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# Clinical covariates that improve surgical risk prediction and guide targeted prehabilitation: an exploratory, retrospective cohort study of major colorectal cancer surgery patients evaluated with preoperative cardiopulmonary exercise testing

Vladimir Bolshinsky<sup>1,2\*</sup>, Hilmy Ismail<sup>3</sup>, Michael Li<sup>3</sup>, Jarrod Basto<sup>3</sup>, Robert Schier<sup>4</sup>, Anna Hagemeyer<sup>4</sup>, Kwok-Ming Ho<sup>5</sup>, Alexander Heriot<sup>3</sup> and Bernhard Riedel<sup>3</sup>

## Abstract

**Background:** Preoperative risk stratification is used to derive an optimal treatment plan for patients requiring cancer surgery. Patients with reversible risk factors are candidates for prehabilitation programmes. This pilot study explores the impact of preoperative covariates of comorbid disease (Charlson Co-morbidity Index), preoperative serum biomarkers, and traditional cardiopulmonary exercise testing (CPET)-derived parameters of functional capacity on postoperative outcomes after major colorectal cancer surgery.

**Methods:** Consecutive patients who underwent CPET prior to colorectal cancer surgery over a 2-year period were identified and a minimum of 2-year postoperative follow-up was performed. Postoperative assessment included: Clavien-Dindo complication score, Comprehensive Complication Index, Days at Home within 90 days (DAH-90) after surgery, and overall survival.

**Results:** The Charlson Co-morbidity Index did not discriminate postoperative complications, or overall survival. In contrast, low preoperative haemoglobin, low albumin, or high neutrophil count were associated with postoperative complications and reduced overall survival. CPET-derived parameters predictive of postoperative complications, DAH-90, and reduced overall survival included measures of VCO<sub>2</sub> kinetics at anaerobic threshold (AT), peakVO<sub>2</sub> (corrected to body surface area), and VO<sub>2</sub> kinetics during the post-exercise recovery phase. Inflammatory parameters and CO<sub>2</sub> kinetics added significant predictive value to peakVO<sub>2</sub> within bi-variable models for postoperative complications and overall survival ( $P < 0.0001$ ).

\* Correspondence: [bolshinsky@gmail.com](mailto:bolshinsky@gmail.com)

<sup>1</sup>General Surgery, Peninsula Health, Frankston, VIC, Australia

<sup>2</sup>Surgical Health Specialists, Frankston, VIC, Australia

Full list of author information is available at the end of the article



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**Conclusion:** Consideration of modifiable ‘triple low’ preoperative risk (anaemia, malnutrition, deconditioning) factors and inflammation will improve surgical risk prediction and guide prehabilitation. Gas exchange parameters that focus on  $VCO_2$  kinetics at AT and correcting peak $VO_2$  to body surface area (rather than absolute weight) may improve CPET-derived preoperative risk assessment.

**Keywords:** Prehabilitation, CPET, Cardiopulmonary exercise testing, Functional capacity, Colorectal cancer surgery

## Introduction

Technical advances in surgery and anaesthesia have led to colorectal cancer surgery being performed on increasingly older patients, often with extensive comorbid disease (Findlay et al., 2011). For the growing numbers of high-risk patients for whom surgery still forms the cornerstone of cancer treatment appropriate preoperative risk stratification is essential to enable clinicians and patients to formulate a shared treatment plan.

Decreased functional capacity (caused by factors such as lifestyle choice, ageing, cancer biology, and neoadjuvant chemo-radiotherapy) increases postoperative morbidity and mortality (Silver & Baima, 2013; West et al., 2014). Functional capacity is a modifiable risk factor: a Delphi survey of anaesthetists and consumers identified preoperative fitness training as a top-ten research priority in anaesthesia (Bainbridge et al., 2012; Boney et al., 2015). Most promising is that a number of recent studies report a substantial reduction in postoperative complications following targeted prehabilitation in patients with modifiable risk, including deconditioning (poor fitness levels), anaemia, and malnutrition (Bolshinsky et al., 2018). Even in elderly patients, published data demonstrated that in the limited window of optimization prior to major gastrointestinal cancer surgery, prehabilitation is feasible and that this translates into measurable benefits in pre and post-operative functional capacity and reduction in postoperative complications (Tsimopoulou et al., 2015; Jack et al., 2011; Barberan-Garcia et al., 2018; Howard et al., 2019).

Importantly, improved surgical risk prediction for postoperative morbidity and mortality will help identify patients that would benefit most from prehabilitation, but also guide informed decision-making in those patients at highest risk. Risk prediction can be aided by a thorough understanding of patients’ burden of comorbid disease (e.g. Charlson Co-morbidity Index or the American College of Surgeons National Surgical Quality Improvement Program [NSQIP] Surgical Risk Calculator (Bilimoria et al., 2013; Chang et al., 2016), preoperative blood tests (to identify modifiable risk factors such as anaemia, malnutrition, and inflammation) (Vardy et al., 2018; Chen et al., 2017; Edwards et al., 2011), and through assessment of functional capacity.

Functional capacity can be quantified using a static survey, e.g. Duke Activity Status Index (DASI), dynamic

field walk tests, or the gold standard of cardiopulmonary exercise testing (CPET) (Moonesinghe et al., 2013). CPET is attractive in that in addition to objective assessment of preoperative functional capacity, it also provides diagnostic insight into the underlying cause of exercise limitation, and assists with exercise prescription.

Over the past two decades, CPET-derived gas exchange parameters have been increasingly studied for preoperative risk stratification, albeit in isolation and often with limited consideration of other preoperative parameters (Hightower et al., 2010). These perioperative CPET studies have generally focused on the kinetics of oxygen consumption ( $VO_2$ ) during the active cycling phase of CPET—namely  $VO_2$  at anaerobic threshold (AT),  $VO_2$  at peak exercise (p $VO_2$ ), and typically dichotomised  $VO_2$  (ml/kg/min) at AT and at peak exercise to predict postoperative morbidity and mortality (Wijeyesundera et al., 2018). Few studies have explored the kinetics of carbon dioxide elimination ( $VCO_2$ ) during the active cycling phase ( $CO_2$  elimination relative to minute ventilation [ $Ve/VCO_2$ ] at AT or end-tidal  $CO_2$  [ $P_{ET}CO_2$ ] at AT) (Moran et al., 2016; Levett & Grocott, 2015), the kinetics of heart rate related to the exercise (Hightower et al., 2010) and gas exchange parameters during the recovery phases of CPET ( $VO_{2R}$ ,  $VCO_{2R}$ ) in relation to postoperative outcomes (Ackland et al., 2019).

