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RESEARCH

A retrospective analysis of the association of effort-independent cardiopulmonary exercise test variables with postoperative complications in patients who underwent elective colorectal surgery

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Abstract

Purpose This study aimed to investigate the association of effort-independent variables derived from the preoperative cardiopulmonary exercise test (CPET) with 30-day postoperative complications after elective colorectal surgery.

Methods A multicenter (n=4) retrospective explorative study was performed using data of patients who completed a preoperative CPET and underwent elective colorectal surgery. The preoperative slope of the relation between minute ventilation and carbon dioxide production (VE/VCO_2-slope) and the oxygen uptake efficiency slope (OUES), as well as 30-day postoperative complications, were assessed. Multivariable logistic regression analyses and receiver operating characteristic (ROC) curves were used to investigate the prognostic value of the relationship between these preoperative CPET-derived effort-independent variables and postoperative complications.

Results Data from 102 patients (60.1% males) with a median age of 72.0 (interquartile range 67.8–77.4) years were analyzed. Forty-four patients (43.1%) had one or more postoperative complications (of which 52.3% general and 77.3% surgical complications). Merely 10 (9.8%) patients had a general complication only. In multivariate analysis adjusted for surgical approach (open versus minimally invasive surgery), the VE/VCO_2-slope (odds ratio (OR) 1.08, confidence interval (CI) 1.02–1.16) and OUES (OR 0.94, CI 0.89–1.00) were statistically significant associated with the occurrence of 30-day postoperative complications.

Conclusion The effort-independent VE/VCO_2-slope and OUES might be used to assist in future preoperative risk assessment and could especially be of added value in patients who are unable or unwilling to deliver a maximal cardiorespiratory effort. Future research should reveal the predictive value of these variables individually and/or in combination with other prognostic (CPET-derived) variables for postoperative complications.

Trial registration number ClinicalTrials.gov NCT05331196

Keywords Preoperative care · Preoperative risk assessment · Cardiopulmonary exercise testing · Oxygen uptake efficiency slope · Abdominal surgery · Anaerobic threshold · Peak oxygen uptake

Introduction

Risk assessment for the risk of adverse postoperative outcomes is an important predictive step in the preparation of patients for major (abdominal) surgery. Following resection for a colorectal carcinoma (CRC), approximately 30% of the patients develop a surgical or non-surgical (general) postoperative complication [1]. Particularly patients with a low preoperative aerobic fitness are at risk for postoperative complications after major elective intra-abdominal surgery [2–5]. Complication rates in these patients can be as high as ~70% [6].

A cardiopulmonary exercise test (CPET) is considered the gold standard for assessing aerobic fitness. In contrast to static and organ-specific risk assessment tests (e.g., echocardiography, spirometry, blood biomarkers), a CPET offers an objective dynamic assessment of the

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integrative response to exercise (i.e., mimicking the surgical stress response) of the cardiovascular, pulmonary, and neuromuscular system [7]. Oxygen uptake (VO_2) at peak exercise (VO_{2peak}) and VO_2 at the ventilatory anaerobic threshold (VO_{2VAT}) are the most commonly used preoperative CPET variables that are associated with postoperative outcomes [8], with lower values (i.e., lower aerobic fitness and thus a lower physiological reserve capacity) reflecting a higher risk for adverse patient-related and treatment-related outcomes. However, determination of VO_{2peak} and VO_{2VAT} bear some limitations. VO_{2VAT} is not determinable in all patients [9, 10] and methods for its determination are complex [11] leading to higher inter-observer variability than VO_{2peak} [9, 10]. To obtain a valid VO_{2peak}, a volitional maximal effort is needed. Attaining a maximal effort is influenced by several factors. For instance, by instructions and motivational support of the assessor, as well as by motivation, pain, or fatigue of the patient, in combination with the substantial stress of performing a maximal effort, a volitional maximal effort cannot be accomplished by all patients [12].

