ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original article

Health-related quality of life and disease progression in PAH patients: a 3-year study

Laurence Halimi, Carey M. Suehs, Gregory Marin, Clement Boissin, Anne-Sophie Gamez, Isabelle Vachier, Nicolas Molinari, Arnaud Bourdin

Please cite this article as: Halimi L, Suehs CM, Marin G, *et al*. Health-related quality of life and disease progression in PAH patients: a 3-year study. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00617-2020).

Health-related quality of life and disease progression in PAH patients: a 3-year study

Authors and their affiliations
Laurence Halimi[1]*, Carey M. Suehs[1, 2], Gregory Marin[2], Clement Boissin[1], Anne-Sophie Gamez[1], Isabelle Vachier[1], Nicolas Molinari[2, 3], Arnaud Bourdin[1, 4]

1 Department of Respiratory Diseases, Univ Montpellier, CHU Montpellier, Montpellier, France
2 Department of Medical Information, Univ Montpellier, CHU Montpellier, Montpellier, France
3 IMAG, CNRS, Univ Montpellier, CHU Montpellier, Montpellier, France
4 PhyMedExp, Univ Montpellier, CNRS, INSERM 1046, CHU Montpellier, Montpellier, France

Corresponding author
Laurence Halimi, PhD, Department of Respiratory Diseases, Hôpital Arnaud de Villeneuve, 371, av. du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France.
E-mail: l-halimi@chu-montpellier.fr
Tel: +33467330745
Fax: +33467634581

Author Contributions: L.H., I.V., N.M. and A.B. designed and wrote the study protocol. L.H., C.B., A-S.G. and A.B. included and/or monitored patients and acquired data. N.M., G.M. and C.M.S. performed data wrangling and statistical analyses. L.H wrote the first draft of the manuscript. All authors participated in data interpretation, manuscript revision and approved the final version of the manuscript.

Sources of support for the project
The HyPsy protocol (clinicaltrials.gov: NCT01380054; https://osf.io/8qduc/) was partially funded by an unrestricted grant from GlaxoSmithKline. GlaxoSmithKline took no part in study design, data acquisition, analysis or interpretation of results.

Total word count (max 3000): 3021

Take home message

Baseline subscale SF-36 Physical Functioning questionnaire for PAH patients is independently associated with disease progression at 3 years. HRQoL should be considered as a complement to risk assessment criteria. The related depression requires specific attention.

Abstract

The role of health-related quality of life (HRQoL) and psychological variables in pulmonary arterial hypertension (PAH) progression remains poorly quantified.

Objectives

We aimed to investigate the relationship between disease progression in PAH patients and HRQoL and psychological characteristics.

Methods

A three-year longitudinal cohort was initiated. Patients with stable PAH (groups I-IV ineligible for angioplasty/endarterectomy) were included (N=55). Standard clinical variables including invasive hemodynamic parameters were prospectively recorded. A battery of questionnaires was used to characterize the psychological status of patients upon study initiation, and HRQoL was quantified using the SF-36 questionnaire every 3 months for 24 months, and then again at 36 months. Guideline-defined disease progression and progression free survival were recorded for 36 months.

Measurements and Main Results

Psychological distress was highly prevalent at baseline. The Physical Component Summary (PCS) and the Mental Component Summary (MCS) of HRQoL were poor (PCS=37.13±8.18; MCS=42.42±10.88) but stable over 3 years of follow-up. Among PCS subscales, Physical Functioning (PF) (p=.012) was identified as independently associated with disease progression (cox-survival model), along with mean pulmonary arterial pressure (p=.003) and cardiac output (p=.005). Depression was the unique independent psychological characteristic associated with PF (p=.0001).

Conclusions

PAH patients have poor HRQoL. In addition to already known criteria related to disease severity, the HRQoL Physical Functioning subscale is independently associated with disease progression in PAH. This may be explained by depression.

Abstract word count: 224

Key words: pulmonary arterial hypertension; progression-free survival; health-related quality of life; physical functioning; depression

Introduction

Pulmonary arterial hypertension (PAH) is a rare and progressive disease caused by persistent elevation of pulmonary arterial pressure leading to right-side heart failure [1]. At onset of PAH, symptoms remain nonspecific (fatigue, shortness of breath on exertion and exercise limitations) and a delay in diagnosis is frequent, emptying patients of their psychological resources. According to the national data registry, there were approximately 1700 PAH patients in France in 2006, and between 15 and 50 cases per million individuals worldwide [2]. In the past three decades, medical treatments have been developed and overall prognosis has improved [3] but mortality remains high and increasing survival remains a research priority. Improving health-related quality of life (HRQoL) has also become an essential objective supported by patients [4, 5].

Most clinical assessments during follow-up are integrated within a prognostic evaluation system based on right atrial pressure, cardiac output, 6-minute walking distance, pericardial effusion and right atrial surface, N-terminal pro-B-type natriuretic peptide, maximal oxygen uptake, symptoms [New York Heart Association (NYHA), syncope] and their progression. Though poor HRQoL is reported in this disabling disease, whether or not HRQoL should be considered as a prognostic criterion has not been addressed. In incident patients, HRQoL is a prognostic marker [5] which can change with time along with the health context [6]. However, systematic longitudinal evaluation by clinicians is not practiced [7] and even in research situations, repeated evaluations remain rare. To our knowledge, no PAH study has regularly monitored HRQoL over a relatively long time span.

The most common generic HRQoL evaluation is the Medical Outcomes Study short-form health survey (SF-36) questionnaire [8] for which minimally important differences have been determined in PAH [9]. Several studies have found improved or unchanged SF-36 scores

following various treatment trials in PAH [5, 10]. A systematic review underlines the heterogeneity of results, as well as the limited availability of data concerning their prognostic significance [11]. It is therefore still unclear whether poor HRQoL in PAH should be seen as a co-factor and eventually as an expected consequence of the disease or if it should be seen as a prognostic criteria.

The self-assessment of HRQoL is a cognitive process, and therefore open to the influence of psychological factors [12]. PAH impacts involving anxiety and depression have been repeatedly demonstrated [13, 14]. Current guidelines therefore stress the association between anxiety and depression and poor HRQoL [4]. Other psychological factors have the potential to expand our understanding of HRQoL [15]. Within this context, we initiated a three-year study to evaluate HRQoL in PAH patients with stable disease versus those who had acute disease aggravation. Associations with baseline clinical and psychological characteristics were also tested.

Methods

The study population

The HyPsy protocol (clinicaltrials.gov: NCT01380054; https://osf.io/8qduc/) included 55 PAH patients from May 2011 to November 2012 at the Arnaud de Villeneuve Hospital (Montpellier University Hospitals, France). The study was approved by an independent ethics committee (*Comité de Protection des Personnes – SudMéditerranée III;* reference number: 2011.04.01) and all patients gave their informed consent to enter the study in accordance with French law. Briefly, this 3-year longitudinal study included patients 18 to 80 years of age who had stable PAH for at least 3 months and no prior psychological care/support.

