)	19.6 (5.1)
Combined	13.5 (3.4)	18.6 (4.9)	14.9 (4.1)	19.9 (5.1)
	<u>30-Day Mortality</u>			
	Yes		**No**	
	AT	**$\dot{V}O_2$Peak**	**AT**	**$\dot{V}0_2$Peak**
Sinclair	13.8 (2.3)	17.4 (3.6)	14.9 (4.4)	19.5 (5.1)
Whibley	11	14.2	11.8 (2.1)	18.3 (3.1)
Lam	-	-	12.4 (2.8)	21.3 (4.4)
Combined	13.1 (2.3)	16.8 (3.4)	13.6 (3.9)	20.1 (4.8)
	<u>90-Day Mortality</u>			
	Yes		**No**	
	AT	**$\dot{V}O$Peak**	**AT**	**$\dot{V}0_2$Peak**
Sinclair	13.1 (4.0)	16.5 (4.6)	15.0 (4.3)	19.5 (5.0)
Whibley	10.6 (0.6)	15.0 (1.1)	11.8 (2.1)	18.4 (3.1)
Lam	10.9 (2.2)	19.9 (5.5)	12.4 (2.8)	21.2 (4.4)
Combined	11.9 (3.2)	17.5 (4.9)	13.6 (3.8)	20.2 (4.7
	<u>12-Month Mortality</u>			
	Yes		**No**	
	AT	**$\dot{V}O_2$Peak**	**AT**	**$\dot{V}0_2$Peak**
Sinclair	14.5 (3.9)	18.4 (4.7)	15.0 (4.5)	19.7 (5.1)
Whibley	11.5 (1.8)	18.5 (4.5)	11.8 (2.1)	18.1 (2.7)
Lam	12.3 (2.5)	21.0 (3.9)	12.4 (2.9)	21.0 (3.9)
Combined	13.5 (3.5)	19.3 (4.6)	13.6 (3.9)	20.3 (4.8)

Table 4: ROC curve analysis for each outcome of interest by CPET predictor.

Outcome	Predictor	AUC (95% CI)	Cut-off value	Sensitivity (%)	Specificity (%)	Youden index
Cardiopulmonary complications	AT	0.55 (0.51, 0.60)	13.1	61.2	53.3	0.15
	$\dot{V}O_2$Peak	0.57 (0.53, 0.61)	17.9	47.4	68.0	0.15
Non-cardiopulmonary complications	AT	0.50 (0.46, 0.55)	10.7	83.7	23.8	0.08
	$\dot{V}O_2$Peak	0.53 (0.48, 0.57)	15.4	86.5	16.5	0.03
Unplanned ICU readmission	AT	0.58 (0.51, 0.65)	13.3	52.4	62.3	0.15
	$\dot{V}O_2$Peak	0.60 (0.52, 0.67)	17.2	45.2	68.5	0.14
90-day mortality	AT	0.65 (0.50, 0.80)	11.1	56.3	75.1	0.31
	$\dot{V}O_2$Peak	0.66 (0.51, 0.82)	16.3	58.8	81.3	0.40
12-month mortality	AT	0.53 (0.46, 0.59)	10.7	26.7	80.2	0.07
	$\dot{V}O_2$Peak	0.56 (0.49, 0.62)	15.8	27.1	84.5	0.12

AUC = Area under the curve; PPV = Positive predictive value; NPV = Negative predictive value

Table 5: ROC curve analysis for each outcome of interest by CPET predictor, by timing of CPET.

CPET at diagnosis						
Outcome	**Predictor**	**AUC (95% CI)**	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**	**Youden index**
Cardio complications	AT	0.63 (0.57, 0.68)	13.0	53.8	67.8	0.22
	$\dot{V}O_2$Peak	0.62 (0.56, 0.67)	18.8	61.6	56.4	0.18
Non-cardio complications	AT	0.49 (0.42, 0.56)	20.3	11.5	95.4	0.07
	$\dot{V}O_2$Peak	0.49 (0.43, 0.56)	25.1	17.5	86.8	0.04
ICU re-admission	AT	0.58 (0.49, 0.67)	13.3	52.4	62.3	0.15
	$\dot{V}O_2$Peak	0.56 (0.47, 0.65)	17.2	45.2	68.5	0.14
12-month mortality	AT	0.53 (0.44, 0.62)	15.5	74.5	37.0	0.11
	$\dot{V}O_2$Peak	0.58 (0.49, 0.67)	16.0	35.8	80.2	0.16
CPET prior to surgery						
Outcome	**Predictor**	**AUC (95% CI)**	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**	**Youden index**
Cardio complications	AT	0.50 (0.43, 0.58)	12.3	49.1	55.7	0.05
	$\dot{V}O_2$Peak	0.48 (0.41, 0.56)	23.0	35.2	74.8	0.10
Non-cardio complications	AT	0.55 (0.47, 0.63)	10.7	78.9	35.7	0.15
	$\dot{V}O_2$Peak	0.51 (0.43, 0.59)	16.6	90.1	21.5	0.12
12-month mortality	AT	0.51 (0.40, 0.62)	10.9	45.7	70.0	0.15
	$\dot{V}O_2$Peak	0.50 (0.40, 0.61)	17.0	29.7	80.0	0.10

Figure 1: ROC curves of CPET variables by outcomes of interest.