Effort-independent CPET variables, such as the slope of the relation between minute ventilation and carbon dioxide production (VE/VCO_2-slope) and the oxygen uptake efficiency slope (OUES), might improve preoperative risk assessment. They can be derived even when no maximal cardiorespiratory effort was performed, meaning that these variables are determinable in all patients. In addition, inter-observer agreement of both variables is excellent (intra-class correlation coefficient >0.95) [10], as they are objectively determined. The VE/VCO_2-slope is a measure of ventilatory efficiency that is usually determined from the start of the work rate increment phase until the respiratory compensation point [13]. The OUES provides an estimation of the efficiency of the minute ventilation (VE) with respect to the VO_2 throughout the CPET by providing a log-transformed response profile [14]. Determination of the OUES is described in detail by Bongers et al. [15]. In a previous study, it was demonstrated that the preoperative OUES provides a valid effort-independent measure of aerobic fitness in elderly patients scheduled for major colorectal surgery [15]. However, there is no direct evidence regarding the association of the preoperative VE/VCO_2-slope and the OUES with postoperative complications. The primary aim of this explorative study was to investigate the prognostic value of the preoperative VE/VCO_2-slope and the OUES for 30-day postoperative complications after elective colorectal surgery. As the VO_{2peak} and VO_{2VAT} are still the most commonly used CPET-derived variables for preoperative risk assessment, the secondary aim was to investigate the association of VO_{2peak} and VO_{2VAT} with 30-day postoperative complications.

Materials and methods

Participants

The current retrospective explorative study was carried out using data from of patients approaching elective colorectal surgery who performed a preoperative CPET at Medisch Spectrum Twente (MST), Máxima Medical Center (MMC), VieCuri Medical Center (VMC), and Maastricht University Medical Center+ (MUMC+). MST, MMC, and VMC are general teaching hospitals, whereas MUMC+ is a university medical center combining the functions of academic and regional hospital. Inclusion criteria, which differed between hospitals, are depicted in Table 1. Patients performed a CPET as a part of a study [6, 16, 17] in one of the abovementioned centers and were not referred for a CPET due to specific (medical) reasons. Patients who participated in preoperative exercise training or received neoadjuvant therapy between the CPET and surgery were excluded. Ethical committee approval of each of the participating hospitals for the data presented here was granted for the original studies from which the data was extracted under the following registration numbers: MST (NL45001.044.13), MMC (NL54547.015.15), VMC (METCZ20190150), and MUMC+ (NL69473.068.19).

Cardiopulmonary exercise test

An incremental CPET was performed using calibrated electronically braked cycle ergometers in an upright position (see Table 1 for the cycle ergometer used in each hospital); CPET comprised a 2-min rest phase; a 3-min unloaded warm-up phase; an incremental phase with constant work rate increments of 5, 10, or 15 W/min, depending on the patient's subjective physical fitness level and aimed at reaching a maximal effort within 8 to 12 min; and a 5-min cool-down phase. During the CPET, patients were verbally coached by the assessor to maintain a pedaling frequency between 60 and 80 rpm. The protocol continued until the patient's pedaling frequency fell definitely below 60 rpm, despite strong verbal encouragement.

During the CPET, patients breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) connected to a flow-volume transducer and metabolic cart (see Table 1) to calculate breath-by-breath minute ventilation (VE), VO_2, and carbon dioxide (VCO_2) production. Flow-volume and gas calibration were performed before each test. Twelve-lead electrocardiography, blood pressure, and pulse oximetry were continuously monitored. CPET data were interpreted independently by two experienced clinical exercise physiologists (RF and BB). CPET data was averaged into 10-s

Table 1 Inclusion criteria, period, and technical CPET information per center

Center	Inclusion criteria	CPET performed	CPET cycle ergometer	CPET metabolic cart
MST	≥60 years of age AND ≤7 metabolic equivalents of task on the veterans-specific activity questionnaire	February 2013 and December 2018	Ergoselect 100, Ergoline, Bitz, Germany	Oxycon Pro, Jaeger, Hoechberg, Germany
MMC	>18 years of age	June 2016 and June 2017	Lode Corival, Lode BV, Groningen	Vyntus CPX, Vyaire Medical, Hoechberg, Germany
VMC	>18 years of age AND ≤7 metabolic equivalents of task on the veterans-specific activity questionnaire	July 2020 and September 2021	Lode Corival, Lode BV, Groningen	Ergostik, Geratherm Respiratory, Bad Kissingen, Germany
MUMC+	>18 years of age	February 2020 and June 2022	Lode Corival, Lode BV, Groningen	Vyntus CPX, Vyaire Medical, Hoechberg, Germany

Abbreviations: *CPET* cardiopulmonary exercise test, *MMC* Máxima Medical Center, *MST* Medisch Spectrum Twente, *MUMC+* Maastricht Universtity Medical Center+, *VMC* VieCuri Medical Center

intervals [18]. The VE/VCO_2-slope, OUES, VO_{2peak}, and VO_{2VAT} were determined using a guideline-based approach as previously published [10].

Patient characteristics and outcome measures

Baseline patient characteristics included sex, age, body height, body mass, body mass index (BMI), smoking status (current, former, never), tumor location, type and stage of the tumor, American Society of Anesthesiologists (ASA) score (I–IV), and type of surgical resection.