Patient monitoring for three years

Relevant right heart catheterization variables were measured at baseline. Data concerning the baseline 6-minute walking test (6MWT) were also recorded: distance walked (m and classified as above or below a 400m threshold), the associated Borg scale (score from 0 to 10); heart rate at the beginning and end of the test (HR_{start} and HR_{stop}; beats per minute (bpm)), peripheral capillary oxygen saturation (SpO2) at the beginning and end of the test ($SpO2_{start}$ and $SpO2_{stop}$; %), and whether or not the latter two measures differed by at least 4%, indicating a clinically significant change in SpO2 during the 6MWT ($\Delta SpO2_{4\%}$; yes/no).

Baseline psychological assessments included questionnaires describing anxiety and depression, coping mechanisms, perceived social support and beliefs concerning perceived control (Table 1). HRQoL was also measured every three months for 24 months and then again at 36 months using the SF36 questionnaire [8]. Disease progression (defined as aggravation requiring a change in treatment or death) versus disease stability was also monitored for 36 months, and triggered an additional HRQoL evaluation.

Statistics

Quantitative variable distributions were evaluated using Shapiro Wilk's tests, and normal variables summarized via their means and standard deviations. Other quantitative variables were presented as medians accompanied by their interquartile ranges and qualitative variables as numbers and percentages. Baseline characteristics were compared between stable and disease-progression patients with student tests or Mann-Whitney U-tests, as appropriate.

Cox models were used to analyze the relationships between baseline clinical and HRQoL variables and progression-free survival (delay to disease progression or death). Univariate models were first carried out, and variables which p-values <0.15 were entered into a multivariable cox model with forward selection. The coefficients with 95% confidence intervals are provided for the final model including only those variables independently and significantly associated with PFS. A bootstrapping of the cox model was carried out, via case resampling with replacement. One thousand bootstrapped samples were calculated, and the cox models were executed in each sample.

Mixed models were used to study the impact of time, disease stability and potential time×disease stability interactions on subscales (physical functioning (PF), physical composite summary (PCS), mental composite summary (MCS) of the SF-36 HRQoL questionnaire.

In order to better understand the psychological characteristics potentially associated with HRQoL, linear regression models were performed with PF as the dependent variable and baseline psychological variables as independent variables. As with cox models, variables with a univariate result of $P < 0.15$ were retained for analysis at the multivariable level using a forward stepwise method.

Statistical analyses were performed using SAS 9.1 software (SAS Institute, Cary, North Carolina) and R v.3.1.1 (The R Foundation for Statistical Computing), and the statistical bilateral significance threshold was set at 5%.

Results

Baseline description of the population and first results

Demographic characteristics, anxiety and depression (HADS), State and Trait anxiety (STAI-Y), coping (CHIP and WCC) and HRQoL (SF-36) baseline values for the total population have been previously reported in detail [16]. Briefly, the population had a mean age of 57.8±15.3 years, and was 64% women. A slight majority (51%) of patients suffered from anxiety and depression (HADS anxiety and depression scores: 8.7±4.7 and 6.16±3.9, respectively). Patients had moderate to very high state (60%; STAI-Y state anxiety: 48.2±7.5) and trait (64%; STAI-Y trait anxiety: 50.5±14.0) anxiety, especially for men. Stressful-life-event-coping (WCC) and disease-coping (CHIP) strategies focused on problem coping strategies. HRQoL was poor and the mean values for the Physical Component Summary (PCS) (37.1 ± 8.03) and the Mental Component Summary (MCS) (42.4±10.9) were particularly low. Regarding medical parameters, the patients included were fairly representative of the population usually described for PAH [4]. More than 50% were in functional classes I-II and the mean 6MWD ± SD was 382±33 m. The hemodynamic parameters for those patients who were already being treated (58% receiving bi- or tritherapy) corresponded to severe PAH (pulmonary vascular resistance of 10.0 ± 6.6 Wood's units) but with conserved cardiac output. Multivariate analysis showed a significant positive relation between 6MWD and PCS and a significant negative relation between delta SpO_2 ≥4% and MCS. Depression and Trait-Anxiety were associated with a lower physical ($p = 0.001$) and mental ($p < 0.001$) HRQoL, respectively [16].

Differences between progression-free and disease-progression groups

Baseline values for stable and unstable (i.e. patients with no observed disease progression during the 3 years of follow-up versus those who were observed to decline) patient groups are

presented in Tables 2 and 3. Certain clinical variables significantly differed between the two groups, including mean pulmonary arterial pressure, PAH treatments, NYHA class and 6 minute walking test results (distance and oxygen saturation at the beginning and end of the test). Both the PCS and MCS were higher (p = 0.06; p =0.04) in the stable group. All anxiety-related scores (STAI-Y state and trait anxiety scores, the HAD anxiety, depression and total scores) were significantly worse (p = 0.03; p = 0.01; p = 0.05; p = 0.01, p = 0.01, respectively) in the unstable group. The WCC emotion score was significantly higher (p = 0.03) in the unstable group, which indicates that the coping strategies used to manage stressful life events are more focused on emotional responses (Table 3).

Explaining Progression-free survival

The progression-free survival (PFS) curve is presented in Figure 1. 54% of the study population (which included 0% lost-to-follow-up) was progression-free at the end of 3 years of follow-up. According to the survival curve, aggravation occurred linearly. At the univariate level, several clinical variables were found to be associated with PFS: NYHA class, mean pulmonary arterial pressure, cardiac output, right atrium pressure and 6-minute walking test results (distance, the 400m threshold and oxygen saturation at the beginning and end of the test). Regarding HRQoL variables, all the SF-36 questionnaire subscales, except Bodily Pain and General Health, were associated with PFS.

At the multivariable level, mean pulmonary arterial pressure (Hazard Ratio = 1.053 [95% Confidence Interval: 1.023 to 1.084], p-value = 0.0153), cardiac output (HR = 1.559 [95% CI = 1.189 to 2.045], p-value =0.0013) and the Physical Functioning subscale (HR = 0.978 [95% CI =0.962-0.995], p-value = 0.0106) were significantly associated with PFS (Table 4). The bootstrapping approach confirms these results.

Stability of HRQoL over time

When examining the Physical Functioning subscale of the SF-36 questionnaire as a function of time and disease stability via a mixed model, only disease stability versus instability was significantly associated with PF (coefficient=18.53; SE=7.22; p=0.013). No association with time or the interaction term (stability × time) was found, indicating that the PF subscale was stable throughout the 3-years of complete follow-up (Figure 2). PCS and MCS were also stable across time (Figure 3). Given this stability, we further explored the contributions of psychological variables to PF scores at baseline.

Association between Physical Functioning subscale and baseline psychological variables

When examining the relationships between baseline psychological variables and the HRQoL PF subscale, several significant associations were demonstrated at the univariate level (Table 5), including negative associations with anxiety and depression variables and the CHIP Emotion score. At the multivariable level, only the HADS Depression score (coefficient=-3.26; SE=0.79; p=0.0001) was significantly negatively associated with the PF subscale.