This retrospective cohort study set out to further explore the predictive value of the following: (1) preoperative covariates of patient burden of comorbid disease (Charlson Comorbidity Index) and/or preoperative serum biomarkers, and CPET-derived parameters of functional capacity; and (2) exploratory parameters of the recovery phase (after peak exercise) CPET-derived parameters on postoperative outcomes after major colorectal cancer surgery.

## Materials and methods

### Patients

This retrospective cohort study was approved by the institutional review board at the Peter MacCallum Cancer Centre (#16/19R). Consecutive patients who had undergone CPET prior to colorectal cancer surgery over a 2-year period (September 2013–August 2015) were identified within a prospectively maintained hospital database. Surgery type included segmental colorectal resection, proctocolectomy, abdominoperineal resection, pelvic exenteration, and cytoreduction surgery with hyperthermic

intraperitoneal chemotherapy (HIPEC). Patients received standard perioperative care that included enhanced recovery after surgery (ERAS) pathways. The postoperative destination (intensive care, high dependency unit, or regular nursing floor) was determined by the clinical team at the conclusion of surgery for each case.

### Risk stratification

Preoperative risk assessment was estimated by routine clinical examination in the pre-anaesthesia clinic, with routine preoperative blood tests performed (full blood evaluation, urea, creatinine, and electrolytes) as clinically indicated, the Charlson Co-morbidity Index, and CPET derived heart rate and gas-exchange variables. A modified Glasgow Prognostic Score was created by substituting neutrophil count for C-reactive protein (which was not routinely measured), and 1 point was assigned for each neutrophil count  $> 7.5 \times 10^9$  cells/l or albumin levels  $< 35$  g/l. Zero points were assigned if both parameters were normal and 2 points assigned if both parameters were abnormal. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were calculated as a marker of inflammation using the results obtained from the full blood evaluation panel (R Z, 2021).

CPET was performed as per the Perioperative Exercise Testing and Training Society (POETTS) practice guidelines (Levett et al., 2018) within four weeks of patients' scheduled elective surgery. Patients participating in the study were instructed not to eat or drink within 2 h of their scheduled CPET. The exercise test was conducted in five phases. Phase 1: Pulmonary function testing (sitting) to measure static lung function, including forced expiratory volume in 1 second and forced vital capacity. Phase 2: Resting phase—after applying the electrodes for a 12-lead ECG, arterial pressure cuff, pulse oximeter, and gas exchange collection mouth piece patients sat quietly for 3 min on the cycle ergometer for the collection of resting gas exchange derived data (CardiO2/CP System, Medical Graphics Corporation, USA). Phase 3: Unloaded cycling at 60–70 revolutions per minute (RPM) with no resistance for 3 min. Phase 4: Ramp protocol during which patients continue to cycle at 60–70 RPM with progressively increasing pedal resistance at a predetermined work rate (10–20 W/min) individualised to each patient's physical strength. The test was stopped either when the patient fatigued or at the investigator's discretion on the basis of signs or symptoms of cardiopulmonary distress. Phase 5: Recovery phase during which patients continue to pedal at 60–70 RPM with minimal resistance (20 W) for 5 min after peak exercise.

After CPET was completed, the test was analysed by anaesthesiologists accredited in CPET assessment (HI, BR), with independent crosschecking of the CPET data

to ensure accuracy. Traditional perioperative CPET-derived parameters that were analysed included  $\text{VO}_2$  at anaerobic threshold (AT; ml/kg/min) and  $\text{pVO}_2$  corrected to patient body weight (ml/kg/min). Peak  $\text{VO}_2$  data were also corrected to patient body surface area (ml/min/m<sup>2</sup>).  $\text{VO}_2$  at AT was determined according to the POETTS guidelines, using the three-point estimate of modified V-slope, ventilatory equivalents, and increasing end-tidal partial pressure of oxygen ( $\text{P}_{\text{ET}}\text{O}_2$ ) (Levett et al., 2018). Exploratory parameters that were analysed included  $\text{CO}_2$  exchange parameters ( $\text{P}_{\text{ET}}\text{CO}_2$ ,  $\text{Ve}/\text{VCO}_2$ —i.e. minute ventilation to  $\text{CO}_2$  production ratio, also known as ventilatory equivalents) at AT, heart (exercise and recovery phase) kinetics, and  $\text{VO}_2$  recovery in the first 5 min after achieving peak exercise.

### Patient characteristics and postoperative outcomes

Data was extracted from the medical records by three investigators (ML, JB, and VB) and cross-referenced. Extracted data included patient demographic, anthropometric factors, and postoperative complications. Postoperative complications were graded according to the Clavien-Dindo scoring system (Dindo et al., 2004). Using the established Clavien-Dindo scores, the sum of all postoperative complications was calculated using the Comprehensive Complication Index (CCI) to derive a score out of 100 (Slankamenac et al., 2013). A patient-centric measure, Days at Home within 90 days after surgery (DAH-90), was used to account for complications, mortality, and re-admission rates (Myles et al., 2016). This metric has been shown to be very sensitive to quality improvement initiatives (Wijeyesundera et al., 2018). Patients were followed up for a minimum of two years after their surgical procedure for overall survival analysis.

### Statistical analysis

Statistical methods consisted of standard reporting of descriptive baseline statistics and standard statistical regression methods using the base package of the R language for statistical computing (version 3.6.0) and add-on packages (survminer, ggplot2, gdata, graphics, grDevices, Hmisc, R2wd, rJava, utils, and xlsx). Some parameters were scaled as indicated in order to report their hazard ratios and the associated 95% confidence interval (95% CI) on a meaningful scale and were considered both in raw form and dichotomised at critical values where it was considered clinically meaningful to do so. Univariable Cox proportional hazards regression was performed for survival analysis, with survival curves compared by Log-Rank test and shown alongside number at risk ( $P < 0.05$  considered significant).

To explore improved risk prediction using multivariable models, bi-variable models were considered within

this data set due to the limited number of patients and the frequency of missing data. Due to the likelihood of high co-linearity within the various CPET-derived variables and inflammatory biomarkers, only models combining one CPET variable with one inflammatory marker were considered together. The best CPET factor (by univariable *P*-value) was combined with the single most predictive inflammatory marker, being the one which adds the most predictive value to the best CPET factor (again using *P*-value as the metric). This was undertaken for each of CCI, DAH-90, and overall survival as the independent variable. Due to the exploratory nature of this study adjustment for multiplicity was not used to correct for the large number of tests performed.

