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Evaluation of disease-specific health-related quality of life in patients with pulmonary arterial hypertension

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Summary
Background: Pulmonary arterial hypertension (PAH) remains a debilitating and life-threatening disease despite improvements in hemodynamics, exercise capacity and survival with recent therapeutic advances. Health-related quality of life (HRQOL) has, therefore, been proposed as an important outcome for evaluating care. Relatively little, however, is known regarding HRQOL or its determinants in PAH. The Minnesota Living with Heart Failure questionnaire was recently adapted and validated for HRQOL measurement in PAH. We applied this pulmonary hypertension-specific version (MLHF-PH) to a larger population of PAH patients.
Methods: Ninety-three consecutive outpatients with PAH completed the MLHF-PH. Scores were assessed for correlations with demographics, symptoms, hemodynamics and treatments.
Results: Patients with PAH had significantly impaired HRQOL as assessed by the disease-specific MLHF-PH. Each physical and emotional component, as well as total scores on the MLHF-PH indicated severely depressed HRQOL. As compared to other diagnoses, PAH associated with scleroderma had the worst HRQOL. Patients with WHO functional Class II symptoms reported better HRQOL than Class III patients. Fatigue, weakness and abdominal discomfort were each associated with more severely depressed HRQOL, as was current epoprostenol use. With the sole exception of the right atrial pressure, hemodynamic measurements did not correlate with HRQOL scores. Simultaneous evaluation of HRQOL with a non-disease-specific questionnaire (SF-36) revealed a similarly impaired status, although identified fewer associations with patient-specific factors.

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Conclusion: Severely impaired HRQOL is present in this population of patients with PAH evaluated with a disease-specific questionnaire. The availability of a pulmonary hypertension-specific HRQOL questionnaire may enable further targeted investigations of factors that might improve outcomes.

Introduction

Pulmonary arterial hypertension (PAH) is a devastating and progressive condition that frequently causes cor pulmonale and premature death.[1–3] Patients with PAH suffer from breathlessness, decreased exercise capacity, peripheral edema, lightheadedness and syncope. Currently available treatments often cause side effects including worsened edema, nausea and diarrhea, and may require invasive, cumbersome and at times painful modes of administration.[4,5] Further, while effective at improving hemodynamics, exercise capacity and survival, none of these therapies is curative and varying degrees of impairment remain.[6,7] Not surprisingly, health-related quality of life (HRQOL) in patients with PAH is significantly impaired.

HRQOL reflects the impact of health issues on one's satisfaction with life and ability to meet physical and emotional needs. Physicians can use assessments of HRQOL to better define and understand how an illness interferes with a patient's day-to-day living. Identifying disease-specific factors that influence HRQOL may allow physicians to select meaningful therapeutic interventions, improve the quality and delivery of care, and optimize clinical outcomes. Indeed, assessments of HRQOL are now commonly used as clinical trial endpoints of many disease states, particularly chronic conditions where the quality of a patient's life may be viewed as having equal or even greater importance than absolute survival.[8]

Only recently has HRQOL been a specific focus of study in patients with PAH. Preliminary evaluations using non-disease-specific questionnaires have identified profound impairment in the HRQOL of patients with PAH, comparable to that seen in other life-threatening and even fatal disease states.[9–13] Indeed, Shafazand et al. found that despite current therapy, patients with PAH reported a willingness to accept a 29% risk of certain death in exchange for a possible cure.[9] Efforts at improving HRQOL in patients with PAH will require validated and potentially disease-specific assessment tools, to identify factors whose change might positively impact HRQOL.[14]

The Minnesota Living with Heart Failure (MLHF) questionnaire was designed and validated for the assessment of HRQOL in patients with heart failure, and is widely applied in studies of patients treated for left-sided heart dysfunction.[15] As both the symptoms and outcome of patients with PAH are predominantly determined by the consequences of right heart failure, Cenedese et al. recently validated a simple modification of the MLHF to allow HRQOL assessment specifically in patients with pulmonary hypertension.[16] They validated this pulmonary hypertension-specific version of the MLHF in 26 patients with PAH, and additionally demonstrated its reliability and responsiveness to change. We have now applied this disease-specific tool to assess HRQOL in a larger population of patients with PAH than previously studied.

