TITLE: Minute ventilation-to-carbon dioxide slope is associated with postoperative survival after anatomical lung resection

AUTHORS: Takuro Miyazaki[ab], Matthew EJ Callister[c], Kevin Franks[d], Padma Dinesh[a], Takeshi Nagayasu[b], Alessandro Brunelli[a]

INSTITUTIONS:

[a]Department of Thoracic Surgery, St. James's University Hospital, Leeds, UK

[b]Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[c] Department of Respiratory Medicine, St. James's University Hospital, Leeds, UK

[d] Department of Clinical Oncology, St. James's University Hospital, Leeds, UK

Corresponding author: Takuro Miyazaki, MD, PhD,

Department of Surgical Oncology,

Nagasaki University Graduate School of Biomedical Sciences,

1-7-1 Sakamoto, Nagasaki 852-8501, Japan;

Tel: +81-95-819-7304; Fax: +81-95-819-7306;

E-mail: miyataku@nagasaki-u.ac.jp

Abstract

Objectives: The aim of the study was to identify whether ventilation-to-carbon dioxide output (V_E/V_{CO2}) slope obtained from cardiopulmonary exercise test (CPET) as part of the preoperative functional workup was an independent prognostic factor for short and long-term survival after major lung resection.

Patients and Methods: 974 consecutive patients undergoing lobectomy (n=887) or segmentectomy (n=87) between April 2014 to March 2018 were included. 209 (22%) underwent CPET, and pulmonary function tests and several clinical factors including age, sex, performance status and comorbidities were retrospectively investigated to identify the prognostic factors with a multivariable Cox regression analysis.

Results: Among the patients with measured V_E/V_{CO2}, the incidence of cardiopulmonary complications in patients with high V_E/V_{CO2} slope (>40) was 37% (19 of 51) vs. 27% (33 of 121) in those with lower slope values (p=0.19). The 90-day mortality in patients with high V_E/V_{CO2} slope (n=8) was 16% vs. 5% (n=6) in those with lower slope values (p=0.03). No overall difference in 2-year mortality was identified between the two groups (VE/VCO2 >40: 70% (54-80) vs. VE/VCO2 ≤40: 72% (63-80), log-rank test, p=0.39). In a Cox regression analysis V_E/V_{CO2} values were associated with poorer 2-year survival (HR 1.05, 95% CI 1.01-1.10, p=0.030).

Conclusions: We found that V_E/V_{CO2} slope was an independent prognostic factor for the 90-day mortality and 2-year survival after anatomic pulmonary resection. This finding may assist during the multidisciplinary treatment decision-making process in high-risk patients with lung cancer.

Key Words: Lung Cancer, Surgery, Cardiopulmonary exercise test.

1. Introduction

Assessment of the aerobic capacity using cardiopulmonary exercise test (CPET) is recommended as a second line test dependent on results of initial pulmonary function tests and low technology fitness tests (e.g. stair climbing or shuttle walk test) to stratify the risk of surgery [1].

Low values of maximal oxygen consumption (V_{O2} max) have been associated with high risk of mortality and long-term disability following major lung resection as they reflect the impairment in the oxygen transport system caused by deficits of one or more of its components (i.e. heart, lungs, and skeletal muscles) [1,2]. Recently, however, in a case matched analysis from European Society of Thoracic Surgeons (ESTS) database, low V_{O2} max was not associated with increased morbidity and mortality after video-assisted thoracic surgery (VATS) lobectomy [3].

Although, in clinical practice, V_{O2} max is still the most used and reliable variable for patient selection, the ratio of minute ventilation (V_E) to carbon dioxide output (V_{CO2}), is gaining interest. V_E/V_{CO2} slope is the relationship between VE, plotted on the Y axis, and V_{CO2}, on the X axis, both measured as L/min. It can be determined in submaximal tests and relates to changes in the ventilation-perfusion relationship or hyperventilation [4, 5]. The increased V_E/V_{CO2} slope is considered as a prognostic factor in patients with pulmonary hypertension, heart failure [6, 7] and respiratory failure [8].

