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Early View

Original article

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EmPHasis-10 health-related quality of life score predicts outcomes in patients with idiopathic and connective tissue disease-associated pulmonary arterial hypertension: results from a UK multi-centre study

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Abstract

Health-related quality of life (HRQoL) scores assess symptom burden in pulmonary arterial hypertension (PAH) but data regarding their role in prognostication and risk stratification are limited. We assessed these relationships using the emPHasis-10 HRQoL measure.

1745 patients with idiopathic or connective tissue disease-associated PAH who had completed emPHasis-10 questionnaires between 2014-17 at 6 UK referral centres were identified. Correlations with exercise capacity and WHO functional class (FC) were assessed, and exploratory risk stratification thresholds were tested.

Moderate correlations were seen between emPHasis-10 scores and 6-minute walk distance (r=-0.546), incremental shuttle walking distance (r=-0.504) and WHO FC (r=0.497; *p* all <0.0001). Distribution of emPHasis-10 differed significantly between each WHO FC (*p* all <0.0001). At multivariate analysis, emPHasis-10, but not WHO FC, was an independent predictor of mortality. In a risk stratification approach, scores of 0-16, 17-33 and 34-50 identified incident patients with one-year mortality of 5%, 10% and 23%, respectively. Survival of patients in WHO FC III could be further stratified using an emPHasis-10 score ≥34 (*p*<0.01). At follow-up, patients with improved emPHasis-10 had improved exercise capacity (*p*<0.0001), and patients who transitioned risk groups demonstrated similar survival to patients originally in those risk groups.

The emPHasis-10 score is an independent prognostic marker in patients with idiopathic or connective tissue disease-associated PAH. It has utility in risk stratification in addition to currently used parameters. Improvement in emPHasis-10 score is associated with improved exercise capacity.

Introduction

Pulmonary arterial hypertension (PAH) is a rare condition, characterised by increased pulmonary vascular resistance and progressive right ventricular failure leading to premature death (1). Exertional breathlessness and limitation in physical activity are typically the earliest reported symptoms and may be caused by a number of mechanisms (2, 3). Exercise limitation may be objectively assessed by exercise testing, but limitations of day-to-day physical activity are typically assessed by healthcare professionals using the World Health Organisation (WHO) functional class.

The importance of assessing patient reported outcome measures (PROMs) in patients with pulmonary hypertension (PH) is now recognised (4, 5) and three PH-specific tools for assessing health-related quality of life (HRQoL) have been developed (6-8). One of these tools, emPHasis-10, is comprised of 10 fields (resulting in a score out of 50, where a higher score represents a higher symptom burden) which can be quickly completed by patients and is free to use and so is well suited to routine clinical use (7). The emPHasis-10 score was found to correlate strongly with measures of HRQoL, breathlessness and psychological morbidity and has high test-retest and internal consistency (7). In addition, the emPHasis-10 questionnaire has been translated into a number of other languages (9, 10). A previous single-centre study of emPHasis-10 in patients with PAH (predominantly congenital heart disease-associated) and chronic thrombo-embolic PH demonstrated prognostic significance and a correlation with WHO functional class (FC) (11). Although risk stratification has an established central role in the management of patients with PAH, PROMs are not incorporated in current risk assessment tools (12-14).

Routine HRQoL assessment using a PH-specific tool has been a mandatory field in the UK National Audit of Pulmonary Hypertension since 2014 (15). We performed a multi-centre study on a large cohort of patients with idiopathic and connective tissue disease (CTD)-associated PAH, to further assess the relationship between emPHasis-10 score and mortality, identify correlations with clinical parameters, including exercise capacity, and determine whether a threshold approach for risk stratification could be applied.

Methods

Local databases for 6 out of the 7 UK pulmonary hypertension referral centres, which together manage 94% of adult patients with a diagnosis of PAH, were interrogated (15). Patients with PAH were diagnosed as per contemporaneous international guidelines (mean pulmonary arterial pressure ≥25mmHg and pulmonary arterial wedge pressure ≤15mmHg in the absence of thromboembolic disease or conditions associated with other forms of pulmonary hypertension) (16). Anonymised demographic, haemodynamic, spirometric, exercise, emPHasis-10 and mortality data were retrieved for all patients with a diagnosis of idiopathic, drug-associated or heritable PAH (hereafter grouped as IPAH) or PAH related to CTD (CTD-PAH) with at least one recorded emPHasis-10 score between January 1st 2014 and 31st May 2018. Incident patients were required to have an emPHasis-10 score at the point of diagnosis, which was possible if diagnosed from 2014 onwards since its clinical use was introduced in the UK during that year. For prevalent patients (i.e. those diagnosed prior to 2014 or for whom no emPHasis-10 score was available at the time of diagnosis) the first available emPHasis-10 score was used. In either group, the first emPHasis-10 score was described as the baseline measurement. All patients were under regular clinical follow-up and the outcome measured was death or transplant by 31st May 2019. Follow-up data were retrieved for the first visit between 3 and 12 months after baseline emPHasis-10 score.

