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Beyond the slope: prognostic utility of the VE/VCO$_2$ intercept in chronic heart failure

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ABSTRACT

Aims Cardiopulmonary exercise testing (CPET) parameters are used for heart failure (HF) prognostication. While the ventilation to carbon dioxide production (VE/VCO$_2$) slope ≥34 identifies high risk, patients with intermediate values remain heterogeneous. The VE/VCO$_2$ Y-intercept, reflecting dead space ventilation at rest and its changes during effort, may refine prognostication.

Methods We retrospectively analysed 2642 HF. Follow-up was 26 (9–63) months. The study endpoint was the composite of all-cause death, urgent transplant or left ventricular assist device implantation.

Results Median age was 62 (53–70) years and left ventricular ejection fraction (LVEF) 33% (27%–39%). 27% of patients were New York Heart Association class III–IV. During follow-up, 534 events occurred. Both VE/VCO$_2$ slope and peakVO$_2$ were associated with outcome in univariable and multivariable models (HR 1.04, 95% CI 1.03 to 1.06; HR 0.90, 95% CI 0.88 to 0.93, p<0.001, respectively). Y-intercept was not prognostic univariately but added independent value in multivariable models (HR 1.08, 95% CI 1.04 to 1.13, p<0.001). Prognosis and clinical profiles improved from group A (VE/VCO$_2$ slope ≥34, n=858) to B (28–34, n=943) to C (<28, n=841). Group A versus C patients had lower LVEF (30% (25%–36%) vs 35% (30%–40%), p_{trend}<0.001), peakVO$_2$ (12.7 (10.06–15.3) vs 17.7 (14.6–21.6) mL/kg/min, p_{trend}<0.001) and higher N-terminal pro-B-type natriuretic peptide (1400 (572–3122) vs 454 (174–1081) pg/mL, p_{trend}<0.001). Only within group B, a high median Y-intercept (B1≥3.9 L/m) clearly identified patients with higher HF severity and worse survival than B2 (<3.9 L/m, log-rank p<0.001).

Conclusion An increase in the VE/VCO$_2$ slope is associated with a progressive lower survival. Y-intercept enhances risk assessment in HF with intermediate VE/VCO$_2$ slope values.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The ventilation to carbon dioxide production (VE/VCO$_2$) slope is a well-established prognostic marker in heart failure, with values ≥34 associated with adverse outcomes. However, patients with intermediate VE/VCO$_2$ slope values remain clinically heterogeneous.

WHAT THIS STUDY ADDS

⇒ This study shows that the VE/VCO$_2$ Y-intercept provides additional prognostic information in heart failure patients with non-high-risk VE/VCO$_2$ slope values (<34), particularly in those with intermediate ventilatory inefficiency.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The VE/VCO$_2$ Y-intercept is an easily obtainable extension of standard cardiopulmonary exercise testing interpretation that may improve risk stratification in heart failure patients below the conventional high-risk VE/VCO$_2$ slope threshold.

INTRODUCTION

Cardiopulmonary exercise testing (CPET) plays a pivotal role in the risk assessment of patients with heart failure (HF).[1 2] Among CPET-derived parameters, evaluation of ventilatory inefficiency[3–6] by the ventilation to carbon dioxide production (VE/VCO$_2$) slope ≥34 has consistently been associated with adverse outcomes.[4 5 7–9] However, the use of a binary evaluation based on a single cut-off value may be criticised and not applicable to all clinical conditions leading to HF.[10–12] Indeed, patients with intermediate VE/VCO$_2$ slope values below the high-risk

