EFFECT OF GENDER ON HEALTH RELATED QUALITY OF LIFE IN SARCOIDOSIS

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ABSTRACT. *Background*: Sarcoidosis has different phenotypic manifestations which may have a diverse effect on functional status and quality of life. There are few studies in sarcoidosis addressing gender disparity and its effect on Health-Related Quality of Life (HRQL) and functional status. *Objective*: The purpose of this study was to investigate the effects of gender on HRQL and to identify associations between poor HRQL and the results of common clinical tests. *Design*: We assessed HRQL for 221 patients with sarcoidosis in a prospective, cross-sectional study using the Short Form-36 Health Survey and Sarcoidosis Health Questionnaire. We evaluated the association between the scores of these measures with patient characteristics, pulmonary function test (PFT) and 6-minute walk test (6MWT) data. *Results*: Women had lower scores than men on every measure of HRQL and weaker associations to findings from PFT and 6MWT. Multivariate linear regression analyses demonstrated that reduced 6MWT distance and DLCO were significantly associated with poor HRQL in both genders but the sensation of dyspnea played a significant role in women only. *Conclusions*: Our results indicate that women with sarcoidosis have a lower HRQL score and a greater degree of functional impairment than men. The factors that are associated with poor HRQL differ by gender. Predictors of poor HRQL include reduction in DLCO and 6MWT distance and an increased sensation of dyspnea. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 96-102)*

KEY WORDS:

INTRODUCTION

Sarcoidosis is a chronic, multisystem disease with a highly variable phenotypic expression, natural history, prognosis, and response to treatment (1). It is well known that the clinical picture of sarcoidosis depends on the patient's gender, race and ethnic-

ity, duration and activity of illness, and the site and extent of organ involvement (1, 2). This varied array of potential symptoms leads to a diverse effect on both physical and functional status.

Quality of life may be influenced by numerous factors. Several studies have been carried out to identify predictors of poor quality of life. Associations have been noted between measures of functional status and the extent of organ involvement, disease activity and 6-minute walk distance (3-5). Other aspects of the disease, such as degree of obstruction on spirometry, ethnicity, duration of disease and treatment with steroids, have shown mixed results and are not reliable predictors of poor quality of life (6-11).

Although it is recognized that there are differences in the mode of presentation and clinical characteristics between the sexes, there is a paucity of studies addressing gender disparity and its effect on Health-Related Quality of Life (HRQL) and functional status. The purpose of this study was to identify associations between HRQL measures and objective clinical data derived from 6-minute walk and pulmonary function testing and to compare such associations based on gender.

Methods

Patients with sarcoidosis were prospectively recruited from the Sarcoidosis and Interstitial Lung Disease Clinic at Wayne State University/Detroit Medical Center in Detroit, Michigan. Adult patients between 18 and 75 years with a biopsy proven diagnosis of sarcoidosis for more than 3 months were invited to participate between December 2005 and May 2009. Patients who were pregnant, organ transplant recipients and those with known COPD, active cancer, or severe cardiomyopathy were excluded to avoid confounding comorbidities. Patients were not invited to participate if they were not fluent in English or had a physical impairment that prevented the completion of questionnaires. The Institutional Review Board of Wayne State University approved this study and informed consent was obtained from all participants. There was no external funding for this study.

Clinical assessment and HRQL measurements

All participants self-administered two questionnaires, the Sarcoidosis Health Questionnaire (SHQ) and the Medical Outcomes Study 36-item Short Form survey (SF-36) (9, 12). The SF-36 is a generic survey of health status that assesses eight health concepts, including bodily pain, mental health, vitality and physical, social and role functioning (12). The online scoring system was used to normalize individual scores and these values were used for statistical analyses (13). The SHQ is a disease-specific HRQL measure for sarcoidosis that has 29 questions with three domains: daily, physical and emotional functioning (9). The scores were calculated as previously described (9).

Variables chosen for investigation as possible indicators of health status included chest radiography, pulmonary function test (PFT) and 6-minute walk test (6MWT) data. Chest radiography was interpreted as stage 0-4 (1,14). PFTs were performed in a licensed laboratory following guidelines established by the American Thoracic Society (15). All studies were performed as described previously (16). All patients included in analyses completed at least one 6MWT, performed by a licensed respiratory therapist following a standardized protocol (17). 6MWT data used in analyses included Borg Dyspnea Scale score (BDSS), oxygen saturation, 6-minute walk distance (6MWD) and the percent-predicted distance. The oxygen saturation was measured and percent-predicted 6MWD was calculated as described previously (16).