Methods

Study design and patients

We performed a cross-sectional assessment of HRQOL using a disease-specific HRQOL tool. Newly referred and established patients were asked to complete HRQOL questionnaires between July 2004 and December 2005. Only patients with World Health Organization (WHO) Group 1 disease (PAH) as defined by the 2003 World Symposium on PH were included.[17,18] Patients were evaluated according to standard guidelines, including confirmation of a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg with exertion and exclusion of significant left heart or respiratory disease.[19,20] Patients completed HRQOL questionnaires without prompting during outpatient appointments. Physicians and nurses providing care were unaware of patient responses.

Patient demographics, symptoms, and medications on the day of HRQOL evaluations were obtained by chart review. Cardiac catheterization results within 12 months were recorded.

Health-related quality of life measurements

We administered a modification of the MLHF disease-specific HRQOL survey validated for assessment of patients with pulmonary hypertension (MLHF-PH).[16] In place of ''your heart failure,'' patients are asked to report the degree to which ''your pulmonary hypertension'' affects various aspects of daily life (see Appendix I). The MLHF-PH has 21 questions and is scored from zero to 105, with higher scores indicating worse HRQOL. The survey yields a total score, providing an overall assessment of satisfaction with life as influenced by health. The MLHF-PH also specifically evaluates physical and emotional HRQOL separately as physical and emotional domain scores. A patient without PH, or who does not attribute any symptoms to it, should have a MLHF-PH score of zero.

For comparison to disease-specific HRQOL evaluations, we simultaneously administered the Medical Outcomes Survey 36 Item Short Form health survey (SF-36).[21] This validated non-disease-specific questionnaire is widely used to assess HRQOL in multiple diseased populations. The SF-36 has 36 questions yielding scaled scores in 8 physical/mental health domains and overall physical and mental component summary scores. In contrast to the MLHF-PH, higher scores on the SF-36 indicate better HRQOL.

Statistical analysis

HRQOL scores of the MLHF-PH and SF-36 were calculated according to published instructions, including imputation for missing data.[21,22] To facilitate comparison across domains,

SF-36 subscale scores were normalized to a mean of 50 and SD of 10 based on the normal US population.[21] Normative values for the MLHF and MLHF-PH do not exist as these surveys are specifically designed for patients with CHF and PH, respectively. A patient whose HRQOL is unaffected by CHF (for the MLHF) or PH (for the MLHF-PH) would have a score of zero.

Data were entered into Access 5.1 (Microsoft Corporation) and analysis performed using SAS 9.1 (SAS Institute; Cary, NC). Differences were assessed using an independent *t*-test for binary predictors, ANOVA for categorical predictors, and correlation coefficients for continuous measures. Comparisons between patient groups were limited to the MLHF-PH physical, emotional and total scores, and the SF-36 physical and mental component summary scores. Significant associations were defined as $p \leq 0.05$ without adjustment for multiple comparisons in this hypothesis-generating evaluation.[23] Prior to modeling, we examined the distributions of the three MLHF-PH scales and the two SF-36 scales, each of which was near normal. The Shapiro–Wilk statistic, which ranges from 0 to 1, where values near 1 indicate near normality, ranged from 0.93 through 0.99 for the SF-36 and MLHF-PH scales in our sample, indicating near normality of the outcome measures and the use of parametric statistical tests.[24] While our analytic methods utilized parametric tests, additional confirmation was performed with secondary nonparametric tests (Spearman correlation and Wilcoxon rank sum as appropriate) to account for any deviations of the assumed normality as well as the sampling process.

This study was approved by the Institutional Review Board of the University of Pennsylvania.

Results

Patient characteristics

HRQOL was assessed in 93 outpatients with PAH (WHO Group 1 disease). The population was 80% female with an average age of 50 years, ranging from 18–81. More than half of the patients were married and 16 percent reported living alone. Approximately one-half had idiopathic PAH (IPAH), and nearly all had NYHA/WHO functional Class II or III symptoms as assessed by their physicians. Thirteen percent of patients completed HRQOL surveys at their initial evaluation in a PH specialty clinic, whereas the remainder of assessments were made in patients followed for up to one, three and five years in 15, 27 and 32 percent of patients, respectively. The rest (13 percent) had received care specifically for PAH for more than five years. Table 1 shows other physical/social characteristics of the population.

