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Prognostic role of cardiopulmonary exercise testing in pulmonary hypertension: a systematic review and meta-analysis

Abstract

Introduction: Several studies have evaluated the relation between variables of cardiopulmonary exercise testing (CPET) and major clinical events in pulmonary hypertension (PH) patients, although the results were conflicting. The main objective of this study was to investigate the prognostic value of the CPET derived parameters on all-cause mortality or urgent transplantation in PH patients.

Material and methods: A meta-analysis of time-to-event outcomes were performed from observational studies that evaluated the predictive value of CEPT-related variables [peak oxygen uptake (VO_2) and the ventilation to CO_2 production slope (VE/VCO_2)] in PH patients, reporting data from mortality or urgent transplantation, after searching the PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar, and Cochrane databases. A fixed or random-effects meta-analysis model was then applied.

Results: Nine eligible studies, including 986 patients, were identified and considered eligible for the quantitative analyses. This meta-analysis showed that high peak VO_2 was associated with a lower mortality or transplant occurrence (HR: 0.81; 95% CI: 0.78–0.85, $I^2 = 29\%$). In addition, high VE/VCO_2 slope was associated with a higher incidence of the primary endpoint (HR: 1.04; 95% CI: 1.02-1.06, $I^2 = 78\%$). The sensitivity analysis showed that the results were robust.

Conclusions: Our data suggest that in a population with PH the CPET-related variables have predictive capacity regarding mortality and the risk of transplantation. Future studies should establish the best cut-off points for these CPET-related variables.

Key words: cardiopulmonary exercise testing, pulmonary hypertension, meta-analysis, mortality, transplantation

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Introduction

The term pulmonary hypertension (PH) includes a heterogeneous group of diseases characterized by a progressive increase in pulmonary arterial resistance, which causes a decrease in quality of life, right heart failure and premature death [1]. According to the current European Society of Cardiology and European Respiratory Society (ESC/ERS) guidelines, PH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg; and pulmonary arterial hypertension (PAH) as a clinical condition characterized by the presence of pre-capillary PH and pulmonary vascular resistance > 3 Wood units (Wu), in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases assessed by right heart catheterization [2]. Recently, a Task Force revisited the definition of PH, suggesting a new pressure level to define an abnormal elevation in the mPAP (> 20 mmHg) and the need for pulmonary vascular resistance ≥ 3 Wu [3].

Cardiopulmonary exercise testing (CPET) is well recognized as the gold standard aerobic exercise testing assessment [4]. It can discriminate cardiovascular, ventilatory, and musculoskeletal limitations during exercise by monitoring

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disturbances in key variable responses such as oxygen, carbon dioxide, minute ventilation, and heart rate [5].

PH is associated with hyperventilation at rest and at exercise, an increase in physiologic dead space and dynamic arterial O_2 desaturation [6]. In addition, maximal cardiac output depends on right ventricular function and critically determines the exercise capacity. Consequently, a reduction in peak oxygen uptake (VO_2) and an increase in the ventilation to CO_2 production slope (VE/VCO_2) are frequently observed in PH patients [1, 7].

In the general population, cardiorespiratory fitness is a predictor of morbidity and mortality [8, 9]. Likewise, the predictive value of the CPET has been demonstrated in various cardiovascular conditions, especially in heart failure [10]. In addition, due to the prognostic ability of key variables, the usefulness of the CPET in patients with PH has been considered [11].

Several observational studies have evaluated the relation between variables of CPET with major adverse clinical events occurrence (all-cause mortality or urgent lung or heart/lung transplantation) in PH patients, although the results were conflicting [12–20]. To date, there are no published meta-analyses that have evaluated this topic.

Therefore, the main objective of the present systematic review and meta-analysis was to investigate the prognostic value of the CPET derived parameters on all-cause mortality or urgent transplantation in PH patients.

Material and methods

Data extraction and quality assessment

The Meta-analysis Of Observational Studies (MOOSE) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to check the reporting of observational studies [21, 22].

