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TITLE

The role of percent predicted six-minute walk distance in pulmonary arterial hypertension

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ABSTRACT

Absolute six-minute walk distance (6MWD) predicts mortality in pulmonary arterial hypertension (PAH), but varies greatly between normal individuals due to physiological factors such as age, gender, height and weight. Percent predicted 6MWD adjust for these factors and may predict mortality more reliably. The aim of the study was to compare the strength of mortality prediction by absolute and % predicted 6MWD in PAH at baseline and on treatment.

Percent predicted 6MWD was calculated using four different reference equations in 137 PAH patients (idiopathic and connective tissue disease associated) diagnosed between November 2000 and November 2009. Cox proportional hazards and receiver-operating characteristic (ROC) analyses were used to compare the prognostic strength of absolute and % predicted 6MWD.

Percent predicted 6MWD was predictive of all-cause mortality at baseline (HR: 0.74-0.83 per 10% increase, $p<0.05$) and on treatment (0.67-0.75 per 10% increase, $p<0.01$), but each respective area under the ROC curve was not different from that of absolute 6MWD for predicting 2-year mortality at baseline (absolute versus % predicted: 0.74 versus 0.71-0.75) or on treatment (0.77 versus 0.72-0.78).

In conclusion, % predicted 6MWD may help clinicians interpret the six-minute walk test, but its prognostic value is not superior to that of absolute 6MWD.

KEYWORDS

Mortality

Pulmonary hypertension

Six-minute walk distance

INTRODUCTION

Absolute six-minute walk distance (6MWD) has been established as the principal clinical outcome measure in pulmonary arterial hypertension (PAH) and has been used as the primary end-point in most clinical trials of new PAH therapies [1]. As a measure of submaximal exercise capacity, it correlates with variables of maximal cardiopulmonary exercise testing such as peak oxygen uptake and oxygen pulse [2,3] and metabolic equivalent measured at exercise treadmill testing [4]. In addition, it correlates with markers of disease severity in PAH such as World Health Organisation functional class (WHO FC) and pulmonary haemodynamics [3]. Most importantly, the ability of baseline 6MWD to predict mortality has been demonstrated in a 12-week randomised controlled trial of intravenous epoprostenol therapy in idiopathic pulmonary arterial hypertension (IPAH) [5], the only clinical trial showing a survival benefit of PAH-specific therapies. This was confirmed by subsequent observational studies on the long-term impact of PAH-specific therapies [6-9]. However, there is ongoing debate as to whether % predicted 6MWD should be used instead of absolute 6MWD as it gives a more accurate reflection of the functional impact of disease on an individual.

As with other measurements of physical function such as lung function and cardiopulmonary exercise capacity, 6MWD varies greatly between individuals due to physiological factors such as age, gender, height and weight, and pathological factors such as cardiopulmonary and musculoskeletal diseases. Adjusting for physiological variation should help clinicians interpret the result of the six-minute walk test (6MWT) and estimate the degree of exercise impairment due to disease in an individual. Several reference equations already exist to calculate % predicted 6MWD

based on an individual's age, gender, height and weight [10-13]. They have been derived from healthy adults sampled from populations in North America and Europe. What is not known is whether % predicted 6MWD is superior to absolute 6MWD at predicting mortality in PAH. The aim of this study was therefore to compare the relative strength of mortality prediction by absolute and % predicted 6MWD in PAH measured at baseline and on treatment respectively using four different published reference equations.

METHODS

Study population

The study cohort was derived by a retrospective case note review of patients treated in the Scottish Pulmonary Vascular Unit which provides the tertiary pulmonary hypertension service for the whole population in Scotland. All consecutive incident cases of IPAH and connective tissue disease associated pulmonary hypertension (CTDPH) treated with PAH-specific therapy between November 2000 and November 2009 were identified. The diagnosis of PAH was based on right heart catheterisation carried out by the pulmonary vascular team in our institution. PAH was defined as mean pulmonary artery pressure (mPAP) >25 mmHg at rest or >30 mmHg on exercise, with pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units [14]. For patients diagnosed after August 2009, PAH was defined as mPAP ≥ 25 mmHg at rest with PCWP ≤ 15 mmHg, and normal or reduced cardiac output [1]. Patients with recorded 6MWD at diagnosis or within 12 months of starting treatment were included in this study. Patients with significant lung disease as defined by forced expiratory volume in one second <60% predicted or forced vital capacity <60% predicted or total lung capacity

<60% predicted (based on European Coal and Steel Community reference values) were excluded [15]. Ethical review was considered unnecessary by the West Glasgow Research Ethics Committee.

Treatment and follow-up

All patients received conventional therapies such as supplemental oxygen, diuretics and warfarin. PAH-specific monotherapies (prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase-5 inhibitors) were initiated after confirmation of diagnosis at right heart catheterisation. Treatment response was assessed after a period of 3-6 months by means of clinical assessment, WHO FC and 6MWD. Patients were subsequently followed up at 3-6 month intervals in out-patient clinics. Right heart catheterisation was not routinely repeated during follow-up. Baseline data including age, height, weight, lung function, 6MWD, WHO FC, mean right atrial pressure (mRAP), mPAP, PVR, cardiac index (CI) and mixed venous saturation (S_vO_2), and follow-up data including 6MWD, WHO FC and all-cause mortality were collected.