Statistical Analysis

Statistical analysis was performed using SPSS v26 (IBM, Chicago) and GraphPad Prism v8. Continuous data were displayed as either mean ± standard deviation, or median (first quartile, third quartile) for non-parametric data. Demographics were compared using paired and unpaired T-test for parametric data, and Wilcoxon signed-rank and Mann-Whitney U-tests for non-parametric data. Frequencies were compared using X^2. For Cox regression modelling, parameters of known prognostic significance in PAH were utilised: age, gender, presence of CTD (rather than IPAH), mean right atrial pressure, cardiac index and walking distance. Collinearity was assessed by measuring the variance inflation factor and tolerance between variables. EmPHasis-10 score was entered as a continuous variable in the multivariable model. Multivariate Cox regression analysis was performed in a forward direction on all parameters with a p value <0.2 at univariate analysis. Data were scaled to the mean and hazard ratios were based on the z-score. Two types of walking test were used (the 6-minute walking test (6MWT) and incremental shuttle walking test (ISWT)) and so for multivariate modelling, distances were converted to a z-score and combined as a single variable. For all statistical tests other than multivariate analysis, a p value of <0.05 was considered significant. Kaplan-Meier survival

curves were compared using log rank X^2, and were truncated at 4 years, based on the census date. Correlations were assessed using either Pearson or Spearman rank, as appropriate. Risk models were compared using the c-statistic identified from receiver operating characteristic (ROC) curve analysis. The minimal detectable change (MDC) for emPHasis-10 score was calculated using the formula: MDC = 1.96 x √2 x standard error of measurement.(17)

Ethical approval was granted (IRAS 254446).

Results

A total of 1745 patients with IPAH (n=994) or CTD-PAH (n=751) who had at least one recorded emPHasis-10 score were identified. There was a female predominance (73%), and 35% of patients were incident and treatment-naïve at the time of baseline emPHasis-10 score. The median emPHasis-10 score was higher in patients with CTD-PAH (median 30 (19, 38)) than patients with IPAH (28 (17, 37)); *p*=0.001. Baseline demographics are displayed in table 1.

Correlation with clinical parameters

Moderate correlations (*p* all <0.0001) were seen between baseline emPHasis-10 score and WHO FC (r=0.50), 6MWT distance (6MWD; r=-0.55) and ISWT distance (ISWD; r=-0.50), table 2. In incident patients with right heart catheter data available (n=591), there were weak correlations with mean right atrial pressure (mRAP; r=0.21), cardiac index (r=-0.21) and pulmonary vascular resistance (PVR; r=0.17); *p* all <0.0001. Correlations were similar in subgroups of IPAH and CTD-PAH, apart from PVR where correlation was significant in CTD-PAH (r=0.21; *p*<0.0005) but not in IPAH (r=0.11; *p*=0.8). Correlations between WHO FC and walk distance and haemodynamics are also shown in table 2.

Distribution of emPHasis-10 score by WHO FC at baseline is shown in figure 1; median emPHasis-10 scores were 3, 19, 31 and 40 in WHO FC I, II, III and IV, respectively, with highly significant differences between the scores in each functional class (*p* all <0.0001).

Risk Stratification

During the course of the study 674 (39%) patients died, of which 240 (14%) died within one-year of baseline emPHasis-10 score; one-year mortality in incident and prevalent patients was 16% and 12%,

respectively. An exploratory three-level score was developed based on a tertile group approach: scores of 0-16 were defined as low-risk, 17-33 as intermediate-risk, and 34-50 as high-risk. Using these thresholds, 22% of all patients were defined as low-risk, 41% as intermediate-risk and 37% as high-risk of one-year mortality. Survival curves for these risk groups are shown for incident patients in figure 2a, prevalent patients in figure 2b, and for all patients in figure 2c. In incident patients, one-year mortality for the low, intermediate and high-risk groups was 5%, 10% and 23%, respectively, and in prevalent patients one-year mortality for the low, intermediate high-risk groups was 4%, 13% and 20%, respectively. In all patients, one-year mortality for the low, intermediate and high-risk groups was 4%, 12% and 21%, respectively. In all patients with IPAH, one-year mortality in low, intermediate and high-risk groups was 4%, 9% and 18%, whereas in CTD-PAH, one-year mortality was 6%, 15% and 25%, respectively. Incident patients in functional class III who were in low/intermediate emPHasis-10 risk groups (emPHasis-10 score 0-33) had superior survival than those in the high-risk group (emPHasis-10 score 34-50) with 1 and 3-year survival of 90% and 67% vs 81% and 56%; $p<0.01$; figure 3). Very similar observations were made in functional class III patients at their first follow-up visit.