A literature search was performed that identified observational studies of CPET related variables in PH patients. Two independent reviewers searched the electronic PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar, and Cochrane Controlled Trials databases using "pulmonary hypertension" or "pulmonary arterial hypertension" terms combined with the following terms: "cardiopulmonary exercise testing", "exercise test", "peak oxygen uptake", "ventilation to CO2 production slope" and "oxygen consumption".

The following inclusion criteria were used to select eligible studies: 1) observational studies with a cohort design (prospective or retrospective). No case-series, cross-sectional or case-control studies were included, 2) studies that included patients with PH confirmed by right heart catheterization, 3) studies that evaluated the relationship between variables of CPET and the risk of major adverse clinical events. Peak VO_2 and VE/VCO_2 slope were chosen as CPET-related variables for this meta-analysis.

The primary endpoint of the study was major adverse clinical events incidence. These events were defined according to the reported events within the selected studies, being a combination of all-cause mortality or urgent lung or heart/lung transplantation.

The quality of the included studies was assessed by two independent review authors using the Newcastle-Ottawa Scale (NOS) [23]. We consider that the studies showed a low, moderate or high quality, when the obtained score was 1 to 4, 5 to 6 or equal to or more than 7 points, respectively. Any discrepancy between the two reviewers was resolved through discussion and by involving a third reviewer.

This meta-analysis was registered in PROSPERO.

Statistical analysis

Since the number of events in the subgroups according to the levels of the CPET parameters were not reported in most studies, a meta-analysis of time-to-event outcomes was performed [24]. Hazard ratios (HRs) and 95% confidens intervals (CIs) were abstracted from each individual study and standard error were calculated. All study-specific estimates were combined using an inverse variance method for pooling. The logarithm of the HRs and their standard errors were used. The summary effect on the endpoints were calculated.

Measures of effect size were expressed as HRs, and the I^2 statistic was calculated to quantify between-studies heterogeneity and inconsistency. Depending on the value of I^2, a fixed effects model ($I^2 < 40\%$) or a random effects model ($I^2 > 40\%$) was chosen. Statistical analyses were performed using the R software for statistical computing version 3.5.1 with additional specific packages [25]. The level of statistical significance was set at a 2-tailed alpha of .05.

Sensitivity analyses

The sensitivity analysis consists of replicating the results of the meta-analysis, excluding in each step 1 of the studies included in the

