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Health-related quality of life of patients with pulmonary arterial hypertension associated with CHD: the multicenter cross-sectional ACHILLE study

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Background: The aim of this study was to assess health-related quality of life in patients with pulmonary arterial hypertension associated with CHD and correlations with clinical status.
Methods: This prospective cross-sectional observational study included CHD patients with pulmonary arterial hypertension in 14 tertiary-care centres in France. We used two health-related quality of life questionnaires – SF-36 and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) – and one anxiety/depression Hospital Anxiety and Depression Scale (HADS) questionnaire.
Results: Clinical data were collected for the 208 included patients (mean age: 42.6 years, range from 15.1 to 85.8 years, 69.7% female). Most patients were in NYHA functional class II (48.1%) and III (37.5%). Patients' phenotype was classified as Eisenmenger syndrome (70.7%), pulmonary arterial hypertension associated with systemic-to-pulmonary shunts (12.0%), with small defects (3.4%), or after corrective cardiac surgery (13.9%). In total, 76.4% of the patients were receiving pulmonary arterial hypertension-specific treatments. SF-36 scores showed impairment compared with normalised data.Health-related quality of life scores were significantly lower in females than in males for most dimensions of both questionnaires and were independent of the patients' phenotype, even after gender adjustment – except for CAMPHOR functioning – but significantly depended on NYHA functional class. The Hospital Anxiety and Depression Scale (HADS) scores suggested anxiety and depression associated with increasing NYHA functional class but independent of patients' phenotype. NYHA functional class, 6-minute walk distance, HADS, gender, and recent stressful event significantly affected quality of life in the multivariate analysis.
Conclusions: This study showed impairment of quality of life in a large cohort of patients with pulmonary arterial hypertension associated with CHD with both generic and specific questionnaires. NYHA functional class and HADS scores were predictive of most quality of life scores.

Keywords: Health-related quality of life; pulmonary arterial hypertension; CHD; Eisenmenger syndrome; CAMPHOR

CHD are the most common of all congenital malformations with an estimated incidence of 8/1000 births.1 As a consequence of paediatric medical advances, prevalence of adults with CHD has been progressively increasing throughout the past two decades.[2] The median age at death for complex CHD has switched from childhood to adulthood and, for instance, increased from 2 to 23 years in the Canadian registry.[3] Pulmonary arterial hypertension is a severe and frequent (5–10%) complication of CHD[4] involving vascular re-modelling, increased pulmonary vascular resistance, and elevated pulmonary arterial pressure.[5] In CHD patients, a diagnosis of pulmonary arterial hypertension multiplies by two the risk of mortality, by three the risk of cardiac event, and by five the risk of hospitalisation in ICUs.[6] At present, patients developing pulmonary arterial hypertension associated with CHD are managed in tertiary-care centres, where the introduction of advanced specific therapies is expected to improve survival.[7] In this new epidemiologic context, the quality of life of CHD patients with pulmonary arterial hypertension deserves investigation. Indeed, these patients suffer from altered physical abilities and must bear the emotional and psychological consequences of a progressive disease.[8,9] Health-related quality of life evaluation has become an emerging research theme in congenital cardiology and an important end point among patientreported outcomes in pulmonary hypertension clinical studies;[10,11] however, limited health-related quality of life data are available for CHD patients with pulmonary arterial hypertension.[12–17] The ACHILLE – Adults adolescents CHD with pulmonary arterial hypertension quality of life assessment – study aimed to evaluate health-related quality of life in a large population of CHD patients with pulmonary arterial hypertension using a generic (SF-36) and a pulmonary hypertension-specific (Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)) instrument.

Materials and methods

Study design This prospective, cross-sectional, observational study was carried out in 14 tertiary-care CHD centres in France, and enrolled patients from May, 2012 to June, 2013.

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. In accordance with French law, formal approval from an ethical committee was not required for this observational study. Patients or their guardians gave their oral consent.

Population Patients over 15 years of age with pulmonary arterial hypertension associated with CHD were asked to participate in the study during routine follow-up. Pulmonary arterial hypertension was confirmed by right heart catheterisation, and pulmonary arterial hypertension associated with CHD was classified according to the Dana Point clinical classification[18] as Eisenmenger syndrome, pulmonary arterial hypertension associated with systemic-to-pulmonary shunts, pulmonary arterial hypertension associated with small defects, and pulmonary arterial hypertension after corrective cardiac surgery. Patients with typical Eisenmenger syndrome – long-standing left-to-right shunt reversed into a right-to-left shunt – could be enrolled on the basis of the echocardiography. Patients were not eligible if they had undergone heart transplantation, cardiac surgery without subsequent control, planned corrective heart surgery, and recent surgical or interventional catheter procedures (<6 months). Patients who were not able to fill out the questionnaires were excluded. Patients with Down syndrome or any other

mental disorder were eligible if, upon the investigator's statement, they were able to understand and fill out the questionnaires by themselves.