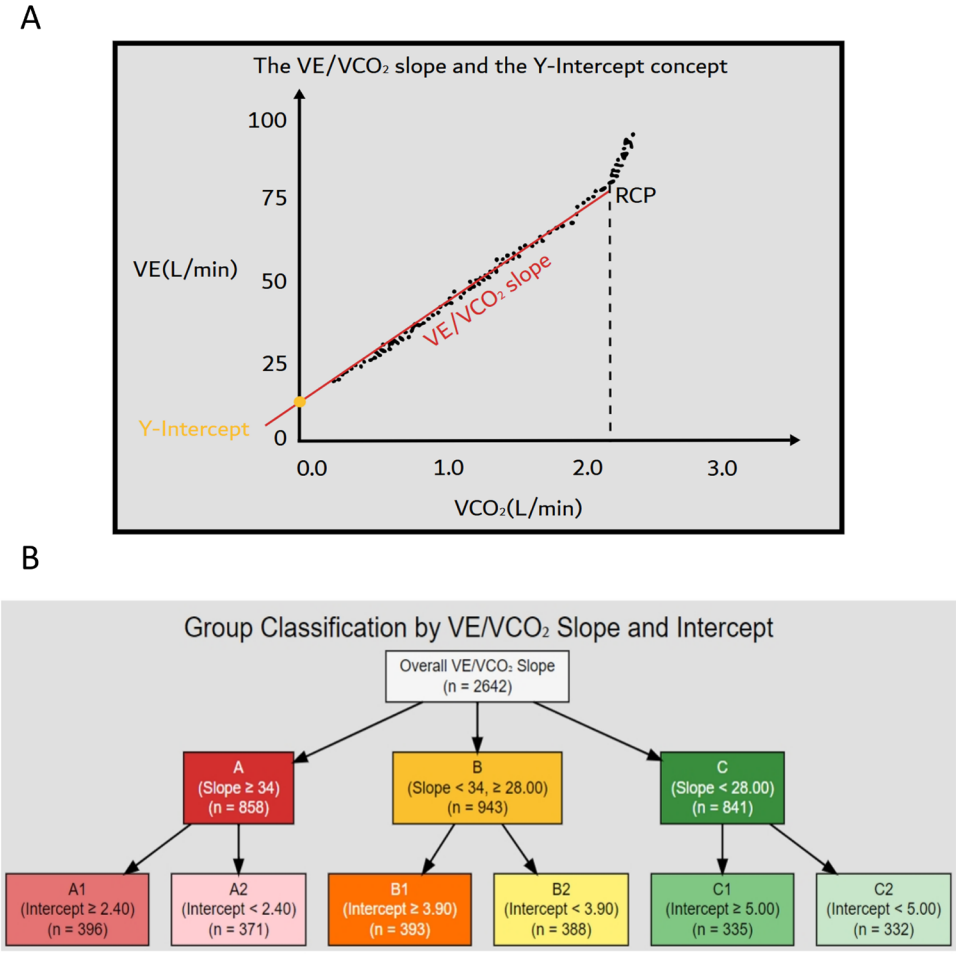

Figure 1 (A) Measurement of the VE/VCO_2 slope. This figure illustrates the derivation of the VE/VCO_2 slope and the Y-intercept in cardiopulmonary exercise testing. The slope is obtained by fitting a linear regression to the relationship between VE and VCO_2 from the beginning of exercise up to the respiratory compensation point, beyond which the ventilatory response becomes non-linear. The Y-intercept is defined as the extrapolated VE value when VCO_2 equals zero. (B) Grouping by the VE/VCO_2 slope and its Y-intercept. This flow diagram illustrates the hierarchical classification of the study cohort (n=2642) based on ventilatory efficiency parameters derived from cardiopulmonary exercise testing (CPET). Participants were initially grouped by VE/VCO_2 slope into three categories: group A (slope ≥34, n=858), group B (slope <34 and ≥28, n=943) and group C (slope <28, n=841). Each group was further stratified according to the VE/VCO_2 Y-intercept using group-specific medians where available (missing Y-intercept in A: 11%, B: 17%, C: 21%): group A into A1 (intercept ≥2.40, n=396) and A2 (Y-intercept <2.40, n=371); group B into B1 (Y-intercept ≥3.90, n=393) and B2 (Y-intercept <3.90, n=388); group C into C1 (intercept ≥5.00, n=335) and C2 (Y-intercept <5.00, n=332). RCP, respiratory compensation point; VE, minute ventilation; VCO_2, carbon dioxide output.

threshold may still present a broad spectrum of clinical risk.[13–1813–15 17]

However, the VE/VCO_2 slope is only one of the two components of the linear relationship linking VE and VCO_2 in a ramp protocol CPET, with the VE axis Y-intercept being the second. Indeed, the VE axis Y-intercept, defined as the point where the extrapolated regression line of the VE/VCO_2 relationship intersects the Y-axis (online supplemental graphical abstract and figure 1A), reflects the combination of dead space volume at rest as well as its changes during exercise.[19 20] Of note, an elevated dead space as well as its increase during exercise are linked to dyspnoea, a cardinal symptom of HF.[21 22] Regardless, the VE axis Y-intercept has received limited attention in the scientific community.[20 23 24] although it allows for separating HF patients with respiratory comorbidities from those without.[25 26] At present, it is unknown whether the VE/VCO_2 slope Y-intercept carries prognostic information in HF.

Therefore, we evaluated, in a sizeable HF population, the prognostic relevance of the VE/VCO_2 slope and assessed whether the Y-intercept adds prognostic power.

METHODS

The Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score registry is a multicentre observational study conducted and still ongoing across several HF units. Inclusion/exclusion criteria for the MECKI score registry have been published elsewhere.[13] In brief, inclusion criteria were: previous or current HF symptoms (New York Heart Association

(NYHA) class I–III, American College of Cardiology/American Heart Association stage C), documented left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF) <40%), stable clinical conditions, ability to perform CPET, and no planned major cardiovascular intervention. Exclusion criteria included history of pulmonary embolism, moderate-to-severe aortic or mitral stenosis, pericardial disease, severe obstructive lung disease, exercise-induced angina, significant ECG abnormalities and any comorbidity limiting exercise performance.

For the present analysis we re-evaluated all CPET to assess the VE/VCO_2 slope Y-intercept which was originally not reported. Seven Italian HF centres participating in the MECKI score registry agreed and assessed the Y-intercept from the VE/VCO_2 relationship.[13 27 28]

Population

We analysed patients recruited between 1993 and 2024 who underwent CPET in a clinically stable condition. Inclusion criteria required a documented history of HF with reduced ejection fraction, absence of scheduled major cardiovascular interventions, and no changes in medical therapy for at least 3 months.

Exercise testing

CPET (Vyntus CPX, Vyaire Medical or Quark CPET, COSMED or Vmax Encore System) was performed as standard[27] on electronically braked cycle ergometers using patient-specific ramp protocols designed to reach maximal exertion within 8–12 min. All tests were symptom-limited. Breath-by-breath gas exchange data were collected. Vital parameters, including heart rate, blood pressure and ECG, were monitored.

Peak oxygen uptake (VO_2) was defined as the highest 30 s averaged value recorded during the final minute of exercise. Per cent-predicted $peakVO_2$ was calculated according to Hansen *et al*.[28] The anaerobic threshold was identified using the V-slope method and confirmed by visual inspection of ventilatory equivalents and end-tidal partial pressure curves for oxygen and carbon dioxide. The VE/VCO_2 slope was assessed as the linear relationship between minute VE and VCO_2, calculated over the linear portion of the curve. The Y-intercept was calculated from the linear regression of the VE/VCO_2 relationship extrapolated to the Y-axis (figure 1A), representing the theoretical VE when VCO_2 equals zero.

Follow-up and outcome

Patient follow-up was conducted prospectively as part of routine care at the enrolling centres, with no predefined time limit. Specifically, in the MECKI score registry, the date of patients enrolment was the date of CPET while the follow-up end was the last clinical visit.[13] For the present study, follow-up was truncated at 150 months to limit the influence of outliers with exceptionally long survival. The composite outcome consisted of all-cause death, urgent heart transplantation or left ventricular assist device (LVAD) implantation.

Statistical analysis

Data analysis was performed in steps. First, we assessed the overall prognostic power for the composite outcome by evaluating the HRs of the VE/VCO_2 slope, Y-intercept and $peakVO_2$ in the entire cohort. Cox proportional hazards models were used to evaluate the prognostic value of the VE/VCO_2 slope, Y-intercept and $peakVO_2$. In the overall cohort, univariate models for evaluating the composite outcome were fitted for the VE/VCO_2 slope, Y-intercept, $peakVO_2$, age and sex. A multivariable model was then constructed accordingly. Following Cox modelling we compared the VE/VCO_2 slope with $peakVO_2$ (mL/kg/min) using receiver operating characteristic (ROC) curves with DeLong testing to assess differences between the areas under the curves (AUCs). Similarly, we compared the VE/VCO_2 slope alone to a model including the Y-intercept, using ROC curves and DeLong testing. AUCs were reported as point estimates with 95% CIs obtained using percentile bootstrap resampling (500 iterations).

Second, patients were stratified into three prognostic groups based on their VE/VCO_2 slope. Group A included patients with a slope ≥34. Among those with a slope <34, patients with slope values ≥the subgroup-specific median were assigned to group B, and those below to group C, to enable a more granular stratification.

Within each group further stratification by the median Y-intercept yielded subgroups A1, B1 and C1 (Y-intercept≥median) and A2, B2 and C2 (Y-intercept<median) (figure 1B).

Continuous variables were summarised as mean±SD when normally distributed, otherwise as median (IQR). Categorical variables were reported as counts and percentages. Normality of continuous variables was assessed using both the Shapiro-Wilk test and graphical methods, including histograms overlaid with Gaussian curves. For comparison among groups A versus B versus C, one-way analysis of variance was used for normally distributed continuous variables, the Kruskal-Wallis test for non-normal variables and the χ^2 test or Fisher's exact test for categorical variables. Trends across A to C were tested using Jonckheere-Terpstra for continuous/ordinal variables and Cochran-Armitage for binary variables. For A1 versus A2, B1 versus B2 and C1 versus C2 Welch's t-tests were used for normal continuous variables, the Mann-Whitney U test for non-normal and Fisher's Exact test or χ^2 test for categorical variables, as appropriate. P values were adjusted using Benjamini-Hochberg procedure, applied separately for each set of comparison set.