In our specialty, previous reports have shown that patients with V_E/V_{CO2} slope exceeding 35 had a significant higher incidence of respiratory complications and mortality after major pulmonary resection, while V_{O2} max was not associated with respiratory complications [9]. Moreover, some reports [10- 12], which were almost consistent with our previous results [9], demonstrated the efficacy and importance of

V_E/V_{CO2} slope for predicting surgical complications in patients with chronic obstructive pulmonary disease (COPD).

However, these reports were limited to COPD patients and acute postoperative complications only. Evidence of the association between this parameter and longer term outcomes (i.e. 90-day mortality and beyond 1-year survival) are missing. Therefore the purpose of this retrospective study was to verify the association between V_E/V_{CO2} slope value and short (90-day) and long term (2-year) survival of NSCLC patients after major pulmonary resection.

2. Patients and Methods

This is the retrospective analysis performed on a prospectively maintained institutional database used for quality of care monitoring and clinical service evaluation. All 974 patients who underwent anatomical lung resection including lobectomy and segmentectomy in St. James's Hospital, Leeds, UK, from April 2014 to March 2018 were analysed. For the purpose of this analysis wedge resections were excluded due to minimal invasiveness, and pnemonectomies were also excluded due to excessive invasiveness. The study was reviewed by the Research and Innovation Department of our hospital, which waived NHS Research Ethics Committee review and classified it as a service evaluation.

All patients were selected for pulmonary resection according to current functional guidelines and after discussion during a multidisciplinary tumour board meeting [13]. A preoperative symptom-limited CPET on an electronically braked cycle ergometer was performed to detect the deficit in their oxygen transport system when the postoperative predicted (ppo) FEV1 or $ppoDL_{CO}$ (or both) are <30%, or if the distance walked during shuttle walk test was shorter than 400 meters, according to the locally

accepted guidelines [1, 14].

Patients were operated by specialist thoracic surgeons through a muscle-sparing, nerve-sparing thoracotomy or VATS. Following the operation, the patients were extubated in the operating room and transferred to an intensive care unit for constant monitoring where they spent the first postoperative night. They were subsequently transferred to a dedicated general thoracic surgical ward. Postoperative treatment focused on early as possible mobilization, chest physiotherapy, and physical rehabilitation administered by a specialized physiotherapist. Surgical pain was managed with a combination of intravenous patient controlled and local paravertebral analgesia. The details of this enhanced recovery pathway was previously described elsewhere [13].

The exercise test involved the patient undertaking a symptom limited CPET test with heart (ECG) monitoring. After measurement of resting data, patients commenced unloaded cycling on a Lode Corival ergometer (Netherlands) until oxygen uptake stabilised. They then cycled at a constant rate of 60 rpm on a ramping protocol, which increased by 1 watt every 6 seconds until either they reached their maximally tolerated level or the test was stopped due to significant ECG or blood pressure changes.

Peak power output (measured in watts), oxygen uptake (VO2), the ratio of dead space to tidal volume (Vd/Vt) and the ventilation (VE) to carbon dioxide output (VCO2) slope (VE/VCO2 slope) were measured during the CPET test using an Ultima CPET metabolic cart (Medical Graphics, UK).

The VE/VCO2 slope was calculated using the slope calculation option of the software package both to anaerobic threshold (if obtained) and to peak VO2. For the purpose of this study the value at anaerobic threshold was considered. If AT was not

reached, the value at peak VO2 was considered.

2.1 Statistical analysis

Risk factors and outcomes were defined and standardized at database outset and in keeping with the joint Society of Thoracic Surgeons and European Society of Thoracic Surgeons statement [15]. The following complications occurring in hospital or within 30 days from the operation were included in the major cardiopulmonary morbidity outcome: adult respiratory distress syndrome, pneumonia, pulmonary embolism, pulmonary oedema, atelectasis requiring bronchoscopy, respiratory failure (needing longer than 24 hours mechanical ventilation or needing re-intubation after surgery), arrhythmia requiring electrical or medical cardioversion, myocardial ischemia, cardiac failure, stroke and acute renal failure.