For the exploratory analysis of the recovery phase parameters, serial changes in HR (HRR, heart rate recovery),  $VO_2$ , and  $CO_2$  exchange parameters ( $P_{ET}CO_2$ ,  $V_e/VCO_2$ ) from the time point of peak exercise through to the 5-min recovery period were analysed by repeated measures ANOVA (to avoid multiple statistical comparisons). In the univariate analyses, cases with missing data required for the analyses concerned were excluded and in the repeated measures of 2-way ANOVA and comparisons of slopes, all cases were included and only the missing data points were not considered in the overall analysis. Area-under-the-receiver-operating-characteristic (AUROC) curve was used to assess the ability of the rate (or slope) of recovery of each CPET parameter to discriminate between patients with and without mortality.

## Results

The study cohort was representative of a complex colorectal surgical practice at a quaternary cancer centre. Eighty-four consecutive patients that underwent CPET prior to major colorectal cancer surgery during a 2-year period (August 2013 and September 2015) were identified and a minimum of 2-year postoperative follow-up for overall survival was performed in this cohort. Two patients required emergency surgical intervention prior to elective surgery at an external institution and consequently the number of patients available for overall survival analysis was 82 patients, with a greater male representation (55%). Baseline patient characteristics, surgical procedures, and postoperative complications are detailed in Table 1.

### Complexity of surgical disease

This cohort of patients had a high burden of comorbid disease (Charlson Co-morbidity Index; median [IQR] = 6 [3–6]). Preoperative metastatic disease was documented in 39% of patients undergoing surgical intervention. More than half of the patients underwent intervention for rectal cancer, with an aggressive surgical

**Table 1** Baseline demographic factors, surgical procedures, and postoperative outcomes

Variable	Count (%) / value
<b>Preoperative variables</b>	
• Age (years)	62 [56–70]
• Gender (M/F)	46 (55%)/38 (45%)
• Smoker (yes/no)	11 (13%)/73 (87%)
• Charlson Co-morbidity Index	6 [3–6]
• Evidence of metastatic disease at time of surgery	32 (39%)
<b>Surgical procedures</b>	
• Rectal cancer resection	42 (51%)
• Cytoreduction and HIPEC	23 (28%)
• Abdominal multi-visceral resection	34 (41%)
• Total pelvic exenteration	14 (17%)
<b>Intraoperative outcomes</b>	
Intraoperative blood transfusion	17 (21%)
<b>Postoperative outcomes</b>	
• Re-look operative intervention during index admission	5 (6%)
• Postoperative complications (by highest Clavien-Dindo grading)	
0	25 (34%)
I–II	25 (34%)
III–IV	21 (29%)
V	2 (3%)
• Composite Complication Index	24.2 [16.1–39.7]
• DAH-90	75 [58–79]

Continuous not normally distributed variables are presented as median with interquartiles range (IQR), categorical variable are presented as absolute and relative frequencies *n* (%)

HIPEC, hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; DAH-90, Days at home within 90 days of surgery

approach. Multi-visceral resection was required in 41% of patients. One-third of the study cohort underwent cytoreduction and HIPEC. Intraoperative blood transfusion was required in 21% of patients and 5 patients required a re-look laparotomy. Two-thirds of patients suffered postoperative complications (CCI; median [IQR] = 24.2 [16.1–39.7]), and median DAH-90 was 75 (IQR, 56–79) days.

### Postoperative complications

Univariable linear regression assessed the association between Charlson Co-morbidity Index, traditional preoperative laboratory values, CPET-derived variables, and postoperative complications (assessed by the CCI; Table 2).

The Charlson Co-morbidity Index was a poor discriminator of postoperative complications. In contrast, low preoperative haemoglobin and albumin (potential modifiable

**Table 2** Postoperative complications. Association between the Comprehensive Composite Index (CCI) and continuous or dichotomised preoperative variables, including the Charlson Co-morbidity score, laboratory biomarkers, and CPET-derived variables. Analysis was done using linear regression analysis

Preoperative parameters	Dichotomised reference level	N	beta	95%CI	P-value
<b>A. Univariable analysis</b>					
<b>Charlson Co-morbidity Index</b>					
<i>i. Continuous</i>		79	- 0.29	- 2.24, 1.67	0.780
<i>ii. Dichotomised</i>	< 5	79	- 1.02	- 9.67, 7.62	0.820
<b>Laboratory parameters</b>					
<i>i. Continuous</i>					
• Haemoglobin (g/l)		58	- 0.31	- 0.59, - 0.03	0.031
• White cell count ( $\times 10^9/l$ )		58	2.46	0.52, 4.40	0.013
• Neutrophils ( $\times 10^9/l$ )		58	3.17	0.87, 5.47	0.007
• Albumin (g/l)		34	- 1.29	- 2.18, - 0.41	0.004
• Modified (neutrophil-albumin) Glasgow Prognostic Score		34	12.00	4.32, 19.70	0.002
<i>ii. Dichotomised</i>					
	<b>Risk cut-point</b>				
• Haemoglobin (g/l)	< 110	58	- 9.39	- 21.40, 2.67	0.130
• White Cell Count ( $\times 10^9/l$ )	> 11	58	23.50	3.63, 43.30	0.020
• Neutrophils ( $\times 10^9/l$ )	> 7.5	58	26.10	8.66, 43.60	0.003
• Platelets ( $\times 10^9/l$ )	> 350	58	6.74	- 8.42, 21.90	0.380
• Albumin (g/l)	< 35	34	- 12.2	- 23.0, - 1.46	0.026
<i>iii. Ratios</i>					
• Neutrophil-lymphocyte ratio (NLR)	> 4	58	2.91	- 0.80, 13.80	0.600
• Platelet-lymphocyte ratio (PLR)	> 160	58	3.15	- 8.20, 14.50	0.590
<b>CPET-derived parameters</b>					
<i>i. Continuous</i>					
• Peak $VO_2$ (ml/kg/min)		79	- 0.74	- 1.60, 0.12	0.090
• Peak $VO_2$ (ml/min/m <sup>2</sup> ) ( $\times 100$ )		79	- 2.63	- 4.82, - 0.44	0.019
• $VO_2$ @ AT (ml/kg/min)		79	- 0.50	- 1.93, 0.93	0.490
• $Ve/VCO_2$ @ AT		79	0.63	- 0.09, 1.36	0.088
• $P_{ET}CO_2$ @ AT (mmHg)		79	- 0.74	- 1.44, - 0.04	0.038
<i>ii. Dichotomised</i>					
	<b>Risk cut-point</b>				
• Peak $VO_2$ (ml/kg/min)	< 16	79	- 10.20	- 18.90, - 1.53	0.021
• Peak $VO_2$ (ml/min/m <sup>2</sup> )	< 710	79	- 11.70	- 20.00, - 3.46	0.005
• $VO_2$ @ AT (ml/kg/min)	< 12	79	- 3.74	- 12.60, 5.07	0.410
• $Ve/VCO_2$ @ AT	A.1.1.1.1. > 35	79	12.70	0.95, 24.40	0.034
• $P_{ET}CO_2$ @ AT (mmHg)	< 35	79	- 15.50	- 28.00, - 2.93	0.016
<b>B. Bi-variable analysis</b>					
• Peak $VO_2$ (ml/min/m <sup>2</sup> )	< 710	41	- 15.00	- 24.00, - 5.90	0.001
• Neutrophils ( $\times 10^9/l$ )			3.10	0.92, 5.20	0.005
• Neutrophils ( $\times 10^9/l$ )	> 7.5	5	22.00	5.20, 39.00	0.010
• Peak $VO_2$ (ml/min/m <sup>2</sup> )	< 710	41	- 13.00	- 23.00, - 4.00	0.005
• Neutrophils ( $\times 10^9/l$ )	> 7.5	5	24.00	6.60, 42.00	0.007
• $Ve/VCO_2$ @ AT	> 35	12	7.30	- 5.80, 21.00	0.280
• Heart rate change: baseline to peak (beats per minute)	< 25	76	- 30.00	- 51.00, - 9.20	0.005
• Peak $VO_2$ (ml/kg/min)	< 710	41	- 9.30	- 17.00, - 1.20	0.024