Six-minute walk test protocol

Six-minute walk test was performed by a trained respiratory physiologist on a twenty-metre corridor with no prior practice walks. Patients were instructed to walk to cover as much ground as possible in six minutes. After 2003, standardised encouragement at one-minute intervals was given as described in the American Thoracic Society guidelines and before that, 6MWT was performed without encouragement [16]. Predicted 6MWD in each patient was calculated based on their age, gender, height

and weight using each of four reference equations (Table 1). Absolute 6MWD was expressed as a percent of predicted 6MWD.

Statistical analysis

Statistical analysis was performed using Statview version 5.0.1 (SAS Institute, NC, USA) and Graphpad Prism version 5.00 (Graphpad Software, CA, USA). Quantitative data were tested for normality using D'Agostino and Pearson omnibus normality test. Parametric data were described by the mean and standard deviation, and compared using paired or unpaired Student's t-test. Non-parametric data were described by the median and interquartile range and compared using Mann-Whitney *U* test. Qualitative data were described by number (%) and compared by Chi-square test. The relationship between 6MWD (absolute and each expression of % predicted 6MWD) and other clinical markers of disease severity was determined by Spearman correlation coefficients. A two-tailed p value less than 0.05 was defined as significant.

Survival time was defined as time from the date of right heart catheterisation to death or data cut-off on 30th November 2009. Patients who received lung transplantation or who were lost to follow-up were censored at the time of procedure or last clinical contact (clinic visit, telephone contact or renewal of drug prescription). Univariate Cox proportional hazards analysis was carried out to determine the association between all-cause mortality and age, gender, aetiology, lung function, haemodynamics, WHO FC, absolute 6MWD and each expression of % predicted 6MWD at baseline, and WHO FC, absolute 6MWD and each expression of % predicted 6MWD on treatment. Multiple bivariate Cox models, one for absolute 6MWD and one for each expression of % predicted 6MWD at baseline, were derived

by including variables with $p<0.2$ in the univariate analysis to adjust for the effect of confounding. Correlation between candidate variables and the predictor of primary interest (absolute or % predicted 6MWD) was checked to limit collinearity. The variables would not be considered for inclusion if $r>0.70$. The same variables were included to adjust 6MWD in each model to facilitate comparison. The bivariate Cox analysis was repeated for absolute 6MWD and each expression of % predicted 6MWD on treatment. Date of follow-up 6MWD was used as the index date for determining survival time for the analysis on treatment.

To compare the relative prognostic strength among expressions of 6MWD against each other at baseline and on treatment respectively, and each corresponding expression of 6MWD at baseline versus on treatment, receiver-operating characteristic (ROC) analysis was used to determine their respective area under the ROC curves (AUC) for predicting 2-year mortality. The significance of differences in AUC was assessed using a paired z test [17]. Optimal thresholds were identified by selecting the data point closest to the coordinate x=0 (1-specificity) and y=1 (sensitivity) on the ROC curves.

RESULTS

Patient characteristics

One hundred and thirty seven patients were included in the cohort (IPAH 86, CTDPH 51). The baseline characteristics of the study patients are outlined in Table 2. During follow-up (median 2 years, range 1.2 months to 8.8 years), 41 patients died from all causes (IPAH 20, CTDPH 21), 2 patients were lost to follow-up and 2 patients received lung transplantation. After receiving PAH-specific monotherapy (7%

prostacyclin analogues, 46% endothelin receptor antagonists and 47% phosphodiesterase-5 inhibitors) for 4.1±1.8 months (median 3.5, range 2.2 to 11 months), absolute 6MWD and each expression of % predicted 6MWD were 311±111 metres, 59±18% (Enright), 48±15% (Troosters), 48±16% (Gibbons) and 58±19% (Chetta) respectively (N=110, all $p<0.0001$ versus baseline). The distribution of absolute 6MWD at baseline, on treatment and the distance changed are shown in Figure 1 in the online supplement. On treatment, 41% of patients were in WHO FC II, 54% in III and 4% in IV (N=123, $p<0.005$ versus baseline). At the time of death or censoring, 69% of patients remained on monotherapy and 31% were on combination therapy.

Correlation with other markers of disease severity at baseline

Baseline absolute and % predicted 6MWD correlated weakly with mRAP (absolute 6MWD $r= -0.23$, $p<0.01$ versus % predicted 6MWD by all equations $r= -0.23$ to -0.25, $p<0.01$), CI ($r= 0.24$, $p<0.01$ versus $r= 0.21$ to 0.22, $p<0.05$), S_vO_2 ($r= 0.21$, $p<0.05$ versus $r= 0.19$-0.21, $p<0.05$) and WHO FC ($r= -0.33$, $p<0.0005$ versus $r= -0.32$ to -0.34, $p<0.005$). Only % predicted 6MWD by Enright and Troosters equations correlated weakly with PVR ($r= -0.23$ and $r= -0.19$, both $p<0.05$). Neither absolute 6MWD nor % predicted 6MWD correlated with mPAP.