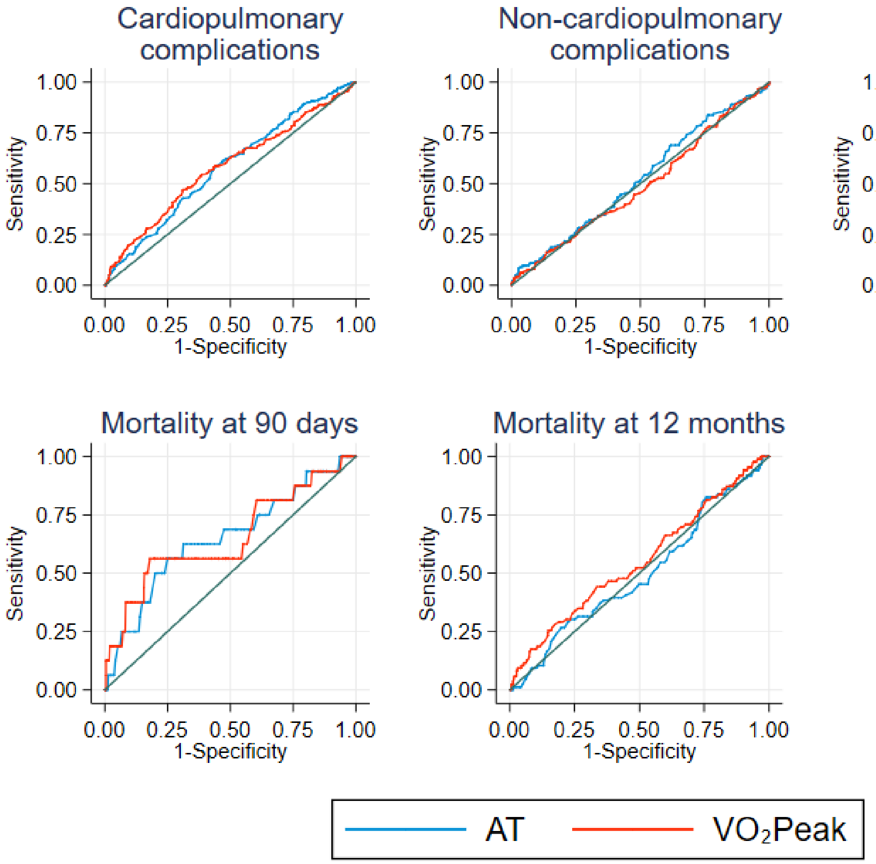
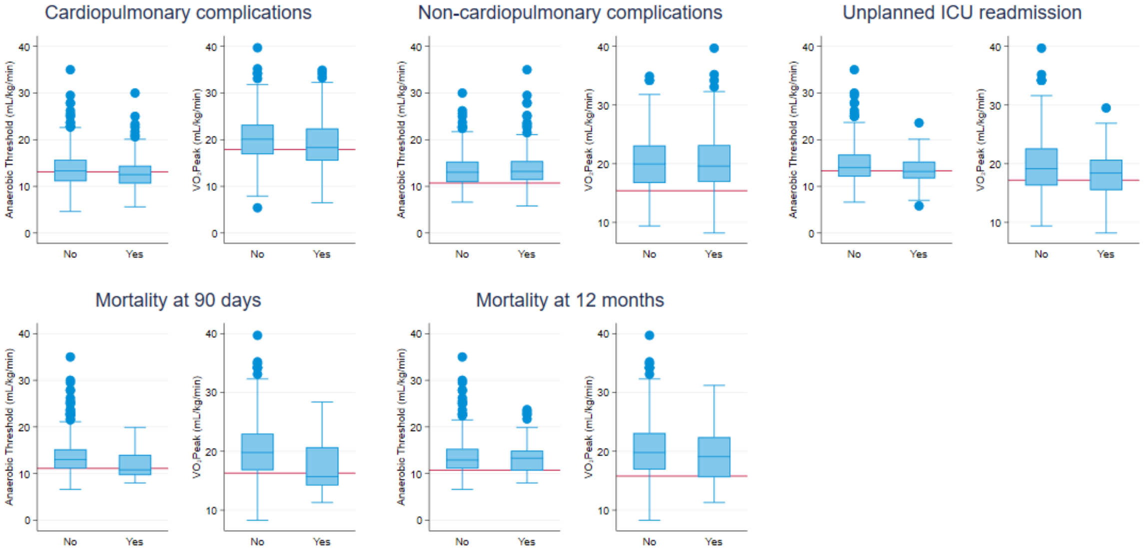


Figure 2: Boxplots for CPET variables by outcomes of interest.



Boxplot charts showing distribution of AT and V̇O2peak with respect to each outcome. The red line indicates the threshold value determined from ROC curve analysis.