Postoperative complications and length of hospital stay were retrieved from the original studies (MST, MMC, and VMC) [6, 16, 17] or from the Dutch ColoRectal Audit (MUMC+). Postoperative surgical complications included anastomotic leakage, perineal wound complication, rectal stump abscess, intra-abdominal abscess, fistula, sepsis, ileus, abdominal wound complication, intestinal necrosis, stoma complication, urological complication, bleeding, iatrogenic intestinal injury, or iatrogenic vascular injury. General complications were scored as cardiovascular, pulmonary, renal, or neurological. The severity of any postoperative complication was scored using the Clavien-Dindo classification of complications. The Clavien-Dindo classification grades the severity of a complications in five grades (grade 1–5) based on the treatment required to treat the complication [18]. A grade 3–5 complication was defined as a severe complication [19, 20].

Statistical analysis

Data were analyzed with the Statistical Package for the Social Sciences for Windows (version 23.0; IBM, SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean ± standard deviation, or as median with interquartile range [IQR], as appropriate. Categorical data were summarized by frequency and percentage. Odds ratios (OR) are presented with 95% confidence intervals (CI). To investigate the univariate association between baseline characteristics, the CPET-derived variables, and 30-day postoperative complications, and length of hospital stay, the Fisher's exact test or chi-square test for categorical variables and the independent samples *t*-test (normal distribution) or Mann-Whitney *U* test (no normal distribution) for continuous variables were used, as appropriate. First, a univariate logistic regression was performed and subsequently four forward stepwise multivariate logistic regression analyses were performed to investigate the individual prognostic value of the preoperative VE/VCO_2-slope, OUES, VO_{2peak}, and VO_{2VAT} for any 30-day postoperative complication (Clavien-Dindo grade 1 or higher). Baseline characteristics were selected as potential confounder when they were associated with 30-day postoperative complications, as well as with the VE/VCO_2-slope, OUES, VO_{2peak}, and VO_{2VAT} ($P<0.200$). Age, sex, and ASA score were considered potential confounders based on previous literature [21]. The logistic regression models were adjusted for these potential confounders in a forward stepwise procedure. A variable was entered in the model when $P<0.200$ and excluded when $P\geq0.200$. The maximum number of variables identified as covariates that could be included for the multiple logistic regression model was based on 10 events per variable. Receiver operator characteristic (ROC) curve analysis was used to assess the independent ability of the VE/VCO_2-slope, OUES, VO_{2peak}, and VO_{2VAT} to discriminate between patients with and without 30-day postoperative complications. The optimal cutoff point was based on our preference to have

primarily a high sensitivity (>0.8) with a reasonable specificity (>0.5). A $P<0.05$ was considered statistically significant.

Results

Data of 102 patients who underwent a preoperative CPET before colorectal surgery were included in the current study. Median [IQR] age of these 62 men and 40 women was 72.0 [67.8–77.4] years.

Patient characteristics of the whole study cohort, as well as stratified for patients with and without complications are shown in Table 2. Patient characteristics categorized per hospital are depicted in Online Resource 1. A total of 44 (43.1%) patients experienced a postoperative complication, of whom 22 (50.0%) patients had more than 1 complication and 17 (38.6%) patients had a Clavien-Dindo ≥3 complication. Of the patients who had one or more postoperative complications, 34 (77.3%) had one or more surgical complications and 23 (52.3%) had one or more general (non-surgical) complications. Of the 23 patients with general complications, 13 (56.7%) had both a surgical and a general complication leaving only 10 patients (9.8%) with general complications only. Median length of hospital stay of all patients (n=102) was 5 (IQR 4–8) days, 8 (IQR 5–16) days for patients with (n=44) postoperative complications and

Table 2 Patient characteristics and postoperative outcomes in relation to 30-day postoperative complications following colorectal surgery