Discussion

This study demonstrates a positive, independent association between progression free survival and the SF-36 HRQoL Physical Functioning subscale score in a 55-patient PAH cohort with no loss-to-follow-up over a three-year period. Unexpectedly, Physical Functioning and both the mental and physical component summary scores were stable over the entire study period. Progression free survival was associated with clinical findings comprising negative relationships with mean pulmonary arterial pressure and cardiac output. A battery of baseline psychological tests further demonstrated differences between the stable and disease progression patient groups that complement differences in HRQoL. Specifically, depression was negatively associated with the Physical Functioning subscale.

Risk assessment in PAH currently relies on parameters from clinical, hemodynamic, echographic, cardiopulmonary exercise testing and specific biomarker assessments. HRQoL has never been previously assessed in this regard. Surprisingly, HRQoL did not statistically decline over time. However, baseline values were associated with disease progression. This reinforces the results of a retrospective study by McCabe et al suggesting that the predictive value of the CAMPHOR questionnaire is also restricted to baseline values [17]. These results suggest that HRQoL monitoring can provide additional useful and complimentary information to the traditional PAH work-up, but does not need to carried out at overly-frequent intervals.

In addition, several psychological variables differed between the progression-free and disease-progression groups at baseline, indicating that the latter individuals have stronger anxiety (trait and state anxiety) and depression and resort more often to emotional coping strategies for dealing with daily stressors. However, at the multivariable level, the only psychological variable that associated with HRQoL was depression. The reader should note that the study

cohort included one-quarter incident patients, and these patterns may be specific to patients in the process of disease discovery.

As specifically concerns coping with stressful life events (WCC) and with the disease (CHIP), baseline values for the total population highlighted strategies that were primarily problem-focused, indicating a tendency to want to control the situation [16]. However, in the disease-progression group, such coping strategies (WCC) were more focused on emotional responses. Additionally, when examining the relationships between baseline psychological variables and the HRQoL Physical Functioning subscale, a significant negative association with the CHIP Emotion score was demonstrated.

People living with PAH are particularly vulnerable when they are newly diagnosed or when they have to deal with the loss of a fellow patient or with a change in treatment. Emotion-focused coping may be the only realistic option when the source of stress is outside the person's control. Furthermore, emotion-focused coping is usually linked to poor health-related quality of life and associated with symptoms of depression and anxiety [18], as for our PAH disease-progression group.

Previous studies have remarked upon the presence of presumably state anxiety, which can be observed to accumulate or peak during (i) the waiting-for-a-diagnosis period [19], (ii) the moment when a PAH diagnosis is announced, or just prior to (iii) key progression-determining exams such a right heart catheterization [20] or 6 minute walking tests (in our clinical experience). An additional key moment is (iv) the initiation of prostacyclin treatment as well-demonstrated by Shafazand, where state anxiety decreases during treatment [13]. An amelioration of mood disorders following PAH diagnosis and treatment has been previously observed [21].

Our results place a new-found importance on trait anxiety, i.e. a non-modifiable and functional personality trait. Patients with an anxious personality type are likely to have a

poorer HRQoL, and this regardless of incident/prevalent status or therapy type (bi or tri therapies) [16]. This observation in PAH is important because in-depth work on their life story will be more beneficial than exposure to fears as in behavioral and cognitive therapies designed to help manage state-anxiety.

It is also quite interesting that depression was associated with the HRQoL Physical Functioning score during multivariable analysis. The association of depression with decreased physical functioning has already been reported [22], and depression has been previously demonstrated as a predictor of reduced HRQoL [23]. Depression is common following the diagnosis of a serious illness. Depression disturbs thought and action and these problematic side effects may interfere with a PAH patient's already compromised health-related quality of life. Associated directions of causality (does physical degradation automatically lead to depression? Are non-depressed patients adapting better to PAH? Does depression lead to a more pessimistic self-assessment of HRQoL Physical Functioning?) remain to be determined.

The Physical Functioning subscale is designed to examine a person's perceived limitation in performing any physical activity [8]. It reflects a wide range of physical disability which can cause significant changes in family life, financial situations and social interactions. All such perceived physical limitations can cause depression or be accentuated thereby; for example, certain patients may give up walking exercises to avoid the anxiety they cause. Fatigue and lack of energy may therefore be due to PAH and/or depression. Depression, like PAH, is difficult to recognize and understand, and in depression as in PAH, the suffering is internal with few visible external signs. Identifying and treating depression is therefore essential.

The limitations of this study include its observational, single-center nature and sample size, though the latter is actually quite large compared to most PAH studies and reflects the relative rarity of the disease. In addition, disease-specific quality-of-life tools, such as the CAMPHOR [24], have not been validated in French. As a result and due to a lack of a minimally clinical

important difference (MCID) for the CAMPHOR [7] and a demonstrated lack of predictive value for repeated CAMPHOR measures [17], we chose a generic measure (the SF-36). The latter, though known to be highly correlated with the Camphor [25], may not be as sensitive to changes in PAH populations [26]. In this case, the patterns in this paper can be considered as conservative in nature. Many authors in the domain have chosen the SF-36 over disease specific tools even when the latter exist in their languages because it is better-known, rapid, easy and reliable [5, 7]. Additionally, the SF-36 has been demonstrated as responsive to change in PAH drug trials [27]. It is also surprising to find that six-minute walking test distance >400m was not retained at the multivariate level (Table 4) as it has been demonstrated as quite predictive in past studies [28]. However, this is likely due to the small sample sizes involved. Utmost care was also taken to convince patients to participate in follow-up activities, and our dataset reports no loss-to-follow-up, which is a great strength. A further strength is the power-supporting, repeated, every-3-month measures of HRQoL, which, to our knowledge, have not been previously reported for PAH populations.

Finally, the patients included in this cohort were treated for anxiety and depression, including in-house psychological support every three months if needed and at times of acute disease decline in accordance with current recommendations [4]. Guidelines for the use of psychological tests stress that the administration of psychological assessments via telephone, via postal mail, in the presence of a doctor, or in the absence of a psychologist without knowledge of the patient's psychological status on a given day are all sources of bias that commonly appear in the literature [29] and that do not apply to the present study. How this might have affected our results in comparison with previous studies should be taken into account.

In conclusion, the positive independent association between the HRQoL Physical Functioning subscale and progression-free survival starts at baseline, indicating that HRQoL is important

complementary information in the work-up of PAH patients. The frequency of psychological symptoms is relatively high, but only depression is independently associated with HRQoL. Lastly, it is interesting to note that HRQoL, which was stable over time in the present cohort, was associated with depression that is also known to be potentially chronic over time. Identifying and treating depression is a major issue in the management of PAH. The patient's point-of-view regarding his/her health status is essential in decision-making procedures, and future studies by our team will focus on the words patients use to describe their disease, moods, behaviors and health-related quality of life. Given its independent association with decline, HRQoL should be further studied to elucidate its prognostic potential.

