Predictors of health-related quality of life in patients with systemic lupus erythematosus associated pulmonary arterial hypertension

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Abstract

Objective

Understanding health-related quality of life (HRQoL) is important in the management of patients with systemic lupus erythematosus associated pulmonary arterial hypertension (SLE-APAH), however, little is known about HRQoL and its determinants in these patients.

Methods

A total of 60 female SLE-APAH patients with mean age of 33.5 years were prospectively recruited from May 2013 to November 2014. Right heart catheter, SF-36 generic questionnaire, disease activity and functional status were assessed in all patients.

Results

The median duration of SLE was 5 years. Thirty-five participants were with low disease activity (SLEDAI: 0-4). Patients with SLE-APAH reported significant impairment in HRQoL. The mean physical component summary (PCS) and mental component summary (MCS) scores were 46.4 and 56.9, respectively. Among haemodynamic measurements, higher pulmonary vascular resistance and lower cardiac output (CO) were associated with worse HRQoL. Lower body mass index (BMI), lower mean blood pressure and higher disease activity were also associated with poor HRQoL. Multivariate analysis revealed that lower SLEDAI and higher mean blood pressure were predictors for better PCS. However, higher CO (CO≥4L/min) was the only parameter independently associated with both better PCS and MCS.

Conclusion

Self-reported HRQoL was impaired in patients with SLE-APAH. Higher CO was the most important predictor for better HRQoL in these patients.

Key words

quality of life, pulmonary artery hypertension, systemic lupus erythematosus, haemodynamics, disease activity

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Received on June 9, 2015; accepted in revised form on November 23, 2015.

Competing interests: none declared.

Introduction

Pulmonary artery hypertension (PAH) is a severe complication of systemic lupus erythematosus (SLE) with significant morbidity and mortality (1, 2). The prevalence of PAH associated with SLE (SLE-APAH) was up to 3.8% (3), accounting for 38% of connective tissue disease associated PAH in China (4).

An improved understanding of health-related quality of life (HRQoL) and its determinants in SLE-APAH population will be essential as HRQoL instruments provide sensitive indicators for monitoring disease progression and effectiveness of therapeutic interventions on daily performance. Focused assessments of HRQoL itself, however, were lacking and a systematic evaluation of the impact factors had not been reported in these patients. Here we assessed a cohort of SLE-APAH patients and identified demographic, clinical and haemodynamic factors associated with HRQoL.

Methods

Patients

Between May 2013 and November 2014, patients who underwent right heart catheterisation (RHC) for SLE-APAH were consecutively enrolled. PAH was defined as mean pulmonary arterial pressure (mPAP) >25 mmHg with a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units on RHC (5). SLE was diagnosed according to the revised American Rheumatism Association (ARA) criteria (6). Patients with valvular heart disease, atrial fibrillation, coronary artery disease or impaired left ventricular (LV) systolic function (defined as LV ejection fraction<50%) were excluded. SLE activity was assessed by the SLE disease activity index (SLEDAI) (7), and SLEDAI <5 was considered as low SLE disease activity.

Haemodynamic measurements

Haemodynamic assessments were obtained by RHC with a 6-lumen 8-F Swan-Ganz catheter (Edwards Lifesciences World Trade, Irvine, CA USA). Mean right atrial pressure (mRAP), mPAP, and PCWP were measured. Cardiac output (CO) was measured in triplicate with the thermodilution technique (Edwards Lifesciences World Trade). PVR was calculated using the standard haemodynamic formulas as follows: PVR= (mPAP-PCWP) / CO.

Quality-of-Life measurements

HRQoL was evaluated by the Mandarin version of SF-36, which was proved to be reliable and valid in the previous surveys in China (8, 9). All patients were requested to complete SF-36 questionnaires including eight domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Scores for SF-36 were summarised into physical component summary (PCS) score and mental component summary (MCS) score ranging from 0 (worst) to 100 (best). Because Chinese normative data was not available, we used previously reported SF-36 scores of Chinese women from a population-based survey (9).