Independent effect on mortality

Age and diffusing capacity for carbon monoxide (DLco) at baseline, absolute and % predicted 6MWD at baseline and on treatment, and WHO FC on treatment predicted all-cause mortality in univariate Cox proportional hazards analysis (Table 3). The predictive value of absolute and % predicted 6MWD at baseline remained significant

after adjusting for age, gender, aetiology of PAH but not DLco in bivariate Cox proportional hazards analysis (Figure 1). Absolute 6MWD, Gibbons and Chetta % predicted 6MWD predicted mortality after adjusting for mRAP but Enright or Troosters % predicted 6MWD did not. On treatment, absolute and % predicted 6MWD was predictive of mortality independently of WHO FC (except Enright equation), age, gender, aetiology, baseline DLco and mRAP (Figure 2). When combined with absolute or % predicted 6MWD on treatment, DLco at baseline no longer predicted mortality.

Relative strength of mortality prediction

Receiver-operating characteristic curves of absolute 6MWD and % predicted 6MWD by each of four reference equations at baseline and on treatment are shown in Figure 3. There were no significant differences in AUC of absolute versus each expression of % predicted 6MWD for predicting 2-year mortality at baseline or on treatment (Table 4). In addition, there were no significant differences in AUC among % predicted 6MWD by the four reference equations. The optimal thresholds of absolute 6MWD and each expression of % predicted 6MWD at baseline and on treatment for predicting 2-year mortality had modest sensitivity and specificity. The thresholds of absolute 6MWD and % predicted 6MWD by Troosters, Gibbons and Chetta equations on treatment had slightly higher sensitivity and specificity than those at baseline, but the respective differences in AUC between baseline and treatment did not reach statistical significance. This analysis was repeated including only patients diagnosed from 2003 onwards as the 6MWT protocol changed at that point and the results were similar (Table 1 and Figure 2 in the online supplement).

DISCUSSION

This study addresses an important clinical issue regarding the role of % predicted 6MWD in the management of PAH. The data analysis showed that % predicted 6MWD at baseline derived from currently available reference equations predicts all-cause mortality but its prognostic ability is not superior to that of absolute 6MWD despite adjusting for physiological inter-subject variance. In addition, there is no difference in the prognostic ability between each of the four studied reference equations. Assuming that the long-term prognosis of patients improves with PAH-specific therapy, 6MWD on treatment may be a stronger predictor of mortality than that at baseline, and hence the difference in the relative prognostic strength between absolute and % predicted 6MWD may be more apparent on treatment. However, this is not supported by the results of this analysis. Percent predicted 6MWD was not more predictive of mortality than absolute 6MWD on treatment.

Percent predicted 6MWD calculated from Troosters and Gibbons equations was slightly lower than that from Enright and Chetta equations. This disparity is due to differences in the 6MWT protocol used in the studies such as the length of corridor, type and frequency of encouragement and the number of practice walks. A 50-metre corridor was used in Troosters equation and the best of 4 walks in Gibbons equation, which resulted in higher predicted absolute 6MWD. The equations were also derived from healthy adults in different age groups. Patients younger than 40 years of age were included in Chetta and Gibbons equations only. This highlights the importance of giving consideration to the characteristics of the study population and the 6MWT protocol used in deriving the reference equation when applying predicted values. The American Thoracic Society guidelines on 6MWT recognise that % predicted 6MWD

is under-utilised due to a lack of optimal reference equations [16]. Only 40-66% of physiological inter-subject variance of 6MWD is explained by the currently available equations. Therefore, there are other factors influencing the performance at the 6MWT that have not been identified or accounted for. This may partly explain the failure to demonstrate the superiority of % predicted 6MWD by any of the four reference equations to absolute 6MWD in predicting mortality.

There are other potential explanations for the negative findings in this study. It might be possible for patients with low or high 6MWD to dominate the analysis, thereby obscuring any prognostic difference between absolute and % predicted 6MWD. However, this was not the case as the 6MWD data were normally distributed with few patients at either end of the range. The use of all-cause mortality rather than disease-specific mortality may also be relevant as this could shift the comparison of prognostic strength in favour of absolute 6MWD. For example, consider the case of a 40-year old man with severe PAH (height 186 cm, weight 90 kg) and an 80-year old woman with mild PAH (height 157 cm, weight 60 kg) both of whom walk the same 6MWD of 300 metres and survive for 5 years. This walk distance corresponds to 40% and 75% predicted using Enright equation respectively, reflecting more severe disease in the man. The 40-year old man is more likely to die from PAH whereas the 80-year old woman is more likely to die from other causes as she approaches the natural limit of life expectancy. In this scenario, absolute 6MWD is the better predictor of all-cause mortality as it has automatically incorporated the influence of age on mortality, with age being the most important physiological determinant of 6MWD. On the other hand, % predicted 6MWD would be expected to perform better at predicting disease-

specific mortality. All-cause mortality was used in this study to avoid the subjectivity associated with disease-specific mortality.