References

1. Thenappan T, Ormiston ML, Ryan JJ, Archer SL. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ* 2018; 360: j5492.

2. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier J-F, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. *Am. J. Respir. Crit. Care Med.* 2006; 173: 1023–1030.

3. Humbert M, Lau EMT, Montani D, Jaïs X, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation* 2014; 130: 2189–2208.

4. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur. Respir. J.* 2015; 46: 903–975.

5. Fernandes CJCS, Martins BCS, Jardim CVP, Ciconelli RM, Morinaga LK, Breda AP, Hoette S, Souza R. Quality of life as a prognostic marker in pulmonary arterial hypertension. *Health Qual. Life Outcomes* 2014; 12: 130.

6. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc. Sci. Med. 1982* 1995; 41: 1403–1409.

7. Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related Quality of Life and Survival in Pulmonary Arterial Hypertension. *Ann. Am. Thorac. Soc.* 2016; 13: 31–39.

8. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med. Care* 1992; 30: 473–483.

9. Gilbert C, Brown MCJ, Cappelleri JC, Carlsson M, McKenna SP. Estimating a minimally important difference in pulmonary arterial hypertension following treatment with sildenafil. *Chest* 2009; 135: 137–142.

10. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ, Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am. J. Respir. Crit. Care Med.* 2002; 165: 800–804.

11. Rival G, Lacasse Y, Martin S, Bonnet S, Provencher S. Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. *Chest* 2014; 146: 686–708.

12. Rapkin BD, Schwartz CE. Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. *Health Qual. Life Outcomes* 2004; 2: 14.

13. Shafazand S, Goldstein MK, Doyle RL, Hlatky MA, Gould MK. Health-related quality of life in patients with pulmonary arterial hypertension. *Chest* 2004; 126: 1452–1459.

14. McCollister DH, Beutz M, McLaughlin V, Rumsfeld J, Masoudi FA, Tripputi M, Yaeger T, Weintraub P, Badesch DB. Depressive symptoms in pulmonary arterial hypertension: prevalence and association with functional status. *Psychosomatics* 2010; 51: 339–339.e8.

15. Hall H, Côté J, McBean A, Purden M. The experiences of patients with pulmonary arterial hypertension receiving continuous intravenous infusion of epoprostenol (Flolan) and their support persons. *Heart Lung J. Crit. Care* 2012; 41: 35–43.

16. Halimi L, Marin G, Molinari N, Gamez A-S, Boissin C, Suehs CM, Vachier I, Bourdin A. Impact of psychological factors on the health-related quality of life of patients treated for pulmonary arterial hypertension. *J. Psychosom. Res.* 2018; 105: 45–51.

17. McCabe C, Bennett M, Doughty N, MacKenzie Ross R, Sharples L, Pepke-Zaba J. Patient-reported outcomes assessed by the CAMPHOR questionnaire predict clinical deterioration in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 2013; 144: 522–530.

18. Graven LJ, Grant JS. Coping and health-related quality of life in individuals with heart failure: an integrative review. *Heart Lung J. Crit. Care* 2013; 42: 183–194.

19. Tsangaris I. Improving patient care in pulmonary arterial hypertension: addressing psychosocial issues. *J. Clin. Hypertens. Greenwich Conn* 2014; 16: 159–161.

20. Harkness K, Morrow L, Smith K, Kiczula M, Arthur HM. The effect of early education on patient anxiety while waiting for elective cardiac catheterization. *Eur. J. Cardiovasc. Nurs. J. Work. Group Cardiovasc. Nurs. Eur. Soc. Cardiol.* 2003; 2: 113–121.

21. Somaini G, Hasler ED, Saxer S, Huber LC, Lichtblau M, Speich R, Bloch KE, Ulrich S. Prevalence of Anxiety and Depression in Pulmonary Hypertension and Changes during Therapy. *Respir. Int. Rev. Thorac. Dis.* 2016; 91: 359–366.

22. Looper KJ, Pierre A, Dunkley DM, Sigal JJ, Langleben D. Depressive symptoms in relation to physical functioning in pulmonary hypertension. *J. Psychosom. Res.* 2009; 66: 221–225.

23. Yorke J, Deaton C, Campbell M, McGowen L, Sephton P, Kiely DG, Armstrong I. Symptom severity and its effect on health-related quality of life over time in patients with pulmonary hypertension: a multisite longitudinal cohort study. *BMJ Open Respir. Res.* 2018; 5: e000263.

24. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual. Life Res. Int. J. Qual. Life Asp. Treat. Care Rehabil.* 2006; 15: 103–115.

25. Gastelurrutia P, Lupón J, Altimir S, de Antonio M, González B, Cabanes R, Cano L, Urrutia A, Domingo M, Zamora E, Díez C, Coll R, Bayes-Genis A. Effect of fragility on quality of life in patients with heart failure. *Am. J. Cardiol.* 2013; 112: 1785–1789.

26. Twiss J, McKenna S, Ganderton L, Jenkins S, Ben-L'amri M, Gain K, Fowler R, Gabbay E. Psychometric performance of the CAMPHOR and SF-36 in pulmonary hypertension. *BMC Pulm. Med.* 2013; 13: 45.

27. Pepke-Zaba J, Gilbert C, Collings L, Brown MCJ. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. *Chest* 2008; 133: 183–189.

28. Souza R, Channick RN, Delcroix M, Galiè N, Ghofrani H-A, Jansa P, Le Brun F-O, Mehta S, Perchenet L, Pulido T, Sastry BKS, Sitbon O, Torbicki A, Rubin LJ, Simonneau G. Association between six-minute walk distance and long-term outcomes in patients with pulmonary arterial hypertension: Data from the randomized SERAPHIN trial. *PloS One* 2018; 13: e0193226.

29. International Test Commission. International Test Commission (2001). International Guidelines for Test Use, International Journal of Testing, 1(2), 93-114. 2001; .

30. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 1983; 67: 361–370.

31. Lépine JP, Godchau M, Brun P, Lempérière TH. Evaluation de l'anxiété et de la dépression chez des patients hospitalisés dans un service de médecine interne. *Ann Med Psychol Paris* 1985; 143: 175–189.

32. Spielberger CD, Jacobs G, Russell S, Crane RS. Assessment of anger: The state-trait anger scale. *Adv. Personal. Assess.* 1983; 2: 159–187.

33. Spielberger CD, Bruchon-Schweitzer M, Paulhan I. Inventaire d'anxiété État-Trait: Forme Y. Paris: ECPA, les Éditions du centre de psychologie appliquée; 1993.

34. Montel S, Bungener C. [Validation of CHIP (a coping questionnaire) in French patients with neurological disorders]. *Rev. Neurol. (Paris)* 2010; 166: 54–60.

35. Endler NS, Parker JD, Summerfeldt LJ. Coping With Health Problems: Developing a Reliable and Valid Multidimensional Measure. *Psychol. Assess.* 1998; 10: 195–205.