The third step of the analysis included survival analyses and Cox proportional hazards regression models, even adjusted for potential confounders. Kaplan-Meier estimates were used to construct event-free survival curves, and group differences were assessed using log-rank tests.

Since only B1 versus B2 showed relevant survival differences only within Group B, univariate models were fitted for the Y-intercept, VE/VCO_2 slope, age, sex, peakVO_2 and per cent predicted forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), followed by a multivariable model.

All analyses were performed using R V.4.4.2 ('Pile of Leaves', The R Foundation). Complete case analysis was employed, excluding observations with missing values for key variables (group-classification variables or follow-up information) without imputation. Variables with high rate of missingness (>30% and ≤50% or >50%) were flagged descriptively in the tables. A two-sided p value <0.05 was considered statistically significant for all analyses.

Assuming an event incidence of 20%, a sample of 2640 subjects is required to detect an HR of at least 1.275 as statistically significant (alpha=0.05) with 80% statistical power.

RESULTS

A total of 2682 patients were screened from eight centres that participated in the MECKI score registry. After excluding those with missing VE/VCO_2 slope values (n=23) and incomplete time-to-event data (n=17), a final cohort of 2642 patients was included in the analysis (table 1). Mean age was 61±13 years, and 81% were male. Mean LVEF was 33±9 and 27% of patients were classified as NYHA functional class III or IV. Prevalence of diabetes was comparable between groups (p>0.05). Median pulmonary function was preserved with FEV_1 and FVC being above 80% of predicted (FEV_1: 84% (71%–95%), FVC: 87% (76%–99%)). PeakVO_2 was 15.1 (12.1–18.7) mL/kg/min being 59% (47%–70%) of predicted, and the median VE/VCO_2 slope was 30.4 (26.9–35.9) with a Y-intercept of 3.8 (2.20–5.30).

Most patients were on guideline-directed medical therapy, including β-blockers (92%), renin–angiotensin–aldosterone system inhibitors (88%) and mineralocorticoid receptor antagonists (58%). Device therapy was common, with 42% of patients having an implantable cardioverter defibrillator (ICD) and 17% a CRT device. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and BNP levels (availability depending on date of inclusion) were elevated, with a median of 759 (336–1725) pg/mL and 263 (103–597), respectively.

Prognostic power of the VE/VCO_2 slope, its Y-intercept and peakVO_2

The VE/VCO_2 slope and peakVO_2 were significant predictors of the composite outcome (table 2). VE/VCO_2 slope was associated with increased risk in univariate (HR: 1.06, 95% CI 1.05 to 1.07, p<0.001) and multivariable analysis (HR 1.04, 95% CI 1.03 to 1.06, p<0.001). Similarly, peakVO_2 was a predictor in univariate (HR 0.87, 95% CI 0.85 to 0.89, p<0.001) and multivariable models (HR 0.90, 95% CI 0.88 to 0.93, p<0.001). VE/VCO_2 Y-intercept was not associated with prognosis in univariate analysis (HR 1.01, 95% CI 0.97 to 1.05, p=0.667), but added independent prognostic value in the multivariable model (HR 1.08, 95% CI 1.04 to 1.13, p<0.001, table 2).

ROC analysis (online supplemental figure 1) demonstrated that peakVO_2 had the highest discriminative ability (AUC=0.699, 95% CI Bootstrap 0.672 to 0.726), followed by the VE/VCO_2 slope (AUC=0.612, 95% CI Bootstrap 0.581 to 0.642; p<0.001, panel A). Adding the VE/VCO_2 Y-intercept to the VE/VCO_2 slope improved the AUC from 0.612 to 0.653 (95% CI Bootstrap 0.624 to 0.684) (p=0.062, panel B). When comparing the AUC of peak VO_2 with that of the VE/VCO_2 slope+Y-intercept, a statistical difference was evident (p=0.024, panel C). Finally, combining peak VO_2 with the VE/VCO_2 slope and the Y-intercept the AUC rose to 0.716 (95% CI Bootstrap 0.689 to 0.742) compared with 0.699 (95% CI Bootstrap 0.672 to 0.726) (p=0.003, panel D) for peak VO_2 alone.

In the analysis of submaximal effort, marked by a respiratory quotient of <1.05 in HF, both peak VO_2 slope and VE/VCO_2 slope demonstrated good discriminative ability (online supplemental figure 2).

Stratification by VE/VCO_2 slope: group A versus B versus C

Patients were classified (figure 1B) into three groups based on VE/VCO_2 slope. Group A included patients with a slope ≥34 (n=858), corresponding to the highest risk profile. Among those with a slope <34 (n=1784), individuals with values ≥to the subgroup-specific median[28] were assigned to group B (n=943), for example, intermediate slope group, and those below assigned to group C (n=841).

Across the A–C gradient, a progressive improvement in patient characteristics was evident (table 1). Patients in group C were significantly younger (56±14 years vs 66±11 years in group A, p_{trend}<0.001), had better LVEF (35±8% vs 31±9% in group A, p_{trend}<0.001), superior exercise capacity (peak VO_2 17.7 (14.6–21.6) mL/kg/min vs 12.7 (10.6–15.3) mL/kg/min in group A, p_{trend}<0.001), less chronotropic incompetence (75% (67%–83%) vs 68% (58%–78%) of predicted peak heart rate in group A, p_{trend}<0.001) and more favourable NYHA functional class distributions (NYHA III–IV 17% vs 41% in group A, p_{trend}<0.001). Moreover, the peak end-tidal carbon dioxide partial pressure ($PetCO_2$) improved stepwise from group A to C (p_{trend}<0.001). Of note VE/VCO_2 relationship Y-intercept progressively increased from group A to C.

Cardiac biomarkers showed strong gradients, with BNP and NT-proBNP levels highest in group A and lowest in group C (p_{trend} for both <0.001). Haemoglobin and renal function (serum creatinine) improved progressively from A to C (table 1). The overall prognosis as assessed by the MECKI score was 3.55% in the entire population and 9.81%, 3.13% and 1.48% (p_{trend}<0.001) in group A, B and C, respectively.

Therapeutic patterns also reflected disease severity as reported in table 1.