The fact that there is a considerable amount of unexplained physiological variance in 6MWD raises concerns about its reliability as an outcome measure in PAH. Some clinicians propose that 6MWD should be used instead to set a treatment goal in individual patients based on their starting parameters, where inter-subject variance is not as relevant. To set an appropriate goal, the knowledge of predicted 6MWD in an individual is essential. Therefore, despite having no added prognostic information, % predicted 6MWD would help clinicians to ascertain the degree of improvement achievable should a goal-oriented treatment strategy be adopted. There is also a suggestion that 6MWD should be replaced altogether by alternative outcome measures that are more directly linked to right heart function or pulmonary haemodynamics such as cardiac magnetic resonance or non-invasive cardiac output measurements. There is no doubt that more robust exercise outcome measures than 6MWD are needed in PAH, but until they are developed and validated, 6MWD on balance remains the best available option in the appropriate setting given its proven prognostic value and simplicity.

The prognostic value of DLco in PAH has been explored in a large retrospective study which showed that DLco at baseline predicted mortality after adjusting for age, CTDPH aetiology, WHO FC, haemodynamics and lung abnormalities on computed tomography [18]. However, the finding of DLco predicting mortality more strongly than 6MWD at baseline in this analysis is of interest and to our knowledge has not

been reported before. It would be interesting to explore the predictive value of DLco on treatment but such data were not available in this study cohort.

The study has a number of limitations. Firstly, selection bias cannot be excluded as this is a retrospective study and gaps due to missing data are unavoidable. Fourteen (10%) patients with no 6MWD data at baseline or within 12 months of starting treatment were excluded from the analysis. This is unlikely to have affected the main outcome of the analysis, namely the comparison between absolute and % predicted 6MWD. Secondly, patients were recruited over a relatively long period of time during which treatment approaches had evolved. This may have led to differences in prognosis of patients diagnosed in the earlier years compared to those diagnosed more recently. Whilst this cannot be excluded, it is worth pointing out that there is as yet conclusive evidence to support improved prognosis with the widespread use of oral agents in the last few years compared to the epoprostenol era. Thirdly, the 6MWT protocol changed during the study period and encouragement may have significantly influenced 6MWD. However, the results were similar with patients diagnosed after 2003 only. Lastly, the reference equations were derived from healthy populations with differing age groups and hence no single equation was perfectly applicable to the study patients.

In conclusion, % predicted 6MWD may help clinicians quantify the functional impact of disease on an individual, but its prognostic ability is not superior to that of absolute 6MWD. In addition, the prognostic ability of currently available reference equations is similar. To explore the role of % predicted 6MWD in the management of PAH further, efforts should be made to develop more robust reference equations using a

standardised 6MWT protocol and sampling healthy adults from more representative populations particularly in relation to age.

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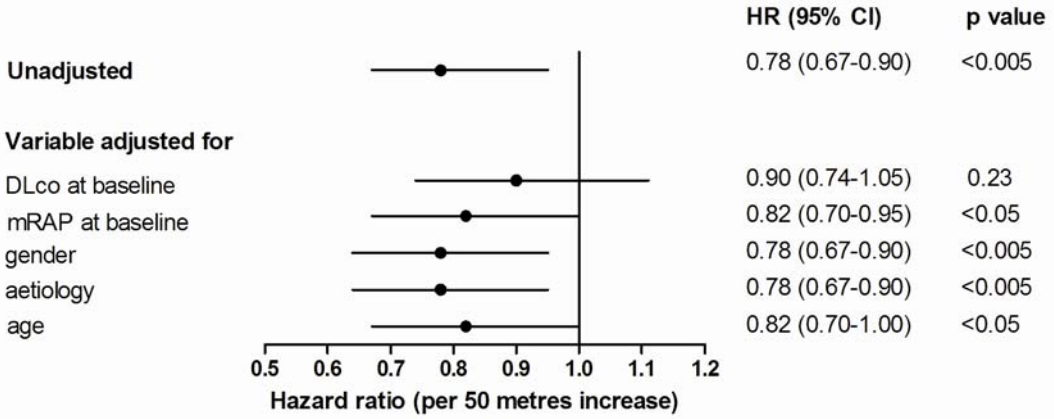
FIGURE LEGENDS