Parameter	Total (n=102)	Postoperative complications		P-value
		Yes (n=44)	No (n=58)	
Age (years)	72.0 [67.8–77.4]	74.8 [68.0–79.6]	71.5 [67.8–75.4]	0.081[a]
<75 years	62	23 (37.1%)	39 (62.9%)	
≥75 years	40	21 (52.5%)	19 (47.5%)	0.125[b]
Sex				
Male	62	26 (41.9%)	36 (58.1%)	
Female	40	18 (45.0%)	22 (55.0%)	0.760[b]
Body mass index (kg/m^2)	28.0 [25.3–30.9]	27.9 [25.4–31.4]	28.0 [25.0–30.8]	0.760[a]
≤27 kg/m^2	44	18 (40.9%)	26 (59.1%)	
>27 kg/m^2	58	26 (44.8%)	32 (55.2%)	0.692[b]
Smoking[d]				
Yes	15	7 (46.7%)	8 (53.3%)	
No	65	29 (44.6%)	36 (55.4%)	0.886[b]
ASA score				
I and II	89	37 (41.6%)	52 (58.4%)	
III and IV	13	7 (53.8%)	6 (46.2%)	0.404[b]
Tumor localization				
Right colon	47	19 (40.4%)	28 (59.6%)	
Left colon	42	18 (42.9%)	24 (57.1%)	
Rectal	10	6 (60.0%)	4 (40.0%)	0.537[c]
Type of surgery				
Open	21	12 (57.1%)	9 (42.9%)	
Minimally invasive[e]	81	32 (39.5%)	49 (60.5%)	0.146[b]
Pathological tumor stage (AJCC)				
0 and I[f]	24	8 (33.3%)	16 (66.7%)	
II	33	19 (51.5%)	17 (48.5%)	
III	38	16 (42.1%)	22 (57.9%)	0.387[b]

Values are presented as median and interquartile range [IQR] or as numbers and (%)

ASA American Society of Anesthesiologists, *AJCC* American Joint Committee on Cancer

[a]Mann-Whitney *U* test

[b]Pearson's chi-square test

[c]Fisher's exact test

[d]Data of 22 patients were missing, so in this case n=80

[e]Including robot-assisted surgery

[f]1 patient had an AJCC stage 0 tumor, 4 patients did not have a carcinoma, 2 patients unknown, 1 patient had a double tumor, so in this case n=95

4 (IQR 4–5) days for those without (n=58) postoperative complications (P<0.001). None of the patient characteristics were statistically significant different between patients with and without a postoperative complication (Table 2).

The median time-interval between the preoperative CPET and surgery was 14 (IQR 9–22) days and the median duration of the ramp phase of the CPET was 568 (IQR 475–617) seconds or 9.5 (IQR 7.9–10.3) minutes. A maximal effort was accomplished by 85 (83.3%) patients and the median respiratory exchange ratio (RER) at peak exercise was 1.12 (IQR 1.11–1.23). VO_{2VAT} was undeterminable in 2 (0.9%) patients, whereas the VE/VCO_2-slope and the OUES were determinable in all patients. Median values of the CPET-derived variables were 30.6 (27.4–35.0) for VE/VCO_2-slope, 22.4 (18.1–28.2) for OUES/kg, 18.4 (15.1–24.4) mL/kg/min for VO_{2peak}, and 11.9 (10.2–14.4) mL/kg/min for VO_{2VAT} (Fig. 1). The preoperative VE/VCO_2-slope was statistically significantly higher, and the OUES/kg, absolute VO_{2peak}, and VO_{2peak} and VO_{2VAT} relative to body mass were statistically significant lower in patients with postoperative

