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

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] and Arnaud Bourdin [1,4]

[1]Dept of Respiratory Diseases, Université de Montpellier, CHU Montpellier, Montpellier, France. [2]Dept of Medical Information, Université de Montpellier, CHU Montpellier, Montpellier, France. [3]IMAG, CNRS, Université de Montpellier, CHU Montpellier, Montpellier, France. [4]PhyMedExp, Université de Montpellier, CNRS, INSERM 1046, CHU Montpellier, Montpellier, France.

Corresponding author: Laurence Halimi (l-halimi@chu-montpellier.fr)

Abstract

Objectives The role of health-related quality of life (HRQoL) and psychological variables in pulmonary arterial hypertension (PAH) progression remains poorly quantified. We aimed to investigate the relationship between disease progression in PAH patients and HRQoL and psychological characteristics.

Methods A 3-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 haemodynamic parameters, were prospectively recorded. A battery of questionnaires was used to characterise 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 the 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=0.012) was identified as being independently associated with disease progression (Cox survival model), along with mean pulmonary arterial pressure (p=0.003) and cardiac output (p=0.005). Depression was the unique independent psychological characteristic associated with PF (p=0.0001).

Conclusions PAH patients have poor HRQoL. In addition to already known criteria related to disease severity, the HRQoL PF subscale is independently associated with disease progression in PAH. This may be explained by 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, draining 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]. Over 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-min walking distance (6MWD), 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. Although 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] that can change with time, together with the health context [6]. However, systematic longitudinal evaluation by clinicians is not practised [7] and even in research situations, repeated evaluations remain rare. To our knowledge, no PAH study has regularly monitored HRQoL over a relatively long timespan.

The most common generic HRQoL evaluation is the Medical Outcomes Study 36-item 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 underlined 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 cofactor and eventually as an expected consequence of the disease or if it should be seen as a prognostic criterion.

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 3-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
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 aged 18 to 80 years who had stable PAH for at least 3 months and no prior psychological care/support.

Patient monitoring for 3 years
Relevant right heart catheterisation variables were measured at baseline. Data concerning the baseline 6-min walk test (6MWT) were also recorded: distance walked (in metres and classified as above or below a 400 m 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 (S_{pO_2}) at the beginning and end of the test ($S_{pO_2}start$ and $S_{pO_2}stop$; %), and whether or not the latter two measures differed by at least 4%, indicating a clinically significant change in S_{pO_2} during the 6MWT ($\Delta S_{pO_2}4\%$; 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 3 months for 24 months and then again at 36 months using the SF-36 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 the Shapiro–Wilk test, and normal variables summarised *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 t-tests or Mann–Whitney U-tests, as appropriate.

Cox models were used to analyse 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 with p-values <0.15 were entered into a multivariable Cox model with forward selection. The coefficients with 95% confidence intervals (CI) are provided for the final model including only those variables independently and significantly associated with progression-free survival. A bootstrapping of the

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 Global score: 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 anxiety: 56–65 Average anxiety: 46–55 Low anxiety: 36–45 Very low anxiety: ⩽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, minimise 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 subscale. 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 Checklist [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 nine 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

Cox model was carried out, *via* case resampling with replacement. 1000 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 Component Summary (PCS), Mental Component 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, NC, USA) 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 initial results

Demographic characteristics, anxiety and depression Hospital Anxiety Depression Scale (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 PCS (37.1±8.03) and the 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 haemodynamic parameters for those patients who were already being treated (58% receiving bi- or tri-therapy) 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 relationship between 6MWD and PCS and a significant negative relationship between delta $S_{pO_2} \geqslant 4\%$ 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 6MWT 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 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 progression-free survival: NYHA class, mean pulmonary arterial pressure, cardiac output, right atrium pressure and 6MWT results (distance, the 400 m 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 progression-free survival.

At the multivariable level, mean pulmonary arterial pressure (hazard ratio (HR) 1.053; 95% CI 1.023–1.084; p=0.0153), cardiac output (HR 1.559; 95% CI 1.189–2.045; p=0.0013) and the PF subscale (HR 0.978; 95% CI 0.962–0.995; p=0.0106) were significantly associated with progression-free survival (table 4). The bootstrapping approach confirms these results.