Survival Analysis

Three multivariate analysis models were developed in the incident population (table 3). Model 1 utilised accepted prognostic parameters: age, gender, CTD-PAH rather than IPAH, WHO FC, mRAP and cardiac index. EmPHasis-10 and exercise capacity were sequentially added into models 2 and 3. Unlike WHO FC, emPHasis-10 score was an independent predictor of outcome in models 2 (scaled HR 1.565; $p<0.0001$) and 3 (scaled HR 1.226; $p<0.05$). There was no significant collinearity between parameters used in the model.

Magnitude of change

The MDC for emPHasis-10 score was calculated to be 9. Follow-up emPHasis-10 data were available for 1068 patients (61%). EmPHasis-10 score changed by at least 9 points in 33% of patients (IPAH 32%, CTD-PAH 34%) between baseline and follow-up. Thirty-seven percent of patients moved risk groups, of which 19% improved at least one risk group. In patients who moved from high-risk to intermediate or low-risk, the median change in emPHasis-10 score was -12 (-6, -19) points, and in patients who deteriorated to high-risk the median change was +13 points (+8, +17). Patients who

either improved to low or intermediate-risk, or deteriorated to high-risk demonstrated similar long-term survival to patients originally in those risk groups (figure 2d).

At paired testing in patients with a follow-up emPHasis-10 score, those who improved emPHasis-10 score by ≥ the MDC of 9 points had significantly improved walk distances at follow-up; ISWD increased by 30m (0, 90; p<0.0001, figure 4a) while 6MWD increased by a median distance of 32m (-4, +113; p<0.005, figure 4b). A significant fall in ISWD of -20m (-60, 0; *p*<0.0001, figure 4a) and no significant change in 6MWD (0m (-29, +57), figure 4b) was observed in patients whose emPHasis-10 score deteriorated by at least 9 points. In the remaining patients in whom there was a change of <9 points there was no significant change in either ISWD (0m (-30, +20)) or 6MWD (0m, (-11, +53)). The relationship between change in emPHasis-10 and change in walk distance differed depending on whether patients were incident or prevalent at the time of their baseline walk (relationship being stronger in incident patients) and whether they performed the ISWT or 6MWT (relationship being stronger in patients who performed the ISWT). In patients whose emPHasis-10 score deteriorated by ≥9 points, ISWD fell significantly in both incident and prevalent populations. In patients whose emPHasis-10 score improved ≥9 points ISWD increased significantly in incident, but not prevalent, patients (figure 4c and 4e). In patients in whom a 6MWT was performed, an improvement was observed in incident patients whose emPHasis-10 score either improved or deteriorated by ≥9 points (figure 4d), while no significant change was seen in prevalent patients (4f).

Discussion

To our knowledge, this is the largest study to assess the role of quality of life scores in patients with PAH, and in this multi-centre study we report on data from centres treating the vast majority of the adult PAH population in the UK. We have demonstrated that the emPHasis-10 score is an independent predictor of outcomes when adjusting for haemodynamics and WHO FC and also has utility in risk stratification, including within patients in WHO FC III. We have also observed moderate correlations with WHO FC and exercise capacity and weaker correlations with pulmonary haemodynamics. Furthermore, we have also demonstrated that improvement in emPHasis-10 score, as opposed to a static or worsening score, is associated with improvements in exercise capacity.

Generic (Short Form Health Survey (SF-36)), heart failure-specific (Minnesota Living with Heart Failure questionnaire), and PAH-specific (emPHasis-10 and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)) PROMs have previously been identified as having prognostic importance in PAH (11, 18-20). Correlations between CAMPHOR and SF-36 and 6-minute walking test distance have also been demonstrated (19, 21, 22). The widespread clinical use of the

CAMPHOR score may, however, be limited by its length (65 fields over 3 domains: symptoms, functioning and quality of life) and lack of open access (23). A third PH-specific PROM, the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) tool, which consists of 22 fields over 2 domains (symptoms and impacts) has also been developed (8). Although PAH-SYMPACT is responsive to change, its relationship to haemodynamics and survival is not known (24).

A previous single-centre study involving 687 patients (314 PAH associated with congenital heart disease, 109 IPAH, 111 CTD-PAH and 131 chronic thromboembolic PH) assessed the relationship between emPHasis-10 and survival (11). In that study, Cox regression analysis demonstrated emPHasis-10 to be predictive of survival, independent of WHO FC, in PAH associated with congenital heart disease, but not in IPAH and CTD-PAH. In our study, which included much larger numbers of patients with IPAH and CTD-PAH, emPHasis-10 was an independent prognostic marker in IPAH and CTD-PAH, even when allowing for a number of variables known to be strongly prognostic in PAH including mRAP and cardiac index. This was not the case for WHO FC and it is interesting to note that Boucly *et al* also observed that baseline WHO FC was not an independent predictor of outcome in their paper from the French Registry (14).