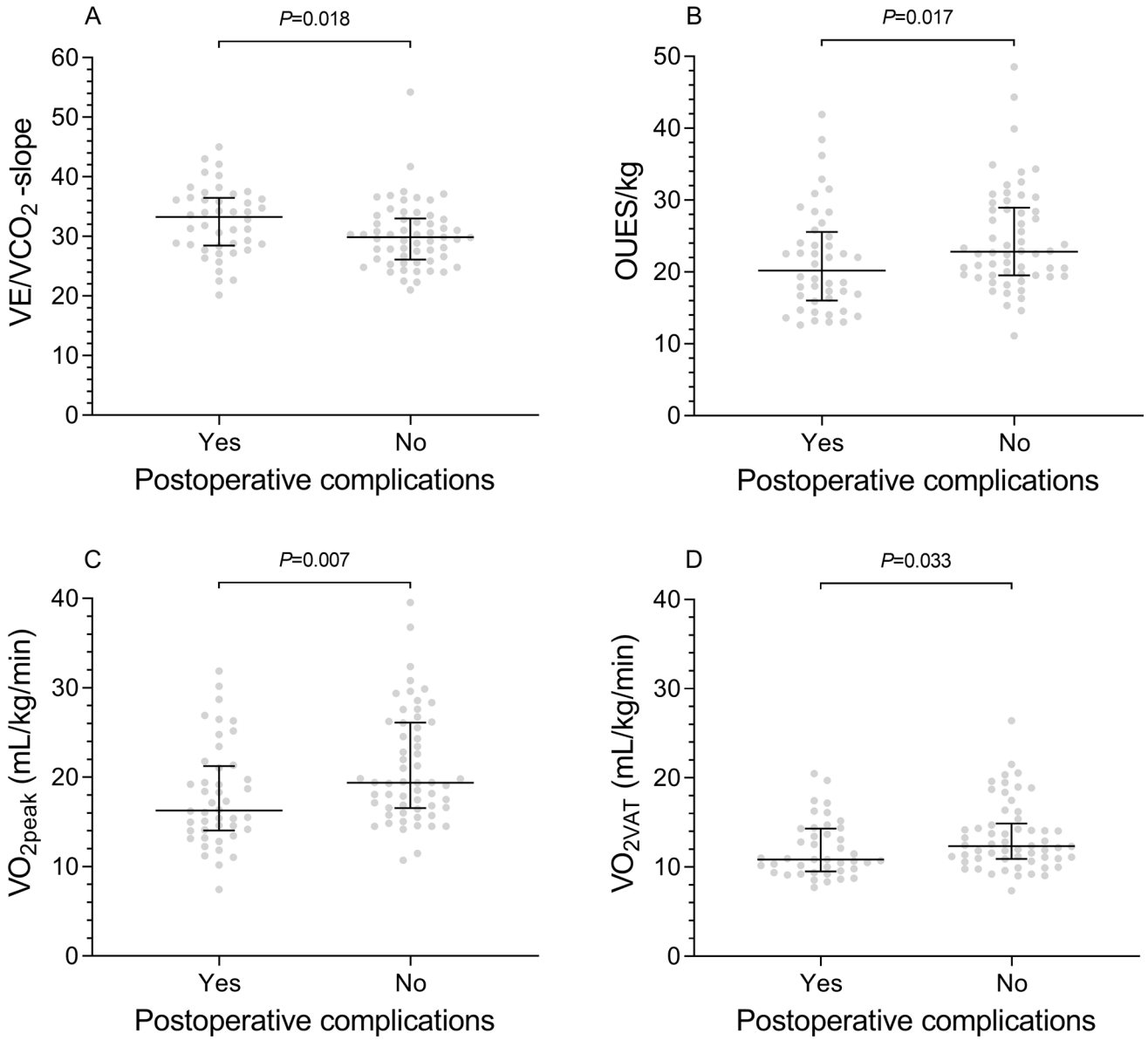

Fig. 1 CPET outcomes of patients with (Yes) and patients without (No) 30-day postoperative complications following colorectal surgery. Gray dots represent individual patients. Horizontal lines with error bars represent the median and interquartile range. Statistically significance was tested using the Mann-Whitney U test. Abbreviations: OUES/kg, oxygen uptake efficiency slope normalized for body mass; VE/VCO_2-slope, the slope of the relation between minute ventilation and carbon dioxide production up to the respiratory compensation point; VO_{2peak}, oxygen uptake at peak exercise; VO_{2VAT}, oxygen uptake at the ventilatory anaerobic threshold

complications compared to those without complications. Preoperative CPET results are presented in Table 3.

In univariate logistic regression analyses, age >75 years, male sex, ASA score (III and IV), open surgery, VE/CO_2-slope, OUES/kg, VO_{2peak} relative to body mass, and VO_{2VAT} relative to body mass were tested for their prognostic value for postoperative complications. Of these variables, the VE/VCO_2-slope (OR 1.08, 95% CI 1.00–1.16), OUES/kg (OR 0.94, 95% CI 0.89–1.00), and VO_{2peak} relative to body mass (OR 0.91, 95% CI 0.85–0.98) were statistically significant associated with postoperative complications. VO_{2VAT} relative to body mass seemed to be associated with postoperative complications (OR 0.88, 95% CI 0.78–1.00); however, it was only borderline significant (P=0.051). In addition to the VE/VCO_2-slope, OUES/kg, VO_{2peak}, and VO_{2VAT}, the variables age >75 years (P=0.127*)* and open surgery (P=0.150) were included in the multivariate logistic regression analyses (all P<0.200 in univariate analyses). Four multivariate regression models were constructed to investigate the individual prognostic value for each CPET-derived variable separately. The variables age, sex, and ASA score were not retained in the final models, as they were not associated with postoperative complications at a P-value <0.200. The VE/VCO_2-slope (model 1, OR 1.08, 95% CI 1.02–1.16; P=0.046), OUES/kg (model 2, OR 0.94, 95% CI 0.94–1.00; P=0.046), VO_{2peak} relative to body mass (model 3, OR 0.91, 95% CI 0.85–0.98; P=0.014), and VO_{2VAT} relative to body mass (model 4, OR 0.88, 95% CI 0.78–1.00; P=0.048) were all statistically significant associated with postoperative complications in the multivariate logistic regression analysis when adjusting for type of surgery (see Table 4). ROC analyses did not reveal any cutoff points for the variables VE/VCO_2-slope (area under the curve (AUC) 0.64, 95% CI 0.53–0.75), OUES/kg (AUC 0.64, 95% CI 0.53–0.75), or VO_{2peak} relative to body mass (AUC 0.66, 95% CI 0.55–0.77), and VO_{2VAT} relative to body mass (AUC 0.63, 95% CI 0.51–0.74) that met the predefined preferred sensitivity and specificity of at least 80% and 50%, respectively. However, if an optimal cutoff point had to be defined (i.e., Youden's index) for the VE/VCO_2-slope, this would be 30.5, with 64% sensitivity and 59% specificity. For the OUES/kg, this cutoff point would be 22.7, with a sensitivity of 66% and a specificity of 52%. For VO_{2peak} and VO_{2VAT} relative to body mass, these cutoff points were respectively 19.4 mL/kg/min (71% sensitivity and 48% specificity) and 12.2 mL/kg/min (62% sensitivity and 53% specificity).