Stability of HRQoL over time

When examining the PF 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.

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
Female, 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
Aetiology, 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)	
Bi-therapy		26 (47)		18 (72)		8 (26.7)	
Tri-therapy[#]		8 (15)		3 (12)		5 (16.7)	
Oxygen, n (%)	55	24 (44)	25	13 (52)	30	11 (36.67)	0.253
Comorbidities, n (%)	55	38 (69)	25	17 (68)	30	21 (70)	0.253
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 catheterisation							
Cardiac output (L·min⁻¹)	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-min walk test							
Distance (6MWD)	52	386±131	23	336±116	29	425±131	**0.013**
6MWD <160 m, n (%)		3 (5.8)		2 (8.7)		1 (3.5)	**0.081**
160 m⩽6MWD⩽400 m, n (%)		29 (55.8)		16 (69.6)		13 (44.8)	
6MWD >400 m, n (%)		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 S_{pO_2}⩾4%	33	25 (76)	12	11 (92)	21	14 (67)	0.282

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association; mPAP: mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; RAP: right arterial pressure; PVR: pulmonary vascular resistance; 6MWD: 6-min walking distance; S_{pO_2}: oxygen saturation measured by pulse oximetry. [#]: ERA, IPDE-5, PGI2.

Association between PF 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 PF subscale score in a 55-patient PAH cohort with no loss to follow-up over a 3-year period. Unexpectedly, PF and both the MCS and PCS 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 PF subscale.

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 Checklist							
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

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. PCS: Physical Composite Summary; MCS: Mental Composite Summary.

Risk assessment in PAH currently relies on parameters from clinical, haemodynamic, 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. [17] suggesting that the predictive value of the CAMPHOR Questionnaire is also restricted to baseline values. These results suggest that HRQoL monitoring can provide additional useful and complementary information to the traditional PAH work-up, but does not need to be 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 to deal with daily stressors. However, at the multivariable level, the only psychological variable 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
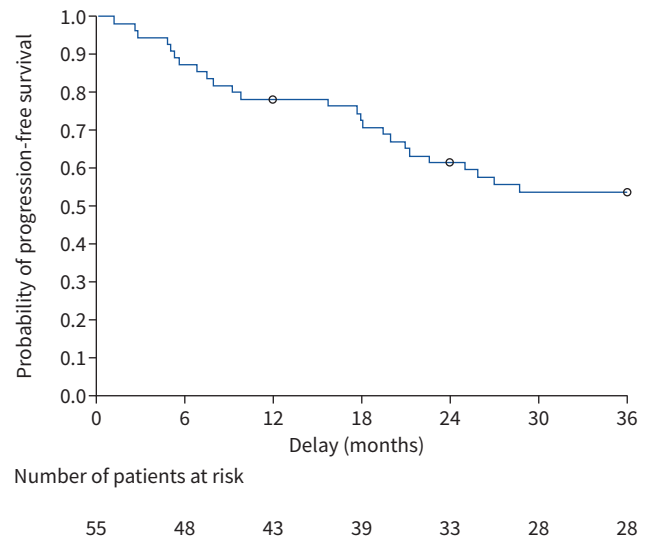
FIGURE 1 Progression-free survival. Aggravation occurred linearly.

TABLE 4 Univariate and multivariable Cox model results describing associations between baseline clinical variables and progression-free survival

