Title: Predictive value of NT-proBNP combined with exercise capacity variables in pulmonary artery disease: Insights from a Spanish cohort.

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Pulmonary hypertension (PH) is a uniformly progressive, fatal disease characterized by right-ventricle failure and defined by levels of mean pulmonary arterial pressure (mPAP) ≥25mmHg [1]. The term *pulmonary arterial hypertension* (PAH) implies a patient subset with pre-capillary PH, being levels of pulmonary artery wedge pressure (PAWP) ≤15mmHg and pulmonary vascular resistance (PVR) >3U/m [1]. A greater understanding of the disease has led to important therapeutic advances [2]. Yet the mean survival rates of PAH patients at 1, 3, 5 and 7yrs has been recently estimated at 91%, 74%, 65% and 59%, respectively [3]. Identification of valid predictors of survival is thus of paramount importance to help monitoring these patients and guiding their treatment.

Non-invasive survival predictors derived from cardiopulmonary exercise testing (CPET) and 6-min walk distance (6MWD) have gained attention in recent years. However, there is yet no consensus on which variable or variable combination is more informative. Here we determined the 2yr and 4yr predictive value of CEPT-related variables and 6MWD in a relatively large cohort of PAH Spanish patients, representing ~27% of the national registry.

Informed consent was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. We performed a cohort-retrospective analysis of PAH patients referred to the ‘12 de Octubre’ Hospital (Madrid, Spain), which is where all assessments took place (June 2006-June 2013) and meeting the following criteria: mPAP≥25mmHg, PAWP≤15mmHg, PVR>3U/m, aged >18yrs and having performed CPET followed by 6MWD within 1wk. CPET was performed using an electromagnetically-braked cycle-ergometer adhering to the American Thoracic Society guidelines (ATS/ACCP Statement on Cardiopulmonary exercise

testing, 2003) and gas-exchange variables were collected breath-by-breath and averaged over 10sec. 6MWD was measured according to a standardized protocol following ATS guidelines [4].

We compared 6MWD, CPET-variables and N-terminal pro-B-type natriuretic peptide (NT-proBNP) blood levels among survivors and non-survivors at 2 and 4yr follow-up from baseline (i.e., from time of CPET), with an unpaired *t*-test. For those variables showing statistical significance at 2 or 4yrs, we calculated the Receiver-Operator Curve (ROC). The optimal cut-off point for predicting survival was determined by the Youden Index. Areas under the curve (AUC), 95% confidence interval (95%CI), specificity and sensitivity were calculated. Values of AUC=1, ≥0.90, =0.80-0.90, =0.70-0.79 and <0.70 are indicative of perfect, excellent, good, fair and poor prediction, respectively. Cox proportional hazard analyses were also performed. Kaplan-Meier survival analyses from CPET (right-censored) and from time of diagnosis (left-truncated and right-censored) were calculated for those variables with an AUC>0.5.

We followed 148 patients (30%male) during a mean of 2380(range: 2242-2519) days with the main etiologies being idiopathic (67%), and connective tissue (17%) or congenital heart disease (10%). Their baseline characteristics were: age (mean±SD) age 49±13yrs (18-83), WHO-categories I(23%), II(55%), III(21%) and IV(1%), NT-proBNP (mean interquartile range)=602(66-792)pg/ml, 6MWD=474±100meters, and peak oxygen uptake (VO_2peak)=17±6ml/kg/min. Treatment strategies were standardized with main medications at baseline being diuretics (57% of patients), anticoagulants (81%), digoxin (11%), oxygen supplementation (25%) prostacyclin analogues (39%), bosentan/sitaxsetan (45%) and sildenafil (59%).

Thirteen patients died [heart failure (n=8), infection (n=1), sudden death (n=1), cerebral vascular accident (n=1), or unknown reason (n=2)] and 6 were scheduled for lung transplantation over the 4yr follow-up. The best predictor was the NT-proBNP, which showed good and fair ability for predicting non-survival at 2 (≥917pg/mL) and 4yrs (≥914pg/mL), respectively (**Table 1**). None of the equations defined by further logistic regression analysis for combinations of the different exercise-related variables proved better predictors of 2 or 4yr survival (all AUC<0.75) than these variables individually (data not shown for simplicity purposes).