FIGURE 1

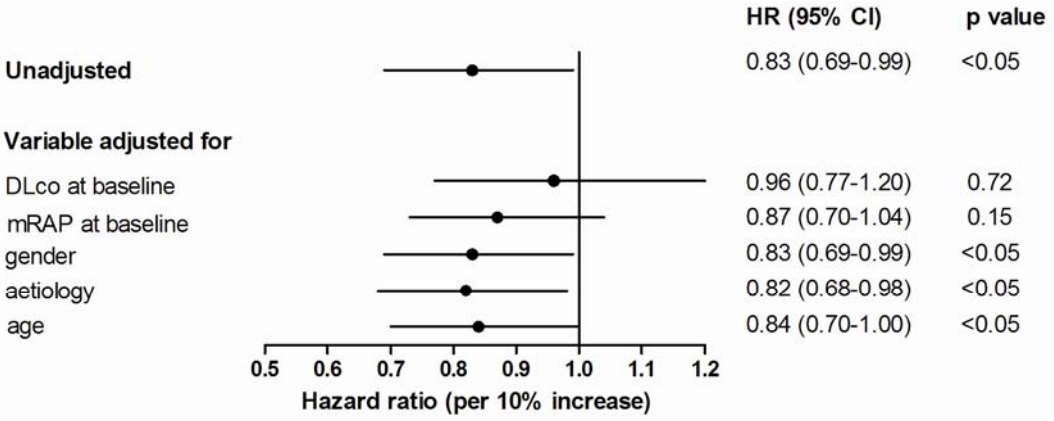
Title: Bivariate Cox proportional hazards models of absolute and percent predicted six-minute walk distance by four different reference equations at baseline

Caption: 6MWD=six-minute walk distance, DLco=diffusing capacity for carbon monoxide, mRAP=mean right atrial pressure. The unadjusted and adjusted hazard ratios (HR) of 6MWD are indicated by closed circles and the 95% confidence interval (CI) by error bars. Adjusted hazard ratios of DLco are 0.76-0.79 per 10% predicted increase, all $p<0.05$.