36. Lazarus RS, Folkman S. Coping and adaptation. *Handb. Behav. Med.* 1984; 282325.

37. Bruchon-Schweitzer M, Cousson F, Quintard B, Nuissier J, Rascle N. French adaptation of the Ways of Coping Checklist. *Percept. Mot. Skills* 1996; 83: 104–106.

38. Sarason IG, Levine HM, Basham RB, Sarason BR. Assessing social support: The social support questionnaire. *J. Pers. Soc. Psychol.* 1983; 44: 127.

39. Bruchon-Schweitzer M. Psychologie de la santé: modèles, concepts et méthodes. Paris: Dunod; 2003.

40. Wallston KA, Stein MJ, Smith CA. Form C of the MHLC scales: a condition-specific measure of locus of control. *J. Pers. Assess.* 1994; 63: 534–553.

Figure legends

Figure 1. Progression-free survival.

Aggravation occurred linearly.

Figure 2. Physical Functioning subscale of SF-36 values over time.

No association with time or the interaction term (stability × time) was found, indicating that the PF subscale was stable throughout the 3-years of complete follow-up.

Figure 3. Mental Composite Summary and Physical Composite Summary values over time.

No association with time or the interaction term (stability × time) was found, indicating that PCS and MCS were stable throughout the 3-years of complete follow-up.

Figure 1

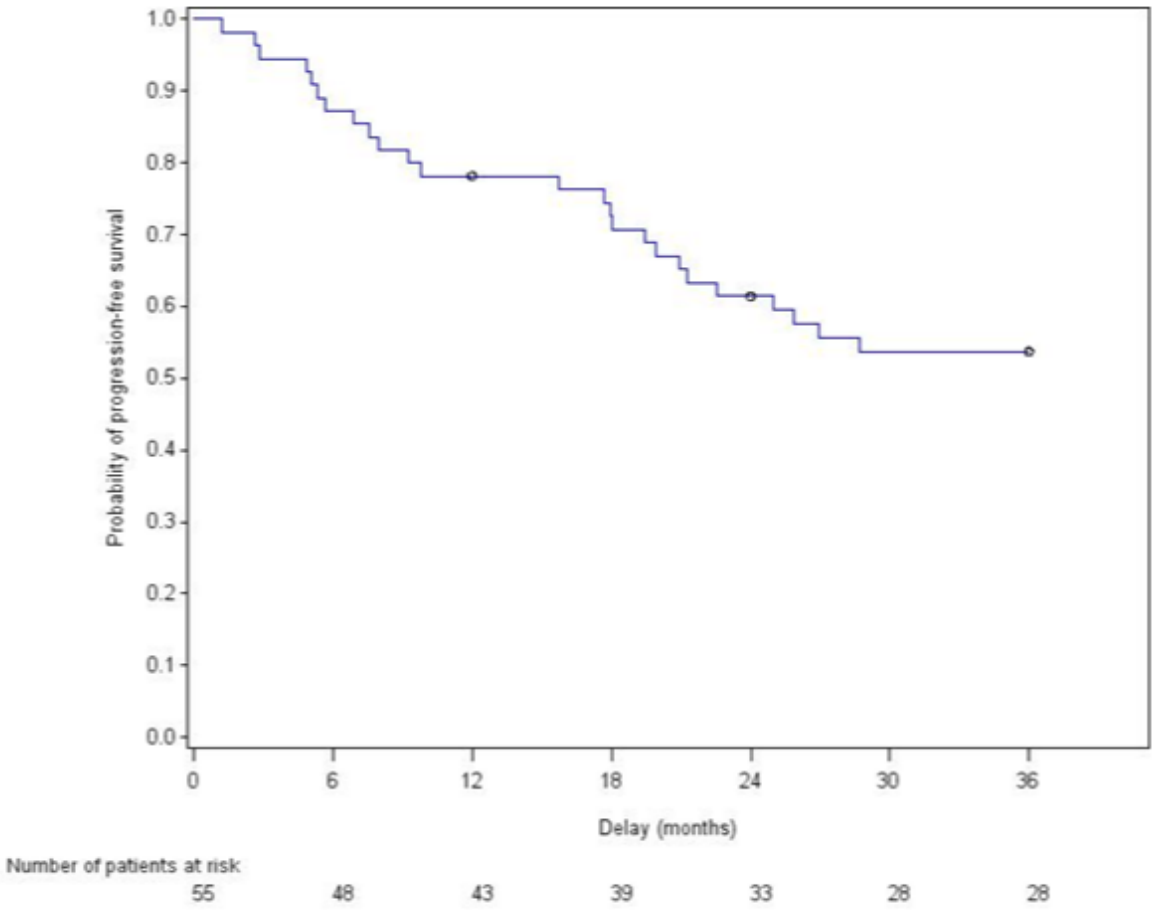

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Probability of progression-free survival
0
6
12
18
24
30
36
Delay (months)
Number of patients at risk
55
48
43
39
33
28
28