Table 1 Patient characteristics stratified by the VE/VCO_2 slope

	Overall (N=2642)	A (N=858)	B (N=943)	C (N=841)	P_{trend} value	FDR-adjusted P_{trend} value*	Group p value	FDR-adjusted group p value*
Patient characteristics								
Age, years	60.75±13.17	65.7±11.3	60.68±12.54	55.79±13.76	<0.001	<0.001	<0.001	<0.001
Male sex, n (%)	2143 (81)	715 (83)	715 (76)	713 (85)	0.464	0.527	<0.001	<0.001
Height, cm	171.23±8.41	170.58±8.39	170.67±8.29	172.54±8.44	<0.001	<0.001	<0.001	<0.001
Weight, kg	78.55±15.4	75.78±14.34	78.77±15.31	81.16±16.07	<0.001	<0.001	<0.001	<0.001
Clinical status and aetiology								
MECKI score, %	3.55 (1.37–9.09)	9.81 (4.55–18.68)	3.13 (1.46–6.43)	1.48 (0.71–3.18)	<0.001	<0.001	<0.001	<0.001
NYHA, n (%)					<0.001	<0.001	<0.001	<0.001
I	534 (20)	81 (10)	199 (21)	254 (30)				
II	1388 (53)	419 (49)	521 (55)	448 (53)				
III	671 (25)	326 (38)	213 (23)	132 (16)				
IV	46 (2)	30 (4)	9 (1)	7 (1)				
Aetiology, n (%)					<0.001	<0.001	<0.001	<0.001
Idiopathic	1124 (44)	276 (34)	389 (44)	459 (56)				
Ischaemic	1062 (42)	430 (52)	375 (42)	257 (32)				
Valvular	89 (4)	34 (4)	36 (4)	19 (2)				
Other	254 (10)	83 (10)	91 (10)	80 (10)				
Systolic blood pressure, mm Hg	115.61±17.59	111.05±16.8	117.66±18.09	117.91±16.92	<0.001	<0.001	<0.001	<0.001
Diastolic blood pressure, mm Hg	72.42±10.21	69.91±9.8	73.23±10.33	74.05±10.01	<0.001	<0.001	<0.001	<0.001
Echocardiography								
LVEF, %	33.14±8.71	30.77±8.92	33.51±8.47	35.15±8.16	<0.001	<0.001	<0.001	<0.001
End-diastolic volume, mL	171 (131–214)	179 (131–225)	170 (132–214)	168 (130–204)	<0.001	0.001	<0.001	<0.001
End-systolic volume, mL	113 (84–152)	123 (90–167)	111 (83–151)	108 (80–138)	<0.001	<0.001	<0.001	<0.001
Systolic PAP, mm Hg	32 (26–42)	37 (29–47)	31 (25–39)	30 (25–35)†	<0.001	<0.001	<0.001	<0.001
Cardiopulmonary exercise testing								
PeakVO_2, mL/kg/min	15.1 (12.1–18.7)	12.7 (10.6–15.3)	15.4 (12.9–18.7)	17.7 (14.6–21.6)	<0.001	<0.001	<0.001	<0.001
PeakVO_2 in % of predicted	59 (47–70)	49 (40–59)	61 (51–72)	66 (55–77)	<0.001	<0.001	<0.001	<0.001
PeakVCO_2, mL/min	1296 (978–1700)	1022 (815–1323)	1338 (1060–1734)	1617 (1241–2049)	<0.001	<0.001	<0.001	<0.001
Peak heart rate, beats/min	115.11±25.32	105.79±24.75	115.98±24.56	123.7±23.46	<0.001	<0.001	<0.001	<0.001
Peak heart rate in % of predicted	71.69±15.89	68.4±16.05	71.95±16.14	74.76±14.77	<0.001	<0.001	<0.001	<0.001
Peak power output, W	81 (59–110)	61 (46–81)	84 (62–107)	104 (77–130)	<0.001	<0.001	<0.001	<0.001
Peak respiratory quotient	1.11 (1.05–1.18)	1.10 (1.03–1.19)	1.11 (1.05–1.18)	1.11 (1.05–1.18)	0.026	0.035	0.033	0.045
Peak $PetCO_2$, mm Hg	32.41±5.62	27.26±3.85	33.05±3.37	37.57±4.13	<0.001	<0.001	<0.001	<0.001
Peak minute ventilation, L/min	50 (40–62)	49 (39–61)	50 (41–62)	51 (41–63)	0.009	0.012	0.030	0.041
Peak respiratory rate, breaths/min	32.31±8.4	34.3±8.5	32.45±8.02	30.14±8.19	<0.001	<0.001	<0.001	<0.001

Continued

Table 1 Continued

	Overall (N=2642)	A (N=858)	B (N=943)	C (N=841)	P_{trend} value	FDR-adjusted P_{trend} value*	Group p value	FDR-adjusted group p value*
VE/VCO_2 slope	30.4 (26.9–35.9)	39.2 (36.0–44.5)	30.3 (29.0–32.0)	25.2 (23.6–26.7)	NA	NA	NA	NA
Y-intercept	3.8 (2.20–5.30)	2.4 (0.4–4.1)	3.9 (2.5–5.2)	5.0 (3.7–6.4)	<0.001	<0.001	<0.001	<0.001
VO_2/work slope, mL/min/W	10.0 (9.0–11.0)	9.1 (8.0–10.3)	10.0 (9.0–11.1)	10.3 (9.3–11.3)	<0.001	<0.001	<0.001	<0.001
Pulmonary function								
FEV_1, L	2.39 (1.87–2.96)‡	2.31 (1.87–2.90)‡	2.50 (1.93–3.04)‡	2.35 (1.78–2.97)‡	0.720	0.768	0.201	0.234
FEV_1, % predicted	84 (71–95)‡	83 (70–95)‡	86 (73–96)‡	82 (69–95)‡	0.468	0.527	0.222	0.252
FVC, L	3.20 (2.56–3.84)‡	3.13 (2.52–3.76)‡	3.29 (2.62–3.93)‡	3.15 (2.46–3.88)‡	0.568	0.631	0.215	0.247
FVC, % predicted	87 (76–99)‡	86 (76–98)‡	89 (79–100)‡	87 (73–99)‡	0.898	0.909	0.190	0.224
Laboratory values								
Serum creatinine, mg/dL	1.10 (0.90–1.33)	1.21 (1.00–1.52)	1.08 (0.89–1.30)	1.01 (0.87–1.19)	<0.001	<0.001	<0.001	<0.001
BNP, pg/mL	263 (103–597)†	555 (274–982)†	217 (108–448)†	108 (54–255)†	<0.001	<0.001	<0.001	<0.001
NT-proBNP, pg/mL	759 (336–1725)‡	1400 (572–3122)‡	610 (321–1287)‡	454 (174–1081)‡	<0.001	<0.001	<0.001	<0.001
Haemoglobin, g/L	138.8±17	135.6±18.6	139±16.2	141.8±15.3	<0.001	<0.001	<0.001	<0.001
Electrocardiography/device therapy								
Atrial fibrillation, n (%)	497 (19)	258 (31)	139 (15)	100 (12)	<0.001	<0.001	<0.001	<0.001
ICD, n (%)	1105 (42)	438 (51)	397 (42)	270 (32)	<0.001	<0.001	<0.001	<0.001
CRT, n (%)	436 (17)	197 (23)	153 (16)	86 (10)	<0.001	<0.001	<0.001	<0.001
Pharmacological therapy								
β-blocker, n (%)	2417 (92)	778 (91)	870 (92)	769 (91)	0.679	0.734	0.527	0.560
RAAS-inhibitor, n (%)	2317 (88)	701 (82)	838 (89)	778 (93)	<0.001	<0.001	<0.001	<0.001
Diuretics, n (%)	1945 (74)	719 (84)	685 (73)	541 (65)	<0.001	<0.001	<0.001	<0.001
Statin use, n (%)	1207 (48)	446 (54)	415 (46)	346 (44)	<0.001	<0.001	<0.001	<0.001
Mineralocorticoid receptor antagonist, n (%)	1530 (58)	583 (68)	512 (54)	435 (52)	<0.001	<0.001	<0.001	<0.001
Digitalis, n (%)	323 (13)	120 (14)	113 (12)	90 (11)	0.047	0.063	0.126	0.158
Amiodarone, n (%)	830 (32)	322 (39)	273 (30)	235 (29)	<0.001	<0.001	<0.001	<0.001