In incident patients, an exploratory risk stratification approach separating emPHasis-10 scores into three bands based on an equal range of scores in each group (thresholds of ≤16, 17-33 and ≥34) identified distinct risk groups with significant survival differences (corresponding one-year mortality of 5%, 10% and 23%, respectively). These levels of one-year mortality are very similar to risk thresholds of low (<5%), intermediate (5-10%) and high-risk (>10%) proposed by the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for risk stratification in PAH. Using these risk thresholds, we identified that patients who either improved to intermediate or low-risk, or deteriorated to high-risk at follow-up emPHasis-10 assessment had a similar longer-term survival to patients who were originally in those risk groups. This effect has been seen in a number of other risk stratification parameters and scores (25-27), and the importance of achieving specific PROM thresholds in PAH has also been observed with the generic SF-36 (28). The majority of patients are in WHO FC III at the time of diagnosis and we were therefore interested whether the emPHasis-10 score could refine these patients into higher and lower risk groups. We observed that a threshold score ≥34 was indeed able to identify functional class III patients at higher and lower risk of one-year mortality at both diagnosis and at first follow-up.

We observed moderate correlations between emPHasis-10 and exercise capacity (r=0.55 and 0.50) and WHO FC (0.50) and only weak correlations with pulmonary haemodynamics (r ranging between 0.17 and 0.21). The correlations with exercise capacity compare favourably with some reports

regarding the other 2 PH-specific PROMs; Gomberg-Maitland *et al* reported weaker correlations between 6MWD and the 3 domains of CAMPHOR (symptoms r=0.35, functioning 0.45, HRQoL 0.33) in 147 PAH patients while Chin *et al* observed weak to moderate correlations between domains of the PAH-SYMPACT and 6MWD (r =-0.14 to -0.57) in 278 PAH patients (24). More recently, however, Reis *et al* observed stronger correlations between 6MWD and the 3 CAMPHOR domains (r=-0.67, -0.74 and -0.61) in 49 patients with PAH or chronic thromboembolic PH (22, 29). To date, there have been no previous reports of correlations of PH-specific PROMs and pulmonary haemodynamics. The correlations we observed were, however, comparable to those observed by Mathai *et al* between components of the SF-36 generic HRQoL tool and haemodynamics in 87 patients with PAH (although in their study, many of these correlations were non-significant) (18).

Finally, we have demonstrated that an improvement in emPHasis-10 score of at least the MDC (≥9) at follow-up was associated with an increase in exercise capacity in incident patients whereas a reduction in emPHasis-10 score by ≥9 was associated with a decrease in exercise capacity when assessed by the ISWD. The vast majority of incident patients will have been started on PAH therapies, whereas in prevalent patients there may have been no treatment change between assessments, which may partly explain the stronger relationship between change in walk distance and change in emPHasis-10 score in the incident group. The reason for the stronger relationship between change in ISWD (as opposed to 6MWD) and change in emPHasis-10 is not clear but may reflect the different nature of the tests; the ISWT is an externally-paced measure of maximal exercise capacity while the 6MWT is an internally-paced assessment of sub-maximal exercise capacity. These data suggest that emPHasis-10 is responsive to change, however further work is needed to define the minimal clinically important difference.

Limitations

While this study was able to demonstrate important associations between emPHasis-10 score and time to death or transplantation, other measures of clinical deterioration including hospitalisation due to heart failure and escalation of therapy were unavailable. In addition, while emPHasis-10 scores were prospectively collected, this was a retrospective study and there were some data availability issues. Treatment data were not available; it is possible that PAH-specific therapies may affect HRQoL both negatively, in terms of side effects and the effects of complex treatments on lifestyle, but also positively, in terms of improvements in right ventricular function translating into amelioration of symptoms. Finally, data regarding comorbidities, such as the presence and extent of parenchymal lung disease in patients with CTD-PAH, were unavailable. Assuming that comorbidities

such as lung disease adversely affect HRQoL the inclusion of patients with parenchymal lung disease would likely weaken the relationships between emPHasis-10 and functional parameters, treatment response and survival.

Conclusion

The emPHasis-10 score correlates with WHO FC, exercise capacity and haemodynamics and is an independent prognostic marker in patients with IPAH and CTD-PAH. It has utility in risk stratification in addition to currently used parameters. The survival of patients within WHO FC III can be further stratified using emPHasis-10 score. Improvement in emPHasis-10 is associated with improvement in exercise capacity, although further work to determine the minimal clinically important difference is required.