Figure 2

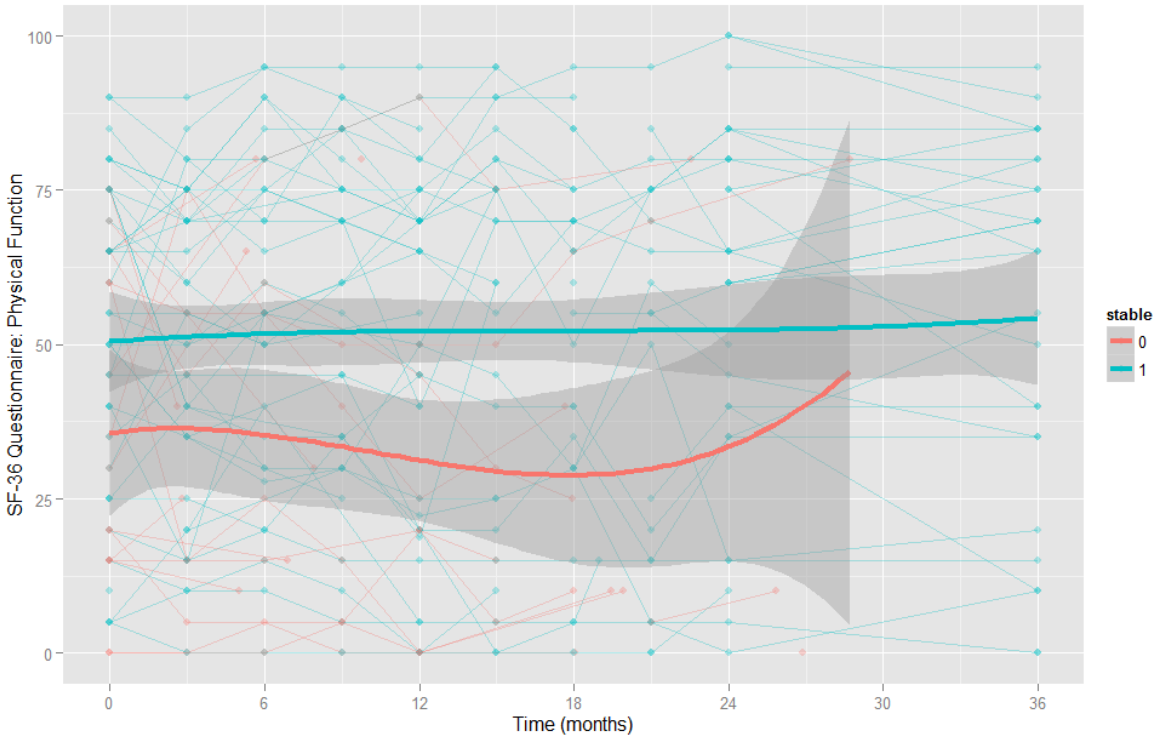
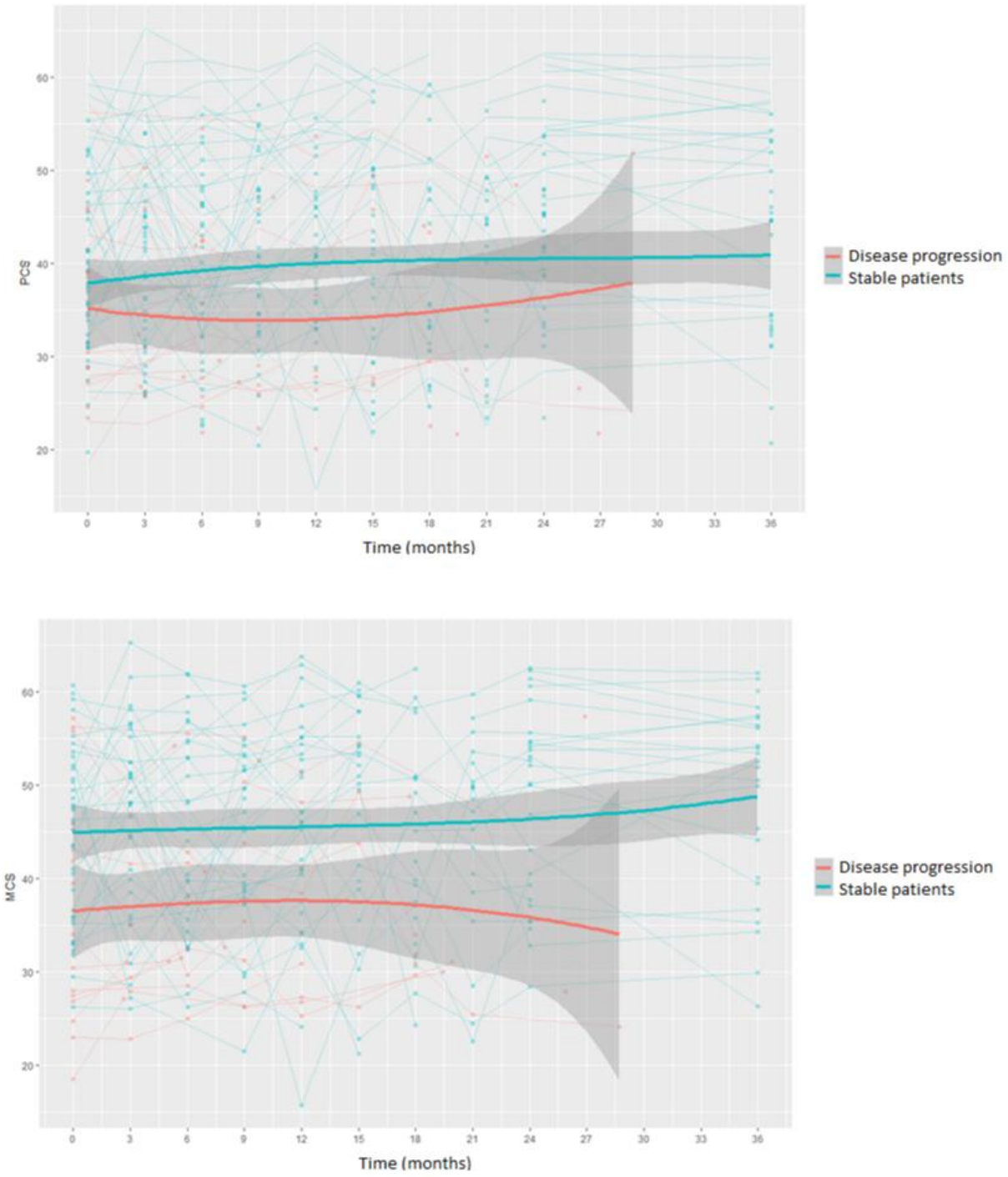

SF-36 Questionnaire: Physical Function
100
75
50
25
0
0
6
12
18
24
30
36
Time (months)
stable
0
1

Figure 3


PCS
60
50
40
30
20
0
3
6
9
12
15
18
21
24
27
30
33
36
Time (months)
Disease progression
Stable patients
MCS
60
50
40
30
20
0
3
6
9
12
15
18
21
24
27
30
33
36
Time (months)
Disease progression
Stable patients

Tables

Table 1. Presentation of psychological evaluation tools used.