Pulmonary hypertension disease-specific HRQOL scores

Assessments of each physical, emotional and overall HRQOL using the pulmonary hypertension-specific MLHF-PH questionnaire revealed severe impairments (Fig. 1). The total MLHF-PH score indicated significant problems in HRQOL ($p < 0.001$). Both the mean physical and emotional dimension scores of the MLHF-PH also were elevated ($p < 0.001$ each), indicating patients' assessment of the effects of pulmonary hypertension on satisfaction with life and ability to function as desired.

Factors associated with HRQOL scores on the MLHF-PH

Demographics

To facilitate comparisons, significant differences in HRQOL scores according to patient-specific factors are summarized in Table 2; full results are presented in Appendix II. As compared with other forms of PAH, patients with disease associated with scleroderma had significantly worse HRQOL. Physical dimension and total summary scores on the MLHF-PH for patients with scleroderma were more severely impaired than those of patients with idiopathic PAH. Patients with NYHA/WHO functional Class II symptoms had better physical, emotional and total summary scores than patients with NYHA/WHO Class III symptoms. Living alone was also associated with worse emotional dimension scores on the MLHF-PH. Neither gender, race, nor marital status was associated with better or worse HRQOL scores.

Symptoms

Certain symptoms were associated with worsened HRQOL. Abdominal complaints (e.g., bloating and ''fullness'') and symptoms of fatigue or weakness were associated with significantly worse physical dimension scores. Abdominal complaints were additionally associated with worse total summary scores. Symptoms of weakness or fatigue occurred more frequently with more severely impaired emotional and total summary scores. Chest pain was associated with worse emotional scores but not physical and total summary scores. Other commonly reported symptoms including leg swelling (35% of patients) and lightheadedness (26%) were not associated with MLHF-PH scores. Common side effects of epoprostenol therapy (diarrhea, jaw pain) were not related to HRQOL scores.

Therapies

Therapies were also assessed. Patients treated with continuously infused epoprostenol reported significantly worse effects of PAH on HRQOL. As compared with other patients, physical dimension, emotional dimension, and total summary MLHF-PH scores were worse. No differences in HRQOL scores were found according to the use or non-use of either calcium channel antagonists or bosentan. Small numbers treated with sildenafil precluded evaluation. Patients receiving warfarin reported significantly worse physical and total summary scores. No such associations were found according to the use of oxygen, digoxin or diuretics.

Hemodynamic values

Although increases in the mean right atrial pressure correlated with worsened physical dimension scores (correlation = 0.29, $p = 0.05$) and total summary scores (correlation = 0.36, $p = 0.01$), no other relationship to hemodynamic values was identified. Neither mean PA pressures, cardiac output/index, nor pulmonary vascular resistance values was correlated with any of the three MLHF-PH quality of life measurement scales (Fig. 2).

Table 1 Population characteristics

Physical characteristics (*n*, % except as indicated)		Social characteristics (*n*,%)	
Patients, *n*	93	*Marital status*	
Age, years (mean ± SD)	50 ± 13	Single	24 (26)
Female	74 (80)	Married	54 (58)
Caucasian	65 (69)	Separated	3 (3)
African American	14 (15)	Divorced	6 (6)
Hispanic	3 (3)	Widowed	4 (6)
Asian	1 (1)	Unknown	2 (2)
Other	12 (12)	Lives alone	15 (16)
PAH diagnosis		*Substance abuse*	
Idiopathic (PAH)	44 (47)	Prior alcohol	7 (8)
Familial	3 (3)	Current alcohol	6 (6)
Systemic sclerosis	16 (17)	Prior smoking	30 (32)
Other CVD	3 (3)	Current smoking	5 (15)
Anorectic agent use	3 (3)	*Treatments (n,%)*	
Liver disease	6 (6)	Epoprostenol	26 (28)
HIV	2 (2)	Bosentan	46 949)
Congenital heart disease/shunt lesions	14 (15)	Calcium channel blocker	44 (47)
PVOD	2 (2)	Sildenafil	3 (3)
NYHA CLASS I	4 (4)	Warfarin	46 (49)
NYHA CLASS II	45 (48)	Digoxin	31 (33)
NYHA CLASS III	42 (45)	Diuretics	53 (57)
NYHA CLASS IV	1 (1)	Oxygen, continuous	24 (26)
Hemodynamics (mean ± SD)			
Mean RA pressure (mmHg)	9.1 ± 6.1		
Mean PA pressure (mmHg)	45 ± 14		
Cardiac output (liters/min)	4.9 ± 1.9		
Cardiac index (liters/min/m^2)	2.7 ± 0.9		
PVR (dynes × sec × cm^{-5})	689 ± 494		
Symptoms (# of patients/% reporting)			
Lower extremity swelling	33 (35)		
Abdominal fullness	14 (15)		
Pre-syncope/lightheadedness	24 (26)		
Chest pain	19 (20)		
Fatigue/weakness	47 (51)		
Diarrhea	8 (9)		
Jaw pain	9 (10)		