Statistical Analysis

Continuous variables are expressed as mean ± SEM. Means were compared using the Student's t-test. Discrete variables were compared using Fisher exact test. Pearson correlation coefficient (r) was calculated to measure the relationship between the clinical variables and the SHQ and SF-36 scores. Baseline characteristics, SF-36, SHQ scores, PFT and 6MWT data were compared by gender using two-sample Student's t-tests. Multivariate linear regression analyses were performed to examine the association between HRQL measures and PFT and 6MWT values for the whole group and for each gender separately using a stepwise, descending method for factors with significance on univariate analyses. The analysis was normalized for age, BMI and smoking status. Data processing and analyses were performed using standard statistical software (SPSS for Windows, version 18.0). Statistical significance was defined as p value < 0.05.

Results

221 patients with a tissue proven diagnosis of sarcoidosis consented to participate in the study and completed both the SHQ and SF-36 questionnaires on the same day, in addition to a PFT and 6MWT. Table 1 presents patient characteristics. The average age of the study group was 46 years and was not sig-

Table 1. Patient characteristics

Age (Mean±SD)	46±10.6	Disease, N (%)	
BMI (Mean±SD)	32±8.2	Inactive	61 (27.6)
Gender, N (%)		Active/Symptomatic†	160 (72.4)
Male	64 (29)	Organ Involvements N (%)	
Female	157 (71)	Lung	205 (93)
Race, N (%)		Skin	60 (27.1)
African American	200 (90)	Eye	33 (15)
White	21 (10)	Heart	11 (5)
CXR stage, N (%)		Liver	19 (8.2)
0	19 (8.6)	CNS	12 (5)
1	40 (18.1)	PAH*	27 (12.2)
2	86 (41.5)	Medication, N (%)	
3	30 (14)	Steroidal	76 (33.7)
4	46 (18.2)	IMD‡	68 (42.3)
Non-smokers	167 (76)	Steroidal+IMD	63 (49.3)

Values are means unless otherwise noted. N=Number of patients, parenthesis percent.
* PAH: pulmonary arterial hypertension, diagnosed by right cardiac catheterization.
† Active defined as an increased requirement for steroid in last 6 months.
‡ IMD: Immune modifying drugs; methotrexate, azathioprine and others.

nificantly different between men and women. 76% of subjects were nonsmokers (167), 71% were female (157) and 90% were African American (200). The average BMI was 32, but there was a significant difference between men and women. The mean BMI for female subjects was 33.5 while it was 28 in male subjects (p < 0.001), suggesting obesity is much more prevalent in our female population. The majority of patients had active disease (72%), with 34% requiring steroid therapy and 49% requiring both steroids and immune modulating medications. In 205 patients (93%), pulmonary involvement was observed. Thirty-two patients (14.5%) required oxygen supplementation, among them 27 (84%) were female.

The PFT and 6MWT results are demonstrated in Table 2 and differentiated based on gender. For PFTs, there were no significant differences between genders except that male subjects had significantly lower FEV1/FVC (p = 0.007) values, while female subjects had lower DLCO values (60% vs. 64.5%; p = 0.049). Men had a significantly higher 6MWD (p = 0.001) but significance was not retained when subjects were analyzed by their percent-predicted 6MWD. The BDSS at 6 minutes was significantly higher (worse) for women (p = 0.04).

Men had significantly higher (better) HRQL scores than women, as demonstrated in Table 3. On every aspect of the SF-36, men had better scores than women with the most prominent differences noted in the areas relating to physical health. There was a less significant difference between the scores of men and women on the total SHQ. There was no difference between male and female subjects' emotional and daily SHQ scores but there was a highly

Table 2. Gender and PFT /6MWT values

Variables	Female		Male		
	N	Mean ± SD	N	Mean ± SD	p
BMI	157	33.5 ± 8.5	64	28 ± 5.3	<0.001†
Age	157	45.2 ± 11	64	43.8 ± 8	0.1
FVC%	157	73 ± 17	64	71 ± 20	0.4
FEV1%	157	74 ± 18	64	68 ± 20	0.09
FEV1/FVC	157	77.8 ± 9	64	73 ± 12	0.007†
TLC%	157	78 ± 15	64	80 ± 17	0.23
DLCO%	157	60 ± 18	64	64.5 ± 21	0.049*
6MWD	157	409 ± 93	64	470 ± 91	0.001†
6MWD%	157	76 ± 16	64	73 ± 15	0.15
BDSS 0 minutes	157	1.8 ± 1.6	64	1.5 ± 2.6	0.26
BDSS 6 minutes	157	4.8 ± 1.8	64	3.7 ± 0.9	0.04*