Clinical, functional and cardiopulmonary characteristics across VE/VCO_2 slope groups A (slope ≥34), B (slope <34 and ≥27.80) and C (slope <27.80). Continuous variables are expressed as median (IQR) and were compared using the Kruskal-Wallis test or one-way ANOVA, as appropriate. Ordinal variables were evaluated using the Jonckheere-Terpstra trend test. Categorical variables were assessed using the χ^2 test or Fisher's exact test, and trends in binary proportions were tested with the Cochran-Armitage trend test. Benjamini-Hochberg false discovery rate (FDR) correction was applied to both trend and groupwise p values to account for multiple testing.
*FDR-adjusted p value based on the Benjamini-Hochberg procedure.
†>30%missing.
‡>50% missing.
AF, atrial fibrillation; ANOVA, analysis of variance; BNP, B type natriuretic peptide; bpm, beats per minute; CRT, cardiac resynchronization therapy; FDR, false discovery rate; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICD, implantable cardioverter defibrillator; LAH, left anterior hemiblock; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; PAP, pulmonary artery pressure; $PetCO_2$, partial pressure of end-tidal CO_2; RBBB, right bundle branch block; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.

Table 2 Cox regression models evaluating predictors of the composite outcome

	Univariate			Multivariable		
Predictors	**Estimates**	**CI**	**P value**	**Estimates**	**CI**	**P value**
Cox regression models in the overall cohort						
VE/VCO_2 slope	1.06	1.05 to 1.07	<0.001	1.04	1.03 to 1.06	<0.001
Y-intercept	1.01	0.97 to 1.05	0.667	1.08	1.04 to 1.13	<0.001
$PeakVO_2$	0.87	0.85 to 0.89	<0.001	0.9	0.88 to 0.93	<0.001
Age	1.04	1.03 to 1.05	<0.001	1.03	1.02 to 1.04	<0.001
Male sex	1.45	1.13 to 1.85	0.004	1.56	1.17 to 2.07	0.002
Observations				2210		
R^2 Nagelkerke				0.138		
Cox regression models for group A						
Y-intercept	1.06	1.01 to 1.11	0.026	1.08	1.02 to 1.14	0.005
Age	1.03	1.01 to 1.04	<0.001	1.02	1.00 to 1.03	0.009
$PeakVO_2$	0.86	0.82 to 0.90	<0.001	0.91	0.87 to 0.96	0.001
Male sex	1.84	1.21 to -2.81	0.005	1.54	0.96 to 2.47	0.076
VE/VCO_2 slope	1.05	1.03 to 1.06	<0.001	1.04	1.02 to 1.06	<0.001
FEV_1 (% pred.)	0.99	0.98 to 1.00	0.136			
FVC (% pred.)	1	0.99 to 1.01	0.503			
Observations				765		
R^2 Nagelkerke				0.11		
Cox regression models for group B						
Y-intercept	1.14	1.06 to 1.24	0.001	1.1	1.01 to 1.20	0.036
Age	1.04	1.02 to 1.05	<0.001	1.05	1.03 to 1.07	<0.001
$PeakVO_2$	0.9	0.86 to 0.93	<0.001	0.91	0.87 to 0.96	0.001
Male sex	1.39	0.90 to 2.15	0.138			
VE/VCO_2 slope	1.08	0.98 to 1.19	0.12			
FEV_1 (% pred.)	1	0.99 to 1.02	0.611			
FVC (% pred.)	1	0.99 to 1.02	0.762			
Observations				780		
R^2 Nagelkerke				0.087		
Cox regression models for group C						
Y-intercept	1.15	1.04 to 1.26	0.004	1.14	1.03 to 1.26	0.01
Age	1.03	1.02 to 1.05	<0.001	1.05	1.03 to 1.07	<0.001
$PeakVO_2$	0.93	0.89 to 0.97	<0.001	0.94	0.89 to 0.99	0.021
Male sex	1.39	0.90 to 2.15	0.138			
VE/VCO_2 slope	1.05	0.97 to 1.15	0.224			
FEV_1 (% pred.)	0.99	0.98 to 1.01	0.245			
FVC (% pred.)	0.99	0.98 to 1.00	0.187			
Observations	–			666		
R^2 Nagelkerke				0.09		

Cox proportional hazards regression was used to evaluate predictors of the composite outcome (cardiovascular mortality, all-cause mortality, heart transplantation, left ventricular assist device) for the overall cohort and VE/VCO_2 slope/Y-intercept subgroups. Results are presented as HRs (estimates), with corresponding 95% CIs and p values. Model performance is summarised using Nagelkerke's R^2.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; $peakVO_2$, peak oxygen consumption; R^2, coefficient of determination; VE/VCO_2, ventilatory equivalent for carbon dioxide.