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Table 1: Patient characteristics

	All (n = 1745)	I/D/HPAH (n = 994)	CTD-PAH (n = 751)	*p* value	n
Female (%)	73	66	82	<0.0001	1745
Age at diagnosis (yrs)	59 ±17	55 ±18	64 ±13	<0.0001	1745
% incident	35	29	44	<0.0001	618
FEV_1 (%pred)	82 ±21	84 ±19	80 ±23	0.0001	1457
FVC (%pred)	92 ±23	95 ±20	89 ±27	<0.0001	1459
FEV_1/FVC	73 ±13	74 ±13	73 ±14	0.078	1459
mRAP (mmHg)	9 ±6	10 ±6	8 ±5	<0.0001	1503
mPAP (mmHg)	48 ±13	53 ±13	41 ±11	<0.0001	1573
PAWP (mmHg)	9 ±4	9 ±4	9 ±3	0.56	1496
PVR (WU)	10.5 ±5.8	12.0 ±5.7	8.7 ±5.4	<0.0001	1378
Cardiac Output (l/min)	4.2 ±1.5	4.0 ±1.5	4.3 ±1.5	<0.0005	1465
Cardiac Index (l/min/m^2)	2.4 ±0.8	2.2 ±0.8	2.5 ±0.8	<0.0001	1305
emPHasis-10	29 (18, 38)	28 (17, 37)	30 (19, 38)	0.001	1745
WHO FC I/II/III/IV (%)*	3/23/61/13	4/26/57/13	1/20/67/12		1725
6MWD*	310 (180, 408)	340 (192, 432)	241 (141, 360)	<0.0001	659
ISWD*	150 (70, 270)	160 (80, 350)	140 (60, 228)	0.001	797

*Variables were recorded at time of baseline emPHasis-10; other variables were recorded at diagnosis. Baseline 6MWD and ISWD were available in 38% and 46% of patients, respectively, with no overlap.

Abbreviations: I/D/HPAH = idiopathic/drug/heritable pulmonary arterial hypertension, CTD-PAH = connective tissue disease related pulmonary arterial hypertension, mRAP = mean right atrial pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PVR = pulmonary vascular resistance; WHO FC = World Health Organisation functional class; 6MWD = six-minute walking test distance; ISWD = incremental shuttle walking test distance

Table 2. Correlation of emPHasis-10 and WHO functional class with walk distance and pulmonary haemodynamics

	6MWD (m)	ISWD (m)	mRAP (mmHg)	CI (L/min/m^2)	PVR (WU)
emPHasis-10	-0.55* (n=659)	-0.50* (n=797)	0.21* (n=575)	-0.21* (n=525)	0.17* (n=550)
WHO FC	-0.60* (n=653)	-0.59* (n=796)	0.18* (n=572)	-0.18* (n=523)	0.18* (n=548)

Correlations assessed by Pearson or Spearman-Rank tests as appropriate. * = p<0.001.

Abbreviations: 6MWD = 6-minute walking distance, ISWD = incremental shuttle walking distance, mRAP = mean right atrial pressure, CI = cardiac index, PVR = pulmonary vascular resistance, WHO FC = World Health Organisation functional class.

Table 3. Univariate and multivariate analysis in incident patients

	Univariate		**Multivariate**	
Model 1	**Scaled HR**	***p* value**	**Scaled HR**	***p* value**
Age	2.063	<0.0001	2.177	<0.0001
Gender (ref. Female)	1.316	0.054		
CTD-PAH (ref. IPAH)	1.336	0.031	1.444	0.017
WHO FC III (ref I&II)	1.817	0.009		
WHO FC IV (ref I&II)	3.642	<0.0001	2.978	<0.0001
mRAP	1.196	0.006	1.227	0.005
Cardiac Index	0.756	0.001		
Model 2	**Scaled HR**	***p* value**	**Scaled HR**	***p* value**
Age	2.063	<0.0001	2.180	<0.0001
Gender (ref. Female)	1.316	0.054		
CTD-PAH (ref. IPAH)	1.336	0.031		
WHO FC III (ref I&II)	1.817	0.009		
WHO FC IV (ref I&II)	3.642	<0.0001		
mRAP	1.196	0.006		
Cardiac Index	0.756	0.001		
emPHasis-10	1.518	<0.0001	1.447	<0.0001
Model 3	**Scaled HR**	***p* value**	**Scaled HR**	***p* value**
Age	2.063	<0.0001	1.860	<0.0001
Gender (ref. Female)	1.316	0.054		
CTD-PAH (ref. IPAH)	1.336	0.031		
WHO FC III (ref I&II)	1.817	0.009		
WHO FC IV (ref I&II)	3.642	<0.0001		
mRAP	1.196	0.006		
Cardiac Index	0.756	0.001		
emPHasis-10	1.518	<0.0001	1.226	0.047
Walking distance*	0.461	<0.0001	0.574	<0.0001

*Two types of walking test were used (the 6-minute walking test and incremental shuttle walking test). For Cox regression modelling, distances were converted to a z-score and combined.