Resting oxyhemoglobin saturation was inversely correlated with physical dimension scores (correlation = −0.35, $p = 0.001$) and total summary scores (correlation = −0.27, $p < 0.05$). Emotional dimension scores were not associated with oxyhemoglobin saturation.

Comparison with HRQOL scores on non-disease-specific surveys

Simultaneous HRQOL evaluations were made using the non-disease-specific SF-36 in order to compare the utility of pulmonary hypertension-specific and non-disease-specific HRQOL assessments. Like the MLHF-PH, the SF-36 identified severe impairment in each physical and mental HRQOL ($p < 0.001$ for the comparison of each with US population normative scores). Deficiencies were additionally found in each of the eight HRQOL domains assessed by the SF-36, except bodily pain (Fig. 3).

Table 2 summarizes those factors identified as being associated with worse HRQOL by either the disease-specific (MLHF-PH) or non-disease-specific (SF-36) surveys. Each survey similarly identified associations between several patient-specific factors and physical aspects of HRQOL (as indicated by the physical dimension and component scores of the MLHF-PH and SF-36, respectively). In the evaluation of physical aspects of HRQOL, discrepancies between the two modes of evaluation occurred in the associations identified with living alone, the presence of pre-syncope or the use of oxygen (each associated with SF-36 physical component scores but not the MLHF-PH) and the use of warfarin or bosentan (each associated with MLHF-PH but not SF-36 scores). Associations between various factors and emotional HRQOL were more often identified by the disease-specific MLHF-PH than by the SF-36. Use of the MLHF-PH total score for overall HRQOL did not identify additional associations not seen in either the emotional or physical component scores.

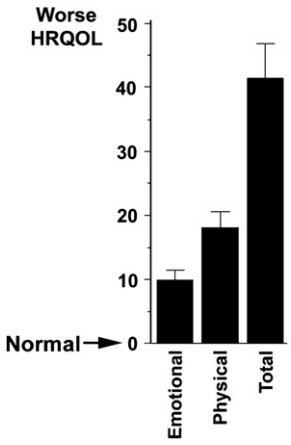

Figure 1 Pulmonary hypertension-specific HRQOL scores. Shown are mean ± SD scores for each the emotional and physical components of the MLHF-PH, as well as the total score evaluating overall HRQOL. Higher scores indicate worse HRQOL. Each mean score indicates significant impairment in HRQOL ($p < 0.001$ for each, as compared to the normal score of zero in each scale of the MLHF-PH).

Discussion

Remarkable progress in understanding the pathogenesis of PAH has led to a rapid growth in therapeutic options. Multiple classes of drugs are now available, as well as options for their route of administration. These advances have led to improvements in important endpoints, including hemodynamics, exercise capacity and survival. Expanding therapeutic options might allow consideration of additional factors when deciding a patient's treatment, including the effect of therapeutic choices on HRQOL. Such consideration is particularly important considering the significant impairments in both exercise capacity and survival that persist despite current therapies. Currently, however, little is known regarding the determinants of HRQOL in PAH, including the best means of assessment.