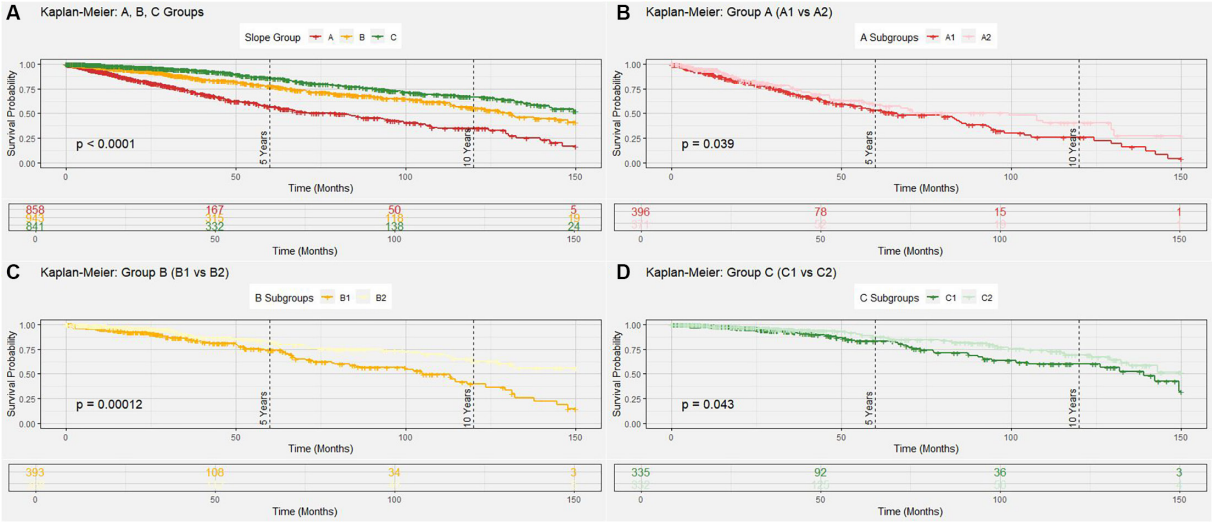

Figure 2 Event-free survival estimates by ventilation to carbon dioxide production (VE/VCO_2) slope and its Y-intercept. Kaplan-Meier curves illustrate event-free survival stratified by VE/VCO_2 slope and Y-intercept. (A) Compares groups A (slope ≥34), B (slope <34 and ≥28) and C (slope <28), showing progressively better outcomes from A to C. (B–D) Subgroup analyses within each slope group based on intercept cut-offs: A1 versus A2 (≥/<2.40), B1 versus B2 (≥/<3.90) and C1 versus C2 (≥/<5.00), respectively. In each group, a lower Y-intercept was associated with better survival.

Stratification by Y-intercept within groups

Within A1 versus A2 and C1 versus C2 KM survival curve showed modest although significant differences with patients with the highest Y-intercept (group A1 and C1) having the worst prognosis (figure 2), only slight differences in clinical profiles, based on the Y-intercept groupings for A and C, can be seen in online supplemental tables. In contrast, within the intermediate slope group, group B (VE/VCO_2 slope <34 but ≥28), further stratification by the group specific median Y-intercept (3.9) yielded two clinically distinct subgroups (table 3): B1 (Y-intercept ≥3.9, n=393) and B2 (Y-intercept <3.9, n=388), as illustrated in figure 1B. Although VE/VCO_2 slope values in both subgroups were closely aligned (30.1 (29.0–31.9) in B1 vs 30.8 (29.3–32.2) in B2), the difference was statistically significant (p=0.001) but not clinically meaningful. Nevertheless, their physiological and clinical profiles markedly diverged.

B2 patients were younger and demonstrated superior exercise performance (table 3). Spirometry was preserved in both groups, but per cent predicted FEV_1 and FVC were better in B2 (table 3). Importantly, NT-proBNP levels were significantly lower in B2 (527 (266–1090) pg/mL vs 863 (394–1635) pg/mL, p=0.039), alongside serum creatinine (1.04 (0.86–1.26) mg/dL vs 1.10 (0.91–1.34) mg/dL, p=0.007). Finally, the MECKI score was not significantly different 3.04% and 2.76% in B1 and B2, respectively.

Clinical history and treatment patterns provided further insight. The low Y-intercept group, B2, had a higher prevalence of idiopathic cardiomyopathy (42% vs 36%) and fewer ischaemic cases (43% vs 50%), along with a lower incidence of atrial fibrillation (12% vs 19%), but comparable prevalence of ICD (44% vs 42%) and CRT (17% vs 15%). Therapeutically, B2 patients were less likely to receive loop diuretics (67% vs 78%) and amiodarone (27% vs 34%).

Prognostic implications of the VE/VCO_2 slope and the Y-intercept

A total of 534 events occurred during the truncated follow-up of up to 150 months (median: 26 (9–63) months), comprising 207 cardiovascular deaths, 59 non-cardiovascular deaths, 43 transplants, 9 LVAD implantations and 216 unclassified events (each being one event of the above).

Kaplan-Meier curves support the prognostic relevance of both VE/VCO_2 slope and its Y-intercept stratification for the composite outcome. As shown in figure 2, patients in group A (slope ≥34) experienced the poorest outcomes, while those in group C (slope <28) had the most favourable survival. Group B patients fell between these extremes (overall p<0.001) while group A and C were only marginally stratifiable by their median Y-intercept (figure 2). Differences in clinical profiles between groups A and C are presented in online supplemental tables 1 and 2.

Within group B, Y-intercept stratification yielded meaningful prognostic separation. As depicted in figure 2, B1 patients (high Y-intercept) experienced significantly worse outcomes compared with B2 (low Y-intercept; p<0.001). This survival gap persisted over the long term.

The combined analysis of groups A, B1, B2 and C (figure 3), revealed a clear and graded hierarchy of survival. Importantly, B2 (low Y-intercept) demonstrated survival probabilities approaching those of group C, while B1 (high Y-intercept) approached patients in group A. A full hierarchical stratification from A1 to C2 can be seen in online supplemental figure 3.

Table 3 Characteristics of patients in VE/VCO_2 slope group B, stratified by the Y-intercept (high vs low Y-intercept)