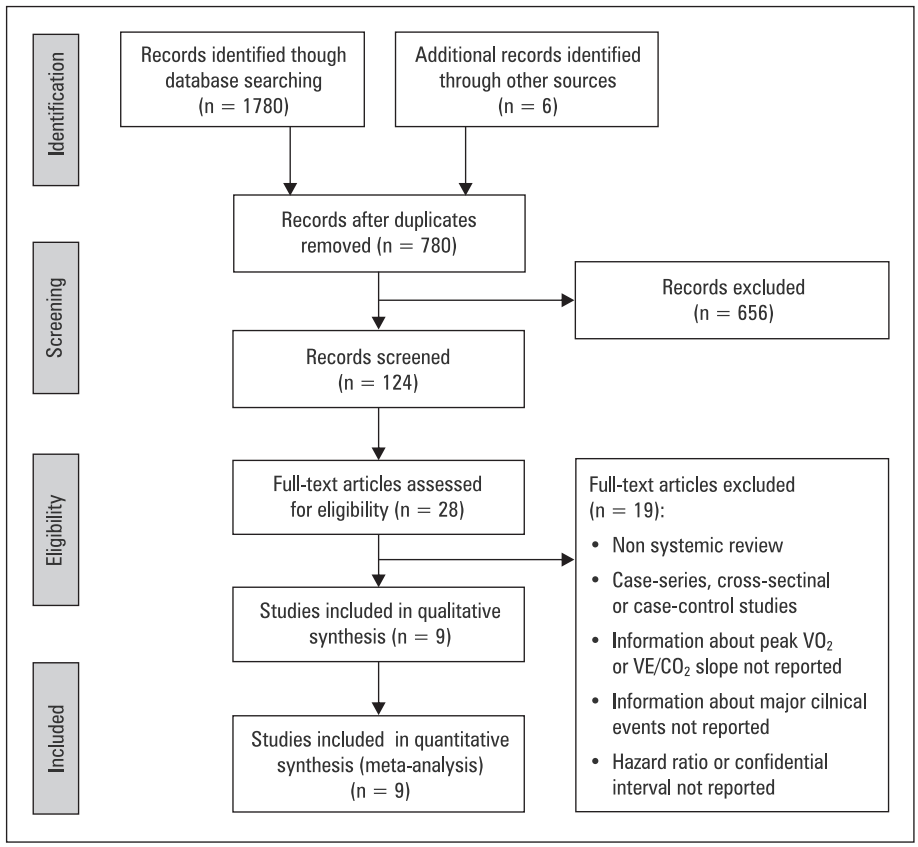

Figure 1. Flow diagram of the study screening process

review. If the results obtained are similar, both in direction and magnitude of the effect and statistical significance, it indicates that the analysis is robust. A sensitivity analysis for the primary endpoint was performed.

Analysis of publication bias

A funnel plot using the standard error (SE) for log HR was created. In addition, Egger's regression intercept tests were done. A p-value less than 0.1 was considered significant for the linear regression test

Results

Nine eligible studies, including 986 patients, were identified and considered eligible for the quantitative analyses. A flow diagram of the study's screening process has been shown in Figure 1.

All included studies were prospective or retrospective observational cohort studies. According to the NOS scale, two studies showed moderate risk of bias and seven studies showed low risk of bias. Likewise, none of the evaluated studies were classified as low quality when applying the NOS tool.

The average age and the proportion of women ranged between 41 and 73 years and between 58.4% and 90%, respectively. Eight studies included patients with idiopathic, familial or associated pulmonary arterial hypertension, while three studies also included patients with chronic thrombo-embolic pulmonary hypertension. Also, two studies included patients with heart failure and PH. Median follow-up duration ranged from 18.6 to 74.5 months. The characteristics of the studies selected for our analysis are summarized in Table 1.

Quantitative analysis showed that high peak VO_2 was associated with a lower mortality or transplant occurrence (HR: 0.81; 95% CI: 0.78–0.85). Statistical heterogeneity was low ($I^2 = 29\%$) (Figure 2). In addition, the meta-analysis showed that high VE/VCO_2 slope was associated with a higher mortality or transplant incidence (HR: 1.04; 95% CI: 1.02–1.06). In this case, the statistical heterogeneity was high ($I^2 = 78\%$) (Figure 3).

The graphical (Figure 4) and analytical evaluation do not suggest publication bias (Egger's asymmetry test, $p = 0.28$. The sensitivity analysis showed that the results were robust (Figures 5 and 6).