Functional assessment

Functional status was registered according to classification of the New York Heart Association (NYHA) modified for pulmonary hypertension by World Health Organisation (WHO) (10). The exercise capacity was determined by six-minute walk distance (6-MWD) according to American Thoracic Society (11).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) and categorical variables as frequency (percentage). The correlations between each domain of SF-36 and the demographic and clinical variables were computed with Pearson or Spearman correlation. Comparisons between groups were made by parametric Student's *t*-test. Chi-square or Fisher's exact test were used to compare categorical data.

All variables identified within the grouped comparison as being significantly associated with the physical and mental component summary scores of the SF-36 ($p<0.05$) were selected for

Table I. Baseline characteristics of SLE disease.

Characteristics	Total (n=60)
Age (years)	33.6 ± 8.2
Duration of SLE (years)	5 (2,11)
Raynaud's phenomenon	38 (63.3)
Kidney involvement	8 (13.3)
Pericardial effusion	13 (21.7)
Accompanying connective tissue disease	17 (28.3)
Anti-dsDNA	31 (51.7)
Anti-Ro/SSA	22 (36.7)
Anti-La/SSB	8 (13.3)
Anti-U1 RNP antibody	32 (53.3)
Anti-phospholipid antibodies*	17/37 (45.9)
SLEDAI 0-4	35 (58.3)
Antimalarial treatment	11 (18.3)
Glucocorticoids	60 (100)
High dose of glucocorticoids (>30 mg/day)	24 (40.0)
Immunosuppressive drugs	38 (63.3)

Data given as mean±SD or n (%).
SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index.
*Anti-phospholipid antibodies including anti-cardiolipin, lupus anticoagulant and anti-β2-glycoprotein-I antibodies were not mandatory tests unless anti-phospholipid syndrome was suspected. The positivity of anti-phospholipid antibodies was defined as at least one positive result of these three assays.

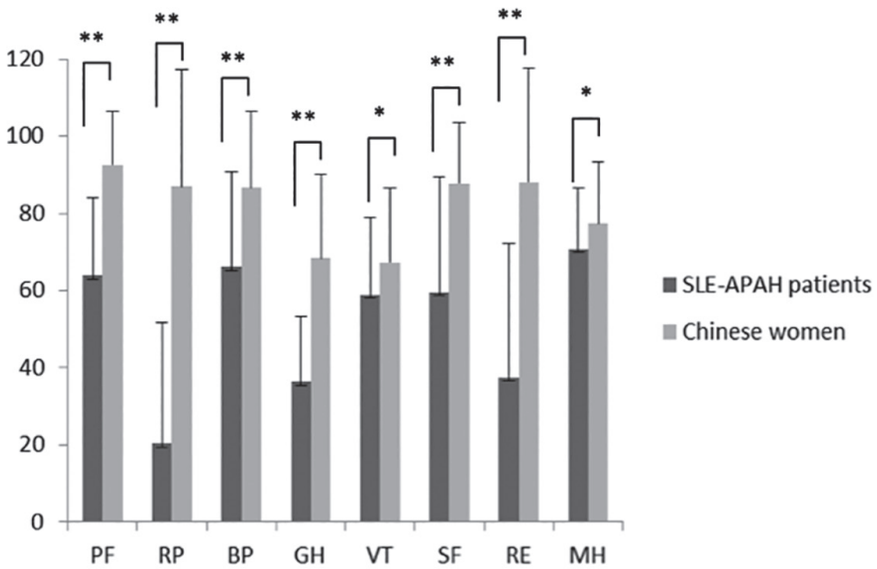

Fig. 1. SF-36 scores obtained in each domain from the study subjects and Chinese women.
Grey bars represent SF-36 scores of Chinese women from the previous report (9).
Black bars represent patients with SLE-APAH. Each bar indicates mean ± SD. *p<0.05, **p<0.001.
Abbreviations: See Tables.

the multivariate step-wise linear regression analysis. A two-tailed p-value of <0.05 was considered as statistically significant. Statistical analysis was performed using SPSS software (SPSS v. 19.0, SPSS, INC., IBM).

Ethics statement

The study protocol was approved by the Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. All participants signed an informed consent prior to enrolment.