Univariate Cox proportional hazard analyses revealed the following significant hazard ratio (HR) values at 2yrs: HR=0.67(95%CI:0.46-0.97;*p*=0.036) for every 12-watt increase in peak watts during CPET; HR=1.07(95%CI:1.00-1.10;*p*=0.020) for the ventilatory equivalent of carbon dioxide at the anaerobic threshold (VE/VCO_2@AT); HR=0.84(95%CI:0.73-0.94;*p*=0.008) for every 30-meter increase in 6MWD; and HR=1.25(95%CI:1.10-1.42;*p*<0.001) for every 300pg/mL increase in NT-proBNP. At 4yrs, a significant HR was found for the abovementioned quantitative changes in peak watts [HR=0.72(95%CI:0.52-1.00;*p*=0.050)], 6MWD [HR=0.84(95%CI:0.743-0.942);*p*=0.003] and NT-proBNP [HR=1.215(95%CI:1.07-1.37);*p*=0.001], as well as for VE/VCO_2@AT [HR=1.063(95%CI:1.01-1.12);*p*=0.014] and end-tidal pressure of carbon dioxide at the anaerobic threshold ($P_{ET}CO_2$@AT) [HR=0.95(95%CI:0.91-0.99); *p*=0.025). In multivariate Cox analyses, 300pg/mL-increases in NT-proBNP yielded a significant HR value, at both 2yrs [HR=1.20(95%CI:1.01-1.42);*p*=0.026] and 4yrs [HR=1.30(95%CI:1.04-1.63);*p*=0.017]. Backward and forward stepwise analyses yielded the same results.

Kaplan-Meier survival analyses showed that patients with both NT-proBNP<914pg/ml and $P_{ET}CO_2$@AT≥30mmHg [87%(65-91)] had a significantly better

prognosis over the 4yr follow-up ($p<0.05$) than those with other value combinations (**Figure 1, left panel**). No events were, in fact, registered for those patients (n=47) with NT-proBNP and $P_{ET}CO_2$@AT values below and above such cut-offs, respectively. Patients with both NT-proBNP<914pg/ml and VE/VCO_2@AT<39 [98%(87-99)] had a significantly better prognosis over the 4yr follow-up ($p<0.05$) than those with other value combinations (**Figure 1, right panel**).

It is urgent to determine useful indicators of mid/long-term survival in large PAH patient cohorts. In this regard, our study is the first of this type in a Spanish cohort and had a comparatively large sample size and a long follow-up with regards to most previous investigations in the field [5-8]. The main insights obtained from our results are three-fold: (1) the NT-proBNP proved better predictor of 2 or 4yr survival than exercise-related variables, although the $P_{ET}O_2$@AT can also provide useful information regarding 4yr-survival (combining good specificity/sensitivity with a fair predictive potential); (2) the combination of NT-proBNP<914pg/ml and $P_{ET}CO_2$@AT≥30mmHg had prognostic value over the 4yr-period; and (3) there does not seem to be a potential algorithm combining 6MWD/CPET variables showing a better predictive capacity compared with individual variables separately, and certainly not compared with NT-proBNP. On the other hand, despite the simplicity and widespread use of the 6WMD, its cut-off value to differentiate survivors vs. non-survivors was not sensitive along time in our cohort, showing a similar value to predict 2 and 4yr survival. A certain 'ceiling effect' in 6MWD may mask treatment efficacy [9,10] and there is yet not a clear consensus about the use of a predictive threshold value.