Table 1. Characteristics of the studies selected

Study	Cut-off of CPET-related variables		N	Population	Follow up (months)	HR (CI 95%)	Primary outcome
Klassen et al. (2017)	VE/VCO_2 slope	Per 10 increases	88	Mean age 73 years. Female 62.5%. HFpEF (LVEF ≥ 45%) and PAH mPAP 31 ± 10.2 mmHg	23.9	2.04 (1.42–2.93)	Mortality
	Peak VO_2	Per 5 mL/min/kg decrease				0.29 (0.10–0.81)	
Blumberg et al. (2013)	VE/VCO_2 slope	Not reported	36	Mean age 54 years Female 58.4% PAH and CTEPH. mPAP 46 ± 11 mmHg	56	1.07 (1.02-1.11)	Mortality Tx
	Peak VO_2					0.75 (0.62–0.91)	
Grünig et al. (2013)	VE/VCO_2	Not evaluated	124	Mean age 54 years	36	—	Mortality
	slope Peak VO_2	> 11.4 mL/min/kg (median value)		Female 70% PAH or CTEPH. mPAP 50 ± 15 mmHg		0.35 (0.16–0.77)	
Wensel et al. (2012)	VE/VCO_2 slope	Best discrimination was calculated using ROC analysis	226	Mean age 49 years Female 69.5% IPAH o familiar PAH. mPAP 54 ± 15 mmHg.	74.5	1.03 (1.02–1.05)	Mortality/Tx
	Peak VO_2					0.81 (0.76–0.86)	
Deboeck et al. (2012)	VE/VCO_2 slope	Best discrimination was calculated using ROC analysis (< 54)	136	Mean age 54 years Female 59.5%	44.2	1.01 (1.00-1.03)	Mortality/Tx
	Peak VO_2	Best discrimination was calculated using ROC analysis (>11.6 ml/min/kg).		IPAH and APAH. mean mPAP 50.5 mmHg		0.84 (0.75–0.94)	
Ramos et al. (2012)	VE/VCO2 slope	< 50	72	Mean age 41 years Female 80% PAH. mPAP 58 ± 18 mmHg.	28	1.07 (1.01–1.13)	Mortality
	Peak VO_2	< 10.3 mL/min/kg				0.78 (0.60–1.03)	
Oudiz et al. (2010)	VE/VCO_2 slope	Per 1 SD increase	103	Mean age 49 years. Female 90% IPAH, familiar PAH or APAH and HF mPAP 54 ± 16 mmHg	56.4	1.48 (1.05–2.09)	Mortality /Tx
	Peak VO_2					0.95 (0.62–1.45)	
Groepenhoff et al. (2008)	VE/VCO_2 slope	Best discrimination was calculated using ROC analysis (< 48)	115	Mean age 48 years. Female 69.5%. PAH or CTEPH.	27.7	1.04 (1,01–1.07)	Mortality
	Peak VO_2	Best discrimination was calculated using ROC analysis (> 13.2 mL/min/kg)		mPAP > 20 mmHg		0.87 (0.78–0.99)	
Wensel et al. (2002)	VE/VCO_2 slope	Best discrimination was calculated using ROC analysis	86	Mean age 46 years. Female 67.4%. PPH. mPAP 60 ± 2 mmHg	18.6	1.03 (1.01-1.04)	Mortality/Tx
	Peak VO_2					0.79 (0.71–0.89)	

APAH — associated pulmonary artery hypertension; CTEPH — chronic thrombo-embolic pulmonary hypertension; HF — heart failure; HFpEF — Heart Failure with preserved ejection fraction; IPAH — idiopathic pulmonary artery hypertension; LVEF — Left ventricular ejection fraction; mPAP — mean pulmonary arterial pressure; PAH — Pulmonary Artery Hypertension; PCWP — pulmonary capillary wedge pressure; PPH — Primary pulmonary hypertension; SD — standard deviation; Tx — lung or heart/lung transplantation

Discussion

In this systematic review, the main observational studies that evaluated the prognostic value of CPET-related parameters in patients with PH have been described. In addition, in this meta-analysis, higher peak VO_2 and lower VE/VCO_2 slope were associated with a lower mortality or transplant incidence.

The normal physiologic response of the pulmonary vasculature to exercise consists of distension of pulmonary arteries and arterioles as