	Hazard ratio	95% CI	p-value
Univariate analysis			
New York Heart Association stage	2.083	1.250–3.470	**0.0048#**
Mean pulmonary arterial pressure (mmHg)	1.039	1.013–1.065	**0.0028#**
Pulmonary capillary pressure (mmHg)	1.043	0.923–1.180	0.4969
Cardiac output (L·min^{-1})	1.267	0.996–1.612	0.0535#
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#**
6-min walk test			
Distance (m)	0.996	0.993–0.999	**0.0080#**
Distance (m) >440 m *versus* ⩽440 m	0.398	0.166–0.954	0.0389#
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#**
End	0.937	0.902–0.974	**0.0010#**
Δ⩾4%	4.144	0.534–32.16	0.1739
SF-36 Questionnaire			
Physical functioning	0.981	0.966–0.996	**0.0142#**
Role-physical	0.986	0.975–0.998	**0.0212#**
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#
Social functioning	0.983	0.968–0.998	**0.0304#**
Role-emotional	0.988	0.978–0.998	**0.0199#**
Mental health	0.976	0.955–0.997	**0.0267#**
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·min^{-1})	1.559	1.189–2.045	**0.0013**

Δ⩾4%: change in oxygen saturation over 4%; SF-36: 36-item Short-Form Health Survey. #: variables with a univariate $p<0.15$ were retained for multivariable analysis.

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 PF 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 HRQoL 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: 1) the waiting-for-a-diagnosis period [19], 2) the moment when a PAH diagnosis is announced, or just prior to 3) key progression-determining exams such as right heart catheterisation [20] or 6MWT (in our clinical experience). An additional key moment is the initiation of prostacyclin treatment as well demonstrated by SHAFAZAND et al. [13], where state anxiety decreases during treatment. 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 nonmodifiable and functional personality trait. Patients with an anxious personality type are likely to have a poorer HRQoL, 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 behavioural and cognitive therapies designed to help manage state anxiety.