The normal distribution of numeric variables was first assessed by the Shapiro-Wilk normality test. Numeric variables with normal distribution were tested by the unpaired Student t test, and those without normal distribution were compared by means of Mann-Whitney test. Categorical variables were tested by the chi-square test or Fisher's exact test (in case of less than 10 observations in at least one cell). No adjustment for multiple testing was performed.

The following variables were tested along with V_E/V_{CO2} for a possible association with 90-day mortality: age, gender, performance status (Eastern Cooperative Oncology Group: PS), forced expiratory volume in one second (FEV1%), carbon monoxide lung diffusion capacity (DL_{CO}%), body mass index (BMI), coronary artery disease (CAD), cerebrovascular disease (CVD), and surgical access (thoracotomy or VATS). Variables were initially screened by univariate analysis. Those with a $p<0.1$ were entered as predictors in a stepwise logistic regression analysis with backward

elimination (p for retention <0.1).

Survival was defined as the interval between surgery to death or last contact. Patients who were not reported as dead at the time of the analysis were censored at the date they were last known to be alive. Survival distribution was estimated by the Kaplan-Meier method. Significant differences in probability of surviving between the groups were evaluated by log-rank test. The Cox multivariate proportional hazard regression model was used to evaluate the effects of the prognostic factors on 2-year overall survival. Follow-up was obtained by data retrieved from the centralized electronic Patient Pathway Manager clinical information system of the hospital. All patients were followed up through March 2018. Median follow up was 738 days (IQR 418-1119).

The following variables were tested along with V_E/V_{CO2} for a possible association with 2-year overall survival: age, gender, PS, FEV1%, DL_{CO}%, body mass index BMI, CAD, CVD, and surgical access (thoracotomy or VATS). In addition, pathological T and N descriptors were also examined to adjust the survival analysis. All statistical tests were performed on the statistical software Stata 15.0 (StataCorp, LP, College Station, Tex).

3. Results

974 patients underwent lobectomy (n=887) or segmentectomy (n=87) during the study period. 801 (82%) operations were performed through VATS. 209 patients had CPET as part of the preoperative functional workup. Table 1 showed the comparison between patients with (n=209, 21%) and without CPET (n=765, 79%). Patients who performed CPET were older (p<0.0001), had lower FEV1 (p<0.0001), lower DL_{CO} (p<0.0001), and higher incidence of CAD (p=0.002) and had a worse performance

status (p=0.01). The incidence of cardiopulmonary complications in patients with CPET was 30% versus 21% in those without (p=0.003). Similarly, the 90-day mortality was more than double in those with CPET (7.7% vs. 2.9%, p=0.002).

3.1 VO2 max

20 patients (10%) had a V_{O2} max lower than 12 ml/kg/min, 75 (35%) between 12 and 15 ml/kg/min, 84 (40%) between 15 and 20 ml/kg/min and 30 patients (15%) equal or greater than 20 ml/kg/min. The incidence of cardiopulmonary complications in these categories was 40%, 29%, 35% and 10%, respectively (p=0.033). The incidence of 90 day mortality was 5%, 11%, 7.1%, 3.3%, respectively (p=0.69). When the groups were collapsed in two lager categories (95 patients: V_{O2}max<15 mL/kg/min; 114 patients: V_{O2}max≥15 mL/kg/min), no differences were observed in cardiopulmonary complications (32% vs. 29%, p=0.68) and 90-day mortality rates (9.5% vs. 6.2%, p=0.43).

3.2 Early outcomes

172 (83%) of 209 patients had their V_E/V_{CO2} estimated during CPET and available for this analysis. The remaining 37 patients without VE/VCO2 data were studied in other centers and their slope values were not estimated at the time of the study. 51 (30%) patients had a V_E/V_{CO2} slope >40.