CPET, cardiopulmonary exercise testing; Peak  $VO_2$ , maximum rate of oxygen consumption measured during incremental exercise;  $VO_2$  @ AT, oxygen uptake at anaerobic threshold;  $Ve/VCO_2$ , minute ventilation relative to carbon dioxide elimination;  $P_{ET}CO_2$  @ AT, partial pressure of end tidal carbon dioxide at anaerobic threshold

risk factors) were associated with increased risk for postoperative complications. A preoperative pro-inflammatory state, depicted by a high preoperative neutrophil count (absolute or dichotomised at  $7.5 \times 10^9$  cells/L), had a strong association with increased postoperative complications. This predictive value was significantly ( $P < 0.01$ ) additive when preoperative neutrophil count was combined with albumin (a modification to the Glasgow Prognostic Score) (He et al., 2018) or considered within a bi-variable model with the CPET-derived parameter  $pVO_2$  (corrected to body surface area).

CPET-derived gas exchange parameters that were most predictive of postoperative complications included  $pVO_2$  (corrected to body surface area) and the measures of ventilation-perfusion (VQ) matching, namely low partial pressure of end-tidal  $CO_2$  ( $P_{ET}CO_2$ ) and high ventilatory inefficiency ( $Ve/VCO_2$ ) both measured at anaerobic threshold. Peak  $VO_2$  (corrected to body surface area) and chronotropic response (heart rate  $> 25$  beats per minute increase during exercise from rest to peak  $VO_2$ ) had additive predictive value within a bi-variable model.

#### Days at Home within 90 days after surgery

Univariable linear regression assessed the association between Charlson Co-morbidity Index, traditional preoperative laboratory values, CPET-derived variables, and Days at Home within 90 days after surgery (DAH-90; Table 3).

The Charlson Co-morbidity Index did not discriminate low versus high DAH-90. In contrast, low haemoglobin and albumin were associated with reduced DAH-90. A preoperative pro-inflammatory state, depicted by a high preoperative neutrophil count (absolute or dichotomised), was also strongly associated with reduced DAH-90. This was also evident when preoperative inflammation was considered in conjunction with albumin (modified Glasgow Prognostic Score) ( $P < 0.001$ ).

The CPET-derived gas exchange parameters that were most predictive of reduced DAH-90 included increased high ventilatory inefficiency ( $Ve/VCO_2$ ) measured at anaerobic threshold and peak  $VO_2$  (corrected to body weight and to body surface area). Within a bi-variable model, the modified Glasgow Prognostic Score (using neutrophil count) and the CPET-derived parameter  $pVO_2$  (corrected to body weight) had significant additive predictive value for reduced DAH-90 after surgery ( $P < 0.001$ ).

#### Overall survival

Univariable linear regression assessed the association between Charlson Co-morbidity Index, traditional preoperative laboratory values, CPET-derived variables, and overall survival within two years after surgery (Table 4).

The Charlson Co-morbidity Index did not discriminate survivors from non-survivors. In contrast, low haemoglobin was strongly associated with reduced overall survival. Similarly, a preoperative pro-inflammatory state, depicted by a high preoperative neutrophil count (absolute or dichotomised), discriminated overall survival.

CPET-derived gas exchange parameters that were most predictive of reduced overall survival included poor  $CO_2$  elimination at AT, namely low partial pressure for end-tidal  $CO_2$  and high ventilatory inefficiency ( $Ve/VCO_2$ ) at anaerobic threshold, and  $pVO_2$  (corrected to body surface area). Comparison of Kaplan-Meier curves (Fig. 1a–d) showed significant difference in survival when  $P_{ET}CO_2$  at AT was dichotomised at 35 mmHg ( $P = 0.001$ ), when  $Ve/VCO_2$  was dichotomised at 35 ( $P = 0.001$ ), when  $pVO_2$  was dichotomised at 710 ml/min/m<sup>2</sup> ( $P < 0.01$ ), and when  $Ve/VCO_2$  and peak  $VO_2$  were considered together. Importantly,  $VO_2$  at AT (dichotomised at 11 ml/kg/min) did not discriminate survivors from non-survivors.

Within bivariate modelling, when inflammation was considered in conjunction with albumin (a modification to the Glasgow Prognostic Score) or neutrophil count considered with peak  $VO_2$  (corrected to body weight) it added significant ability to discriminate between survivors and non-survivors. Similarly, when ventilatory efficiency ( $Ve/VCO_2$ ) was considered within a bi-variable model with the CPET-derived parameter peak  $VO_2$  (corrected to body weight), it also added significant predictive value for reduced survival after surgery (Fig. 1;  $p < 0.0001$ ).