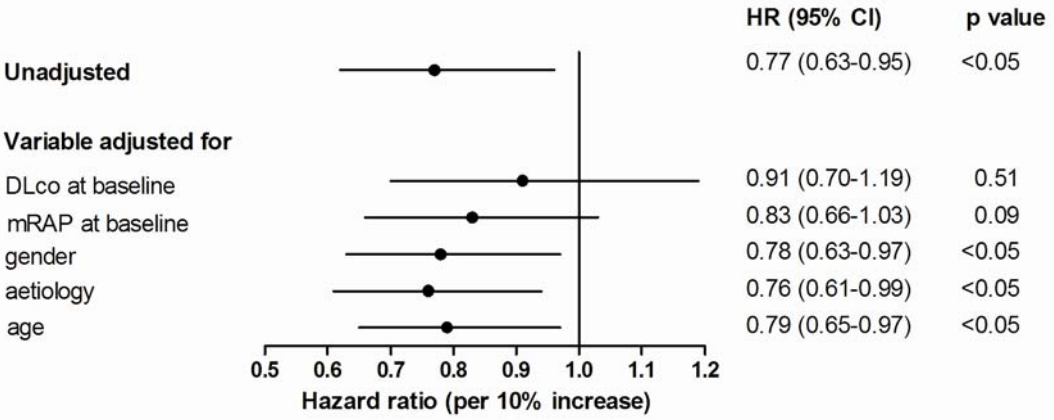
A Absolute 6MWD



B Enright % predicted 6MWD



C Troosters % predicted 6MWD



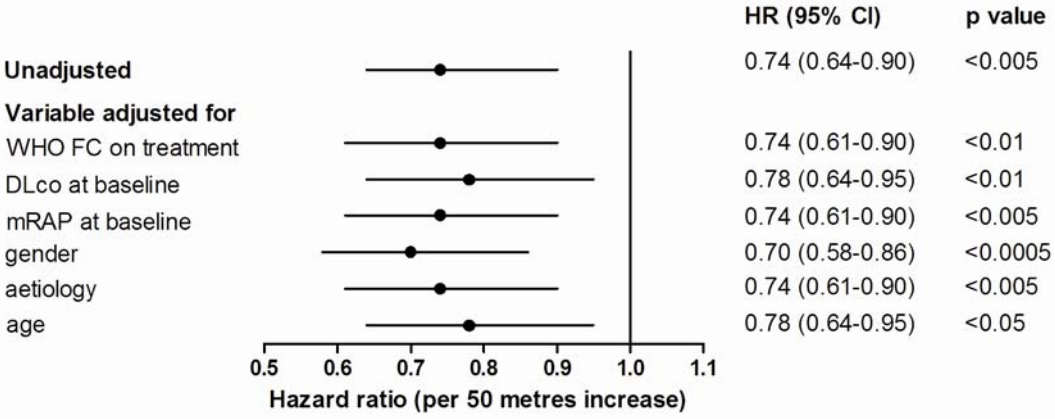
D Gibbons % predicted 6MWD

FIGURE 2

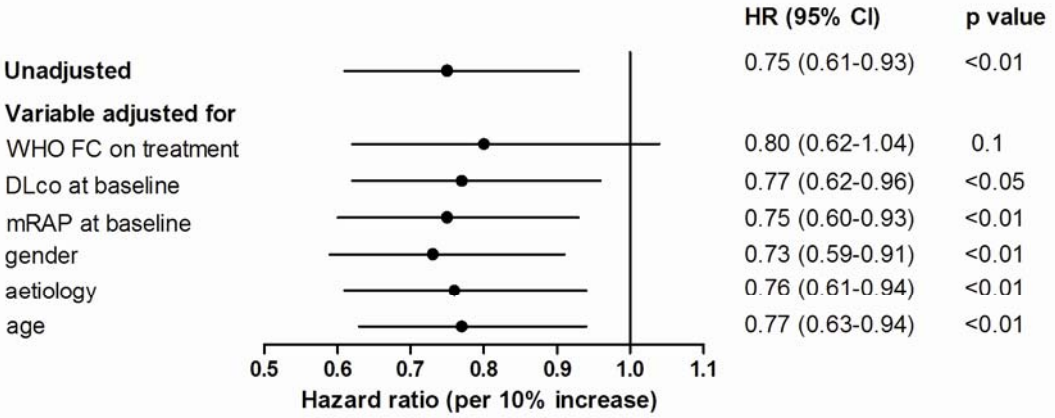
Title: Bivariate Cox proportional hazards models of absolute and percent predicted six-minute walk distance by four different reference equations on treatment

Caption: 6MWD=six-minute walk distance, WHO FC=World Health Organisation functional class, DLco=diffusing capacity for carbon monoxide, mRAP=mean right atrial pressure. The unadjusted and adjusted hazard ratios (HR) of 6MWD are indicated by closed circles and the 95% confidence interval (CI) by error bars.

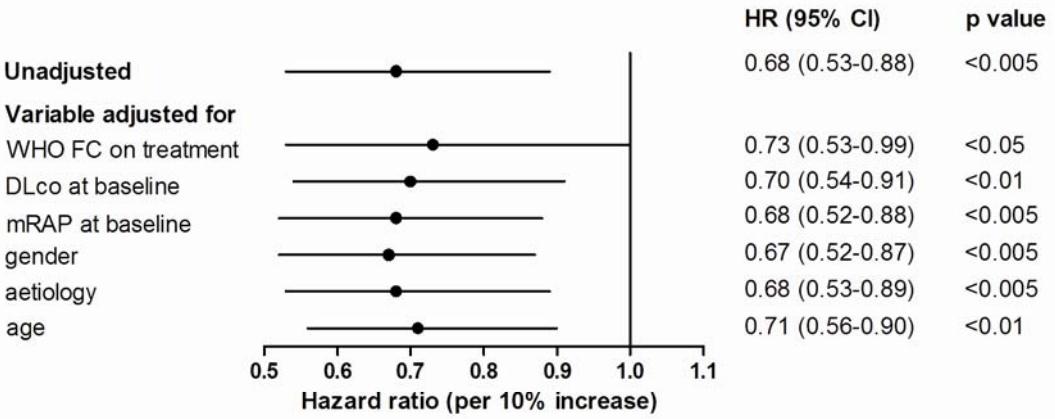
A Absolute 6MWD



B Enright % predicted 6MWD



C Troosters % predicted 6MWD



D Gibbons % predicted 6MWD

FIGURE 3

Title: Receiver-operating characteristic curves of absolute and percent predicted six-minute walk distance by four different reference equations in predicting two-year mortality at baseline and on treatment

Caption: 6MWD=six-minute walk distance. All $p>0.05$ when area under the receiver-operating characteristic curves is compared among expressions of 6MWD at baseline and on treatment respectively by a paired z test.