The incidence of cardiopulmonary complications in patients with V_E/V_{CO2} slope >40 was 37.2% (19 of 51 patients) vs. 27.3% (33 of 121 patients) in those with lower slope values (p=0.19). The 90-day mortality rate in patients with V_E/V_{CO2} slope >40 was 15.9% (8 of 51 patients) vs. 5.0% (6 of 121 patients) in those with lower slope values (p=0.03). Among patients experiencing cardiopulmonary complications during their

hospital stay, 37% of those with V_E/V_{CO2} slope >40 died at 90 days versus 12% of those with lower slope values (p=0.074).

22 (24%) of 93 patients with a V_{O2} max≥15 ml/kg/min had a V_E/V_{CO} slope>40, and 29 (37%) of 79 patients with V_{O2}max<15 ml/kg/min had a slope of or higher than 40 (p=0.062). The incidence of 90-day mortality in patients with high or low V_{O2}max (cut-off 15 ml/kg/min) was not significantly higher when the V_E/V_{CO2} slope was>40 (9.1% vs. 21%, p=0.44). Similarly, in patients with lower values of slope, the 90-day mortality rate was similar in those with high or low V_{O2} max (4.2% vs. 6.0%, p=0.69).

After adjusting for other confounders using a logistic regression analysis, V_E/V_{CO2} slope remained an independent predictor significantly associated with 90-day mortality (OR 1.2, 95%CI 1.1-1.3, p<0.001), whereas V_{O2} max was not associated with 90-day mortality (table 2).

3.3 Long term outcome

Compared to patients with lower V_E/V_{CO2} slope the 1-year survival of patients with V_E/V_{CO2} slope >40 was poorer (p=0.056): 76% (95% confidence interval: CI, 62-85) vs. 87% (95% CI, 81-93). 2-year survival was similar between the two groups (V_E/V_{CO2} >40: 70% (54-80) vs. V_E/V_{CO2} ≤40: 72% (63-80), log-rank test, p=0.39) (figure 1).

A multivariable Cox regression analysis was performed to identify prognostic factors associated with 2-year survival. Higher V_E/V_{CO2} values remained associated with poorer 2-year survival (HR 1.05, 95% CI 1.01-1.10, p=0.030) along with lower values of DL_{CO} (HR 0.98, 95%CI 0.95-1.00, p=0.055), male sex (HR 1.75, 95%CI 0.92-3.34, p=0.089) and p-N2 stage (HR 3.55, 95%CI 1.52-8.29, p=0.003).

4. Discussion

We found that higher V_E/V_{CO2} slope was a useful prognostic factor not only for the 90-day mortality, but also 2-year survival of NSCLC patients after anatomical pulmonary resection after adjusting for other confounders using regression models.

Risk stratification before lung resection in patients with lung cancer is becoming increasingly important in the face of an ever-growing population of elderly patients with frequent underlying comorbidities. The choice of the most appropriate radical treatment for these frail and high risk patients should be a shared decision based on reliable estimation of short and long term risk of mortality and availability of non-surgical treatments. Still the definition of the lowest limit of operability remains equivocal. The use of fitness tests is recommended by current functional guidelines [16] in selected patients and V_{O2} max is so far the most widely used parameter to assess cardiopulmonary function [2, 12]. V_{O2} level is influenced by the combined contribution of the heart, lungs the oxygen transport system, and skeletal muscles to external work [9] and represents a reliable parameter expressing the global fitness of the patients. A low Vo_2 indicates that there is a deficit in the oxygen transport system that needs to be identified and possibly corrected to minimize the surgical risk. In this regard, CPET provides a vast array of direct or indirect parameters, which may assist in precisely identifying the functional problem. Among these parameters, recently V_E/V_{CO2} slope, also known as inefficiency slope, has been one of the most investigated ones. [4-6, 8, 17]. One of the most important characteristics which might make it superior to V_{O2} max was that it was independent of patient effort and can be measured at sub-maximal workload levels [5]. We speculate that the possible mechanism for the relationship between VE/VCO2 and mortality following surgery may be due to the decreased vascular bed after anatomical lung resection that could

exacerbate a V/Q mismatch in patients with latent subclinical pulmonary hypertension or heart failure.