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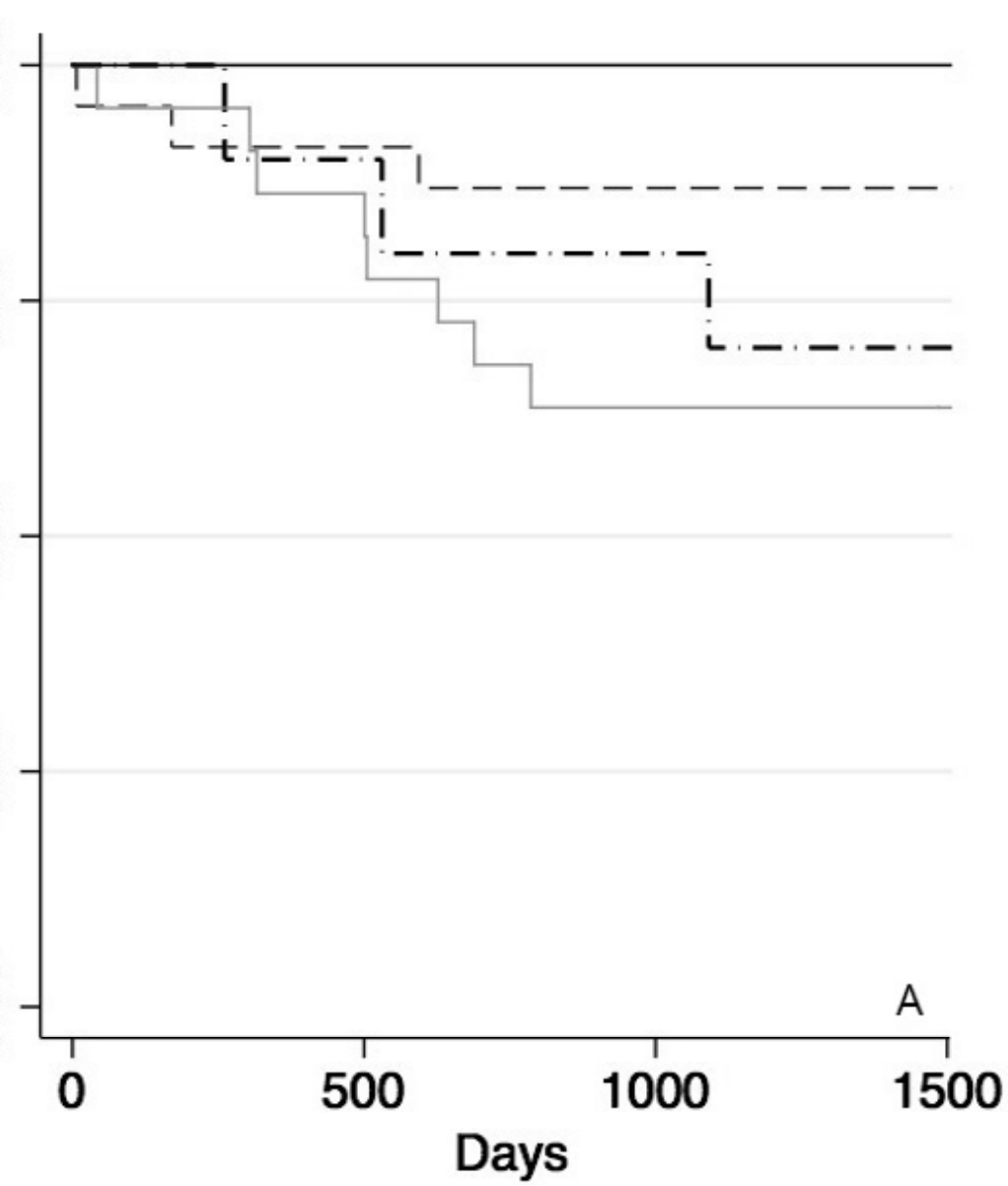
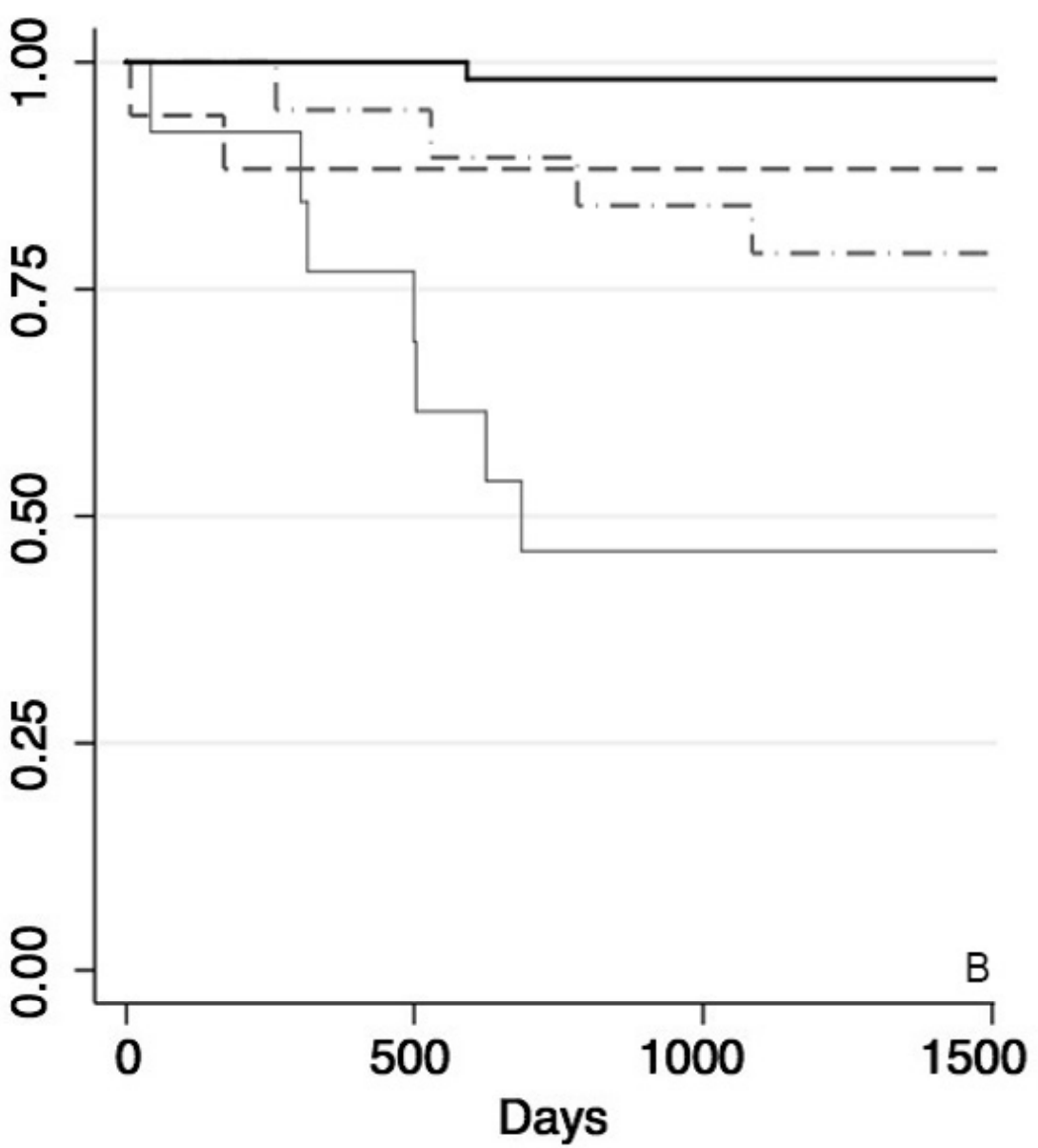
Figure 1 legend. 4yr Kaplan-Meier survival curves. Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; $P_{ET}CO_2$@AT, end-tidal pressure of carbon dioxide at anaerobic threshold; VE/VCO_2@AT, ventilatory equivalent for carbon dioxide at anaerobic threshold.