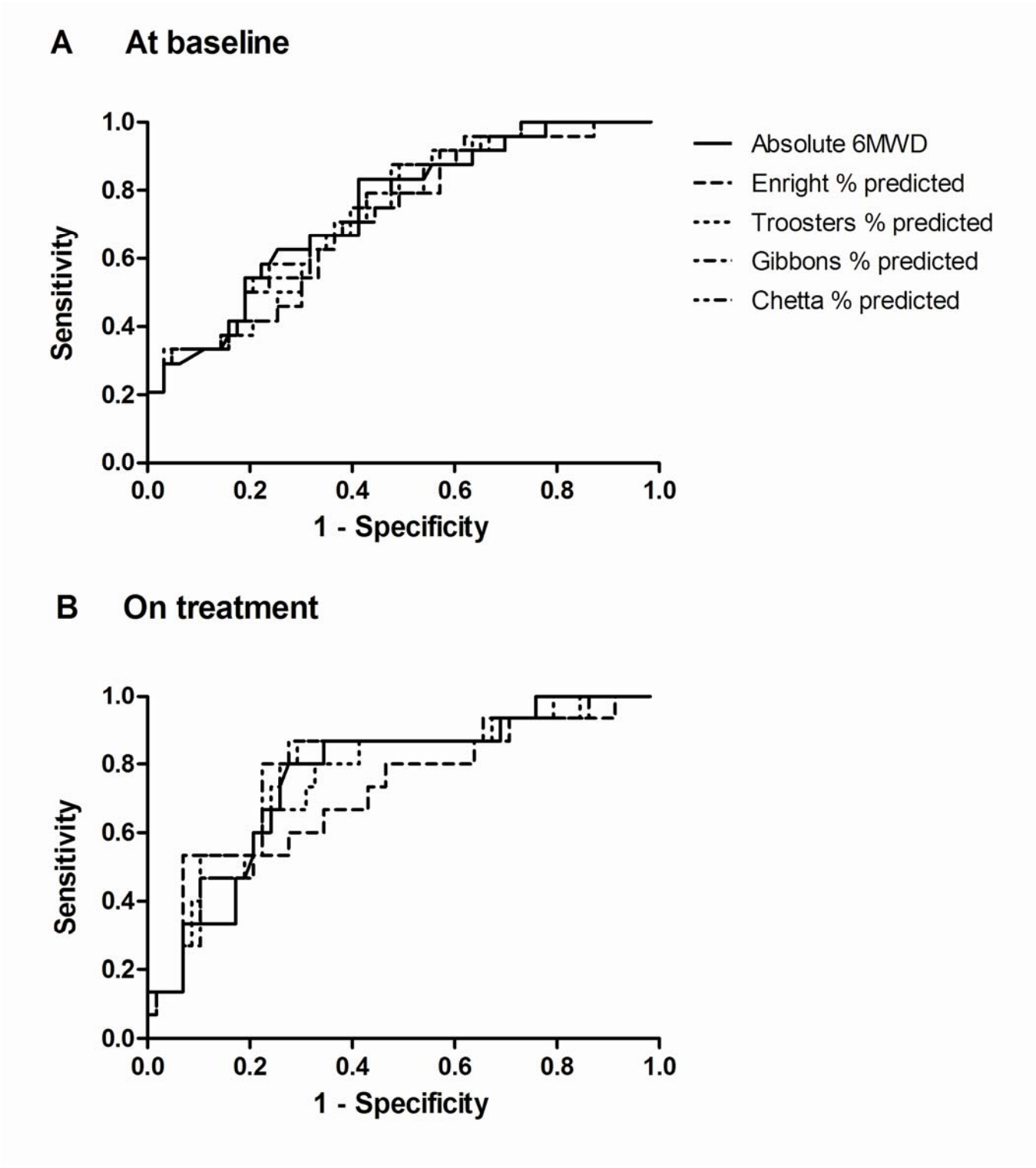


FIGURE 1 (online supplement)

Title: Distribution of absolute 6MWD at baseline, on treatment and the distance changed with treatment

Caption: 6MWD=six-minute walk distance

FIGURE 2 (online supplement)

Title: Receiver-operating characteristic curves of absolute and percent predicted six-minute walk distance by four different reference equations in predicting two-year mortality at baseline and on treatment in patients diagnosed from 2003 onwards

Caption: 6MWD=six-minute walk distance. All $p>0.05$ when area under the receiver-operating characteristic curves is compared among expressions of 6MWD at baseline and on treatment respectively by a paired z test.

TABLE 1 Previously published reference equations for predicting six-minute walk distance in healthy adults based on an individual's age, gender, height and weight

	Study populations	Reference equations	R^2
Enright [11] (1998)	USA 117♂, 173♀ age 40-80	♂: (7.57 x Ht) - (5.02 x age) - (1.76 x Wt) - 309 ♀: (2.11 x Ht) - (5.78 x age) - (2.29 x Wt) + 667	0.40
Troosters [13] (1999)	Belgium 29♂, 22♀ age 50-85	218 + (5.14 x Ht) - (5.32 x age) - (1.8 x Wt) + (51.31 x gender) ♂ = 1, ♀ = 0	0.66
Gibbons [12] (2001)	Canada 41♂, 38♀ age 20-80	868.8 – (age x 2.99) – (gender x 74.7) ♂ = 0, ♀ = 1	0.41
Chetta [10] (2006)	Italy 48♂, 54♀ age 20-50	518.853 + (1.25 x Ht) – (2.816 x age) – (39.07 x gender) ♂ = 0, ♀ = 1	0.42

Ht=height (cm), Wt=weight (kg), ♂=male, ♀=female, R^2 indicates the degree of inter-subject variance explained by the equation.

TABLE 2 Baseline characteristics of all patients and subgroups according to the aetiology of pulmonary arterial hypertension

	All patients (N=137)	Aetiology		p value*
		IPAH (N=86)	CTDPH (N=51)	
Age†, years	60 (22)	60 (29)	62 (13)	0.18
Female, N (%)	95 (69)	54 (63)	41 (80)	<0.05
Lung function (% predicted)				
FEV_1†	87 (22)	88 (19)	85 (24)	0.84
FVC†	99 (23)	101 (22)	98 (32)	0.48
DLco†	43 (32)	45 (38)	41 (18)	0.22
WHO FC, N (%)				
I and II	22 (16)	17 (20)	5 (10)	<0.05
III	104 (76)	59 (69)	45 (88)	−
IV	11 (8)	10 (12)	1 (2)	−
Haemodynamics				
mRAP†, mmHg	6 (7)	6 (7)	7 (8)	0.40
mPAP†, mmHg	48 (19)	50 (18)	42 (19)	<0.01
CI†, l/min/m^2	2.1 (0.9)	2.2 (0.9)	2.0 (0.9)	0.92
PVR†, Wood units	10.5 (8.4)	10.6 (7.8)	9.7 (9.9)	0.36
SvO_2, %	63±8	64±8	63±9	0.60
6MWD (N=130)				
Absolute 6MWD, metres	264±111	271±117	251±102	0.33
% predicted 6MWD				
Enright	50±19	50±20	50±19	0.95
Troosters	41±16	41±16	42±15	0.84
Gibbons	41±16	41±16	40±15	0.81
Chetta	49±19	49±20	49±18	0.92