Data collected Demographic data were recorded. Clinical data included co-morbidities, hospitalisations due to pulmonary arterial hypertension and/or CHD within the last year, stability of the disease status as assessed by the investigator, recent stressful event as reported by the patient, NYHA functional class at inclusion as assessed by the investigator, most recent 6-minute walk distance, and on-going pulmonary arterial hypertension-specific treatments.

Patient reported outcomes In this study we used two health-related quality of life and one anxiety/depression self-reported questionnaires: the Medical Outcome Study 36-item Short Form Health Survey (SF-36v2, Acute, France), the CAMPHOR, and the HADS. The SF-36 is a generic health-related quality of life questionnaire.[19] In addition to change in reported health, the domains assessed are physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. These domains are combined to formtwo higher-order summaries: the physical and mental health component summaries. Each domain and each summary is reported on a 0–100 scale. Higher scores indicate better health-related quality of life. SF-36 scores are normalised to a mean of 50 and an SD of 10 based on the normal United States population.[20] The SF-36 has received linguistic and psychometric validation in French,[21,22] and standard (United States-derived) scoring algorithms are recommended for use in France.[20] The CAMPHOR is a pulmonary hypertensionspecific health-related quality of life questionnaire.[23] It includes three scales designed to assess symptoms, functioning, and quality of life. Scores range from 0 to 25 for the symptom and quality of life scales and from 0 to 30 for the functioning scale. Higher scores indicate greater impairment. The French–Canadian validated version of the CAMPHOR[24] is used in the present study, with permission. The HADS questionnaire[25] is divided into two scales including seven items each for the screening of depression and anxiety. The total scores for depression and for anxiety range between 0 and 21. Higher scores indicate greater depression and/or anxiety. We considered a score $\geqslant 8$ to represent symptoms of anxiety or depression.[26]

Statistical analysis Continuous variables are described as mean±standard deviation. Categorical data are described as numbers and percentages for each modality. Characteristics of patients were compared according to the type of pulmonary arterial hypertension associated with CHD or NYHA functional class by analysis of variance for continuous variables and χ^2 or exact Fisher's test for categorical variables. Pearson's correlation coefficients were estimated between SF-36 dimensions and CAMPHOR dimensions. Univariate and multivariate regression analyses were performed to identify the covariates impacting the health-related quality of life among the following: gender, age per quartile, time since diagnosis of pulmonary arterial hypertension, depression and anxiety scores, 6-minute walk distance, NYHA functional class, at least one hospitalisation due to pulmonary arterial hypertension and/or CHD in the past 12 months, and recent stressful event. All the variables were introduced in the multivariate model without selection. For all statistical tests, a significance level of $p \leqslant 0.05$ was used.

Results

Population characteristics

The characteristics of the 208 evaluated patients are presented in Table 1. Most patients had Eisenmenger syndrome (70.7%). At inclusion, most patients (86.0%) were considered as stable for the previous 3 months, 48.1% were in NYHA functional class II, 37.5% in class III, and 76.4% were receiving pulmonary arterial hypertension-specific treatments. Health-related quality of life scores Mean SF-36 scores were low compared with the normalized mean of 50 for all domains (Fig 1) and also for the summaries indicating decreased health-related quality of life compared with normalised data. When patients were asked to appreciate their health at the time of the study, compared with their health a year before, 59.1% considered their health as stable, 22.1% as better, and 18.8% as worse. SF-36 scores were lower for female than for male patients ($p<0.05$, except for physical component summary: $p=0.053$, role physical: $p=0.07$, and vitality: $p=0.16$), but did not vary significantly with the phenotype of pulmonary arterial hypertension associated with CHD (Table 2), even after gender adjustment. All SF-36 scores – individual domains and summaries – were significantly different between NYHA functional class, with and without gender adjustment (Fig 2).

Table 1. Patient characteristics at inclusion.