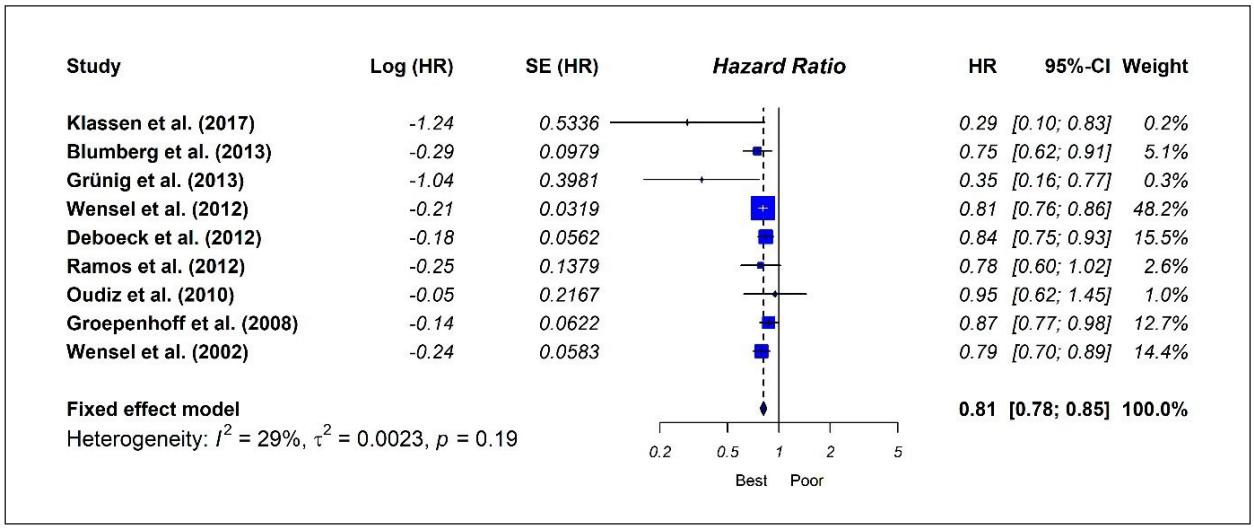

Figure 2. Effect of peak VO_2 on primary endpoint. A fixed-effects, hazard ratios (HR), 95% confidence intervals (CI) and I^2 statistics

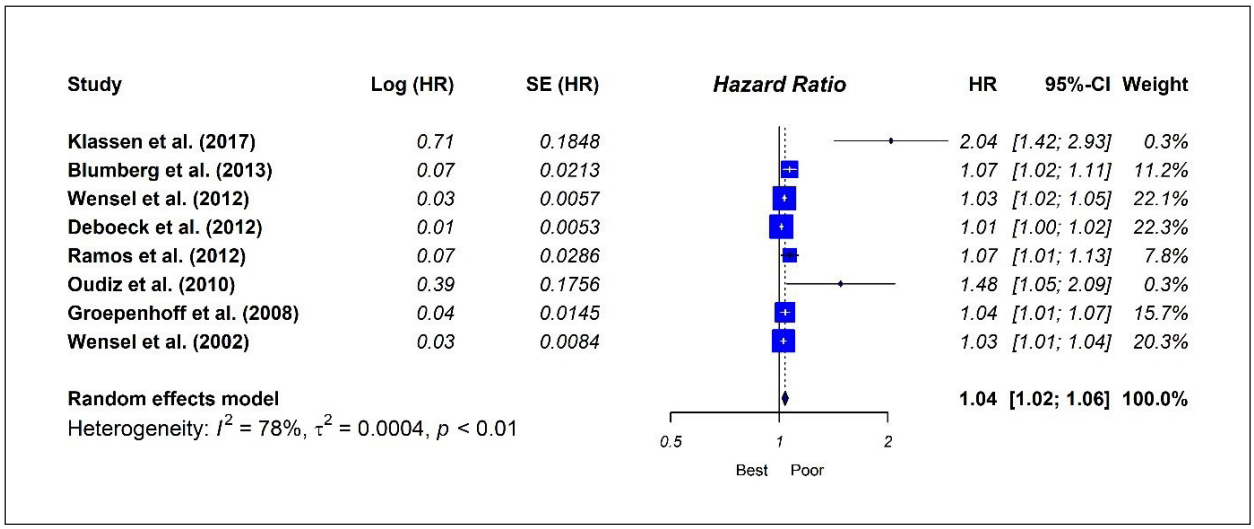

Figure 3. Effect of VE/VCO_2 slope on primary endpoint. Random effects, hazard ratios (HR), 95% confidence intervals (CI) and I^2 statistics

well as recruitment of previously unused vascular beds [26]. In normal subjects, pulmonary artery pressure rises minimally and pulmonary vascular resistance decreases in response to increased blood flow. These mechanisms are impaired in PH patients. Furthermore, patients with PH show increased physiologic dead space and ventilatory requirements and frequently do not increase cardiac output appropriately in response to exercise. Moreover, patients with PH present significant peripheral muscle changes that are partly correlated with their exercise capacity and show profound dyspnea at low levels of exercise [27].