A few recent studies have begun to specifically assess HRQOL in patients with PAH. Evaluations using non-PAH specific questionnaires have consistently demonstrated impaired HRQOL.[9–13,16] Two groups have recently established the validity of PH-specific assessment tools. McKenna and colleagues developed a novel questionnaire (the CAMPHOR) and Cenedese et al. modified a widely used and well-established tool specifically for use in patients with PH (the MLHF-PH).[13,16,25] Both the CAMPHOR and MLHF-PH yield highly reproducible and valid measures of HRQOL in patients with PAH. The MLHF-PH was additionally shown to be a responsive measure with sensitivity to changes in HRQOL with treatment. In a multivariate analysis including common invasive and non-invasive measures, patients' MLHF-PH scores were also shown to be predictive of subsequent clinical worsening, including death. Chua et al. compared the performance of the SF-36, MLHF and the Australian QOL questionnaires and found the SF-36 and MLHF to be sensitive to measures of functional and exercise capacity.[11]

We, therefore, applied the disease-specific MLHF-PH to a larger population of patients with PAH. Severely impaired HRQOL was identified, even among patients using medications known to improve exercise capacity and survival. We identified demographic, symptom, examination, and treatment factors associated with better or worse HRQOL. Significantly impaired HRQOL was also identified by the non-disease-specific SF-36. No clear advantage of either method was seen for evaluating individual patients. Although the MLHF-PH did more often identify associations with emotional domains of HRQOL, the relative utility of these questionnaires as research tools requires prospective studies in additional populations and with attention to change over time and prediction of outcomes. Accordingly, Cenedese et al. have demonstrated the MLHF-PH to be

Table 2 Comparison of HRQOL scores assessed by disease-specific and non-disease-specific questionnaires

	SF-36-physical component	MLHF-PH physical dimension	SF-36-mental component	MLHF-PH emotional dimension	MLHF-PH total summary score
Living alone	X			X	
Abdominal fullness	X	X			X
Pre-syncope	X				
Chest pain				X	
Fatigue/weakness	X	X	X	X	X
Warfarin		X			X
IV epoprostenol		X		X	X
Bosentan			X		
Oxygen	X				
Scleroderma vs. other Group I PAH diagnosis	X	X			
Scleroderma vs. IPAH	X	X			X
NYHA/WHO Functional Class II vs. Class III	X	X		X	X

Indicated are significant ($p < 0.05$) association between the patient factor and worse HRQOL, which was identified by the HRQOL scale. Note that unlike the MLHF-PH, there is no corresponding overall (total) score generated by the SF-36 questionnaire. See Appendix II for full score details in each assessment.