The relationship between higher V_E/V_{CO2} slope and lower V_{O2} max was not always consistent. This indicated a differential interpretation of these two ergometric variables. We may expect that V_{O2} max retains the information that is derived from the lungs, together with the information from other systems involved in work production, while V_E/V_{CO2} slope is the expression of lung efficiency which may or may be not compensated for by the other systems.

In this study, 24% of patients with higher V_E/V_{CO2} slope had normal V_{O2} max (>15 mL/kg/min) and 37% of them had low V_{O2} max, respectively. Although we found a prohibitive rate of 90-day mortality in patients with both low V_{O2} max and high slope value (21%), this rate was not significantly different from the one observed in those with normal values of V_{O2} max and high slope values (9.1%). Therefore, it appears that the estimation of V_E/V_{CO2} slope is useful even in patients with apparently good aerobic capacity. The 90-day mortality rate of these patients after lobectomy or segmentectomy (the majority of them performed through minimally invasive thoracic surgery) was extremely high in this series (9.1%).

Likewise, in patients with lower values of V_E/V_{CO2} slope, the 90-day mortality was not different between those with high or low V_{O2} max (4.2% vs. 6.0%, p=0.69). Therefore, it appeared that in the presence of a reduced V_{O2} max, a normal slope value is protective against adverse events after surgery. The present findings indicate that ventilatory efficiency is more accurate in stratifying the prognosis of patients after lung resection. These findings were consistent with previous reports [9, 11] and suggesting that both parameters should be taken into account of evaluating of high risk pulmonary resections.

At variance with previous reports we selected a higher cut-off value of V_E/V_{CO2} slope. Traditionally and based on studies in other specialties [18], 35 has been previously used as the high risk cut-off value. However, in this series 53% of patients had a slope greater than 35 and a receiver operating characteristics analysis identified a value of 40 as the optimal cut-off for 90-day mortality.

In chronic heart failure [7], V_E/V_{CO2} slope ≥ 32.9 was a strong predictor of cardiac-related mortality by receiver operating characteristics curve. Torchio [11] et al adopted the cut-off of >34 as used in heart failure patients. Shafiek et al [10] also determined cut-off value of V_E/V_{CO2} slope as >35 for predicting postoperative complications. However, they included patients submitted to pneumonectomy, who in our opinion represent a different group of patients and analysed separately from lesser resections for the higher physiologic burden imposed by that operation. This is the reason why we did not include those patients in our analysis.

Unlike previous studies dealing with efficiency slope, we analysed not just early outcomes such as morbidity and mortality but also long term survival. We found that the relationship between V_E/V_{CO2} and survival was biphasic, with a poorer survival in patients with high slope value during the first year after surgery and a subsequent plateauing of the survival curve. At 2 year after surgery, we were not able to find any difference between patients with slope higher or lower than 40. This finding is probably related to a higher mortality rate immediately after surgery and during the first months for causes unrelated to cancer progression (cardiopulmonary causes). This is also in keeping with the relatively small effect of V_E/V_{CO2} slope on survival (although significant) at 2 years found at Cox regression analysis. At this stage other oncologic prognostic factors such as nodal status become predominant. A limitation of this study is the lack of cancer specific survival data due to the absence of the cause

of death, which are not recorded in the centralized electronic hospital system. In light of previous studies reporting an association between physical fitness or quality of life and cancer specific survival [19], future studies will be required to elucidate whether V_E/V_{CO2} slope may be associated with cancer progression and death. Similarly further study are needed to identify how high V_E/V_{CO2} slope would affect the non-cancer related causes of death, quality of life, and also in different subsets of patients (i.e. elderly, COPD, cardiac comorbidities) [5].