	Patients with PAH-CHD (n =208)
Demographics	
Age, years (range)	42.6 ±15.8 (15.1;85.8)
Female gender (n (%))	145 (69.7)
Clinical characteristics	
Age at CHD diagnosis (n (%))	
Fetal	5 (2.4)
<1 month	41 (19.8)
1 month to 1 year	36 (17.4)
⩾1 year	125 (60.4)
Unknown	1
Age at PAH diagnosis (years (range))	25.9 ±20.3 (0;80.0)
PAH-CHD classification (n (%))	
Eisenmenger syndrome	147 (70.7)
PAH with systemic–pulmonary shunt	25 (12.0)
PAH with small defects	7 (3.4)
PAH after corrective cardiac surgery	29 (13.9)
Co-morbidities (n (%))	
Respiratory disorder	20 (9.6)
Neurological disorder	10 (4.8)
Renal disorder	7 (3.4)
Liver disorder	1 (0.5)
Other disorder	31 (14.9)
Recent stressful event as reported by the patient (n (%))	39 (18.8)
At least one hospitalisation in the past 12 months (n (%))*	142 (68.3)
Clinical status stable for the past 3 months (n (%))	184 (86.0)
NYHA FC I: II: III: IV (%)	10.6: 48.1: 37.5: 3.9
6-minute walk distance (m)	431 ±109 (n=147)
PAH-specific treatments (n (%))**	
No treatment	49 (23.6)
Monotherapy	85 (40.9)
Double combination therapy	66 (31.7)
Triple combination therapy	8 (3.9)

FC=functional class; PAH=pulmonary arterial hypertension; PAHCHD= pulmonary arterial hypertension associated with CHD Values are expressed as mean ± standard deviation unless otherwise specified
*Hospitalisation due to PAH and/or CHD
**Endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, and/or prostanoid

The observed trend was a decrease in SF-36 scores with worsening NYHA functional class, except for the small group of patients in NYHA functional class IV (n=8). The evolution of the health status compared with the previous year was more likely to be considered as favourable by patients with a worse NYHA functional class (p =0.01).

Mean CAMPHOR symptom, functioning, and quality of life scores among CHD patients with pulmonary arterial hypertension were 8.8 (SD =5.6), 8.5 (SD=5.0), and 6.7 (SD=5.6), respectively.

CAMPHOR scores were higher for female than for male patients (p=0.001 for symptoms; p=0.01 for activity; p=0.001 for quality of life), but only the functioning score varied significantly with the phenotype of pulmonary arterial hypertension associated with CHD (p=0.03 and p=0.04 with and without gender adjustment, respectively, Table 2).

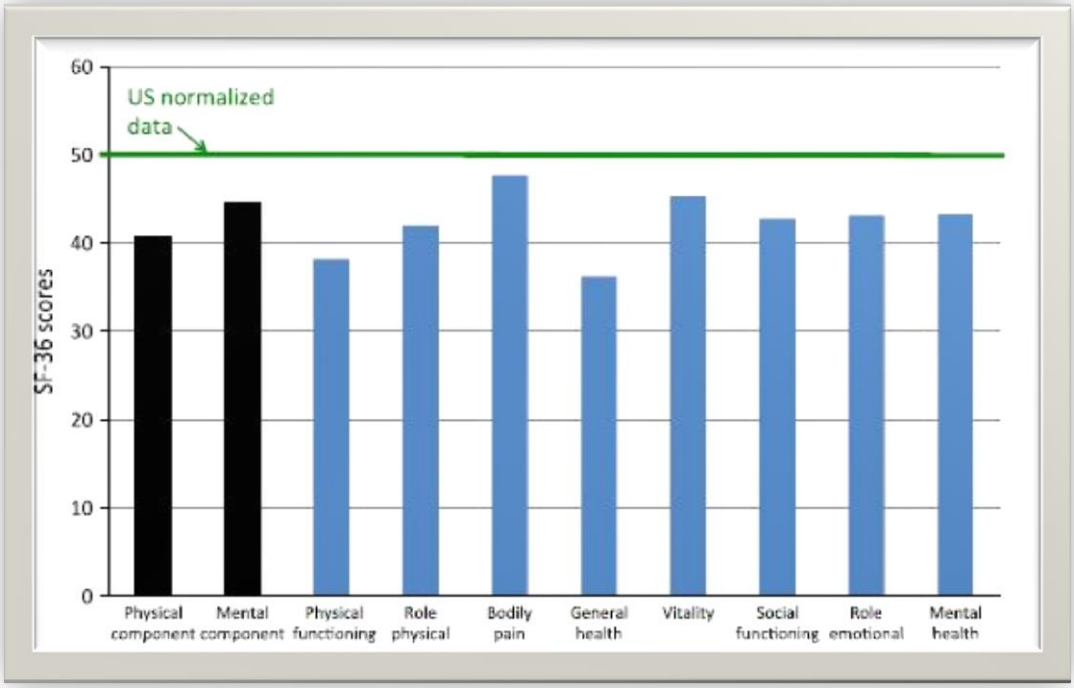

Figure 1. Quality of life impairment assessed by SF-36 in the adults adolescents CHD with pulmonary arterial hypertension quality of life assessment population compared with United States (US) normalised data (n = 208). Aggregate scores are shown in black and individual domains in blue. Higher scores indicate better quality of life. p <0.0001, except for bodily pain: p =0.005.