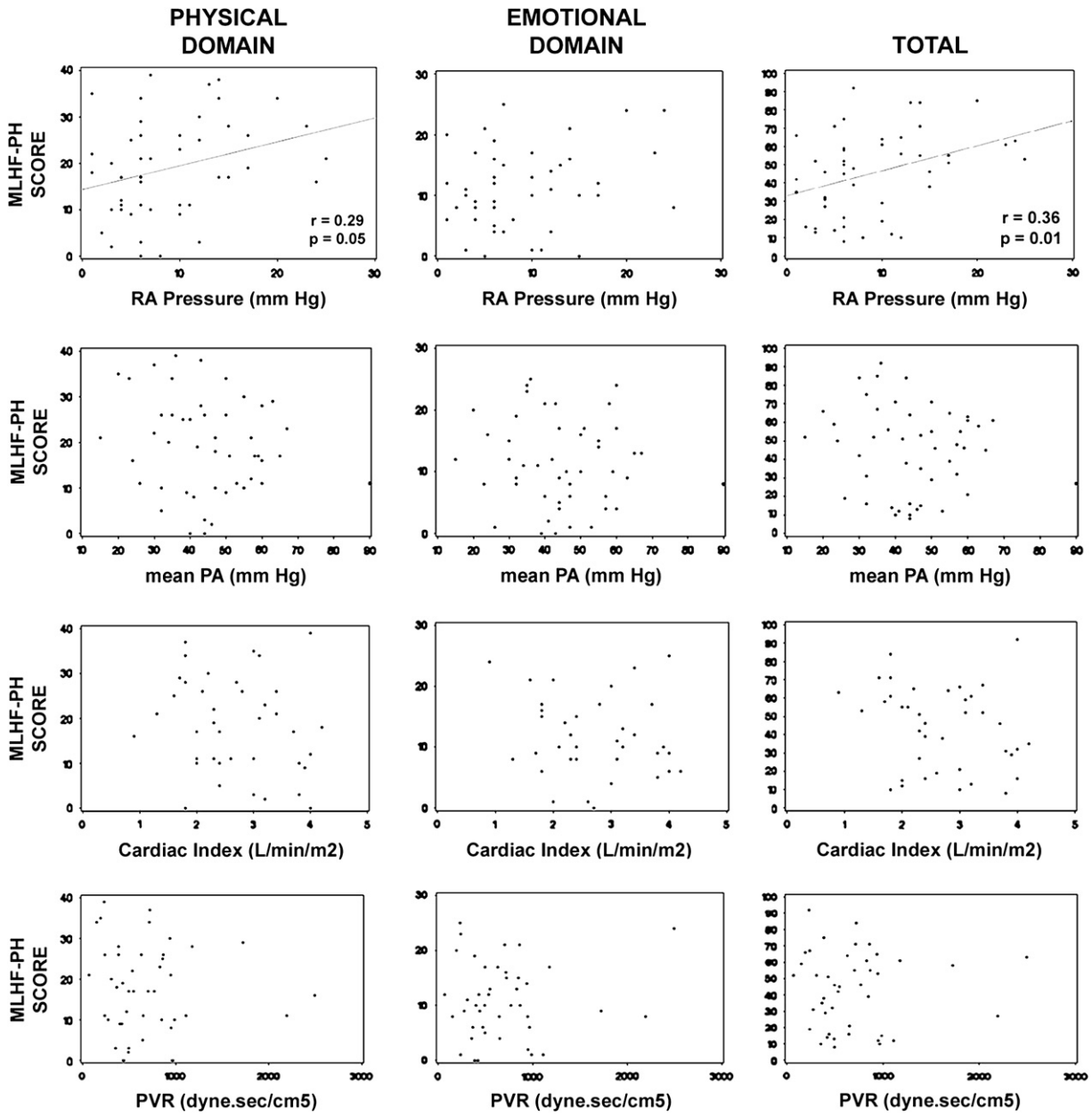

Figure 2 Relationship between MLHF-PH scores and hemodynamic values. Lack of correlation between most hemodynamic values and the scores on each physical domain and emotional domain and total MLHF-PH scores. An association was only identified between the right atrial (RA) pressure and the physical domain and total MLHF-PH scores (with correlation coefficient and corresponding p values as indicated). Nonparametric analysis resulted in similar values ($r = 0.31$, $p = 0.033$ for the association with physical domain score and $r = 0.37$, $p = 0.012$ for the total MLHF-PH score). None of the other hemodynamic values had significant correlations with any of the MLHF-PH scores. PA, pulmonary artery; PVR, pulmonary vascular resistance.

predictive of outcomes, as noted above. Chua et al. compared the ability of each the MLHF, SF-36 and the Australian Quality of Life questionnaires to detect change in HRQOL over time, and found the MLHF and SF-36 to be most responsive, in addition to correlating well with other baseline measures of functional status.[11]

Despite the availability of only a few studies thus far focusing specifically on HRQOL in PAH, quality of life has been consistently impaired regardless of whether assessments are made before or after therapy, or the questionnaire used. Study of HRQOL is important in PAH for several reasons. Patients may perceive the effects of impaired hemodynamic values and six-minute walk distances differently. These differences may be influenced by their pre-morbid status, comorbidities, life-styles and expectations. Further, although improved by current therapies, survival remains significantly reduced for most patients with PAH. It is, therefore, appropriate that factors influencing a patient's satisfaction with overall HRQOL be addressed when evaluating care. Indeed, recent studies have shown that hemodynamic values no longer reliably predict survival in patients