Results

Characteristics of study participants

We enrolled 60 female participants with a mean age of 33.6 years (Table I). The mPAP for all participants was 43.6 mm Hg (Table II). At the time of enrollment, the median duration of SLE was 4 years. There were 35 patients (58.3%) with low disease activity (SLEDAI 0–4).

Scores for the 8 subscales were significantly lower in SLE-APAH patients than in Chinese women, ranging from a low of 20.4±31.4 for RP to a high of 70.8±15.9 for MH (Fig. 1). Of the eight categories, mean scores below 50 were observed in 3 domains including RP, GH, and RE. Average PCS and MCS scores were 46.4 and 56.9, respectively.

Relationship of demographic variables, disease-related factors and haemodynamic measures to HRQoL

No correlations between age and SF-36 scores were observed. A lower BMI (BMI <20.5) was associated with worse scores in GH, VT, MH, PCS, and MCS (Table III). No correlations were found between the duration of SLE and any SF-36 subscales or summary component scores. The scores for PF, BP, and PCS scales were significantly lower in patients with high SLEDAI (SLEDAI≥5) than patients with low SLEDAI (SLEDAI<5). The BP, VT, and PCS scores were lower for patients with lower mean blood pressure (BP) (<88mmHg) compared to those with higher mean BP (≥88mmHg) (Table III).

The haemodynamic measurements associated with a worse PCS score including lower CO (CO<4L/min), higher PVR (PVR≥10 Wood Units), higher End-diastolic volume (EDV>250ml), and lower mixed venous oxygen saturation (SvO2) (SvO2≤70%). Higher CO was the only haemodynamic variable associated with better MCS scores. Neither physical nor mental component summary scores correlated with mean right atrial or mean pulmonary artery pressures.

Predictors of HRQoL

Multivariate linear analysis revealed that active SLE was independently associated with lower PCS, otherwise, mean BP ≥ 88mmHg and CO ≥4L/min

Table II. Baseline characteristics of functional and haemodynamic measures.

Systolic blood pressure	(113 ± 15)
Diastolic blood pressure (mmHg)	(75 ± 10)
Heart Rate (beats/min)	82 ± 14
BMI (kg/m^2)	20.5 ± 2.9
WHO Class II	31 (51.7)
WHO Class III	24 (40.0)
WHO Class IV	1 (1.7)
6MWD (m)	439 ± 115
Right atrial pressure (mmHg)	4.8 ± 4.5
Mean PAP (mmHg)	43.6 ± 9.9
PVR (Wood Units)	9.6 ± 4.1
PVRI (Wood Units · m^2)	15.6 ± 6.8
CO (L/min)	4.1 ± 0.9
Cardiac index (L · min^{-1} · m^{-2})	2.5 ± 0.6
SvO2 (%)	70.9 ± 8.9

Data given as mean±SD or n (%).
BMI: body mass index; HR: heart rate; WHO: World Health Organisation; 6MWD: 6-min walking distance; PAP: pulmonary arterial pressure; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CO: cardiac output; SvO2: mixed venous oxygen saturation.

Table III. SF-36 subscales in patients with different invasive and non-invasive parameters.