All CAMPHOR scores were significantly different between NYHA functional class with and without gender adjustment (Fig 3). The observed trend was an increase in impairment with worsening NYHA functional class. Correlations between the SF-36 and the CAMPHOR are shown in Table 3. All correlations were statistically significant in the anticipated direction. SF-36 summaries and CAMPHOR scores were strongly correlated, with the exception of the CAMPHOR functioning and SF-36 mental component summary, which presented a weaker correlation.

Table 2. SF-36, Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), and Hospital Anxiety and Depression Scale (HADS) scores according to pulmonary arterial hypertension (PAH)-CHD phenotypes.

	Eisenmenger (n =147)	Systemic-topulmonary shunts (n= 25)	Small defects (n= 7)	Corrected defects (n =29)	All PAH-CHD (n= 208)	p-value with/ without adjustment
SF36						
PCS	40.5 ± 9.3	41.6 ± 10.4	38.8 ± 8.4	42.3 ± 11.1	40.8 ± 9.6	ns/ns
MCS	44.5 ± 11.1	44.3 ± 9.2	39.3 ± 9.4	46.4 ± 11.2	44.6 ± 10.8	ns/ns
CAMPHOR						
Symptom	8.8 ± 5.5	9.2 ± 5.9	11.7 ± 3.3	7.7 ± 5.8	8.8 ± 5.6**	ns/ns
Functioning	9.1 ± 5.0	8.0 ± 5.6	6.9 ± 4.1	6.5 ± 4.3	8.5 ± 5.0***	0.03/0.04
Quality of life	6.9 ± 4.6	6.6 ± 4.6	7.1 ± 3.3	5.7 ± 5.7	6.7 ± 5.6***	ns/ns
HADS						
Anxiety	7.1 ± 3.9	7.9 ± 4.0	7.4 ± 2.4	6.8 ± 4.2	7.2 ± 3.9*	ns/ns
Depression	4.1 ± 3.9	4.5 ± 2.7	3.1 ± 1.7	3.4 ± 3.7	4.0 ± 3.7**	ns/ns

MCS= mental component summary of SF-36; PCS=physical component summary of SF-36
Values are expressed as mean ± standard deviation
*n=204
**n=206
***n=207