GROUP B (34>VE/VCO_2 slope≥28)	B1 (high Y-intercept ≥3.90) (N=393)	B2 (low Y-intercept <3.90) (N=388)	P value	FDR-adjusted p value*
Patient characteristics				
Age, years	64.44±11.52	59.6±12.14	<0.001	<0.001
Male sex, n (%)	318 (81)	274 (71)	<0.001	0.007
Height, cm	171.85±8.03	169.96±8.56	0.002	0.011
Weight, kg	79.62±14.95	77.89±15.29	0.111	0.266
Clinical status and aetiology				
MECKI score, %	3.04 (1.42–6.62)	2.76 (1.35–5.52)	0.177	0.313
NYHA, n (%)			0.025	0.083
I	75 (19)	92 (24)		
II	209 (53)	222 (57)		
III	102 (26)	72 (19)		
IV	6 (2)	2 (1)		
Aetiology, n (%)			0.030	0.092
Idiopathic	129 (36)	156 (42)		
Ischaemic	180 (50)	159 (43)		
Valvular	21 (6)	14 (4)		
Other	28 (8)	44 (12)		
Systolic blood pressure, mm Hg	117.95±17.06	118.17±18.79	0.864	0.981
Diastolic blood pressure, mm Hg	73.47±9.94	73.02±10.73	0.539	0.777
Echocardiography				
LVEF, %	33.6±8.27	34.07±8.41	0.434	0.594
End-diastolic volume, mL	172 (132–214)	167 (134–212)	0.856	0.894
End-systolic volume, mL	112 (83–149)	110 (84–145)	0.792	0.875
Systolic PAP, mm Hg	31 (26–42)	30 (25–37)	0.009	0.039
Cardiopulmonary exercise testing				
PeakVO_2, mL/kg/min	15.0 (12.8–19.2)	16.08 (13.2–18.7)	0.078	0.178
PeakVO_2 in % of predicted	61 (49–74)	62 (53–73)	0.344	0.551
PeakVCO_2, mL/min	1326 (1017–1699)	1352 (1097–1741)	0.294	0.489
Peak heart rate, beats/min	113.12±24.61	118.3±23.89	0.003	0.018
Peak heart rate in % of predicted	72.59±14.22	73.82±14.31	0.230	0.404
Peak power output, W	81 (61–104)	86 (65–110)	0.028	0.087
Peak respiratory quotient	1.10 (1.04–1.17)	1.12 (1.06–1.18)	0.020	0.067
Peak $PetCO_2$, mm Hg	32.48±3.3	33.62±3.36	<0.001	<0.001
Peak minute ventilation, L/min	52 (42–64)	51 (41–62)	0.152	0.275
Peak respiratory rate, breaths/min	32.89±7.05	31.7±8.06	0.032	0.107
VE/VCO_2 slope	30.1 (29.0–31.9)	30.8 (29.3–32.2)	0.001	0.009
Y-intercept	5.20 (4.50–6.00)	2.50 (1.40–3.10)	<0.001	<0.001
VO_2/work slope, mL/min/W	10.3 (9.3–11.5)	10.0 (9.0–11.0)	<0.001	0.002
Pulmonary function				
FEV_1, L	2.44 (1.92–2.97)†	2.51 (1.97–3.07)†	0.370	0.569
FEV_1, % predicted	81 (68–95)†	88 (75–97)†	0.017	0.065
FVC, L	3.23 (2.59–3.87)†	3.30 (2.66–3.96)†	0.408	0.594
FVC, % predicted	89 (77–98)†	90 (81–102)†	0.016	0.064

Continued

Table 3 Continued

GROUP B (34>VE/VCO$_2$ slope≥28)	B1 (high Y-intercept ≥3.90) (N=393)	B2 (low Y-intercept <3.90) (N=388)	P value	FDR-adjusted p value*
Laboratory values				
Serum creatinine, mg/dL	1.10 (0.91–1.34)	1.04 (0.86–1.26)	0.007	0.033
BNP, pg/mL	228 (120–492)‡	221 (105–369)†	0.215	0.372
NT-proBNP, pg/mL	863 (394–1635)†	527 (266–1090)†	0.039	0.102
Haemoglobin, g/L	138.5±16	139.6±16.9	0.350	0.594
Electrocardiography/device therapy				
Atrial fibrillation, n (%)	73 (19)	47 (12)	0.019	0.067
ICD, n (%)	164 (42)	170 (44)	0.602	0.732
CRT, n (%)	60 (15)	67 (17)	0.499	0.663
Pharmacological therapy				
β-blocker, n (%)	353 (90)	361 (93)	0.145	0.275
RAAS-inhibitor, n (%)	341 (87)	346 (89)	0.368	0.552
Diuretics, n (%)	301 (78)	261 (67)	0.004	0.023
Statin use, n (%)	183 (48)	179 (51)	0.415	0.594
Mineralocorticoid receptor antagonist, n (%)	225 (58)	226 (58)	0.885	0.906
Digitalis, n (%)	28 (7)	21 (6)	0.375	0.569
Amiodarone, n (%)	132 (34)	101 (27)	0.032	0.092

Comparison of patient characteristics between B1 (high Y-intercept) and B2 (low Y-intercept) subgroups. Continuous variables are presented as median (IQR) and categorical variables as counts (percentages). Group comparisons were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. To correct for multiple testing, Benjamini-Hochberg false discovery rate adjustment was used. The Benjamini-Hochberg procedure was applied to adjust for multiple testing.
*FDR-adjusted p value based on the Benjamin-Hochberg procedure.
†>50% missing.
‡>30% missing.
AF, atrial fibrillation; BNP, B type natriuretic peptide; bpm, beats per minute; CRT, cardiac resynchronization therapy; FDR, false discovery rate; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICD, implantable cardioverter defibrillator; LAH, left anterior hemiblock; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; PAP, pulmonary artery pressure; $PetCO_2$, partial pressure of end-tidal CO_2; RAAS, renin–angiotensin–aldosterone system; RBBB, right bundle branch block; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.

Cox regression confirmed that VE/VCO_2 slope was significantly associated with outcomes (table 2). In the overall cohort, a higher VE/VCO_2 slope was predictive of adverse events (HRs 1.06, 95% CI 1.05 to 1.07; p<0.001), and this association remained robust after multivariable adjustment for age, sex, peakVO_2 and the Y-intercept (HRs 1.04, 95% CI 1.03 to 1.06; p<0.001).

In contrast to the entire study population, within group B, univariate analysis showed that the Y-intercept was associated with a higher risk (HRs 1.14, 95% CI 1.06 to 1.24; p=0.001). This relationship persisted in the multivariable model adjusting for age and peakVO_2, with the Y-intercept remaining an independent predictor of outcome (HRs 1.10, 95% CI 1.01 to 1.20; p=0.022).

DISCUSSION

The present study shows that in HF peakVO_2 emerged as the strongest predictor of adverse outcomes, reinforcing its role as the gold standard parameter in CPET-based risk stratification. The VE/VCO_2 slope also demonstrated independent prognostic value, with its Y-intercept adding value to the VE/VCO_2 slope in patients with an intermediate, ranging between 34 and 28, VE/VCO_2 slope value.

While the VE/VCO_2 slope is an established marker of ventilatory efficiency and adverse outcome,[3–5 22] our study is the first to demonstrate that the Y-intercept, derived from the extrapolated regression line of the VE-VCO_2 relationship, refines risk stratification in individuals with non-high risk (<34/28) VE/VCO_2 slope values.