This study has potential limitations. Firstly, this is a retrospective study from a single centre and the number of patients with CPET (n=209) and estimated V_E/V_{CO2} slope (n=172) was relatively small. This may be particularly critical when analysing rare events such as 90 day mortality (only 14 events). In addition, the result that there was no difference between the complications and mortality between low and high V_{O2} max groups in the high V_E/V_{CO2} groups should be interpreted with caution because there was a trend towards higher complications and mortality in the low V_{O2} max group. The lack of significance might be a reflection of the low numbers of events occurring in these groups. Secondly, the follow-up period (median 628 days) might not be sufficiently long to draw definitive conclusions about the relationship between overall survival of surgically treated NSCLC patients and ergometric variables. Third, the findings of this study are applicable to lobar or anatomic sublobar resection only. Specific studies on pneumonectomies should be performed to verify the association between short term and long term outcomes and the efficiency slope.

Another limitation discussed above is the lack of cause specific mortality, which is a limit inherent to our hospital electronic patient level system. Admittedly, knowing the cause of death would have helped in better understanding the biphasic relationship between efficiency slope and survival. Lastly, although we found that 40 was the best

cut-off value in our series, the optimal cut-off value of V_E/V_{CO2} slope has not been determined yet. To resolve these limitations, a larger possibly multicenter study would be needed.

5. Conclusions

We were able to find that a high value of V_E/V_{CO2} slope was associated with poorer early and long term outcomes following anatomical pulmonary resection. These findings may assist members of the tumour board to select the most appropriate radical treatment for borderline patients. This ergometric parameter, along with V_{O2} max, should be used routinely when CPET is available, to refine risk stratification and as an additional information to share with the patient during the surgical counselling. The present study confirmed previous findings and warrant the inclusion of this parameter in future revisions of functional guidelines to assess fitness for radical treatment of lung cancer.

Figure legend

Figure 1: 2-year survival rates of patients with V_E/V_{CO2} slope >40 and lower. No significant difference was identified between the groups. (log-rank test, p=0.39). V_E/V_{CO2}: the ratio of minute ventilation to carbon dioxide output

Acknowledgments:

The author appreciates for the 1st Japanese Association for Thoracic Surgery fellowship.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Brunelli A, Kim AW, Berger KI, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 143 (2013) e166S–190S.

[2] Brunelli A, Belardinelli R, Refai M, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. Chest. 135 (2009) 1260–1267.

[3] Begum SS, Papagiannopoulos K, Falcoz PE, Decaluwe H, Salati M, Brunelli A. Outcome after video-assisted thoracoscopic surgery and open pulmonary lobectomy in patients with low VO2 max: a case-matched analysis from the ESTS database. Eur J Cardiothorac Surg. 49 (2016) 1054-1058.

[4] Herdy AH, Ritt LE, Stein R, Araùjo CG, Milani M, Menegheli RS, et al. Cardiopulmonary exercise test: background, applicability and interpretation. Arq Bras Cardiol. 107 (2016) 467-481.

[5] Brunelli A. Ventilatory efficiency slope: an additional prognostcator after lung cancer surgery. Eur J Cardiothorac Surg. 50 (2016) 780-781.

[6] Nadruz W, West E, Sengeløv M, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with reduced, midrange, and preserved ejection fraction. J Am Heart Assoc. 6 (2017) e006000.

[7] Shen Y, Zhang X, Ma W, et al. VE/VO2 slope and its prognostic vale in patients with chronic heart failure. Exp Ther Med 9 (2015) 1407-1412.

[8] Vainshelboim B, Oliveria J, Fox BD, et al. Prognostic role of ventilator inefficiency and exercise capacity in idiopathic pulmonary fibrosis. Respir Care. 61 (2016) 1100–1109.

[9] Brunelli A, Belardnelli R, Pompili C, et al. Mintute ventilation-to-carbon dioxide output (VE/V_{CO2}) slope is the strongest predictor of respiratory complications and death after pulmonary resection. Ann Thorac Surg. 93 (2012) 1802-1806.

[10] Shafiek H, Valera JL, Togores B, et al. Risk of postoperative complications in chronic obstructive lung diseases patients considered fit for lung cancer surgery: beyond oxygen consumption. Eur J Cardiothorac Surg. 50 (2016) 772-779.