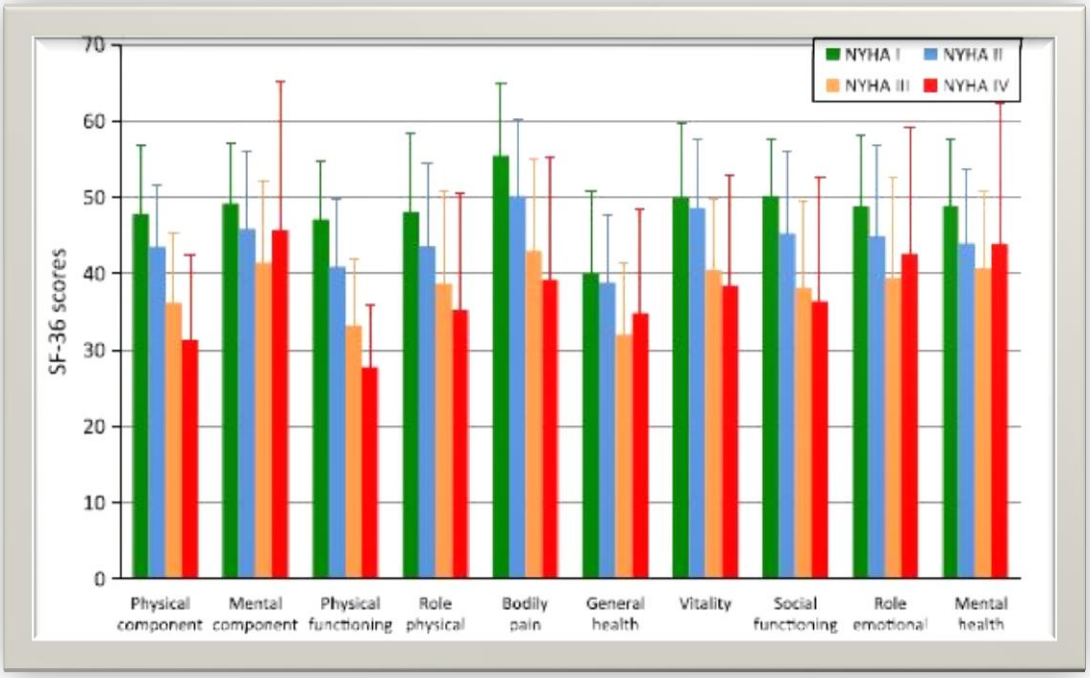

Figure 2. SF-36 scores (mean ± standard deviation) for patients in NYHA functional classes I–IV (n = 208). Higher scores indicate better quality of life. All SF-36 scores were significantly different between NYHA functional classes, with and without gender adjustment by analysis of variance.

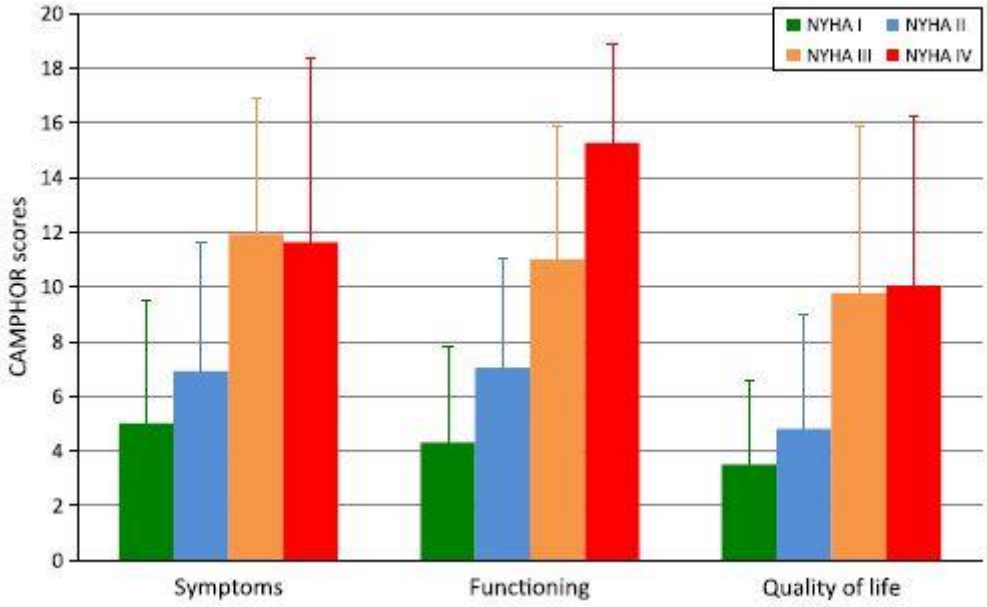

Figure 3. Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) scores (mean ± standard deviation) for patients in NYHA functional classes I–IV (n = 208). Higher scores indicate higher impairment. All CAMPHOR scores were significantly different between NYHA functional classes, with and without gender adjustment by analysis of variance (p <0.001).

HADS questionnaire scores

HADS scores for anxiety and depression were 7.2 (SD=3.9) and 4.0 (SD =3.7), respectively; they were ⩾8 for 64 patients (31.4%) and 19 patients (9.2%), respectively. HADS scores were higher for female than for male patients (p =0.01 and p=0.001, respectively), but did not vary significantly with the phenotype of pulmonary arterial hypertension associated with CHD (Table 2), even after gender adjustment. Scores were significantly different between NYHA functional class for both anxiety and depression with and without gender adjustment (Fig 4). The observed trend was an increase in HADS scores with worsening NYHA functional class, except for the small group of patients in NYHA functional class IV (n =8).

Factors affecting SF-36 and CAMPHOR

The results from univariate and multivariate regression analyses are presented in Table 4. Female gender was a factor affecting the SF-36 physical component summary and mental component summary as well as the CAMPHOR scores in univariate analyses, but significance was not maintained in the multivariate analyses, except for the SF-36 mental component summary.

Table 3. Correlations between SF-36 and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).