This observation is mechanistically plausible, as the VE/VCO_2 slope reflects overall ventilatory efficiency,[22] while the Y-intercept captures resting dead space ventilation and its changes during exercise.[20 24] Therefore, a higher Y-intercept may indicate persistent ventilatory low efficiency or elevated resting dead space, potentially reflecting more advanced pulmonary or haemodynamic impairment. As a matter of fact, the Y-intercept progressively increased from group A to C as the VE/VCO_2 slope

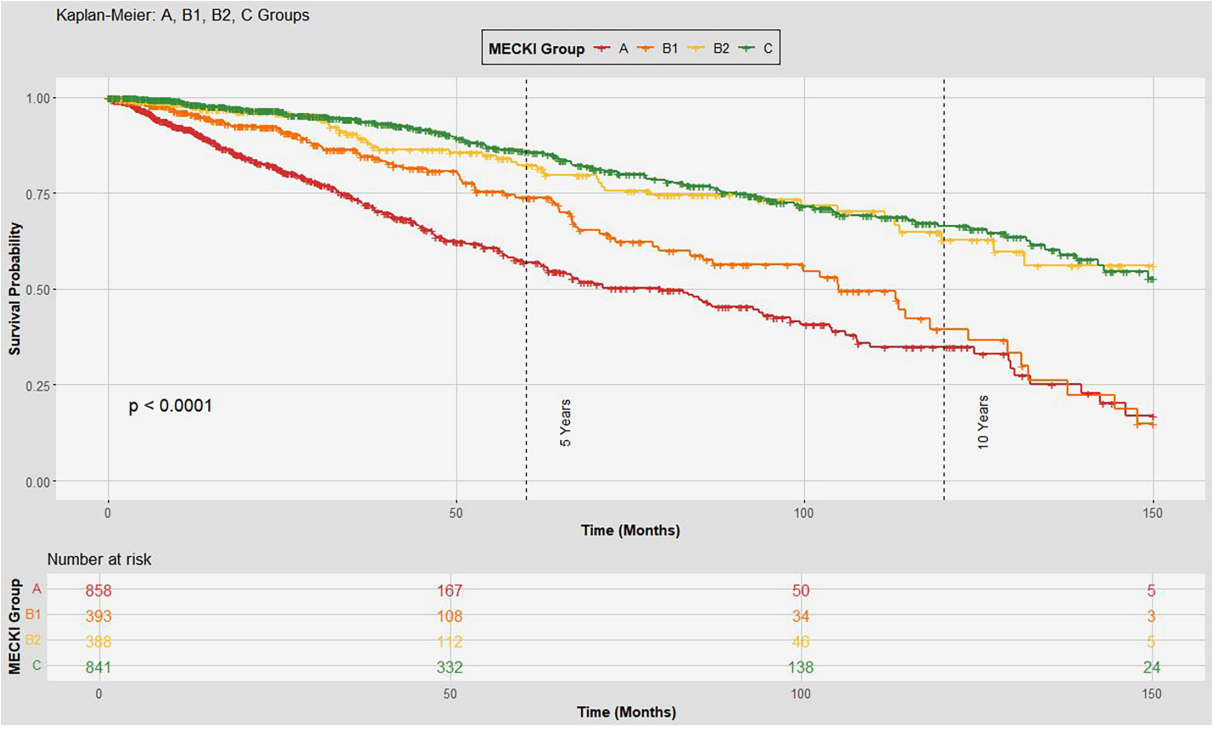

Figure 3 Prognostic stratification across the ventilation to carbon dioxide production (VE/VCO_2) slope-Y-intercept hierarchy (overall+subgroup B). Kaplan-Meier event-free survival curves showing slope groups and subgroup B derived from the combined VE/VCO_2 slope and Y-intercept classification: group A (slope ≥34), group B1 (slope <34 and ≥28, Y-intercept ≥3.90), group B2 (slope <34 and ≥28, Y-intercept <3.90) and group C (slope <28). The survival gradient confirms the prognostic continuum, with progressively lower mortality risk observed from group A to B1 to B2 to C. MECKI, Metabolic Exercise test data combined with Cardiac and Kidney Indexes.

decreased. This is mathematically expected given that the VE/VCO_2 relationship is related to dead space changes during effort so that the greater the dead space increase during exercise, the higher the slope. However, the Y-intercept, but not the slope, is also significantly affected by the resting dead space and its value is not simply a consequence of the VE/VCO_2 slope, but has a physiological meaning independent from the slope.

Importantly, the Y-intercept remained independently associated with the composite outcome after adjusting for key prognostic variables, including age and peakVO_2. The additive value of the Y-intercept was further visible in the four-group stratification (A, B1, B2, C, figure 3), which revealed a clear, stepwise decline in survival probability, indicating a refinement in prognostic granularity adding the Y-intercept to the VE/VCO_2 slope. This stratification suggests that the Y-intercept facilitates a form of 'fate reclassification' where intermediate patients (VE/VCO_2 slope <34 but ≥28) are reassigned towards a more accurate prognostic trajectory. Clinically, this refined approach could support improved risk stratification for a substantial subset of HF patients. However, considering that the Y-intercept is not predictive at univariate analysis it has to be assessed in conjunction with the VE/VCO_2 slope, as indicated by our model of stratification.

The lack of differences in MECKI scores between group B1 and B2, although differences in survival deserve some comments. Indeed, an elevated Y-intercept is related to high dead space at rest or its development during exercise. The former is not considered in any of the MECKI score-generating parameters, while the latter influences VE/VCO_2 slope which is included in the MECKI score. This suggests that parameters reflecting resting dead space may further increase the already very relevant MECKI score prognostic capacity. Indeed, the presence of respiratory abnormalities in HF patients without respiratory diseases has been described for many years.[29–31] As a matter of fact, the present is a hypothesis suggested by our findings which needs to be evaluated by a dedicated study.

Limitations

First, this was a retrospective analysis. Second, although CPET protocols were harmonised, minor differences in equipment and ramp protocols across centres may have affected Y-intercept values. Third, there was a notable lack of data on biomarkers (NT-proBNP), therefore this datum should be interpreted cautiously. Fourth, this study was conducted in patients with HF and reduced ejection fraction, and therefore confirmation in HF with preserved ejection fraction is warranted. Moreover, given the long enrolment period, therapy was not optimised for all patients according to the most recent guidelines, and the broad inclusion timeframe may have influenced outcomes due to suboptimal HF management in some cases. Fifth, we acknowledge that complete-case analysis may have introduced a selection

bias. Indeed, complete-case analysis was restricted to observations missing essential variables for the primary analyses, namely group-classification variables or survival outcome data. Imputation was not performed for group-classification variables and for outcome variables. Finally, it is acknowledged that the definition of the intermediate group is based on median-derived Y-intercept cut-offs. This definition is arbitrary and has not undergone external validation. This raises the possibility of an optimistic separation and the group's boundaries should be considered with caution in the clinical field.

CONCLUSION

The VE/VCO_2 Y-intercept is an easily accessible extension of CPET interpretation that enhances risk assessment in HF, and specifically in patients below the high-risk VE/VCO_2 slope cut-off. Its use should be explored further in prospective and interventional frameworks.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants. The MECKI registry protocol was approved by the institutional ethics committee of each participating centre. Written informed consent was obtained from all participants at enrolment. The study complied with the Declaration of Helsinki (ethical approval: CCM04_21 PA). Participants gave informed consent to participate in the study before taking part.

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