N=number, IPAH=idiopathic pulmonary arterial hypertension, CTDPH=connective tissue disease associated pulmonary hypertension, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, WHO FC=World Health Organisation functional class, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, CI=cardiac index, PVR=pulmonary vascular resistance, SvO_2=mixed venous saturation, 6MWD=six-minute walk distance. Data are expressed as mean±standard deviation or number (percentage) unless otherwise stated. †Median (interquartile range), *Comparing IPAH versus CTDPH patients.

TABLE 3 Univariate Cox proportional hazards analysis

	Hazard ratio	95% CI	p value
Age at diagnosis, per decade increase	1.43	1.11-1.86	<0.005
Gender			
Female	0.61	0.32-1.19	0.14
Male (reference)	–	–	–
Lung function at baseline			
FEV_1, per 10% predicted increase	1.09	0.91-1.31	0.36
FVC, per 10 % predicted increase	1.07	0.91-1.26	0.42
DLco, per 10 % predicted increase	0.75	0.63-0.90	<0.005
WHO FC at baseline			
I/II	0.60	0.18-2.02	0.41
III	0.63	0.24-1.67	0.34
IV (reference)	–	–	–
WHO FC on treatment			
I/II	0.13	0.04-0.43	<0.001
III	0.28	0.09-0.89	<0.05
IV (reference)	–	–	–
Aetiology			
CTDPH	1.63	0.87-3.06	0.12
IPAH (reference)	–	–	–
Haemodynamics at baseline			
mRAP, per 5 mmHg increase	1.19	0.90-1.58	0.21
mPAP, per 5 mmHg increase	1.01	0.91-1.12	0.81
CI, per 1 l/min/m^2 increase	0.83	0.49-1.39	0.47
PVR, per 1 Wood unit increase	1.01	0.96-1.06	0.68
SvO_2, per 5% increase	0.93	0.73-1.19	0.56
6MWD at baseline: N=130			
Absolute 6MWD, per 50 m increase	0.78	0.67-0.95	<0.005
% predicted 6MWD, per 10% increase			
Enright	0.83	0.69-0.99	<0.05
Troosters	0.77	0.62-0.96	<0.05
Gibbons	0.74	0.61-0.90	<0.005
Chetta	0.79	0.66-0.94	<0.01
6MWD on treatment: N=110			
Absolute 6MWD, per 50 m increase	0.74	0.64-0.90	<0.005
% predicted 6MWD, per 10% increase			
Enright	0.75	0.61-0.93	<0.01
Troosters	0.68	0.53-0.89	<0.005
Gibbons	0.67	0.53-0.85	<0.005
Chetta	0.72	0.59-0.88	<0.005

CI=confidence interval, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, WHO FC= World Health Organisation functional class, CTDPH=connective tissue disease associated pulmonary hypertension, IPAH=idiopathic pulmonary arterial hypertension, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, CI=cardiac index, PVR=pulmonary vascular resistance, SvO_2=mixed venous saturation, 6MWD=six-minute walk distance, N=number

TABLE 4 Receiver-operating characteristic analysis comparing the ability of absolute and percent predicted six-minute walk distance to predict two-year mortality

	ROC curve area (95% CI)	Optimal threshold	Sensitivity/specificity	p value
At baseline				
Absolute 6MWD	0.74 (0.63-0.86)	<295 metres	0.83/0.59	<0.0005
% predicted 6MWD				
Enright	0.71 (0.59-0.83)	<51%	0.75/0.56	<0.005
Troosters	0.73 (0.62-0.85)	<43%	0.79/0.57	<0.001
Gibbons	0.75 (0.64-0.85)	<43%	0.75/0.60	<0.0005
Chetta	0.74 (0.63-0.85)	<53%	0.75/0.57	<0.001
On treatment				
Absolute 6MWD	0.77 (0.64-0.90)	<296 metres	0.87/0.66	<0.005
% predicted 6MWD				
Enright	0.72 (0.56-0.87)	<53%	0.67/0.66	<0.01
Troosters	0.76 (0.63-0.90)	<45%	0.80/0.67	<0.005
Gibbons	0.78 (0.64-0.91)	<44%	0.87/0.72	<0.005
Chetta	0.78 (0.65-0.91)	<53%	0.87/0.71	<0.005

ROC=receiver-operating characteristic, CI=confidence interval, 6MWD=six-minute walk distance

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