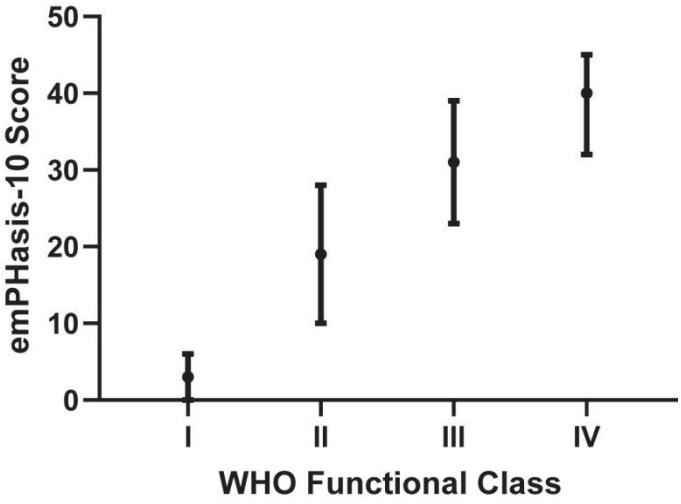
Abbreviations: IPAH = idiopathic pulmonary arterial hypertension, CTD-PAH = connective tissue disease related pulmonary arterial hypertension, WHO FC = World Health Organisation functional class; mRAP = mean right atrial pressure, HR = Hazard Ratio

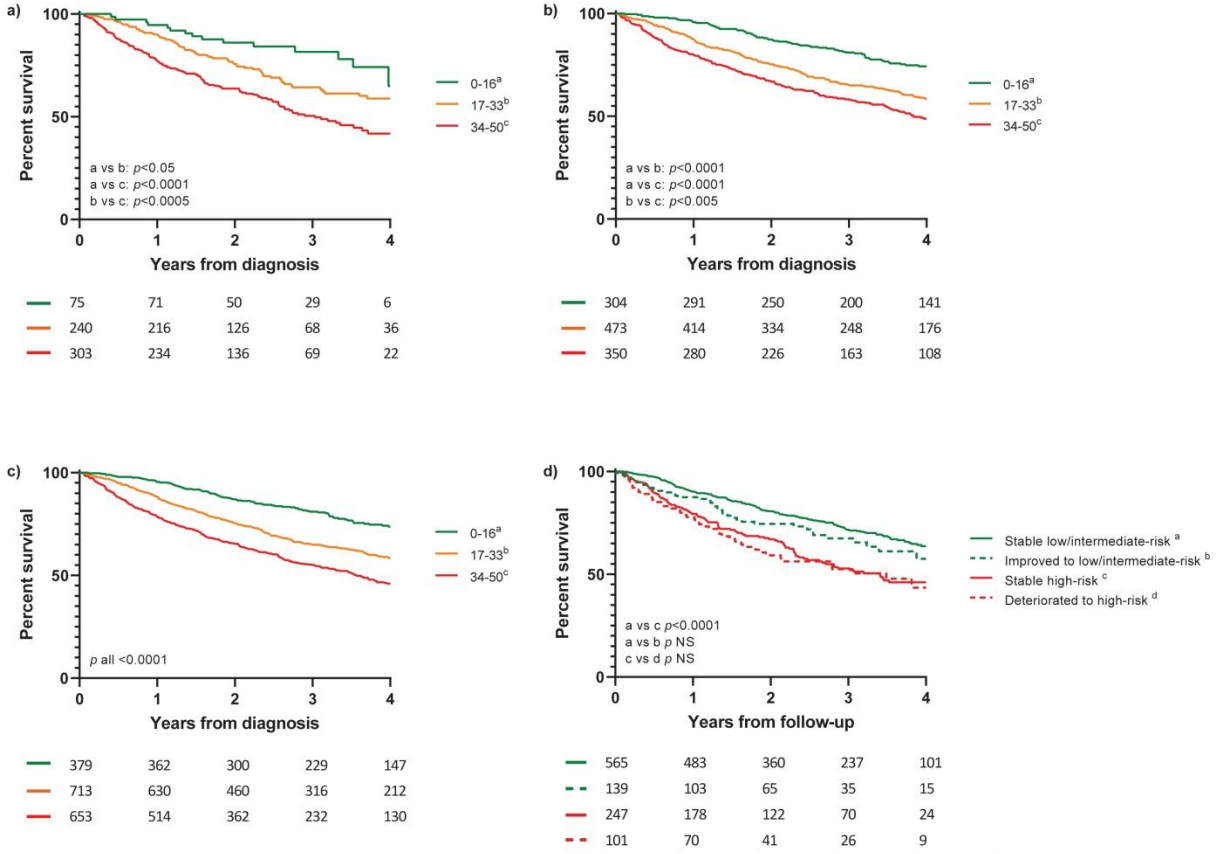
Figure 1: Distribution of emPHasis-10 score by WHO functional class at baseline Abbreviations: WHO = World Health Organisation