Discussion

The aim of this retrospective explorative study was to investigate the prognostic value of the effort-independent and objectively determinable VE/VCO_2-slope and OUES to preoperatively predict postoperative complications following elective colorectal surgery. In the current study, the preoperative VE/VCO_2-slope (OR 1.08) and the OUES/kg (OR 0.94)

Table 3 Preoperative CPET results in relation to 30-day postoperative complications following colorectal surgery

Parameter	Total (n=102)	Postoperative complication		P-value
		Yes (n=44)	No (n=58)	
HR_{peak} (beats/min)	**144 [122–160]**	**141 [116–153]**	**149 [131–166]**	**0.012**[a]
HR_{peak} (% of predicted)	**92.7 [80.2–101.8]**	**89.4 [76.4–100.0]**	**95.8 [83.4–104.1]**	**0.016**[a]
RER_{peak}	1.12 [1.11–1.23]	1.15 [1.11–1.22]	1.18 [1.11–1.23]	0.325[a]
Maximal effort (yes)	85 (83.3%)	37 (84.1%)	48 (82.3%)	0.858[b]
VE/VCO_2-slope	**30.6 [27.4–35.0]**	**33.2 [28.5–36.5]**	**29.9 [26.1–33.1]**	**0.018**[a]
OUES/kg	**22.4 [18.1–28.2]**	**20.2 [16.0–25.6]**	**22.8 [19.5–28.9]**	**0.017**[a]
VO_{2peak} (mL/kg/min)	**18.4 [15.1–24.4]**	**16.3 [14.0–21.3]**	**19.4 [16.6–26.1]**	**0.007**[a]
VO_{2VAT} (mL/kg/min)[a]	**11.9 [10.2–14.4]**	**10.8 [9.5–14.3]**	**12.3 [10.9–14.9]**	**0.033**[a]
VE/VCO_{2VAT}[a]	31.2 [28.4–34.4]	32.7 [28.0–36.4]	30.5 [28.5–32.9]	0.219[a]

Values are presented as median and interquartile range [IQR] or as numbers and (%)

Abbreviations: HR_{peak} heart rate at peak exercise, *OUES/kg* oxygen uptake efficiency slope relative to body mass, RER_{peak} respiratory exchange ratio at peak exercise, VE/VCO_2*-slope* the slope of the relation between minute ventilation and carbon dioxide production up to the respiratory compensation point, VE/VCO_{2VAT} ratio between minute ventilation and carbon dioxide production at the ventilatory anaerobic threshold, VO_{2peak} oxygen uptake at peak exercise, VO_{2VAT} oxygen uptake at the ventilatory anaerobic threshold

[a]Mann-Whitney *U* test

[b]Pearson's chi-square test

[c]Predicted maximal heart rate was based on the formula 208 – (0.7 × age)

[d]The ventilatory anaerobic threshold was undeterminable in 2 patients, so n=42 in the group with postoperative complications

Bold are statistically significant at a level p<0.05

Table 4 Univariate and multivariate logistic regression of variables associated with 30-day postoperative complications following colorectal surgery