* p < 0.05; † p < 0.01

Table 3. Effect of gender on HRQL

Variables	Female		Male		
	N	Mean ± SEM	N	Mean ± SEM	p
Total SF-36	157	42 ±1.80	64	51.5 ± 3.1	0.001†
Physical Health	157	38 ± 1.8	64	47 ± 2.9	0.009†
Mental Health	157	44 ± 1.75	64	52 ± 3.0	0.001†
PCS	157	35 ± 0.8	64	38 ± 1.3	0.001†
MCS	157	40 ± 0.8	64	43 ± 1.7	0.02*
Total SHQ	157	3.7 ± 0.07	64	4.2 ± 0.1	0.01*
Physical SHQ	157	3.4 ± 0.09	64	3.8 ± 0.13	0.008†
Emotional SHQ	157	3.8 ± 0.08	64	4.1 ± 0.1	0.5
Daily SHQ	157	3.8 ± 0.07	64	4.1 ± 0.2	0.1

* $p < 0.05$; † $p < 0.01$

significant difference noted between genders on the physical scores.

Pearson correlation was used to measure the relationship between the clinical variables and the SHQ and SF-36 scores in total and by gender. The results were similar for the SHQ and the SF-36 with no significant differences between the two measures. The results of analysis using the SF-36 are shown in Table 4. Different clinical variables were predictive of HRQL between men and women. For men, the variables with the highest correlation to HRQL scores were DLCO and 6MWD, followed closely by the BDSS at 0 and 6 minutes. No other component of the PFT was significantly associated with HRQL. For women, the variables with highest correlation to HRQL scores were the BDSS at 0 and 6 minutes, closely followed by the 6MWD. Both oxygen saturation at the end of the 6MWT and DLCO showed a weaker correlation to SF-36 scores.

Three sets of multivariate regression analyses were performed to predict total SF-36 and SHQ scores using variables significant in univariate analy-sis and adjusting for BMI, smoking and age. Similar results were found for each HRQL measure and the results of the analyses with SF-36 are presented in Table 5. First, we performed regression analysis to predict SF-36 scores for the whole group. The predictive value was R = 0.59, with BDSS at 6 minutes (p < 0.001; CI -5.1, -1.6), DLCO (p = 0.001; CI -.076, -0.36) and percent-predicted 6MWD (p = 0.003; CI 0.14, 0.54) demonstrating a significant association with SF-36 scores. Similar analysis was performed for each gender. The same variables (BDSS at 6 minutes, DLCO and percent-predicted 6MWD) were significant for the prediction of SF-36 scores for females but produced a lower R value (R = 0.57). Interestingly, when the analysis was performed for males, a much higher R value (R = 0.71) was attained and this was associated only with per-cent-predicted 6MWD (p = 0.015; CI 0.2, 1.1) and DLCO (p = 0.04, CI -2.6, -0.1). BDSS at 6 minutes did not retain significance for men on multivariate analysis.

Table 4. Gender disparity and correlation of SF-36 scores and physiological parameters

Variable	Female		Male	
	r-value	p-value	r-value	p-value
FEV1(L)	0.14	NS	0.21	NS
$DL_{CO\%}$	0.18	0.03*	0.41	< 0.001†
6MWD (m)	0.32	< 0.001†	0.41	< 0.001†
Oxygen sat at 6 minutes	0.18	< 0.01†	0.2	NS
BDSS 0 minutes	-0.34	< 0.001†	0.38	< 0.001†
BDSS 6 minutes	0.36	< 0.001†	0.39	< 0.001†

* Correlation is significant at $p < 0.05$ level (2-tailed test)
† Correlation is significant at $p < 0.01$ level (2-tailed test)
NS Not significant