	SF-36 PCS	SF-36 MCS
CAMPHOR Symptom	R=− 0.65, p <0.0001	R=− 0.59, p <0.0001
CAMPHOR Functioning	R=− 0.69, p <0.0001	R=− 0.31, p <0.0001
CAMPHOR quality of life	R=− 0.57, p <0.0001	R=− 0.56, p <0.0001

MCS= mental component summary; PCS=physical component summary

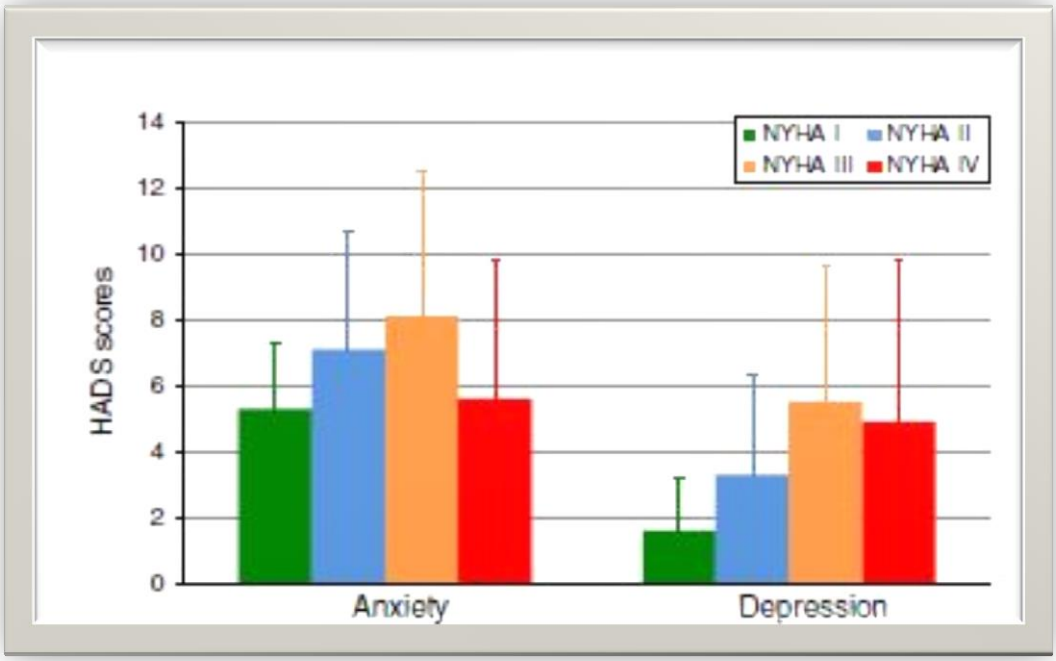

Figure 4. Hospital Anxiety and Depression Scale (HADS) scores (mean ± standard deviation) for patients in NYHA functional classes I–IV (n = 191). Higher scores indicate higher anxiety/ depression. Scores were significantly different between NYHA functional classes for both anxiety and depression ($p = 0.02$ and $p < 0.0001$, respectively) with and without gender adjustment by analysis of variance.

Table 4. Impact of demographic and clinical factors on health-related quality of life.

	p-values from (univariate) multivariate regression analyses				
	SF-36		**CAMPHOR**		
Factors tested for an impact on **HRQoL**	**PCS**	**MCS**	**Symptoms**	**Functioning**	**Quality of life**
Gender	(0.053) 0.68	(0.0002) 0.05	(0.001) 0.56	(0.01) 0.93	(0.007) 0.73
Quartile age	(0.049) 0.86	(0.20) 0.57	(0.12) 0.94	(0.01) 0.13	(0.27) 0.78
Time from PAH diagnosis	(0.63) 0.41	(0.56) 0.89	(0.33) 1.00 0.32	(0.98) 0.54	(0.97)
NYHA functional class III/IV	(<0.0001) 0.045	(0.002) 0.15	(<0.0001) 0.004	(<0.0001) 0.03	(<0.0001) 0.0005
6MWD	(<0.0001) 0.001	(0.9) 0.13	(<0.0001) 0.003	(<0.0001) <0.0001	(0.001) 0.33
At least one hospitalisation* in the past 12 months	(0.004) 0.053	(0.85) 0.33	(0.02) 0.33	(0.62) 0.57	(0.27) 0.90
Recent stressful event	(0.65) 0.96	(<0.0001) <0.0001	(0.50) 0.96	(0.97) 0.23	(0.14) 0.55
HADS anxiety	(0.001) 0.12	(<0.0001) <0.0001	(<0.0001) <0.0001	(<0.0001) 0.04	(<0.0001) 0.0003
HADS depression	(<0.0001) 0.27	(<0.0001) <0.0001	(<0.0001) <0.0001	(<0.0001) 0.03	(<0.0001) <0.0001

CAMPHOR=Cambridge Pulmonary Hypertension Outcome Review; HADS =Hospital Anxiety and Depression Scale; HRQoL =health-related quality of life; MCS =mental component summary; PAH=pulmonary arterial hypertension; PCS=physical component summary; 6MWD=6-minute walk distance *Hospitalisation due to PAH and/or CHD