#### Exploratory CPET parameters

Heart rate at peak exercise and the heart rate recovery (HRR) after peak exercise are higher among the survivors than non-survivors. While change in heart rate and change in  $VO_2$  over the entire testing period were not statistically different between survivors and non-survivors, the recovery phase slopes for HRR and for oxygen consumption ( $VO_2R$ ) were significantly different between survivors and non-survivors (Table 5) with modest ability to predict survival (HRR: AUROC 0.74, 95% CI 0.59–0.89;  $P = 0.002$  and HRR  $> 0.87$  had 69% sensitivity and 81% specificity;  $VO_2R$ : 0.74, 95% CI 0.61–0.86;  $P = 0.008$  and  $VO_2R > 0.57$  had 85% sensitivity and 66% specificity). The recovery phase slopes for CPET-derived  $CO_2$  exchange parameters ( $VCO_2$ ,  $P_{ET}CO_2$ ,  $Ve/VCO_2$ ) were not significantly different between survivors and non-survivors.

#### Discussion

This study demonstrates that a ‘triple low’ state, characterised by low haemoglobin (anaemia), low albumin, and low functional capacity compounded by a pro-inflammatory state, as assessed by routine inflammatory

**Table 3** Days at Home within 90 days after surgery (DAH-90). Association between the DAH-90, a patient centric measure, and continuous or dichotomised preoperative variables, including the Charlson Co-morbidity score, laboratory biomarkers and CPET-derived variables. Analysis was done using linear regression analysis

Preoperative parameters	Dichotomised reference level	N	beta	95%CI	P-value
<b>A. Univariable analysis</b>					
<b>Charlson Co-morbidity Index</b>					
<i>i. Continuous</i>					
		80	- 0.86	- 2.59, 0.86	0.330
<i>ii. Dichotomised</i>					
	< 5	80	- 4.47	- 12.10, 3.14	0.250
<b>Laboratory parameters</b>					
<i>i. Continuous</i>					
• Haemoglobin (g/l)		58	0.24	- 0.01, 0.49	0.060
• White cell count ( $\times 10^9/l$ )		58	- 1.94	- 3.67, - 0.21	0.028
• Neutrophils ( $\times 10^9/l$ )		58	- 2.59	- 4.63, - 0.55	0.013
• Albumin (g/l)		34	1.37	0.57, 2.17	0.001
• Modified (neutrophil-albumin) Glasgow Prognostic Score		34	- 12.50	- 19.40, - 5.48	< 0.001
<i>ii. Dichotomised</i>					
	<b>Risk cut-point</b>				
• Haemoglobin (g/l)	< 110	58	10.6	0.09, 21.00	0.048
• White Cell Count ( $\times 10^9/l$ )	> 11	58	- 26.50	- 43.40, - 9.55	0.002
• Neutrophils ( $\times 10^9/l$ )	> 7.5	58	- 26.90	- 41.80, - 11.90	< 0.001
• Platelets ( $\times 10^9/l$ )	> 350	58	- 6.27	- 19.60, 7.07	0.360
• Albumin (g/l)	< 35	34	10.3	0.02, 20.60	0.050
<i>iii. Ratios</i>					
Neutrophil-lymphocyte ratio (NLR)	> 4	58	- 0.32	- 9.96, 9.33	0.950
Platelet-lymphocyte ratio (PLR)	> 160	58	- 2.76	- 12.70, 7.24	0.590
<b>CPET-derived parameters</b>					
<i>i. Continuous</i>					
• Peak $VO_2$ (ml/kg/min)		80	0.62	- 0.15, 1.39	0.110
• Peak $VO_2$ (ml/min/m <sup>2</sup> ) ( $\times 100$ )		80	2.07	0.12, 4.01	0.038
• $VO_2$ @ AT (ml/kg/min)		80	0.45	- 0.81, 1.71	0.490
• $Ve/VCO_2$ @ AT		80	- 0.56	- 1.21, 0.08	0.088
• $P_{ET}CO_2$ @ AT (mmHg)		80	0.68	0.05, 1.31	0.033
<i>ii. Dichotomised</i>					
	<b>Risk cut-point</b>				
• Peak $VO_2$ (ml/kg/min)	$\leq 16$	80	10.60	3.00, 18.20	0.006
• Peak $VO_2$ (ml/min/m <sup>2</sup> )	< 710	80	9.46	2.08, 16.90	0.012
• $VO_2$ @ AT (ml/kg/min)	< 12	80	1.94	- 5.88, 9.75	0.630
• $Ve/VCO_2$ @ AT	> 35	80	- 13.3	- 23.7, - 3.01	0.011
• $P_{ET}CO_2$ @ AT (mmHg)	< 35	80	11.20	- 0.08, 22.60	0.052
<b>B. Bi-variable analysis</b>					
• Peak $VO_2$ (ml/kg/min)	$\leq 16$	51	19.00	11.00, 27.00	< 0.001
• Modified (neutrophils-albumin) Glasgow Prognostic Score			- 10.00	- 16.00, - 4.50	< 0.001

CPET, cardiopulmonary exercise testing; Peak  $VO_2$ , maximum rate of oxygen consumption measured during incremental exercise;  $VO_2$  @ AT, oxygen uptake at anaerobic threshold;  $Ve/VCO_2$ , minute ventilation relative to carbon dioxide elimination;  $P_{ET}CO_2$  @ AT, partial pressure of end tidal carbon dioxide at anaerobic threshold

markers are associated with poorer postoperative outcomes, including medium-term overall survival. These findings add to the emerging body of evidence that dynamic assessment of physiological fitness using CPET can help predict adverse postoperative outcomes

(including post-operative complications and mortality) in patients undergoing major colorectal cancer surgery. The Charlson Co-morbidity Index appears unreliable for predicting post-operative complications in this patient population.