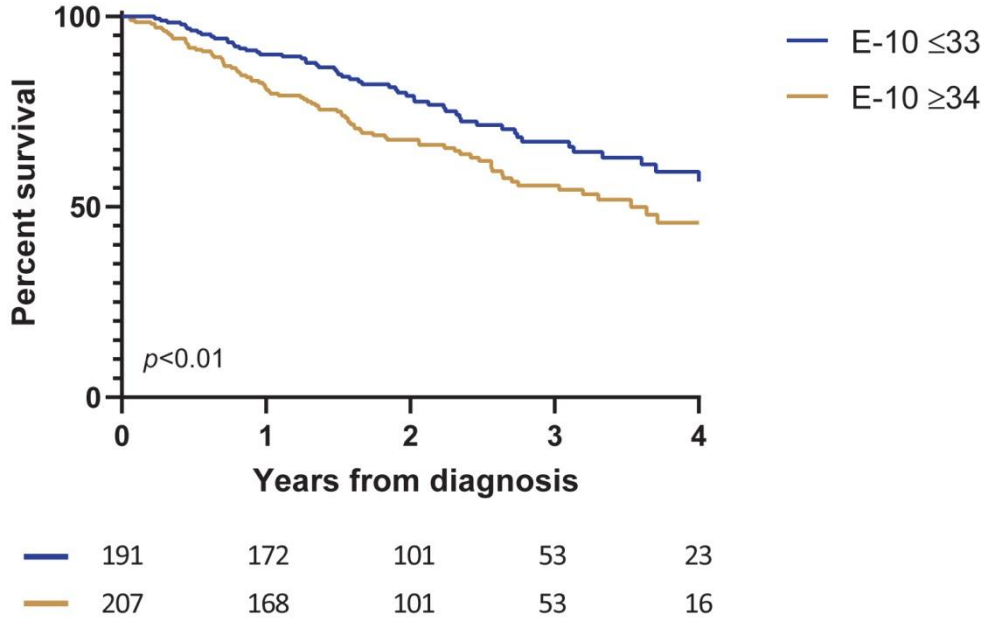
Figure 2: Kaplan Meier survival curves demonstrating survival from baseline emPHasis-10 score for a) incident patients; b) prevalent patients; c) all patients; d) risk transition in all patients between baseline and follow-up emPHasis-10 score Abbreviations: NS = not significant

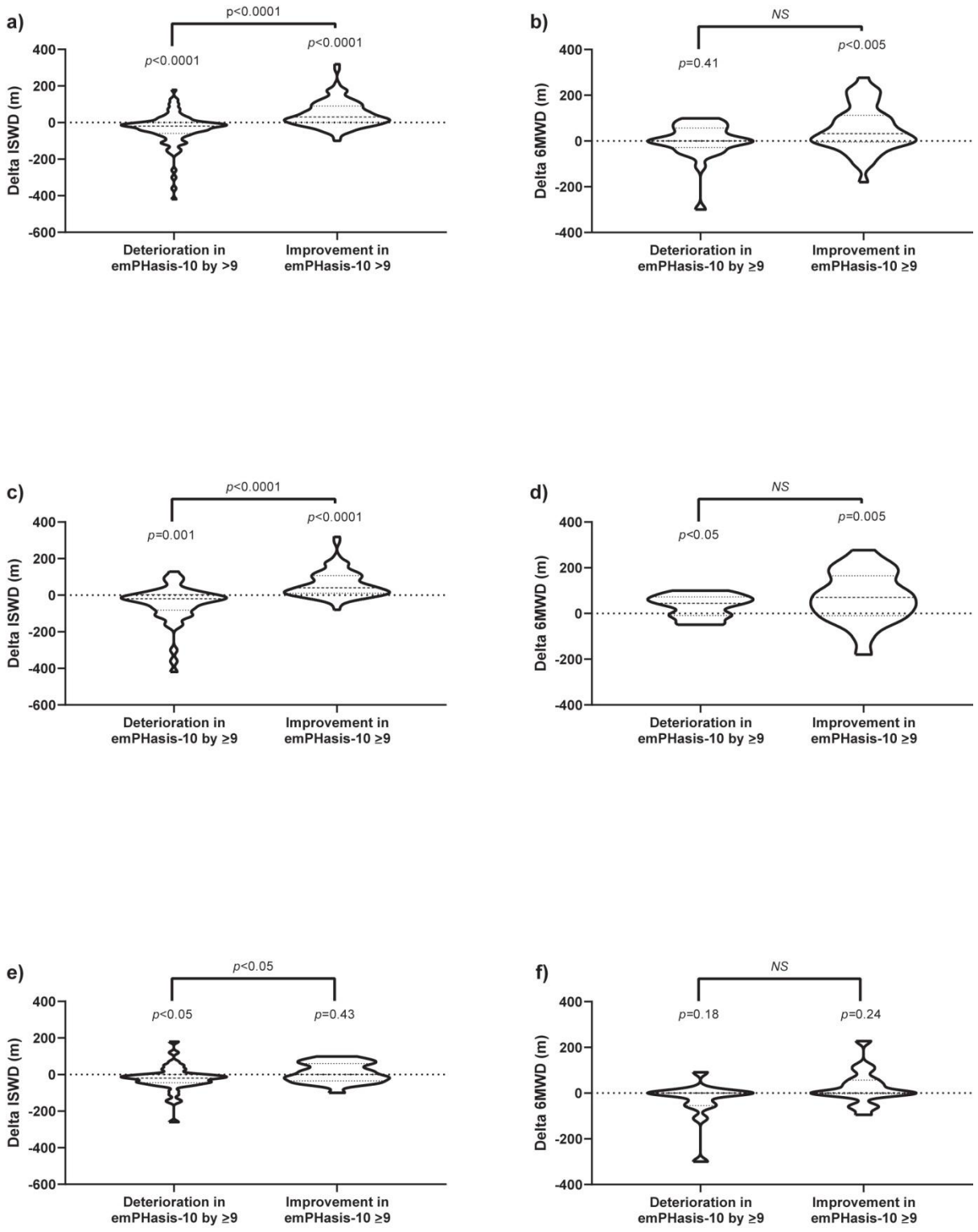
Figure 3: Survival in incident patients with WHO functional class III symptoms, dichotomised by emPHasis-10 score ≤33 or ≥34. Abbreviations: WHO = World Health Organisation, E-10 = emPHasis-10 score