Age only had an impact on the SF-36 physical component summary and CAMPHOR functioning in univariate analyses. The time from diagnosis of pulmonary arterial hypertension had no impact on health-related quality of life. In the multivariate analysis, NYHA functional class III/IV was related to all SF-36 and CAMPHOR scores, with the exception of the SF-36 mental component summary, whereas the 6-minute walk distance was associated with the SF-36 physical component summary and the CAMPHOR symptoms and functioning. HADS scores impacted all health-related quality of life scores in univariate analyses and the effect was confirmed in multivariate analyses except for the SF-36 physical component summary. At least one hospitalisation for pulmonary arterial hypertension and/or CHD during the past 12 months was a factor affecting the SF-36 physical component summary and the CAMPHOR symptoms only in univariate analyses, whereas a recent stressful event affected the SF-36 mental component summary in multivariate analyses.

Discussion

The ACHILLE study is a prospective, cross-sectional, multicentre, observational study, which investigated the health-related quality of life of a large cohort of208 CHD patients with pulmonary arterial hypertensionin 14 specialised CHD centres. Although the patients presented with a stable disease, they had an impaired health-related quality of life as assessedusing both generic and pulmonary hypertensionspecific questionnaires. NYHA functional class and HADS scores were predictive of most health-related quality of life scores.

Health-related quality of life has become a matter of increasing interest in a number of chronic diseases including pulmonary arterial hypertension,[27–29] buta few studies have focussed on patients with pulmonary arterial hypertension associated with CHD. Only one study by Becker-Grunig et al[12] has described the health-related quality of life of 20 patients with pulmonary arterial hypertension associated with CHD. Other studies are small series involving patients with Eisenmenger syndrome.[13–17]

In our study, we included 208 patients presenting with all four clinical phenotypes of pulmonary arterial hypertension associated with CHD:[18] Eisenmenger syndrome, pulmonary arterial hypertension associated with systemic-to-pulmonary shunts, small defects, and corrected defects. In these patients, health-related quality of life was impaired, particularly in the physical domains of the SF-36, which is consistent with the findings of the abovementioned small studies. Although health-related quality of life is compromised in our patients with pulmonary arterial hypertension associated with CHD, impairment appears less severe than in patients with other types of pulmonary arterial hypertension. [27–29] This might be due to the fact that CHD patients with pulmonary arterial hypertension have lived with CHD since childhood and may have adapted to their illness.[30] Besides, some patients might be aware of a better prognosis of their disease's subgroup, and this might influence the way they estimate their quality of life, especially in the mental dimensions.

Patients with pulmonary arterial hypertension associated with CHD are a heterogeneous population, and the four clinical phenotypes have different clinical, functional, and haemodynamic characteristics as well as diverse patterns of survival.[31] We compared the health-related quality of life and level of anxiety/depression of patients across the four phenotypes, but no significant difference was observed except for the functioning dimension of the CAMPHOR. Functional disability was increased in patients with

Eisenmenger syndrome in line with the comparative study of Manes et al,[31] which reported the worst functional capacity and haemodynamics for these patients. The lack of significant difference of other health-related quality of life and anxiety/ depression parameters across subgroups of pulmonary due to the small numbers of patients in some of the subgroups, but it cannot be excluded that pulmonary arterial hypertension is predominantly impairing health-related quality of life, regardless of the associated cardiac defect. This is substantiated by a study by Muller et al[15] who reported that health-related quality of life is more impaired in pulmonary arterial hypertension due to Eisenmenger syndrome associated with a simple cardiac defect than in complex cyanotic CHD with pulmonary stenosis.

In our study, NYHA functional class was an independent predictor for all domains of the CAMPHOR and for the physical component summary of the SF-36, whereas the 6-minute walk distance was only predictive of the symptoms and functioning domains of the CAMPHOR. Such associations between health-related quality of life and measures of the functional status – NYHA functional class and to a lesser degree the 6-minute walk distance – have been demonstrated consistently in patients with pulmonary arterial hypertension.[9,27,29]

Owing to diminished health-related quality of life, decreased exercise capacity, financial burden of treatment, unemployment, and an uncertain prognosis, patients with pulmonary arterial hypertension associated with CHD may be more vulnerable to developing depression and anxiety.[8] The high prevalence of depression and anxiety in patients with pulmonary arterial hypertension has been known for many years.[32–35] In the patients of our study, the HADS anxiety scores were comparable with those reported for patients with various types of pulmonary arterial hypertension,[32,35] whereas depression scores were indicative of a less depressed population. As reported in other studies,[36] we found that mental disorders were significantly associated with health-related quality of life, suggesting that mental disorders should be considered in the management of these patients.