[11] Torchio R, Guglielmo M, Giardino T, et al. Exercise ventilatory insufficiency and mortality in patient with chronic obstructive pulmonary disease undergoing surgery for non-small-cell lung cancer. Eur J Cardiothorac Surg. 38 (2010) 14-20.

[12] Salati M, Brunelli A. Risk stratification in lung resection. Curr Surg Rep. 4 (2016) 37.

[13] Brunelli A, Thomas C, Dinesh P, et al. Enhanced recovery pathway versus standard care in patients undergoing video-assisted thoracoscopic lobectomy. J Thorac Cardiovasc Surg. 154 (2017) 2084-2090.

[14] Fennelly J, Potter L, Pompili C, et al. Performance in the shuttle walk test is associated with cardiopulmonary complications after lung resection. J Thorac Dis. 9 (2017) 789-795.

[15] Fernandez FG, Falcoz PE, Kozower BD, et al. The Society of Thoracic Surgeons and the European Society of Thoracic Surgeons general thoracic surgery database: joint standardization of variable definitions and terminology. Ann Thorac Surg. 99

(2015) 367-376.

[16] Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 28 (2017) iv1-21.

[17] Armstrong HF, Dussault NE, Thirapatarapong W, et al. Ventilatort efficiency before and after lung volume reduction surgery. Respir Care. 60 (2015) 63-71.

[18] Van de Veire NR, Van Laethem C, Philippé J, et al. VE/VCO2 slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVO2. Eur J Cardiovasc Prev Rehabil. 13 (2006) 916-923.

[19] Vijayvergia N, Shah PC, Denlinger CS. Survivorship in non–small cell lung cancer: challenges faced and steps forward. J Natl Compr Canc Netw. 13 (2015) 1151–1161.

Figure 1.

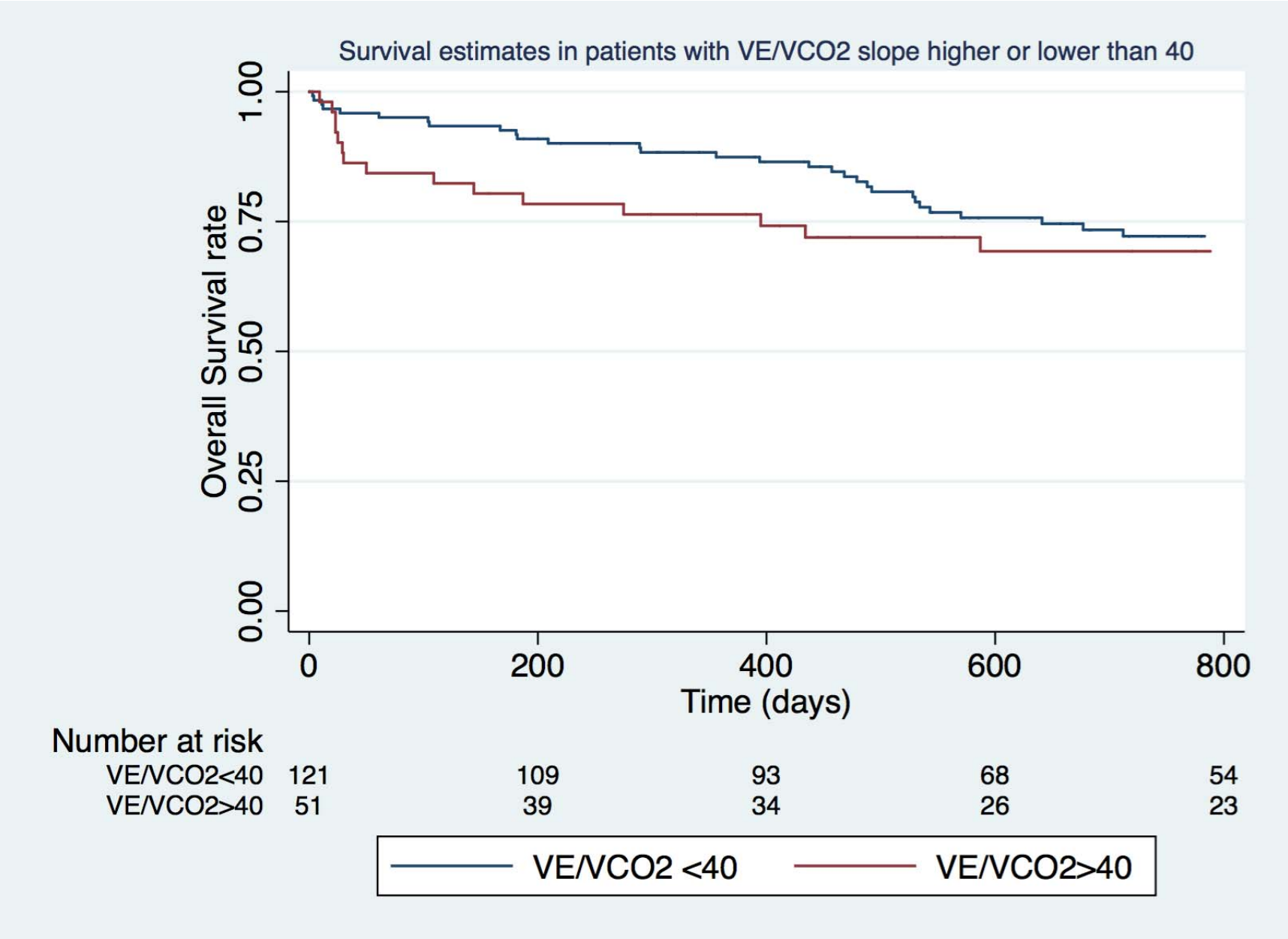
Survival estimates in patients with VE/VCO2 slope higher or lower than 40
Overall Survival rate
0.00
0.25
0.50
0.75
1.00
0
200
400
600
800
Time (days)
Number at risk
VE/VCO2<40 121 109 93 68 54
VE/VCO2>40 51 39 34 26 23
VE/VCO2 <40
VE/VCO2>40