Patients with PH exhibit a CPET profile similar to that observed in heart failure patients as documented by a series of abnormal variables such as reduced work rate, diminished aerobic capacity and impaired ventilatory efficiency [28]. However, the pathophysiologic mechanisms that lead to these exercise related abnormalities are different. CPET reveals the ventilation–perfusion mismatch observated in PH patients. Among others, this characteristic is reflected by elevated VE/VCO_2 slope and decreased peak VO_2, both CPET-related variables considered in this meta-analysis.

In the individual assessment of the included studies the results regarding peak VO_2 were contradictory. Seven studies showed a significant association between this CPET-related parameter and the risk of major clinical events [12, 14–19], while another two studies did not [13, 20]. On

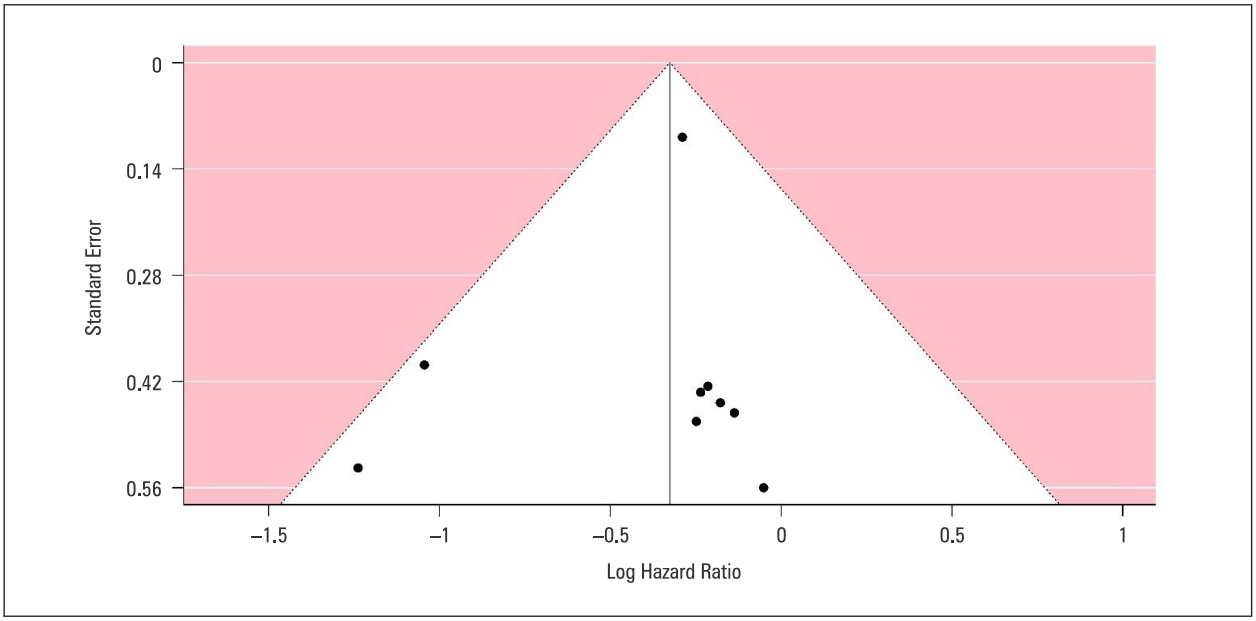

Figure 4. Funnel plot to assess publication bias (VO_2)