Table 5. Multiple regression model to predict SF-36

	Whole group (R=0.59)			Females (R=0.57)			Males (R=0.71)		
	Beta	95% CI	p-value	Beta	95% CI	p-value	Beta	95% CI	p-value
Constant	76	-6.1, 31.4	0.069	34	-59, 12.1	0.4	97	-27, 120	0.08
DLCO%	-1.46	-0.76, -0.36	0.001†	-1.48	-0.79, -0.16	0.004†	-0.9	-2.6, -0.1	0.04*
6MWD%	0.4	0.14, 0.54	0.003†	0.28	0.04, 0.53	0.023*	1.58	0.2, 1.1	0.015*
BDSS 0	-1.9	-4.4, 0.6	0.14	-1.5	4.4, 1.5	0.3	-2.5	-8.2, 2.6	0.4
BDSS 6	-3.4	-5.1, -1.6	<0.001†	-3.8	-5.6, -1.7	<0.001†	1.5	0.12, 1.1	0.3

* p < 0.05; † p < 0.01

Discussion

Significant differences in HRQL between the genders have been noted in some cardiac and respiratory diseases (18-23). However, there is a paucity of literature regarding the effect of gender on HRQL in sarcoidosis. Based on the limited data available, women with sarcoidosis appear to have a more severe impairment in HRQL than men (10, 11). The aim of this study was to further evaluate the gender disparity in HRQL among patients with sarcoidosis. Additionally, we analyzed the components of commonly used clinical tests to identify any associations with impaired HRQL.

Our study demonstrated significant differences between male and female subjects with sarcoidosis in terms of the effects of the disease on health, functional status and quality of life. Female patients scored significantly lower on the HRQL measures SF-36 and SHQ than men and the differences were most profound in the measures related to physical health. This concurs with a previous study that identified being female as a significant negative predictor of HRQL (10). Male subjects with sarcoidosis have previously been shown to score better than females in areas of physical and psychological health (11). In our study, men had significantly better HRQL scores than women in both the physical and mental health domains on the generalized HRQL measure, the SF-36, but only in areas related to physical health on the sarcoidosis-specific HRQL measure, the SHQ.

Our data also suggest that there are gender-specific influences that are associated with impaired HRQL. The factors that predict HRQL in COPD differ by gender and this appears to be true as well for sarcoidosis (22,23). Factors that have been associated with poor HRQL for men with COPD include dyspnea, exercise capacity as calculated by 6MWD, degree of obstruction and hyperinflation, and the presence of comorbidities. In women with COPD dyspnea, oxygenation and 6MWD are the most significant predictors of HRQL with other factors including anxiety and depression also contributing to the impairment (20). In our study, the best predictors of poor HRQL for men with sarcoidosis were DLCO and 6MWD and these factors were strongly associated with HRQL scores. This implies that factors that limit physical capacity are the most influential in determining HRQL for male gender. For women, the best indicator of poor HRQL was the BDSS at 6 minutes, with DLCO and 6MWD also significantly associated with HRQL scores. This suggests that the perception of dyspnea is a strong influential factor in determining poor HRQL in women with sarcoidosis. Our results are in agreement with previous studies showing female patients with COPD and interstitial lung disease are more likely than males to report severe dyspnea, and suggest that women are intrinsically more sensitive to the sensation of dyspnea (20-22).

The common clinical factors that were studied in our population had a much stronger association with the HRQL scores for males than for females (R = 0.71 vs. R = 0.57) and were better predictors of poor HRQL in men. This suggests that factors besides those evaluated in the present study are influencing our female patients' functional status. In COPD, women with evidence of milder disease than men still had more exacerbations, more dyspnea and poorer HRQL scores (24,25). These women scored poorer in areas of mental health and in bodily pain suggesting that variables other than lung function are influencing the HRQL scores (25). Similar factors are likely to be associated with poor HRQL in female sarcoidosis patients.

Multiple factors may be contributing to a functional impairment in female sarcoidosis patients. Women are more likely to report symptoms than