It is also quite interesting that depression was associated with the HRQoL PF 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 HRQoL. Associated directions of causality (Does physical degradation automatically lead to depression? Are non-depressed
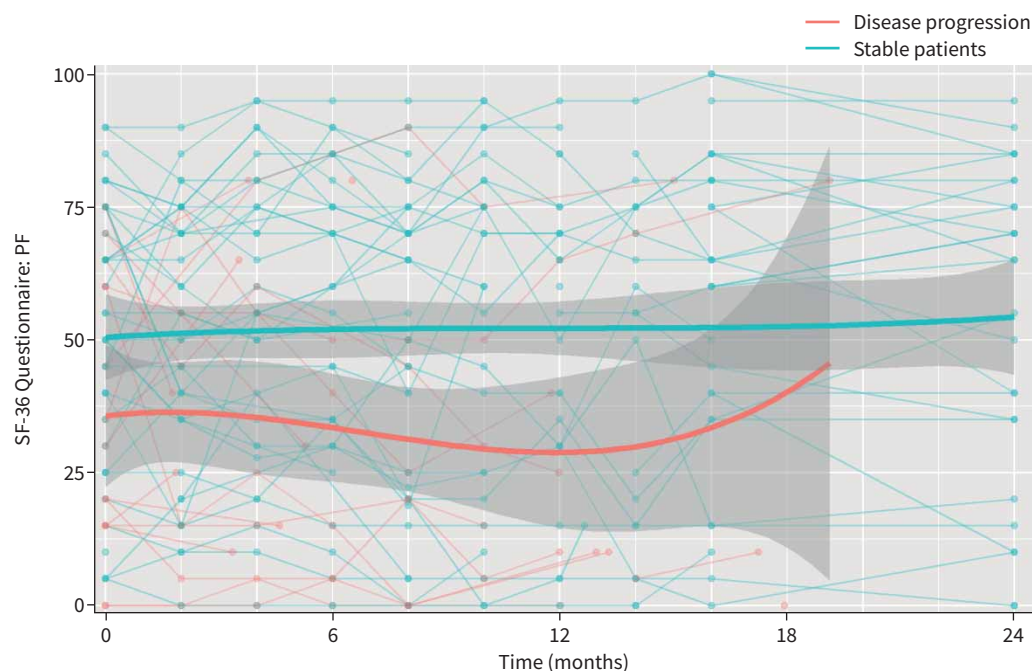
FIGURE 2 Physical functioning (PF) subscale of 36-item Short-Form Health Survey (SF-36) values over time. No association with time or the interaction term (stability × time) was found, indicating that the PF subscale was stable throughout the 3 years of complete follow-up.
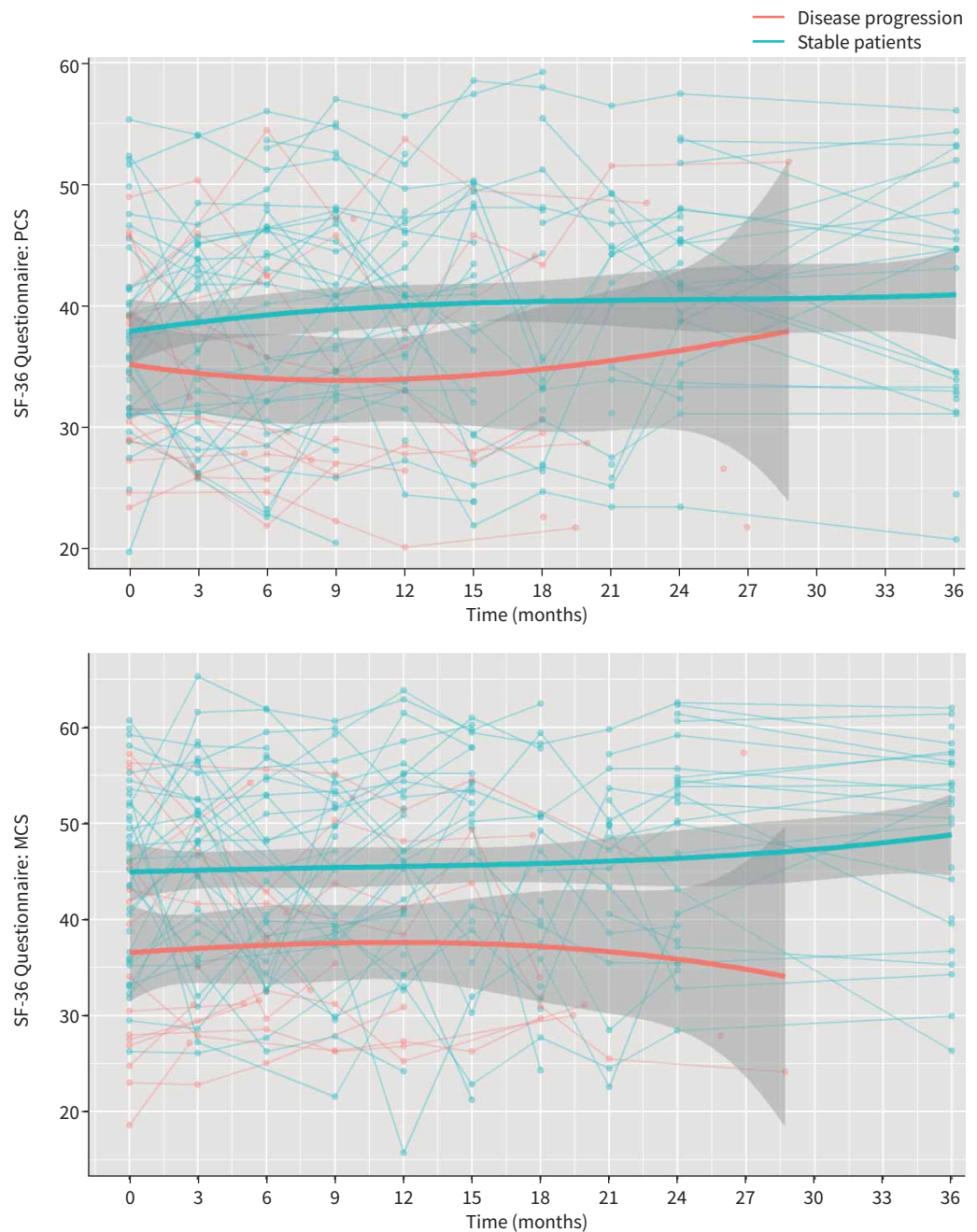
FIGURE 3 Mental Component Summary (MCS) and Physical Component Summary (PCS) values over time. No association with time or the interaction term (stability × time) was found, indicating that PCS and MCS were stable throughout the 3 years of complete follow-up. SF-36: 36-item Short-Form Health Survey.

patients adapting better to PAH? Does depression lead to a more pessimistic self-assessment of HRQoL PF?) remain to be determined.