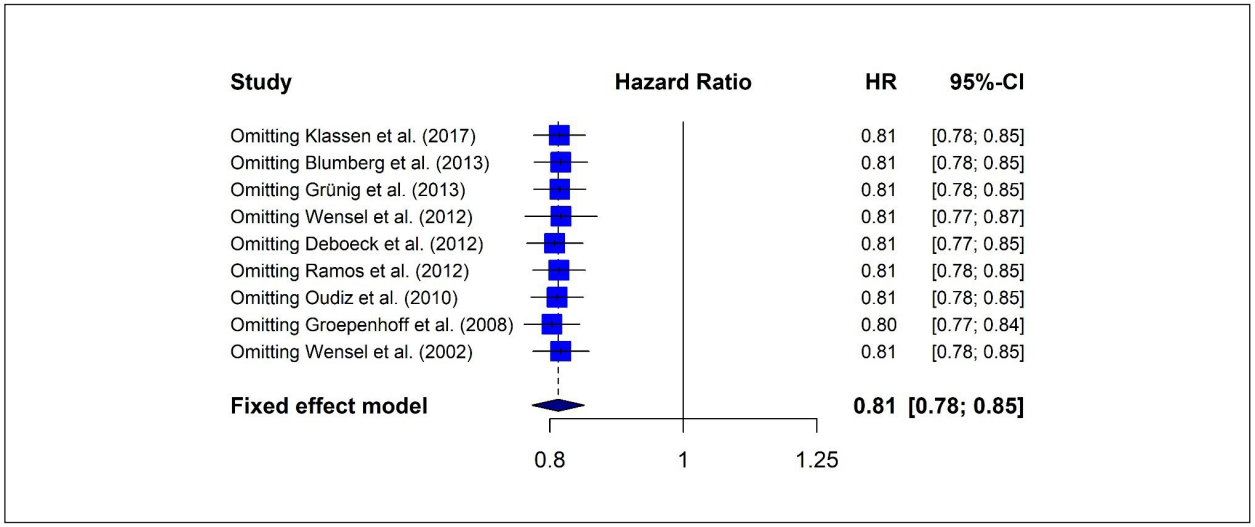

Figure 5. Sensitivity analysis for VO_2. After replicating the results of the meta-analysis, excluding in each step one of the studies included in the review, the results obtained are similar

the other hand, the strength of association between VE/VCO_2 slope and major clinical events in the survival analysis was borderline in many studies. Finally, given the type of disease being evaluated, the number of patients was small in almost all studies. Therefore, it is very useful to jointly analyze all the data using the meta-analysis technique.

Risk stratification in PH patients is crucial for the development of an appropriate treatment strategy, especially in the pulmonary arterial hypertension (idiopathic, heritable or associated forms) [29]. The last European Guidelines for the diagnosis and treatment of PH recommend including the two CPET-related variables included in our meta-analysis as part of the risk stratification [2]. These recommendations suggest that a peak $VO_2 < 11$ mL/min/kg and a VE/VCO_2 slope > 45 stratify the patient with PH as high risk. However, most of the proposed variables' cut-off values are based on expert opinion. Of the studies included in this systematic review, only four reported the optimal cut-off values of VO_2 ($<$ 10.3, $<$ 11.4, $<$ 11,6 and $<$ 13.2 mL/min/kg), and only three informed the optimal cut-off values of VE/VCO_2 slope ($>$ 48, $>$ 50 and $>$ 54) [15, 16].