men, which may suggest that either they are more expressive or that they are more symptomatic (11). Women also tend to suffer from more comorbid chronic diseases that may further alter the expression of sarcoidosis (26). The greatest impact on HRQL in sarcoidosis appears to be caused by nonspecific symptoms that may be hard to objectify, such as fatigue, depression and sleep disturbance (27, 28). Gender differences have previously been demonstrated in other areas that are difficult to objectively define such as pain, body image and amount of positive feelings (11). Depression, fatigue and pain are likely major contributors to the poor HRQL in female sarcoidosis patients. 60% of sarcoidosis patients in one study reported clinical symptoms of depression and the presence of depression was strongly associated with female sex (28). Fatigue has also been demonstrated to be strongly related to all aspects of HRQL, is an important independent predictor of HRQL in both the physical and mental health domains, and is not related to respiratory functional impairment (10, 29). Although pain is highly prevalent in sarcoidosis, it remains poorly studied. The presence of pain has been shown to be associated with a lower HRQL and pain was associated with female sex (30). Although, we did not evaluate fatigue using a standardized fatigue questionnaire, a limited evaluation of fatigue by scoring two questions from the daily physical section of SHQ found female patients had lower scores (worse) for fatigue compared to male patients and this correlated highly with the SF-36 scores for females but less so for males. This finding confirms previous observations that lack of energy and fatigue have a significant impact on HRQL scores in sarcoidosis (4, 7, 10). However, no previous study analyzed the gender differences in this measurement. Interestingly, a comparison study among Dutch and American sarcoidosis subjects found a similar prevalence of fatigue between these two populations but a lack of clinical relation to demographic and clinical parameters in the Dutch but not in the US patients (31).

HRQL is not only affected by disease severity, but also by the social and occupational limitations imposed by the disease. Ethnicity may impact HRQL in conditions like sarcoidosis due to its influence on both disease severity and access to healthcare. One limitation of this study is that the sample consists almost entirely of African American women. Because of minimal variation in ethnicity

there may be racial differences not detected from this data set. Additionally, one study of depression in sarcoidosis demonstrated that African-American women possessed an odds ratio 4 times greater than African-American men for depression (27). Since depression was not studied separately, it is unknown if a high prevalence of depression may have impacted the HRQL scores.

This study is also limited by the fact that we could not account for all comorbid conditions that may affect patients with sarcoidosis despite our attempts to exclude confounding comorbidities. Among the study patients, 12% had known pulmonary hypertension as confirmed by right-sided cardiac catheterization and they were not excluded from participation. Also, women have demonstrated significantly more clustering of chronic illnesses than men and it is unclear how these comorbidities may influence the HRQL of our patients.

HRQL is an important component in the evaluation of patients with chronic disease. Further studies examining the role of gender differences among sarcoidosis patients in HRQL are necessary. The role of nonspecific symptoms such as pain, fatigue and sleeping disturbances in the impairment of HRQL specifically needs to be addressed, especially for female subjects. New approaches may be needed that target different areas of impairment to achieve maximum benefit from treatment.

Our study demonstrated that the results of commonly used clinical tests, such as the PFT and 6MWT, show a much stronger association with HRQL scores for men than for women. For both sexes, the only variable from PFT that was significantly associated with HRQL was the DLCO, suggesting the degree of obstruction or restriction is less influential on functional status and not a good predictor of functional status. The 6MWT appears to be a better test for this purpose, with the percent-predicted 6MWD significantly associated with HRQL measures for both sexes and the degree of dyspnea at the end of the 6MWT most significantly related to poor HRQL scores for women.

In conclusion, our study was performed to identify associations between HRQL measure scores and objective, commonly used clinical testing and to identify specific associations that may differ based on gender. Our results indicate that women have a much greater degree of functional impairment than men

with sarcoidosis. Additionally, the factors that are associated with poor HRQL differ by gender. Factors that limit physical abilities appear to be the most influential in determining HRQL for males. For females, the perception of dyspnea and fatigue were most influential factors in determining poor HRQL. Other nonspecific symptoms are also likely contributing to such impairment. PFT measurements are not strongly associated with these assessments of clinical status and quality of life. This suggests that our reliance on PFT data in determining treatment goals is not likely to improve sarcoidosis patients' quality of life and that new measures to target treatment are needed and may need to be gender-based. Additionally, further studies are needed to evaluate whether there is any utility in developing a gender-specific questionnaire assessing quality of life.

ACKNOWLEDGMENTS

REFERENCES

1. Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999; 160 (2): 736-55.

2. Baughman RP, Tierstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164 (10 Pt 1): 1885-9.

3. Gvozdenovic BS, Mihailovic-Vucinic V, Ilic-Dudvarski A, Zugic V, Judson MA. Differences in symptom severity and health status impairment between patients with pulmonary and pulmonary plus extrapulmonary sarcoidosis. Respir Med 2008; 102 (11): 1636-42.