Questionnaire, purpose and item example	Likert scale used	Subscales /Dimensions	Interpretation rules (if any)
HADS: Hospital Anxiety Depression Scale [30, 31] The HADS detects anxiety and/or depression, evaluates their severity and avoids confusion with somatic illnesses. *I have lost interest in my appearance.*	• 4 levels • 0 to 3	➢ Depression (14 items) ➢ Anxiety (14 items)	Non-cases: 0-7; Possible cases: 8-10; Probable cases: 11-21. <u>Global score:</u> No anxio-depressive disorders: 0-14 Anxio-depressive disorders: 15-42
STAI-Y: State Trait Anxiety Inventory form Y [32, 33] The STAI-Y evaluates anxiety and differentiates the anxiety-trait (AT) from anxiety-state (AS) *I feel satisfied with myself. I have disturbing thoughts.*	• 4 levels • "No" to "Yes" • "Almost never" to "Almost always" • (0 to 3)	➢ State anxiety (20 items) ➢ Trait anxiety (20 items)	Very high anxiety > 65 High = 56-65 Average = 46-55 Low = 36-45 Very low ≤ 35
CHIP: Coping with Health Injuries and Problems [34, 35] The CHIP, specific to health-related problems, refers to the thoughts and actions we use to deal, in order to master, minimize or tolerate stress and threatening situations *I wonder why it happened to me*	• 5 levels • "not at all" to "very much" • (1 to 5)	➢ Distraction Coping (D; 8 items) ➢ Instrumental Coping (I; 8 items) ➢ Emotional Preoccupation (E; 8 items) ➢ Palliative Coping (P; 8 items)	Likert scores are summed per sub-scale. Subscale sums are then transformed according to age and sex. The latter (T-scores) have a mean of 50 and a standard deviation of 10.
WCC: Ways of Coping Check List [36, 37] The WCC identifies, from a stressful situation not linked to the disease (divorce, moving, conflict, etc.), strategies which have been used to confront the situation. *I accepted sympathy and understanding from someone*	• 4 levels • "no" to "yes" • (0 to 3)	➢ Problem-focused (9 items) ➢ Emotion-focused (9 items) ➢ Search for social support (9 items)	Possible scores range from 0 to 27 for each subscale.
SSQ6: Short Form of the Social Support Questionnaire [38, 39] The SSQ intends to quantify the dimensions of perceived availability of and satisfaction with social support *Whom can you really count on to help you feel more relaxed when you are under pressure or tense? (For each item, there is a two-part answer: Part 1: list all the people that fit the description of the question. Part 2: use the Likert scale to indicate satisfaction.)*	• 6 levels • "very satisfied" to "very dissatisfied" • (1 to 6)	➢ Number of available people (N; 6 items with up to 9 people in each item) ➢ Satisfaction (S; 6 items)	SSQ Number score (N): The total score ranges between 0 and 54 SSQ Satisfaction score (S) The total score ranges between 6 and 36
MHLC-C: Multidimensional Health Locus of Control Form C [39, 40] This scale measures health specific locus of control along four dimensions: the extent to which individuals believe that: 1) health is a consequence of their own actions, 2) under the influence of doctors, 3) under the influence of powerful others, 4) due to chance. Form C is designed to be "condition-specific", i.e. used when studying people with an existing health condition. *Other people play a big role in whether my condition improves, stays the same or gets worse.*	• 6 levels • "strongly disagree" to "strongly agree" • (1 to 6)	➢ Internal (I; 6 items) ➢ External: Chance (C; 3 items) ➢ External: Doctors (D; 3 items) ➢ External: Powerful others (O; 6 items).	Possible range: Internal and Chance: 6-36 Doctors and Other powerful people: 3-18

Table 2. Demographic and clinical characteristics for stable (no observed disease progression over the 3 years of follow-up) and disease progression patient groups as guideline-defined.

Characteristics	All PAH patients		Disease progression		Stable		P-value
	N	Centrality	N	Centrality	N	Centrality	
Age (years) *	55	57.8±15.3	25	58.1±16.5	30	57.6±14.7	0.915
Sex (F), n (%)	55	35(64)	25	14(56)	30	21(70)	0.282
Incident/prevalent, n (%)	55	12 (22)/43(78)	25	6(24)/19(76)	30	6(20)/24(80)	0.720
Etiology, n (%)	55		25		30		**0.038**
Congenital		1(1.8)		0(0)		1(3.3)	
Histiocytosis		2(3.6)		1(4)		1(3.3)	
Idiopathic		40(72.7)		22(88)		18(60)	
CTEPH		12(21.8)		2(8)		10(33.3)	
PAH treatments, n (%)	55		25		30		**0.003**
No treatment		1(2)		0(0)		1(3.3)	
Monotherapy		20(36)		4(16)		16(53.3)	
Bitherapy		26(47)		18(72)		8(26.7)	
Tritherapy (ERA, IPDE-5, PGI2)		8(15)		3(12)		5(16.7)	
Oxygen, n (%)	55	24(44)	25	13(52)	30	11(36.67)	0.253
Co-morbidities, n (%)	55	38(69)	25	17(68)	30	21(70)	
NYHA I/II/III/IV, n (%)	55	8(15)/25(45)/19 (35)/3(5)	25	0(0)/12(48)/11 (44)/2(8)	30	8(26.7)/13(43.3)/8 (26.7)/1(3.3)	**0.018**
Right heart catheterization							
Cardiac output (l/min) *	51	5.3±1.9	24	5.8±2.0	27	4.9±1.7	0.114
mPAP (mmHg) **	52	44.5(38.5–51)	25	48(40–64)	27	43(29–48)	**0.012**
Pcwp (mmHg) *	44	9.3±3.6	21	10.1±3.4	23	8.7±3.8	0.221
RAP (mmHg) **	34	8(5–10)	15	10(7–12)	19	8(3–9)	0.058
PVR (Wood's units) **	50	8.6(6.2–11.1)	24	8.7(7.0–12.3)	26	8.4(6.1–9.7)	0.472
6 minute walking test							
Distance (6MWD) *	52	386 ± 131	23	336 ±116	29	425 ±131	**0.013**
6MWD<160m***		3 (5.8)		2 (8.7)		1 (3.5)	**0.081**
160m≤6MWD≤400m***		29 (55.8)		16 (69.6)		13 (44.8)	
6MWD > 400m***		20 (38.5)		5 (21.7)		15 (51.7)	
Max 6MWD Borg score *	52	4.8±2.7	23	4.8±2.9	29	4.8±2.5	0.984
Cardiac frequency (bpm)							
Baseline **	17	77(70–92)	5	75(69–92)	12	78(62-109)	0.966
End **	16	108.5(96–123.5)	6	121.5(97–133)	10	104(95–115)	0.209
Oxygen saturation (%)							
Baseline **	38	95.5(92–97)	14	92.5(87–96)	24	96(94–97.5)	**0.039**
End **	43	88(78–92)	19	79(73–88)	24	89(87–95.5)	**0.002**
Delta SpO_2≥ 4%	33	25(76)	12	11(92)	21	14(67)	0.282

PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; mPAP: mean pulmonary arterial pressure; Pcwp: pulmonary capillary wedge pressure; RAP: right arterial pressure; PVR: pulmonary vascular resistance; 6MWD: 6-min walk distance; SpO_2: pulse oximeter oxygen saturation;Δ SpO_2≥ 4%: change in oxygen saturation over 4%.

* Mean±SD; ** Median (IQR). *** n(%)

Table 3. Health-Related Quality of life and psychological baseline characteristics for stable (no observed disease progression over the 3 years of follow-up) and disease progression patient groups.