	SLEDAI≥5 n=25	SLEDAI<5 n=35	*p*-value	BMI≥20.5 n=31	BMI<20.5 n=29	*p*-value	WHO I ~ II n=35	WHO III ~ IV n=25	*p*-value	BPmean ≥88mmHg n=26	BPmean <88mmHg n=34	*p*-value
PF	55.4±19.7	70.0±18.1	0.004	68.5±19.8	59.0±19.2	0.063	68.3±18.7	57.8±20.5	0.044	68.7±18.4	60.3±20.7	0.109
RP	15.0±29.8	24.3±32.4	0.262	22.6±31.2	18.1±32.0	0.585	25.0±33.2	14.0±28.0	0.183	27.9±34.2	14.7±28.3	0.108
BP	56.4±28.4	73.0±19.3	0.009	70.4±21.4	61.5±27.4	0.163	64.9±25.6	67.8±23.8	0.656	75.9±18.5	58.6±26.4	0.006
GH	31.7±15.8	39.9±17.0	0.065	43.4±16.7	29.0±13.9	0.001	41.0±15.0	30.1±17.6	0.013	39.9±11.6	33.9±19.8	0.172
VT	55.6±22.0	61.4±18.0	0.265	65.5±15.9	52.1±21.4	0.008	62.3±17.3	54.4±22.4	0.129	67.3±15.1	52.6±20.8	0.004
SF	54.2±30.7	63.5±29.2	0.240	65.6±30.4	53.3±28.5	0.111	60.6±30.8	58.2±29.3	0.761	64.5±32.1	55.9±28.1	0.271
RE	28.3±28.8	44.2±37.3	0.069	43.5±30.7	31.2±38.0	0.169	38.9±35.0	35.7±34.8	0.723	46.2±32.7	31.0±35.1	0.094
MH	70.2±17.9	71.2±14.5	0.820	77.2±11.3	64.0±17.4	0.001	70.7±14.0	70.9±18.6	0.975	74.0±15.5	68.4±16.0	0.175
PCS	39.6±18.0	51.3±15.4	0.009	51.2±15.8	41.3±17.8	0.026	49.8±17.4	41.7±16.6	0.077	52.4±14.5	41.9±18.3	0.019
MCS	52.6±16.4	59.9±21.0	0.137	62.0±17.7	51.4±19.9	0.031	57.2±20.6	56.4±17.9	0.877	59.8±19.0	54.6±19.6	0.312

Table III. SF-36 subscales in patients with different invasive and non-invasive parameters *(continued)*.

	PVR≥10 Wood U n=24	PVR<10 Wood U n=36	*p*-value	CO≥4 L/min n=31	CO<4 L/min n=29	*p*-value	EDV >250ml n=21	EDV ≤250ml n=39	*p*-value	SvO2>70% n=35	SvO2≤70% n=25	*p*-value
PF	59.0±21.8	67.2±18.3	0.117	71.3±15.9	56.0±21.1	0.003	62.5±20.6	64.6±20.1	0.706	70.1±16.0	56.8±21.1	0.006
RP	8.3±17.5	28.5±35.9	0.006	33.9±36.8	6.0±14.4	<0.001	10.0±18.8	26.3±35.3	0.025	29.3±34.0	10.0±24.9	0.005
BP	63.0±25.5	68.2±24.3	0.432	72.5±19.1	59.2±28.3	0.035	60.7±21.9	69.5±25.8	0.197	70.5±21.4	63.2±26.3	0.100
GH	31.7±17.8	39.6±15.7	0.074	42.7±13.6	29.8±17.7	0.002	30.7±16.2	39.5±16.9	0.060	42.7±14.9	29.7±14.9	<0.001
VT	55.6±20.1	61.3±19.6	0.285	63.5±19.2	54.1±19.6	0.065	53.3±15.5	61.8±21.5	0.120	64.6±19.5	52.8±18.7	0.009
SF	57.9±22.7	60.8±34.2	0.691	65.2±33.1	53.6±25.4	0.135	63.3±26.3	57.0±31.8	0.445	61.0±31.6	61.7±28.3	0.689
RE	25.0±31.5	45.9±34.5	0.021	52.8±32.7	21.3±29.2	<0.001	25.0±29.9	42.4±34.8	0.062	47.5±35	29.6±30.3	0.008
MH	74.0±17.0	68.7±14.5	0.206	69.3±15.7	15.7±16.3	0.452	75.6±10.8	67.9±17.5	0.078	72.2±15.0	70.8±17.5	0.415
PCS	39.8±12.9	50.9±18.7	0.014	55.1±16.1	37.2±13.6	<0.001	40.1±13.1	50.0±18.6	0.039	52.7±16.3	39.9±15.8	0.001
MCS	54.5±17.8	58.4±20.5	0.450	63.1±19.5	50.2±17.2	<0.001	55.1±18.8	57.1±19.6	0.704	62.3±19.9	51.4±15.8	0.009

Data given as mean±SD. PF: physical functioning; RH: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: Social functioning; RE: role emotional; MH: mental health; PCS: physical component summary; MCS: mental component summary; Bp: blood pressure; EDV: End-diastolic volume; For other abbreviations, see previous Tables.

were independently associated with higher PCS. Furthermore, patients with CO≥4L/min had significantly better MCS scores than those with lower CO (Table IV).