	Univariate		Multivariate stepwise[a]							
			Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age >75 years	1.87 (0.84–4.20)	0.127	Not retained		Not retained		Not retained		Not retained	
Male sex	0.88 (0.37–2.00)	0.760	Not retained		Not retained		Not retained		Not retained	
ASA score III and IV	1.64 (0.51–5.30)	0.407	Not retained		Not retained		Not retained		Not retained	
Open surgery	2.04 (0.77–5.40)	0.150	2.00 (0.74–5.40)	0.170	2.10 (0.76–5.62)	0.157	2.04 (0.74–5.63)	0.171	2.00 (0.72–5.58)	0.181
VE/VCO_2-slope	**1.08 (1.00–1.16)**	**0.041**	**1.08 (1.02–1.16)**	**0.046**						
OUES/kg	**0.94 (0.89–1.00)**	**0.045**			**0.94 (0.89–1.00)**	**0.046**				
VO_{2peak} (mL/kg/min)	**0.91 (0.85–0.98)**	**0.013**					**0.91 (0.85–0.98)**	**0.014**		
VO_{2VAT} (mL/kg/min)	0.88 (0.78–1.00)	0.051							**0.88 (0.78–1.00)**	**0.048**

[a]Four forward stepwise multivariate logistic regression analyses were performed to investigate the prognostic value of the VE/VCO_2-slope (model 1), OUES (model 2), VO_{2peak} (model 3), and VO_{2VAT} (model 4) for any 30-day postoperative complication

Abbreviations: ASA American Society of Anesthesiologists, *OR* odds ratio, *OUES/kg* oxygen uptake efficiency slope relative to body mass, *VE/VCO_2-slope* the slope of the relation between minute ventilation and carbon dioxide production up to the respiratory compensation point, *VO_{2peak}* oxygen uptake at peak exercise, *VO_{2VAT}* oxygen uptake at the ventilatory anaerobic threshold

Bold are statistically significant at a level $p<0.05$

were statistically significantly associated with postoperative complications. In addition, the preoperative CPET variables VO_{2peak} and VO_{2VAT} relative to body mass, corrected for type of surgery, were statistically significant associated (OR 0.91 and 0.88, respectively) with postoperative complications in the current cohort of patients approaching colorectal surgery.

Traditionally, physiological markers of aerobic fitness that are obtained at specific time-points during the preoperative CPET, such as the VO_{2peak} and VO_{2VAT}, are the most commonly used variables used for preoperative risk assessment in major abdominal surgery [3, 5]. However, these variables bear some limitations, as interpretation of VO_{2peak} is difficult when a patient did not continue to exercise until volitional maximal exhaustion (16.7% of the patients in the current study), and methods for the determination of VO_{2VAT} are complex. The findings of the current study provide novel evidence that the effort-independent CPET-derived variables VE/VCO_2-slope and OUES can be used to assist in preoperative risk assessment in patients approaching colorectal surgery. The advantages of the VE/VCO_2-slope and the OUES are that their calculation uses all data (for VE/VCO_2-slope up to the respiratory compensation point) gained during the CPET. Therefore, the VE/VCO_2-slope and OUES might better reflect continuous, dynamic cardiopulmonary responses throughout the CPET as opposed to variables obtained at specific time-points (i.e., VO_{2peak} and VO_{2VAT}). In addition, the VE/VCO_2-slope and OUES are objectively determinable in all patients, and they do not require a maximal effort from the patient. The latter is of great clinical importance, as the VE/VCO_2-slope and OUES can therefore also be prognostic in patients who are unable or unwilling to perform a volitional maximal effort (i.e., due to fatigue, pain, and/or lack of motivation). Individual risk prediction from preoperative CPET-derived data may support collaborative decision-making and guide perioperative preventive interventions (e.g., multimodal prehabilitation) [22]. Exercise prehabilitation can be beneficial in decreasing the incidence of postoperative morbidity after colorectal surgery, especially when aiming at high-risk patients [6, 23].

Although there is no previous research that investigated the association between the preoperative VE/VCO_2-slope and postoperative complications, some studies addressed the prognostic value in this context of the VE/VCO_2 ratio at the ventilatory anaerobic threshold (VE/VCO_{2VAT}) [4]. Similar to the VE/VCO_2-slope, VE/VCO_{2VAT} is a marker of ventilatory efficiency with higher values representing worse ventilation-perfusion matching in the lungs. Previous research [4] has shown that VE/VCO_{2VAT} can be used as a prognostic variable for postoperative complications as measured using the postoperative morbidity survey [24]. Nevertheless, it needs to be noted that although the VE/VCO_2-slope and VE/VCO_{2VAT} are often used interchangeably [22], they are not (always) numerically similar. Interestingly, in the current study, VE/VCO_2-slope but not VE/VCO_{2VAT} differed

statistically significant between patients with and without postoperative complications (Table 2). Therefore, the VE/VCO_2-slope potentially seems a stronger predictor than the VE/VCO_{2VAT}. The observation that the OUES/kg is statistically significantly associated for postoperative complications in the multivariate analysis is not surprising, as previous research has shown that the preoperative OUES/kg is strongly associated (r 0.763) with VO_{2peak} relative to body mass in patients approaching colorectal surgery [15], indicating it reflects a patient's cardiorespiratory fitness.