Figure 4: Change in walk distance (ISWD or 6MWD) in patients whose emPHasis-10 score deteriorated by ≥9 or improved by ≥9 between baseline and follow-up. Figure 4a & b: all patients, figure 4c & d: incident patients, figure 4e & f: prevalent patients. Abbreviations: ISWD = incremental shuttle walking test distance; 6MWD = six-minute walking test distance; E-10 = emPHasis-10. Violin plots: dashed line = median, dotted line = 25th and 75th centile


50
40
30
20
10
0
emPHasis-10 Score
I
II
III
IV
WHO Functional Class


a)
Percent survival
100
50
0
0 1 2 3 4
Years from diagnosis
a vs b: p<0.05
a vs c: p<0.0001
b vs c: p<0.0005
0-16a
17-33b
34-50c
75 71 50 29 6
240 216 126 68 36
303 234 136 69 22
b)
Percent survival
100
50
0
0 1 2 3 4
Years from diagnosis
a vs b: p<0.0001
a vs c: p<0.0001
b vs c: p<0.005
0-16a
17-33b
34-50c
304 291 250 200 141
473 414 334 248 176
350 280 226 163 108
c)
Percent survival
100
50
0
0 1 2 3 4
Years from diagnosis
p all <0.0001
0-16a
17-33b
34-50c
379 362 300 229 147
713 630 460 316 212
653 514 362 232 130
d)
Percent survival
100
50
0
0 1 2 3 4
Years from follow-up
a vs c p<0.0001
a vs b p NS
c vs d p NS
Stable low/intermediate-risk a
Improved to low/intermediate-risk b
Stable high-risk c
Deteriorated to high-risk d
565 483 360 237 101
139 103 65 35 15
247 178 122 70 24
101 70 41 26 9


100
50
0
Percent survival
p<0.01
0
1
2
3
4
Years from diagnosis
E-10 ≤33
E-10 ≥34
191 172 101 53 23
207 168 101 53 16


a)
p<0.0001
p<0.0001
p<0.0001
Delta ISWD (m)
400
200
0
-200
-400
-600
Deterioration in emPHasis-10 by >9
Improvement in emPHasis-10 >9
b)
NS
p=0.41
p<0.005
Delta 6MWD (m)
Deterioration in emPHasis-10 by ≥9
Improvement in emPHasis-10 ≥9
c)
p<0.0001
p=0.001
p<0.0001
Delta ISWD (m)
Deterioration in emPHasis-10 by ≥9
Improvement in emPHasis-10 ≥9
d)
NS
p<0.05
p=0.005
Delta 6MWD (m)
Deterioration in emPHasis-10 by ≥9
Improvement in emPHasis-10 ≥9
e)
p<0.05
p<0.05
p=0.43
Delta ISWD (m)
Deterioration in emPHasis-10 by ≥9
Improvement in emPHasis-10 ≥9
f)
NS
p=0.18
p=0.24
Delta 6MWD (m)
Deterioration in emPHasis-10 by ≥9
Improvement in emPHasis-10 ≥9