Table 1. Patients' characteristics in patients with and without CPET

Variables	With CPET (n=209)	Without CPET (n=765)	P value
Age	72.4 (8.3)	66.9 (10.6)	<0.001
Male sex (n, %)	122 (58%)	327 (43%)	<0.001
PS>1 (n, %)	35 (17%)	77 (10%)	<0.01
FEV1%	78.0 (23.6)	90.6 (22.0)	<0.001
DL_{CO}%	61.7 (17.6)	75.9 (17.5)	<0.001
BMI	25.8 (5.0)	27.5 (5.6)	<0.001
CAD (n, %)	43 (20.6)	94 (12.3)	0.002
CVD (n, %)	18 (8.6)	41 (5.4)	0.08
Thoracotomy (n, %)	46 (22.0)	127 (16.6)	0.07
Cardiopulmonary complications (n, %)	63 (30.1)	157 (20.5)	0.003
90-daymortality (n, %)	16 (7.7)	22 (2.9)	0.002

Results are expressed as means and standard deviations for numeric variables and as count and percentage of the total number of patients within the category for categorical variables. CPET: Cardiopulmonary exercise test, FEV1%: Forced expiratory volume in 1 second, DL_{CO}: Carbon monoxide diffusion capacity of the lung BMI: Body mass index (kg/m^2), CAD: Coronary artery disease, PS: Eastern Cooperative Oncology Group performance status, CVD: Cerebrovascular disease

Table 2. Results of the stepwise logistic regression analysis in patients with VE/VCO2 slope measurement (dependent variable: 90 day mortality). Parsimonious model shown.

Predictors	OR	95%CI	P value	
Age	1.1	1.0-1.2	0.023	
Sex male	9.5	1.4-66.0	0.023	
VE/VCO2 slope	1.2	1.1-1.3	<0.0001	

OR: Odds ratio; CI: Confidence Interval; V_E/V_{CO2}: the ratio of minute ventilation to carbon dioxide output,