4. De Vries J, Drent M. Quality of life and health status in sarcoidosis: a review of the literature. Clin Chest Med 2008; 29 (3): 525-32, ix.

5. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. Chest 2007; 132 (1): 207-13.

6. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. Health-related quality of life of persons with sarcoidosis. Chest 2004; 125 (3): 997-1004.

7. Wirnsberger RM, de Vries J, Breteler MH, van Heck GL, Wouters EF, Drent M. Evaluation of quality of life in sarcoidosis patients. Respir Med 1998; 92 (5): 750-6.

8. Antoniou KM, Tzanakis N, Tzouvelekis A, et al. Quality of life in patients with active sarcoidosis in Greece. Eur J Intern Med 2006; 17 (6): 421-6.

9. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. The Sarcoidosis Health Questionnaire: a new measure of health-related quality of life. Am J Respir Crit Care Med 2003; 168 (3): 323-9.

10. Michielsen HJ, Peros-Golubicic T, Drent M, De Vries J. Relationship between symptoms and quality of life in a sarcoidosis population. Respiration 2007; 74 (4): 401-5.

11. De Vries J, Van Heck GL, Drent M. Gender differences in sarcoidosis: symptoms, quality of life, and medical consumption. Women Health 1999; 30 (2): 99-114.

12. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992; 30 (6): 473-83.

13. SF-36. Scoring and interpreting data. Available from: http://www.sf-36.org

14. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. Br Med J 1961; 2 (5261): 1165-72.

15. Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS Task Force: Standardization of spirometry. Eur Respir J 2005; 26 (2): 319-38.

16. Bourbonnais JM, Samavati L. Clinical predictors of pulmonary hypertension in sarcoidosis. Eur Respir J 2008; 32 (2): 296-302

17. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166 (1): 111–7.

18. Emery CF, Frid DJ, Engebretson TO, et al. Gender differences in quality of life among cardiac patients. Psychosom Med 2004; 66 (2): 190-7.

19. Norris CM, Ghali WA, Galbraith PD, Graham MM, Jensen LA, Knudtson ML; APPROACH Investigators. Women with coronary artery disease report worse health-related quality of life outcomes compared to men. Health Qual Life Outcomes 2004; 2: 21.

20. Han MK, Postma D, Mannino DM, et al. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med 2007; 176 (12): 1179-84.

21. Han MK, Swigris J, Liu L, et al. Gender influences health-related quality of life in IPF. Respir Med 2010; 104 (5): 724-30.

22. Katsura H, Yamada K, Wakabayasi R, Kida K. Gender-associated differences in dyspnea and health-related quality of life in patients with chronic obstructive pulmonary disease. Respirology 2007; 12 (3): 427-32.

23. de Torres JP, Casanova C, Hernandez C, et al. Gender associated difference in determinants of quality of life in patients with COPD: a case series study. Health Qual Life Outcomes 2006; 4: 72

24. de Torres JP, Casanova C, Hernandez C, Abreu J, Aguirre-Jaime A, Celli BR. Gender and COPD in patients attending a pulmonary clinic. Chest 2005; 128 (4): 2012-6.

25. Martin A, Rodriguez-Gonzalez Moro JM, Izquierdo JL, Gobartt E, de Lucas P; VICE Study Group. Health-related quality of life in outpatients with COPD in daily practice: the VICE Spanish study. Int J Chron Obstruct Pulmon Dis 2008; 3: 683-92.

26. Westney GE, Habib S, Quarshie A. Comorbid illnesses and chest radiographic severity in African-American sarcoidosis patients. Lung 2007; 185 (3): 131-7.

27. De Vries J, Drent M. Quality of life and health status in interstitial lung diseases. Curr Opin Pulm Med 2006; 12 (5): 354-8.

28. Chang B, Steimel J, Moller DR, et al. Depression in sarcoidosis. Am J Respir Crit Care Med 2001; 163 (2): 329-34.

29. Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. Chest 2006; 130 (4): 989-94.

30. Hoitsma E, De Vries J, van Santen-Hoeufft M, Faber CG, Drent M. Impact of pain in a Dutch sarcoidosis patient population. Sarcoidosis Vasc Diffuse Lung Dis 2003; 20: 33-9.

31. de Kleijn WP, Elfferich MD, De Vries J, et al. Fatigue in sarcoidosis: American versus Dutch patients. Sarcoidosis Vasc Diffuse Lung Dis 2009; 26 (2): 92-7.