Characteristics	Total population		Disease progression		Stable		P-value
	N	Centrality	N	Centrality	N	Centrality	
SF-36: Health-Related Quality of Life							
PCS *	55	37.13±8.18	25	34.81±7.28	30	39.04±8.50	0.060
Physical Functioning **	55	50.00 (25.0-65.0)	25	32.50 (15.0-62.5)	30	55.00 (40.0-75.0)	**0.013**
Role-Physical **	55	25.00 (0.0-75.0)	25	12.50 (0.0-50.0)	30	50.00 (0.0-75.0)	**0.039**
Bodily Pain **	55	52.00 (41.0-84.0)	25	41.00 (36.0-72.5)	30	52.00 (42.0-84.0)	0.098
General Health **	55	35.00 (30.0-47.0)	25	35.00 (23.5-45.0)	30	35.00 (30.0-50.0)	0.219
MCS *	55	42.42 ± 10.88	25	38.98±11.77	30	45.05±9.39	**0.042**
Vitality *	55	45.64 ± 17.82	25	41.60 ± 18.13	30	49.00 ± 17.14	0.099
Social Functioning **	55	62.50 (50.0-75.0)	25	62.50 (25.0-68.7)	30	62.50 (50.0-75.0)	**0.043**
Role-Emotional **	55	33.33 (0.0-100.0)	25	16.67 (0.0-83.3)	30	66.67 (33.3-100.0)	**0.047**
Mental Health *	55	56.00 ± 18.60	25	50.56 ± 17.51	30	60.53 ± 18.55	**0.016**
HADS: Hospital Anxiety Depression Scale							
Anxiety **	55	9.0 (4.0-12.0)	25	10.0 (8.0-12.0)	30	5.0 (4.0-11.0)	0.054
Depression **	55	6.0 (2.0-10.0)	25	9.0 (5.0-11.0)	30	4.0 (2.0-7.0)	**0.010**
Total score **	55	17.0 (8.0-22.0)	25	18.0 (13.0-23.0)	30	9.5 (3.0-25.0)	**0.015**
STAI-Y: State-Trait Anxiety Inventory Form Y							
State Anxiety *	55	48.48±7.50	25	50.52±7.54	30	46.23±7.01	**0.033**
Trait Anxiety *	55	50.55±14.52	25	55.52±13.68	30	46.40±14.10	**0.018**
CHIP: Coping with Health Injuries and Problems							
Distraction *	55	27.35±6.57	25	26.16±6.57	30	28.33±6.51	0.298
Palliative *	55	26.11±4.76	25	25.56±4.95	30	26.57±4.64	0.737
Instrumental *	55	30.44±6.17	25	29.96±6.19	30	30.83±6.22	0.246
Emotional preoccupation *	55	25.13±7.48	25	26.28±7.27	30	24.17±7.63	0.206
WCC: Ways of Coping Check							
WCC Problem *	53	26.28±5.55	24	26.29±5.15	29	26.28±5.96	0.991
WCC Emotion *	53	23.23±5.79	24	25.04±5.82	29	21.72±5.40	**0.036**
WCC Social support *	53	20.45±5.46	24	19.25±5.57	29	21.45±5.25	0.146
SSQ: Social Support Questionnaire							
SSQ Availability **	53	13.0 (8.0-16.0)	24	14.0 (9.0-15.0)	29	13.0 (8.0-16.0)	0.943
SSQ Satisfaction **	53	30.0 (26.0-34.0)	24	29.5 (24.5-34.0)	29	30.0 (28.0-36.0)	0.181
MHLC-C: Multidimensional Health Locus of Control							
Internal *	55	19.33±6.21	25	19.52±6.20	30	19.17±6.31	0.835
External: Chance *	55	20.65±6.48	25	19.84±6.40	30	21.33± 6.58	0.400
External: Doctors	55	15.00 (12.0-17.0)	25	15.00 (12.0-17.0)	30	15.50 (12.0-17.0)	0.820
External: Others *	55	10.78±3.69	25	11.48±3.86	30	10.20±3.49	0.202

PCS: Physical Composite Summary; MCS: Mental Composite Summary

* Mean± SD; ** Median (IQR)

Table 4. Univariate and multivariable cox model results describing associations between baseline clinical variables and progression-free survival.

	Hazard Ratio	95% Confidence Interval	P-value
Univariate analysis			
New York Heart Association (NYHA) Stage	2.083	1.250-3.470	**0.0048** [R]
Mean pulmonary arterial pressure (mmHg)	1.039	1.013-1.065	**0.0028** [R]
Pulmonary capillary pressure (mmHg)	1.043	0.923-1.180	0.4969
Cardiac output (L/minute)	1.267	0.996-1.612	0.0535 [R]
Pulmonary vascular resistance (Wood's units)	1.008	0.952-1.067	0.7796
Right atrium pressure (mmHg)	1.194	1.048-1.359	**0.0075** [R]
6-minute walking test			
Distance (m)	0.996	0.993-0.999	**0.0080** [R]
Distance (m) >440m vs ≤440m	0.398	0.166-0.954	0.0389 [R]
Borg test	1.006	0.858-1.179	0.9421
Cardiac frequency (bpm)			
Baseline	1.004	0.947-1.064	0.9011
End	1.018	0.985-1.053	0.2852
Oxygen saturation (%)			
Baseline	0.896	0.821-0.977	**0.0132** [R]
End	0.937	0.902-0.974	**0.0010** [R]
Δ≥ 4%	4.144	0.534-32.16	0.1739
SF-36 Questionnaire			
Physical Functioning	0.981	0.966-0.996	**0.0142** [R]
Role-Physical	0.986	0.975-0.998	**0.0212** [R]
Bodily Pain	0.991	0.975-1.008	0.3053
General Health	0.987	0.965-1.009	0.2436
Vitality	0.977	0.953-1.002	0.0705 [R]
Social Functioning	0.983	0.968-0.998	**0.0304** [R]
Role-Emotional	0.988	0.978-0.998	**0.0199** [R]
Mental Health	0.976	0.955-0.997	**0.0267** [R]
Multivariate analysis			
SF-36 Questionnaire: Physical Functioning	0.978	0.962-0.995	**0.0106**
Mean pulmonary arterial pressure (mmHg)	1.053	1.023-1.084	**0.0153**
Cardiac output (L/minute)	1.559	1.189-2.045	**0.0013**

R: variables with a univariate $p<0.15$ were retained for multivariable analysis. Δ≥ 4%: change in oxygen saturation over 4%.

Table 5. Univariate and multivariable linear regression results describing associations between baseline psychological variables and the Physical Functioning subscale from the SF-36 Health-related Quality of Life questionnaire.

	Coefficient	Standard Error	P-value
Univariate analysis			
HADS			
HADS Total	-1.81	0.41	**<0.0001** [R]
HADS Anxiety	-2.08	0.71	**0.0007** [R]
HADS Depression	-3.51	0.77	**<0.0001** [R]
STAI-Y			
State Anxiety	-0.99	0.47	**0.0393** [R]
Trait Anxiety	-0.80	0.22	**0.0007** [R]
CHIP			
Distraction	1.05	0.53	0.0558 [R]
Instrumental	0.84	0.59	0.1539
Emotional Preoccupation	-1.12	0.46	**0.0187** [R]
Palliative	0.20	0.77	0.7995
WCC			
Problem-focused	0.74	0.65	0.2580
Emotion-focused	-1.07	0.61	0.0859 [R]
Search for social support	0.54	0.65	0.4160
SSQ6			
Avaibility	0.28	0.38	0.4692
Satisfaction	-0.12	0.52	0.8204
MHLC-C			
Internal locus of control	0.74	0.57	0.2005
External locus of control			
Chance	0.55	0.56	0.3293
Doctors	0.19	1,00	0.8467
Powerful others	-1.48	0.97	0.1342 [R]
Multivariate analysis			
HADS Depression	-3.26	0.79	**0.0001**

R: variables with a univariate $p < 0.15$ were retained for multivariable analysis.