**Table 4** Survival. Association between overall survival and continuous or dichotomised preoperative variables, including Charlson Co-morbidity score, laboratory biomarkers and CPET-derived variables. Analysis was done using Cox proportional hazards regression analysis

Preoperative parameters	Dichotomised reference level	N	Hazard ratio or (1/hazard ratio) <sup>a</sup>	95%CI	P-value
<b>A. Univariable Analysis</b>					
<b>Charlson Co-morbidity Risk Index</b>					
<i>i. Continuous</i>		82	1.03	0.81, 1.32	0.810
<i>ii. Dichotomised</i>	< 5	82	1.62	0.54, 4.84	0.380
<b>Laboratory parameters</b>					
<i>i. Continuous</i>					
• Haemoglobin (g/l)		58	0.93, <sup>a</sup> 1.08	0.89, 0.98	0.001
• White cell count ( $\times 10^9/l$ )		58	1.29	1.08, 1.55	0.012
• Neutrophils ( $\times 10^9/l$ )		58	1.36	1.10, 1.67	0.010
• Albumin (g/l)		34	0.89, <sup>a</sup> 1.12	0.80, 1.00	0.050
• Modified (neutrophil-albumin) Glasgow Prognostic Score		34	3.16	1.21, 8.27	0.024
<i>ii. Dichotomised</i>					
	<b>Risk cut-point</b>				
• Haemoglobin (g/l)	<110	58	0.232, <sup>a</sup> 4.31	0.06, 0.87	0.032
• White Cell Count ( $\times 10^9/l$ )	> 11	58	4.40	0.91, 21.30	0.110
• Neutrophils ( $\times 10^9/l$ )	> 7.5	58	6.79	1.68, 27.50	0.020
• Platelets ( $\times 10^9/l$ )	> 350	58	2.98	0.74, 11.90	0.150
• Albumin (g/l)	< 35	34	0.22, <sup>a</sup> 4.55	0.04, 1.12	0.051
<i>iii. Ratios</i>					
Neutrophil-lymphocyte ratio (NLR)	> 4	58	1.57	0.42, 5.84	0.510
Platelet-lymphocyte ratio (PLR)	> 160	58	0.92	0.23, 3.67	0.900
<b>CPET-derived parameters</b>					
<i>i. Continuous</i>					
• Peak $VO_2$ (ml/kg/min)		82	0.91, <sup>a</sup> 1.10	0.80, 1.04	0.150
• Peak $VO_2$ (ml/min/m <sup>2</sup> ) ( $\times 100$ )		82	0.65, <sup>a</sup> 1.54	0.45, 0.94	0.012
• $VO_2$ @ AT (ml/kg/min)		82	0.89, <sup>a</sup> 1.12	0.72, 1.10	0.250
• $Ve/VCO_2$ @ AT		82	1.09	1.02, 1.15	0.014
• $P_{ET}CO_2$ @ AT (mmHg)		82	0.89, <sup>a</sup> 1.12	0.82, 0.96	0.004
<i>ii. Dichotomised</i>					
	<b>Risk cut-point</b>				
• Peak $VO_2$ (ml/kg/min)	< 16	82	0.35, <sup>a</sup> 2.86	0.12, 1.00	0.049
• Peak $VO_2$ (ml/min/m <sup>2</sup> )	< 710	82	0.13, <sup>a</sup> 7.70	0.03, 0.56	0.001
• $VO_2$ @ AT (ml/kg/min)	< 12	82	0.69, <sup>a</sup> 1.45	0.23, 2.05	0.490
• $Ve/VCO_2$ @ AT	> 35	82	6.12	2.13, 17.50	0.001
• $P_{ET}CO_2$ @ AT (mmHg)	< 35	82	0.160, <sup>a</sup> 6.25	0.05, 0.47	0.002
<b>B. Bi-variable analysis</b>					
• Haemoglobin (g/l)			0.94, <sup>a</sup> 1.06	0.90, 0.99	0.017
• $Ve/VCO_2$ @ AT	>35	10	2.60	0.63, 11.00	0.180
• Peak $VO_2$ (ml/min/m <sup>2</sup> )	<710	42	0.18	0.04, 0.85	0.013
• $Ve/VCO_2$ @ AT	> 35	13	<sup>a</sup> 5.56, 3.70	1.30,	0.020

**Table 4** Survival. Association between overall survival and continuous or dichotomised preoperative variables, including Charlson Co-morbidity score, laboratory biomarkers and CPET-derived variables. Analysis was done using Cox proportional hazards regression analysis (Continued)

Preoperative parameters	Dichotomised reference level	N	Hazard ratio or (1/hazard ratio) <sup>a</sup>	95%CI	P-value
• Peak VO <sub>2</sub> (ml/min/m <sup>2</sup> )	> 710	28	0.11, <sup>a</sup> 9.09	0.01, 0.87	0.007
• Neutrophils (× 10 <sup>9</sup> /l)			1.40	1.10, 1.70	0.008

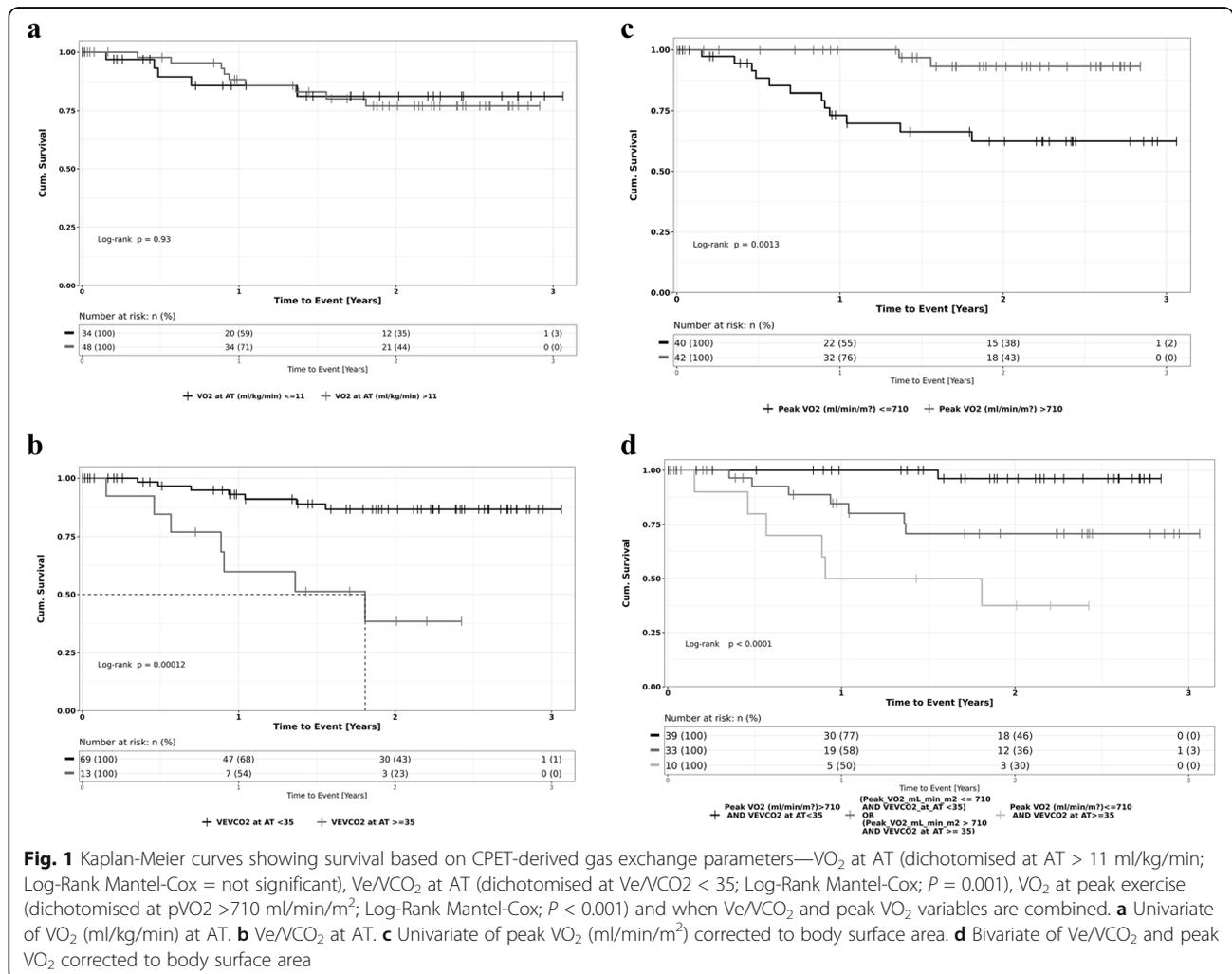
CPET, cardiopulmonary exercise testing; Peak VO<sub>2</sub>, maximum rate of oxygen consumption measured during incremental exercise; VO<sub>2</sub> @ AT, oxygen uptake at anaerobic threshold; Ve/VCO<sub>2</sub>, minute ventilation relative to carbon dioxide elimination; P<sub>ET</sub>CO<sub>2</sub> @ AT, partial pressure of end tidal carbon dioxide at anaerobic threshold