Table IV. Multivariate linear regression analysis of factors associated with PCS and MCS.

	Associated factors	B (95%CI)	*p*-value
PCS	SLEDAI ≥5	-11.04 (-18.61~ -3.47)	0.005
	BPmean ≥88 mmHg	8.32 (0.74 ~ 15.90)	0.032
	CO ≥4L/min	15.23 (7.63 ~ 22.82)	<0.001
MCS	CO ≥4L/min	10.84 (0.75~20.93)	0.036

CI: confidence interval; for other abbreviations, see previous Tables.

Discussion

All aspects of SF-36, both physical and mental, were impaired in SLE-APAH patients. Haemodynamic measurements and SLE activity were associated with HRQoL of SLE-APAH patients. Multivariate analysis showed that CO was independent predictor of PCS and MCS, active SLE and lower mean BP were also independent determinants for lower PCS.

SLE-APAH is a devastating condition that affects predominately young women in the prime of their life. Understanding HRQoL is important in the management of these patients. There are disease-specific HRQoL instruments developed for SLE (12, 13), although these questionnaires may be helpful for a better understanding of patient's perspective, none can be considered as sufficiently complete, furthermore, the use of generic instruments does allow comparisons to be made between SLE patients and healthy people.

The SF-36 is a validated generic measure of HRQoL that has been widely used in PAH and SLE patients, and accepted by clinical, patient, regulatory, and academic communities (14-19). Previous studies showed that HRQoL of SLE patients was consistently lower than that of matched healthy control subjects or the population norm (20, 21). In this study, significantly impaired HRQoL was found in all 8 domains of SF-36 in SLE-APAH patients. Although the SF-36 is sufficiently responsive to evaluate HRQoL in SLE (22), specific and generic questionnaires seemed to be complementary in capturing changing of symptoms and responsiveness of SLE patients, suggesting these tools used together maybe provide more information (23).

One interesting finding was a positive correlation of BMI with several SF 36 subscales including GH, VT, and MH as well as summary scores. However, Almehed *et al*. reported that BMI was negatively associated with PCS in SLE patients (20). Of note, patients in our study had relatively lower BMI than

the report mentioned above (20). In a recent study of Chinese systemic sclerosis patients, BMI was also found to have a positive correlation with physical HRQoL (24). While the reason of this relationship between BMI and HRQoL is unclear, a lower BMI may be an indicator of more severe disease. Patients with severe SLE-APAH are usually underweight as a result of reduced oral intake and malabsorption secondary to oral ulcer, gastrointestinal involvement, and depression.

In this study, active SLE (SLEDAI ≥5) correlated with lower scores for the PF, BP, and PCS. After adjusting other variables, SLEDAI was still independently associated with PCS. This was consistent with previous studies on the relationship of HRQoL and disease activities in SLE patients (15, 25, 26).

Haemodynamic parameters including CO and PVR were observed to be significantly associated with most of the SF-36 parameters in our study. Previous studies have reported that haemodynamic measurements did not correlate with HRQoL scores in PAH patients; however, subjects enrolled in these studies were mostly diagnosed of idiopathic PAH, and patients with SLE-APAH were not included (14, 17). It suggested that inflammation and autoimmunity play an important role in the pathogenesis and progression of SLE-APAH, besides of mechanisms similar to idiopathic PAH (27, 28).

Our results showed that CO was the strongest independent predictor for both physical and mental dimensions of HRQoL in SLE-APAH patients, while SLE disease activity was only independently associated with PCS scores. This suggests that haemodynamic variables are of greater importance in determining HRQoL of SLE-APAH patients than SLE disease activity. Therefore, appropriate recognition and treatment for PAH are essential for improving HRQoL in SLE-APAH patients. These findings, however, require confirmation by further studies with larger sample.

There were several limitations. First, HRQoL can be affected by many residual confounding factors (such as socioeconomic status, education) that we have not analysed, which might have caused biases. Second, the cross-sectional nature of this study limited our ability to understand causal mechanisms. Third, the relatively small sample and hospital-based cohort without a matched control group of SLE patients without PAH might decrease the reliability of our results.

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