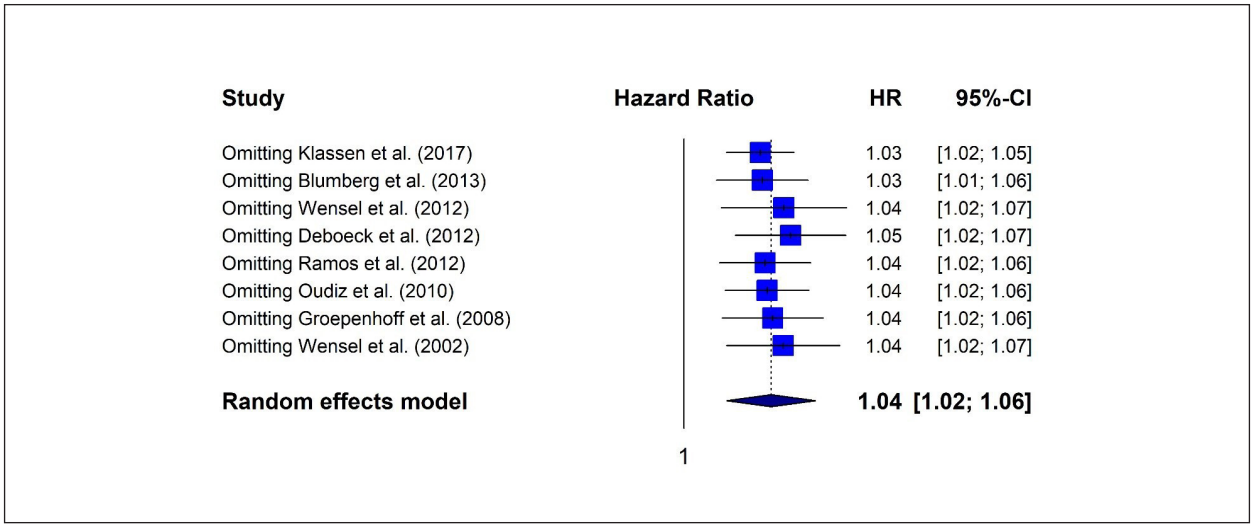

Figure 6. Sensitivity analysis for VE/VCO_2. After replicating the results of the meta-analysis, excluding in each step one of the studies included in the review, the results obtained are similar

Likewise, another study not included in our meta-analysis (the odds ratio was reported instead of hazard ratio) showed that patients with a peak $VO_2 \leq 10.4$ mL/min/kg and with a VE/VCO_2 slope ≥ 60 had 1.5-fold and 5.8-fold increased risk of mortality in the next 24 months, respectability [30]. Hence, to further enhance clinical application, additional research is needed to better define optimal CPET measures and associated cut-off values [31].

This meta-analysis presented several limitations. First, they were related to clinical heterogeneity (popular characteristics, different endpoints definitions and follow-ups). Although peak VO_2 is a universal exponent of impaired physical efficiency in various types of PH, the VE/VCO_2 slope could behave differently in the categories of this disease. Additionally, the different treatments used in the different categories could also influence the prognostic value of CPET. For example, group 2 PH patients have a lower VE/VCO_2 slope compared to PAH. On the other hand, group 4 PH patients have higher VE/VCO_2 slope compared to group 1, as this parameter reflects the dead space ventilation, which is more pronounced in the first case. In addition, dynamic hyperinflation on exertion was observed in PAH patients, but was not confirmed in subjects with heart failure. However, the statistical heterogeneity was low in the VO_2 analysis and the results were robust when performing the sensitivity analysis. Second, our study could not determine which is the optimal cut-off point for the predictive CPET-related variables. We consider it essential to evaluate this point in future studies, to obtain clinically applicable predictive values. Third, our analysis included observational studies. Consequently, the presence of biases and confounders was highly expected. Finally, few studies were included in our analysis. However, until more studies with a larger number of PH patients are performed, this study analyzes the best evidence available to date.

Conclusions

Our data suggest that in a population with PH the CPET-related variables, such as peak VO_2 or VE/VO_2 slope, have predictive capacity regarding mortality and the risk of transplantation. However, future studies should establish the best cut-off points for the CPET-related variables.

Conflicts of interest

None to declared.

Ethical considerations

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Author Contributions

LB and WM participated in the conception and design of the research. LB and WM participated in the data collection. The interpretation of the data and the statistical analysis was done by WM and ML. WM, IB, DI and LB drafted the manuscript. All authors performed a critical review of the final document.

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