<sup>a</sup>Inverse of hazard ratio to show directional change related to overall survival relative to other variables

**Utilisation of CPET parameters**

Previous studies have demonstrated that patients undergoing intra-abdominal surgery with an AT between 10 and 12 ml/kg/min have increased postoperative risk, with an AT of < 10.1 ml/kg/min being a strong predictor of morbidity, and an AT < 10.9 ml/kg/min being a predictor of mortality (Moran et al., 2016). In a recent meta-analysis of objective assessment of physical fitness in patients

undergoing colorectal cancer surgery we reported that deconditioned (AT < 11 ml/kg/min) patients had a three- to five-fold higher incidence of postoperative complications than those patients deemed ‘fit’, but we were unable to identify a pooled cut point to predict postoperative mortality (Lee et al., 2018). While pVO<sub>2</sub> has been demonstrated to be an independent predictor of mortality (Jones et al., 2011), with significant risk of perioperative



**Table 5** CPET-derived recovery phase parameters, with difference between survivors and non-survivors after major colorectal cancer surgery at 1-year follow-up

Variables	Survivors	Non-survivors	AUROC	P-value
VO <sub>2</sub> : slope (IQR)	0.54 (0.46-0.62)	0.61 (0.57-0.70)	0.74	0.008
Heart rate: slope (IQR)	0.81 (0.74-0.87)	0.89 (0.81-0.95)	0.74	0.006
Ve/VCO <sub>2</sub> : slope (IQR)	28.5 (23.90-32.90)	32.1 (24.20-39.40)	0.59	0.318
P <sub>ET</sub> CO <sub>2</sub> : slope (IQR)	0.95 (0.92-1.00)	0.97 (0.92-1.10)	0.60	0.279

Results are presented as median with IQR

A larger 'Ve/VCO<sub>2</sub> slope' implies a slower recovery from peak performance to baseline

VO<sub>2</sub>, maximum rate of oxygen consumption measured during incremental exercise; Ve/VCO<sub>2</sub>, minute ventilation relationship to carbon dioxide elimination; P<sub>ET</sub>CO<sub>2</sub>, end tidal partial pressure of carbon dioxide

complications reported with a pVO<sub>2</sub> of < 15 ml/kg/min (Smith et al., 2009), a recent international prospective cohort study (the METS study) suggested that a low AT or low pVO<sub>2</sub> did not predict for a composite of postoperative cardiac complications and mortality (Wijeyesundera et al., 2018). This same study, however, confirmed the value of peak VO<sub>2</sub> as a bi-variate metric to be predictive of all-cause non-cardiac complications after surgery in a mixed cohort of surgical patients with relative low preoperative risk (Wijeyesundera et al., 2018). In our study cohort of patients having major colorectal cancer surgery, we were unable to demonstrate significant association between VO<sub>2</sub> kinetics at AT and adverse postoperative outcomes. The strongest association between postoperative mortality in our study was seen with VO<sub>2</sub> at peak exercise that was adjusted to body surface area (rather than weight) and for CO<sub>2</sub> kinetics at AT (Ve/VCO<sub>2</sub> or P<sub>ET</sub>CO<sub>2</sub> at AT). In this small cohort, one in two patients with preoperative pVO<sub>2</sub> < 710 ml/min/m<sup>2</sup> and Ve/VCO<sub>2</sub> at AT > 35 had died within one year of surgery (Fig. 1d).

Nagamatsu et al. reported a similar association between pVO<sub>2</sub> adjusted for body surface area and postoperative complications in patients having an oesophagectomy (Nagamatsu et al., 2001; Nagamatsu et al., 1994). Indexing VO<sub>2</sub> to body surface area rather than body weight was performed in order to minimise variability due to extremes of body weight. There is emerging recognition that sarcopenic obesity (obesity with depleted muscle mass), caused by cancer, as well as toxicity of chemotherapy, may be predictive of disease-specific morbidity and mortality (Prado et al., 2008). Our patient cohort included patients with recurrent, or advanced gastrointestinal cancer, commonly having multiple courses of preoperative chemotherapy and potential sarcopenia, making it necessary to index CPET derived variables to body surface area rather than absolute body weight.