NT-ProBNP < 914 pg/ml and $P_{ET}CO_2$ @AT ≥ 30 mmHg

NT-ProBNP < 914 pg/ml and $P_{ET}CO_2$ @AT < 30 mmHg

NT-ProBNP ≥ 914 pg/ml and $P_{ET}CO_2$ @AT ≥ 30 mmHg

NT-ProBNP ≥ 914 pg/ml and $P_{ET}CO_2$ @AT < 30 mmHg

NT-ProBNP < 914 pg/ml and VE/VCO_2 @AT < 39

NT-ProBNP < 914 pg/ml and VE/VCO_2 @AT ≥ 39

NT-ProBNP ≥ 914 pg/ml and VE/VCO_2 @AT < 39

NT-ProBNP ≥ 914 pg/ml and VE/VCO_2 @AT ≥ 39

Table 1. Receiver operating characteristic (ROC) results over the study period.

		Follow-up	Cut-off	AUC	95%CI	*P*-value	Standard Error	Sensitivity (%)	Specificity (%)
Survival	VO_{2peak} (ml/kg/min)	2yrs	≥15	0.64	(0.53,0.76)	0.07	0.06	61	73
		4yrs	≥15	0.70	(0.59,0.80)	**0.01**	0.05	67	74
	6MWD (meters)	2yrs	≥463	0.71	(0.59,0.82)	**0.01**	0.06	57	87
		4yrs	≥464	0.73	(0.62,0.83)	**<0.01**	0.05	56	90
	Peak watts	2yrs	≥63	0.68	(0.57,0.80)	**0.03**	0.06	41	93
		4yrs	≥68	0.66	(0.54,0.76)	**0.04**	0.06	30	100
	$P_{ET}CO_2$@AT (mmHg)	4yrs	≥30	0.72	(0.58,0.85)	**<0.01**	0.07	62	81
Non-survival	NT-proBNP (pg/ml)	2yrs	≥917	0.82	(0.73,0.92)	**<0.01**	0.05	77	80
		4yrs	≥914	0.79	(0.69,0.89)	**<0.01**	0.05	75	77
	VE/VCO_2@AT	2yrs	≥39	0.70	(0.55,0.86)	**0.01**	0.08	71	76
		4yrs	≥39	0.71	(0.57,0.85)	**0.01**	0.07	63	78

Abbreviations: 6MWD, six minute walk distance; 95%CI, 95% confidence interval; AT, anaerobic threshold; AUC, area under the curve; NT-ProBNP, N-terminal pro-B-type natriuretic peptide; $P_{ET}CO_2$@AT, end-tidal pressure of carbon dioxide at anaerobic threshold; VE/VCO_2@AT, ventilatory equivalent for carbon dioxide at anaerobic threshold; VO_{2peak}, peak oxygen uptake. Significant *p*-values are in bold.