The strongest association with postoperative complications in our study was however seen in VO_{2peak}. This is not new, as the preoperative VO_{2peak} has been found to be consistently associated with postoperative complications after colorectal surgery in previous research [3–5]. In the Measurement of Exercise Tolerance before Surgery (METS) study [25], the largest preoperative CPET study so far that included 1401 patients in 25 hospitals across the globe, VO_{2peak} was the only CPET-derived parameter that was predictive for postoperative complications following major non-cardiac surgery. The VO_{2VAT} has also been shown to be prognostic for postoperative complications in several previous studies [3–5].

In the ROC analysis, the independent predictive value of the VE/VCO_2 and OUES/kg was not sufficiently accurate (AUC 0.64 for both variables) to retrieve any relevant cutoff points with the predefined sensitivity of 80% and specificity of 50%. Nevertheless, the cutoff points retrieved in the current study showed comparable sensitivity and specificity with the cutoff point for VO_{2VAT} (sensitivity 68% and specificity 58%) that was found in a previous study by West et al. [4]. In hindsight, it might have been too optimistic to assume that the VE/VCO_2-slope and OUES/kg alone would have strong predictive value for postoperative complications, given the many pre- and postoperative factors that influence postoperative outcomes. Previous research has already shown that CPET outcomes alone have limited predictive performance to assess the perioperative risk [26, 27]. However, in combination with biomarkers such as hemoglobin levels (anemia), albumin levels (malnutrition), inflammatory markers [28], or NT-PRO-BNP [25], and/or embedded within a comprehensive risk score [29], the predictive value of CPET-derived variables might improve as has been shown in previous studies [25, 28, 29]. Unfortunately, inclusion of these biomarkers was not feasible in the current study due to its retrospective nature.

One of the limitations of the current explorative study was that it was based on secondary analysis of data retrieved within different clinical trials. This means that the availability of the data depended on and was restricted to the data that was collected during these trials. The occurrence of postoperative complications is not only influenced by a patient's preoperative physical status, but also by general perioperative measures (e.g., type of anesthesia, surgical duration, postoperative management). These factors should be considered in future research. Secondly, the data collected from the different hospitals was not homogenous regarding patient characteristics as depicted in Online Resource 1. Unfortunately, the sample size precluded us from stratifying for hospital or to perform subgroup analyses. Combining the data from different studies was considered to be representative of those approaching colorectal surgery. Although patients in the current studies were not referred for CPET based on medical reasons, selection bias based on aerobic fitness cannot be ruled out completely. However, aerobic fitness (i.e., VO_{2peak}) of patients in the current study (Fig. 1) are in line with those of healthy individuals [30] of the same age, sex, and body mass, as well as with a relatively large recently published prehabilitation study [31]. Therefore, it is believed that the aerobic fitness levels of patients in the current study is a representative estimate of the total population of patients undergoing colorectal surgery. Nevertheless, results should be interpreted within the explorative nature of this study and should be confirmed in a future prospective study.

Strengths of the current study include that all CPETs of multiple centers were re-analyzed by two clinical exercise physiologists for the purpose of the current study. By doing so, any variability of CPET outcomes coming from inter-rater variability was minimized and detailed analyses of the CPETs was possible. Moreover, the current study assessed postoperative complications until 30 days after surgery, whereas others [3–5] have used complications until day 5 after operation as primary outcome; the latter may have resulted in an underreported postoperative complication rate in previous studies.

In conclusion, results of the current retrospective explorative study in patients approaching elective colorectal surgery show that the preoperatively assessed effort-independent and objectively determinable VE/VCO_2-slope and OUES/kg are associated with postoperative complications and might be useful parameters to assist in preoperative risk assessment, especially in patients who are unwilling or unable to deliver a maximal cardiorespiratory effort during a CPET. As such, the VE/VCO_2-slope and OUES/kg seem promising variables worth investigating in future research with a larger sample size and in combination with other prognostic preoperative (CPET-derived) variables.

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Declarations

Competing interests The authors declare no competing interests.

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