#### Utilisation of preoperative biomarkers

Statistical association of low haemoglobin and low albumin with postoperative complications and overall survival allude to additional modifiable risk factors that may not only add value to CPET-derived risk prediction but also

underpin the need for haematonic and nutritional optimisation within the setting of prehabilitation. The concept of using perioperative biomarkers to stratify surgical risk has its foundations in gauging the risk of postoperative cardiac complications (Edwards et al., 2011). Optimisation of the oxygen-carrying capacity of the surgical patient by addressing anaemia has been shown to increase AT and pVO<sub>2</sub> (Agostoni et al., 2010). Both cancer biology and anticancer therapy are associated with a pro-inflammatory state (de Visser et al., 2006) and relationships between different haematological markers have been previously used to prognosticate cancer risk. Specifically, platelet/lymphocyte (PLR), lymphocyte/monocyte (LMR) and neutrophil/lymphocyte (NLR) ratios have been investigated as preoperative risk indicators (Guo et al., 2017; Templeton et al., 2014; Chan et al., 2017). It has been demonstrated that in patients with operable colorectal cancer, PLR was associated with poor prognosis, whereas LMR was associated with increased overall survival for patients undergoing curative colorectal resections (Guo et al., 2017; Chan et al., 2017). While the ratios of these haematological markers did not demonstrate an association with the postoperative outcomes of interest in our patient population, there was statistically significant association with preoperative neutrophil count, signalling the association between preoperative inflammation and post-operative outcomes. Though our sample sizes were limited for biomarker analysis (haemoglobin/neutrophil count: *n* = 58; albumin count: *n* = 34), larger prospective studies assessing multiple variables alongside CPET are needed to delineate modifiable risk factors that may benefit from intervention preoperatively, within the setting of a multimodal prehabilitation program.

#### Exploratory CPET recovery parameters

Ackland et al. have demonstrated that heart rate recovery (HRR) has good predictive capability for morbidity within five days of surgery (Ackland et al., 2019). We similarly demonstrate that heart rate kinetics during preoperative CPET testing has a modest ability to predict intermediate-term mortality following major intra-abdominal cancer surgery. HRR is an independent

predictor for 6-year all-cause mortality in the epidemiological (non-surgical) population (Cole et al., 1999). Patients with prolonged HRR were more likely to be elderly and also possess cardiac risk factors (Simões et al., n.d.). Furthermore, large studies examining healthy patients without cardiovascular disease have also reported that HRR is directly linked to mortality (Cole et al., 2000; Nishime et al., 2000; Shetler et al., 2001).

Our findings that HRR is a prognostic factor, as a reflection of cardiovascular reserve, or a predictor of autonomic dysfunction (Imai et al., 1994; Perini et al., 1989), is supported by studies showing HRR is associated perioperative morbidity (Ackland et al., 2015; Ackland et al., 2018), improved survival in conditions such as bacterial peritonitis, hypovolemic shock, and myocardial ischaemia (Guarini et al., 2003; Boland et al., 2011; Mioni et al., 2005). Taking all the existing evidence together, HRR measured during the recovery phase of CPET has the potential to be an important marker of parasympathetic activity and a risk predictor of perioperative morbidity and mortality risk and should be further investigated.

#### Limitations of this study

This cohort reflects a gastrointestinal surgical population in a quaternary institution with multiple variables that may affect outcomes and these results may have limited applicability to other major oncological subspecialty procedures. The size of this cohort was limited and therefore some of our negative findings may reflect the power of the study. Given the exploratory nature of this retrospective study, we have restricted our focus to comorbid disease and have a limited description of intraoperative variables. The statistical power of the results may be reduced due to the number of analysed variables. Furthermore, while referral to CPET in the study centre is based on hospital guidelines, the pattern of referral could have introduced an element of selection bias.

#### Conclusion

Patients presenting with a 'triple low' preoperative state (anaemia {low haemoglobin}, malnutrition {low albumin}, and deconditioned {low functional capacity, e.g. low peak  $\text{VO}_2$ }) are at greatest risk of postoperative complications and death. This is further compounded by a pro-inflammatory state. This study demonstrates that in complex colorectal cancer patients undergoing major cancer surgery, one in two patients with a preoperative  $\text{pVO}_2 < 710 \text{ ml/kg/m}^2$  and  $\text{Ve/VCO}_2$  at AT  $> 35$  or  $\text{PETCO}_2$  at AT  $< 35 \text{ mmHg}$  will die within 1 year of surgery. In light of this, the current focus on conventional CPET parameters such as  $\text{VO}_2$  at AT and peak  $\text{VO}_2$  should be superseded by a holistic approach that analyses multiple physiological and biochemical parameters. This will not only improve risk prediction but to identify

opportunity to optimise reversible patient factors within the prehabilitation window. Large, prospective multivariate trials are required to expand our understanding of modifiable risk factors and guide preoperative optimisation prior to major cancer surgery.

#### Abbreviations

AT: Anaerobic threshold; CPET: Cardiopulmonary exercise testing; CCI: Comprehensive Complication Index; DAH-90: Days at Home within 90 days; DASl: Duke Activity Status Index; HRR: Heart rate recovery; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio

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#### Authors' contributions

Vladimir Bolshinsky: Involved in gathering data, data analysis, and drafting of the manuscript. Hilmy Ismail: Involved in CPET interpretation, study design, and drafting of manuscript. Michael Li: Involved in gathering data. Jarrod Basto: Involved in gathering data. Robert Schier: Involved in statistical analysis and drafting of manuscript. Anna Hagemeyer: Involved in statistical analysis and drafting of manuscript. Kwok-Ming Ho: Involved in statistical analysis and drafting of manuscript. Alexander Heriot: Overall supervision of project, study design, and drafting of manuscript. Bernhard Riedel: Overall supervision of project, CPET interpretation, study design, and drafting of manuscript. The authors read and approved the final manuscript.

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#### Availability of data and materials

Please contact author for data request.

#### Declarations

##### Ethics approval and consent to participate

Ethical approval as well as patient consent was obtained for the conduct of this study using the Peter MacCallum Cancer Centre institutional review board (registration number: #16/19R).

##### Consent for publication

Consent for publication of this manuscript has been obtained from all the authors and is available upon request.

##### Competing interests

The authors declare that they have no competing interests.

##### Author details

<sup>1</sup>General Surgery, Peninsula Health, Frankston, VIC, Australia. <sup>2</sup>Surgical Health Specialists, Frankston, VIC, Australia. <sup>3</sup>Peter MacCallum Cancer Centre, Melbourne, VIC, Australia. <sup>4</sup>Universität zu Köln Medizinische Fakultät, Köln, Nordrhein-Westfalen, Germany. <sup>5</sup>Royal Perth Hospital, Perth, Australia.

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