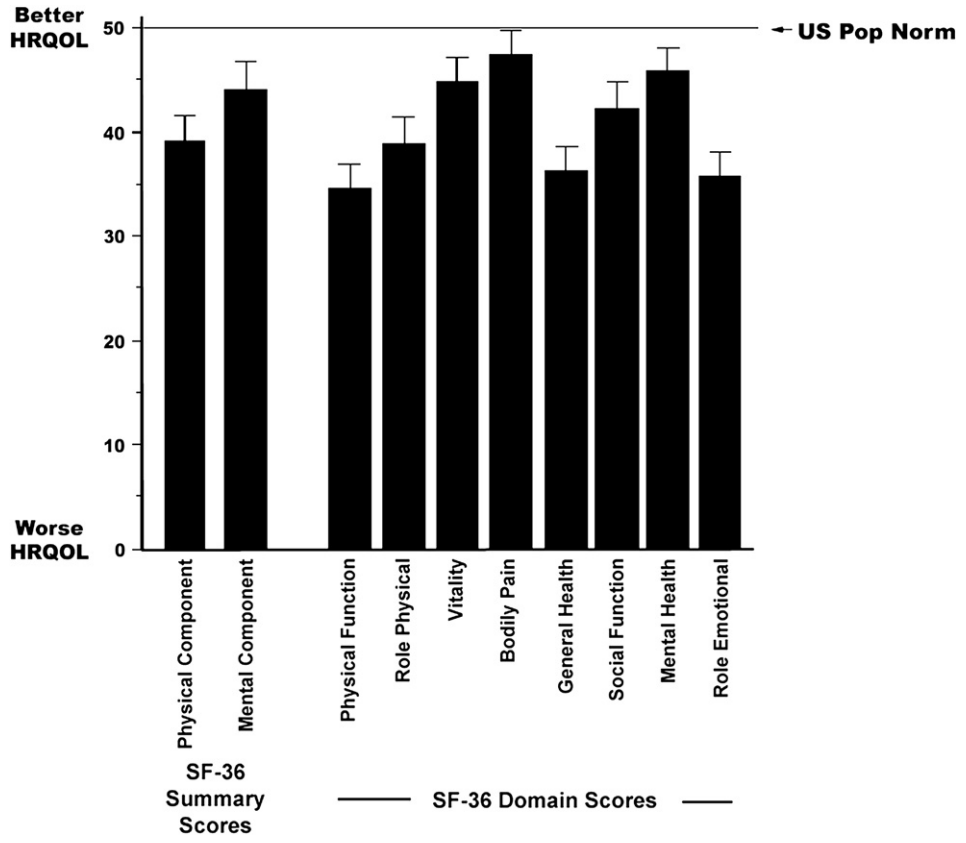

Figure 3 Non-disease-specific HRQOL scores. Shown are the mean ± SD scores on the SF-36. Both physical and emotional component scores (left) and individual domain scores (right) are shown. Each mean score is significantly different from the normal US population score ($p < 0.001$), with the exception of bodily pain. Higher scores on the SF-36 indicate better HRQOL.

with PAH. The identification of previously unrecognized predictors of survival in patients with PAH (e.g., race and socioeconomic status) underscores the importance of evaluating new means of assessing outcomes.[26] Indeed in other populations, impaired HRQOL is associated with markedly increased mortality independent of other medical issues.[27,28]

The present study has several limitations. Retrospective collection of patient data may result in misclassification bias thereby influencing the associations identified. Furthermore, in responding to questions on the MLHF, it is unknown whether patients readily differentiate between symptoms caused by PH and those resulting from comorbidities. The cross-sectional design does not allow evaluation of changes in HRQOL in response to individual treatments. As we are unable to control for differences between patients that influenced the choice of therapies, it is important to recognize that no firm conclusions can be drawn regarding their relative effects on HRQOL. Such comparisons will require prospective studies. The modification made to the MLHF to foster assessment of HRQOL in patients who identify their health problem as ''pulmonary hypertension'' as opposed to ''heart failure'' may limit the ability to compare our results with other studies using the original, non-modified MLHF to assess patients with other causes of heart failure. In addition, it is unknown how discussions between physicians and patients about PAH, or the extent to which patients learn about PAH via available resources (e.g., the internet) impacts HRQOL; study of such potential influences on HRQOL will require additional assessment tools. Additional study is also required to assess whether the MLHF-PH accurately predicts outcome in this population.

In conclusion, we have applied a recently validated pulmonary hypertension-specific HRQOL assessment tool to a larger population of patients with PAH than previously studied by this method. Scores on the MLHF-PH were severely impaired, underscoring the need for future prospective studies aimed at identifying factors which determine and the interventions that might improve HRQOL in patients with PAH. While further study is required to assess whether changes in factors associated with worse HRQOL in the current study can result in improved outcomes, the availability of disease-specific and validated tools, such as the MLHF-PH, should enable continued progress toward this goal.