Health-related quality of life is patients' own expectations and perceptions of how their health affects them. It is therefore subjective and time dependent.

Adjustment to pulmonary arterial hypertension has been reported in other studies,[37] but we did not observe an effect of time since diagnosis on patients' health-related quality of life. Nonetheless, an interesting observation was that patients in NYHA functional class IV tended to perform better in some of the mental domains of the SF-36 and in the HADS than patients in NYHA functional class III. These results could suggest a phenomenon of psychological resilience in patients suffering from an incurable disease at an advanced stage, although they should be interpreted cautiously, given the limited number of patients in NYHA functional class IV.

Measurements of health-related quality of life in patients with pulmonary arterial hypertension have been reported in a number of epidemiological studies[27–29] and clinical trials[38] but they are often overlooked in routine clinical practice, possibly because they are still perceived as subjective, cumbersome, and unreliable. Yet, health-related quality of life questionnaires provide valuable information on the burden of pulmonary arterial hypertension on the patient's day-to-day living and have also been associated with prognosis.[39,40] In our study, the generic SF-36 and pulmonary hypertensionspecific CAMPHOR questionnaires presented strong inter-domain correlations as observed

previously in patients with pulmonary hypertension[41] and were strongly associated with therapeutic objectives as assessed by NYHA functional class and the 6-minute walk distance, supporting their use in clinical practice.

The quality of life assessment of our patients is certainly subjective, but not less essential. Today, few congenital cardiologists evaluate in regular follow-up the actual quality of life of their patients. As in many other chronic diseases, measurement of patient-related outcomes has been given more or more attention in congenital cardiology, but mostly when carrying out clinical research trials.[42] In their routine practice, physicians mostly rely on clinical symptoms and disease complications but usually have a wrong estimation of their patients' overall life satisfaction [43,44]. Yet, approaching the physical and psychosocial aspects of quality of life can enlarge the doctor–patient interaction and help decision making in routine clinical practice.

Therefore, we recommend for pulmonary hypertension CHD specialists to regularly assess the health-related quality of life of their patients – for instance, during the annual or semi-annual medical check-up. A specialist nurse could probably be dedicated to this assessment. As similar results were obtained in our study by both generic and specific questionnaires, we recommend using the SF-36 for clinical routine health-related quality of life assessment. This generic questionnaire is rapidly filled-out, easily scored, and also enables comparison with the healthy population in many countries. Moreover, symptoms of anxiety and/or depression should be systematically evaluated in routine clinical practice. The HADS questionnaire is a simple tool for pulmonary hypertension CHD specialists, but in routine follow-up patients should be evaluated and potentially regularly followed-up by a psychologist or a psychiatrist according to individual needs.

Limitations

This cross-sectional, multicentre, observational study has a number of inherent limitations as it was designed to describe the health-related quality of life of patients with pulmonary arterial hypertension associated with CHD with no investigation of the evolution of this health-related quality of life with time. The patient population is limited to the more severe patients followed-up in selected centres with expertise in pulmonary vascular medicine. Patients with cognitive limitations who could not fill the questionnaire were excluded, and are therefore not represented in our group of patients with pulmonary arterial hypertension associated with CHD. At inclusion, a high proportion of patients (23.6%) did not receive any pulmonary arterial hypertension-specific therapies, which could have had an impact on health-related quality of life. The study enrolled a large number of patients with pulmonary arterial hypertension associated with CHD, but some subgroups were small, such as the subgroup of patients in NYHA functional class IV (n=8) and patients with small defects (n=7), which precluded some statistical analyses and interpretation. Patients' awareness of prognosis might have influenced their self-reported health-related quality of life scores and could represent a possible confounding factor, especially when comparing the different subgroups where prognosis is known to be different; however, data comparing these different prognoses were published after patients were enrolled in the ACHILLE study, suggesting limited bias.[31]

Conclusion

This study shows in a large patient population that CHD with pulmonary arterial hypertension is associated with impaired health-related quality of life, as assessed using both the generic SF-36 and the pulmonary hypertension-specific CAMPHOR

questionnaires. Confronted with numerous life stressors, these patients are also prone to anxiety and depression. Health-related quality of life, anxiety, and depression should be more systematically evaluated in routine clinical practice, as tools have demonstrated validity and reliability and psychological support and/or treatment may be beneficial for the patient.

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Conflicts of Interest
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