The PF 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 recognise and understand, and in depression as in PAH, the suffering is internal, with few visible external signs. Identifying and treating depression is therefore essential.

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[#]**
HADS anxiety	−2.08	0.71	**0.0007[#]**
HADS depression	−3.51	0.77	**<0.0001[#]**
STAI-Y			
State anxiety	−0.99	0.47	**0.0393[#]**
Trait anxiety	−0.80	0.22	**0.0007[#]**
CHIP			
Distraction	1.05	0.53	0.0558[#]
Instrumental	0.84	0.59	0.1539
Emotional preoccupation	−1.12	0.46	**0.0187[#]**
Palliative	0.20	0.77	0.7995
WCC			
Problem-focused	0.74	0.65	0.2580
Emotion-focused	−1.07	0.61	0.0859[#]
Search for social support	0.54	0.65	0.4160
SSQ6			
Availability	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[#]
Multivariate analysis			
HADS depression	−3.26	0.79	**0.0001**

HADS: Hospital Anxiety Depression Scale; STAI-Y: State-Trait Anxiety Inventory Form Y; CHIP: Coping with Health Injuries and Problems; WCC: Ways of coping Checklist; SSQ6: Social Support Questionnaire-6; MHLC-C: Multidimensional Health Locus of Control. Bold indicates significance. [#]: variables with a univariate p<0.15 were retained for multivariable analysis.

The limitations of this study include its observational, single-centre nature and sample size, although 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 the lack of a minimally clinical important difference 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, although 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 6MWT distance >400 m was not retained at the multivariate level (table 4) as it has been demonstrated as quite predictive in previous studies [28]. However, this is probably 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, 3-monthly 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 3 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 PF 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, behaviours and HRQoL. Given its independent association with decline, HRQoL should be further studied to elucidate its prognostic potential.

References

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

2   Humbert M, Sitbon O, Chaouat A, *et al.* 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, *et al.* Advances in therapeutic interventions for patients with pulmonary arterial hypertension. *Circulation* 2014; 130: 2189–2208.

4   Galiè N, Humbert M, Vachiery J-L, *et al.* 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). *Eur Respir J* 2015; 46: 903–975.

5   Fernandes CJCS, Martins BCS, Jardim CVP, *et al.* 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* 1995; 41: 1403–1409.

7   Mathai SC, Suber T, Khair RM, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* Health-related quality of life in patients with pulmonary arterial hypertension. *Chest* 2004; 126: 1452–1459.

14   McCollister DH, Beutz M, McLaughlin V, *et al.* Depressive symptoms in pulmonary arterial hypertension: prevalence and association with functional status. *Psychosomatics* 2010; 51: 339–339.

15   Hall H, Côté J, McBean A, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* The effect of early education on patient anxiety while waiting for elective cardiac catheterization. *Eur J Cardiovasc Nurs* 2003; 2: 113–121.

21   Somaini G, Hasler ED, Saxer S, *et al.* 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, *et al.* Depressive symptoms in relation to physical functioning in pulmonary hypertension. *J Psychosom Res* 2009; 66: 221–225.

23   Yorke J, Deaton C, Campbell M, *et al.* 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, *et al.* 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* 2006; 15: 103–115.

25   Gastelurrutia P, Lupón J, Altimir S, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* 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 Guidelines for Test Use. *Int J Test* 2001; 1: 93–114.

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, *et al.* 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, *et al.* Assessment of anger: The State-Trait Anger Scale. *In:* JN Butcher and CD Speilberger, eds. Advances in Personality Assessment, Vol. 2. Hillsdale, Lawrence Erlbaum Associates, Inc., 1983; pp. 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. *In:* WD Gentry, ed. The Handbook of Behavioral Medicine. New York, Guilford, 1984; pp. 282–325.

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

38   Sarason IG, Levine HM, Basham RB, *et al.* 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.