Conflicts of interest

Darren Taichman receives grant support from Actelion. Harold Palevsky has served as a consultant to Actelion and Gilead. None of the other authors have potential conflicts of interest relevant to the subject of this manuscript.

Supplementary material

Supplementary material can be found, in the online version, at doi: 10.1016/j.rmed.2008.04.016.

References

1. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet* 1998;**352**(9129):719—25.
2. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med* 1987;**107**(2):216—23.
3. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;**115**(5):343—9.
4. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;**126**(Suppl.1):35S—62S.
5. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest* 2007; **131**(6):1917—28.
6. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; **126**(Suppl. 1):78S—92S.
7. Taichman DB, Mandel J. Epidemiology of pulmonary arterial hypertension. *Clin Chest Med* 2007;**28**(1):1—22.
8. Lopez-Campos JL, Failde I, Masa JF, Benitez-Maya JM, Barrot E, Ayerbe R, et al. Factors related to quality of life in patients receiving home mechanical ventilation. *Respir Med* 2008;**102**(4): 605—12.
9. Shafazand S, Goldstein MK, Doyle RL, Hlatky MA, Gould MK. Health-related quality of life in patients with pulmonary arterial hypertension. *Chest* 2004;**126**(5):1452—9.
10. Taichman DB, Shin J, Hud L, Archer-Chicko C, Kaplan S, Sager JS, et al. Health-related quality of life in patients with pulmonary arterial hypertension. *Respir Res* 2005;**6**:92.
11. Chua R, Keogh AM, Byth K, O'Loughlin A. Comparison and validation of three measures of quality of life in patients with pulmonary hypertension. *Intern Med J* 2006;**36**(11):705—10.
12. White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG. Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. *Respir Res* 2006;**7**:55.
13. 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* 2006;**15**(1):103—15.
14. Hoeper MM, Oudiz RJ, Peacock A, Tapson VF, Haworth SG, Frost AE, et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol* 2004;**43**(12 Suppl. S):48S—55S.
15. Rector T, Kubo SH, Cohn JN. Patient self-assessment of their congestive heart failure part 2: content, reliability, and validity of a new measure the Minnesota Living with Heart Failure Questionnaire. *Heart Fail* 1987;**3**:198—209.
16. Cenedese E, Speich R, Dorschner L, Ulrich S, Maggiorini M, Jenni R, et al. Measurement of quality of life in pulmonary hypertension and its significance. *Eur Respir J* 2006;**28**(4): 808—15.
17. Rubin LJ, Galie N. Pulmonary arterial hypertension: a look to the future. *J Am Coll Cardiol* 2004;**43**(12 Suppl. S):89S—90S.
18. Simonneau G, Galie N, Rubin J, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;**43**(12 Suppl. S):5S—12S.
19. McGoon M, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;**126**(Suppl. 1): 14S—34S.
20. Barst RJ, McGoon M, Torbicki A, Sitbon O, Krowka MJ, Olschewski H, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; **43**(12 Suppl. S):40S—7S.
21. Ware J, Kosinski M, Dewey JE. *How to score version 2 of the SF-36 health survey*. Lincoln, RI: QualityMetric Incorporated; 2000. p. 229.
22. Rector TS. Minnesota living with heart failure questionnaire: instructions for data collection and scoring. Available at: http://mlhfq.org; 2004 [accessed 10.13.2004].
23. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;**1**:43—6.
24. Shapiro SS, Wilk MB. An anlysis of variance test for normality. *Biometrika* 1965;**52**:591—611.
25. Gomberg-Maitland M, Thenappan T, Rizvi K, Chandra S, Meads DM, McKenna SP. United States validation of the Cambridge pulmonary hypertension outcome review. *J Heart Lung Transplant* 2008;**27**:124—30.
26. Kawut SM, Horn EM, Berekashvili KK, Garofano RP, Goldsmith RL, Wildlitz AC, et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. *Am J Cardiol* 2005;**95**(2):199—203.
27. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav* 1997; **38**(1):21—37.
28. Benyamini Y, Idler EL. Community studies reporting association between self-rated health and mortality; additional studies, 1995—1998. *Res Aging* 1999;**21**:392—401.