RHEUMATOLOGY

Rheumatology 2013;52:173–179
doi:10.1093/rheumatology/kes311
Advance Access publication 28 November 2012

Original article

Clinical pulmonary involvement in primary Sjögren's syndrome: prevalence, quality of life and mortality—a retrospective study based on registry data

Øyvind Palm[1], Torhild Garen[1], Tone Berge Enger[2], Janicke Liaaen Jensen[2], May-Brit Lund[3,4], Trond Mogens Aaløkken[5] and Jan Tore Gran[1,4]

Abstract

Objective. The aim of the present study was to describe the prevalence of clinical pulmonary manifestations in primary SS (pSS), and based on registry data, to assess quality of life (QoL) and mortality in these patients.

Methods. Patients with pSS consecutively included in the Norwegian systemic CTD and vasculitis registry (NOSVAR) were investigated for pulmonary manifestations when presenting with clinical pulmonary symptoms. Pulmonary involvement was defined as typical abnormalities identified with high-resolution CT (HRCT) and/or pulmonary function tests (PFTs).

Results. Among patients referred from our primary area, Oslo ($n = 117$), lung involvement was found in 26 patients (22%). In our total cohort ($n = 216$), 59 patients (27%) were affected. A higher rate of pulmonary complications and trends towards longer disease duration and higher age indicated a selection of more complicated cases referred from outside our primary area. Abnormal HRCTs were found in 50 patients (23%) and PFTs in 34 patients (16%). The Medical Outcomes Study 36-Item Short-Form Health Survey Physical Functioning subscore, was significantly reduced in patients with lung involvement ($P = 0.03$). Furthermore, a 4-fold increased risk of dying after 10 years of disease among patients with lung involvement ($n = 10$, 17%) compared with those without lung involvement ($n = 7$, 4.5%) ($P = 0.002$) was found.

Conclusion. We found a high population-based prevalence of clinical pulmonary involvement (22%) among patients with pSS. Moreover, patients with lung involvement had reduced QoL represented by the subscale Physical Functioning, and mortality was increased.

Key words: Sjögren's syndrome, pulmonary disease, population register, computed tomography, mortality, quality of life.

Introduction

Primary SS (pSS) is one of the most common CTDs, affecting females about 20 times more often than males [1]. The prevalence of pSS in population-based studies from our region is estimated to be between 0.05% and 3.9% [2, 3]. Typical features of the disease are reduced function of exocrine glands with symptoms of dryness from eyes, mouth and genitalia caused by infiltration of inflammatory lymphocytes in affected glandular and extraglandular organs. Most patients present with serum anti-Ro/SSA- and/or anti-La/SSB antibodies [4]. An excess mortality due to lymphoproliferative malignancy has been found [5].

Pulmonary manifestations are among the most prevalent extraglandular complications, with reported prevalence varying widely (9–75%), depending on the methods of detection and patient selection [6–8]. Lung involvement in pSS may be based on clinical symptoms and high-resolution CT (HRCT) findings [9] or supplemental investigations with pulmonary function tests (PFTs), bronchoalveolar

[1]Department of Rheumatology, Oslo University Hospital, [2]Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, [3]Department of Respiratory Medicine, Oslo University Hospital, [4]Institute of Clinical Medicine, University of Oslo and [5]Department of Radiology, Oslo University Hospital, Oslo, Norway.

Submitted 2 May 2012; revised version accepted 1 October 2012.

Correspondence to: Øyvind Palm, Department of Rheumatology, Clinic for Cancer, Surgery and Organ Transplantation, Oslo University Hospital Rikshospitalet, PO Box 4950 Nydalen, 0424 Oslo, Norway.
E-mail: opalm@ous-hf.no

CLINICAL SCIENCE

lavage (BAL) and histopathology [10]. However, plain chest radiographs have a low sensitivity to detect early lung involvement [11], whereas studies systematically performing HRCTs, even in asymptomatic patients, report higher rates of pulmonary abnormalities compared with studies based on clinical symptoms [9, 12]. Initial symptoms of lung involvement in pSS are dry cough or dyspnoea at exertion, occasionally accompanied by chest pain. Abnormal findings at auscultation are often absent, but inspiratory bibasilar crackles are found in some cases [10]. HRCT may identify ground-glass attenuation, thin-walled cysts, honeycombing, reticular pattern, small nodules and enlarged mediastinal lymph nodes [10, 13]. PFT may reveal reduced levels of forced vital capacity (FVC), reduced forced expiratory volume in 1 s (FEV1) or reduced single breath transfer factor of the lung for carbon monoxide (DL_{CO}) [10]. Some publications have found that lung involvement in pSS is usually mild and stable [14], while others describe a far more severe disease complication with a 5-year mortality of 16% [15], indicating that more studies of prevalence and severity of pulmonary involvement in pSS are needed.

Previous studies have shown that health-related quality of life (QoL) may correlate with the level of autoimmunity [16], and that extraglandular manifestations in general may be essential for impaired QoL in patients with pSS. However, data focusing on associations between lung involvement and QoL are rare [17].

The aim of the present study was to describe the prevalence of clinical pulmonary manifestations in pSS. We also wanted to assess QoL and mortality in patients with and without symptoms and objective findings of pulmonary manifestations.

Patients and methods

Patients

The Norwegian systemic CTD and vasculitis registry (NOSVAR) is a research registry for studying systemic CTDs and vasculitides. The patients are consecutively recruited from our department, which is the only rheumatological department serving patients with pSS within the city of Oslo (population 611 000). We also represent a regional referral centre for CTDs, serving south-eastern Norway with 2.6 million inhabitants. The patients presented in the study were included in NOSVAR since the start of registration in 1999 until final evaluation in December 2010 or until death. Registry data included age, gender, classification criteria, disease duration and complications. In total, 344 patients with a diagnosis of pSS were identified. Of these, 216 (63%; 199 females, 17 males) fulfilled the American–European Consensus Group (AECG) criteria for pSS [18] and were included in the present study. Patient characteristics are listed in Table 1. One hundred and seventeen patients (54%)

Table 1 Characteristics of patients with ($n = 59$) and without ($n = 157$) pulmonary involvement

	Pulmonary involvement			
	Yes	No	*P*-value	Total
All patients, *n* (%)	59 (27)	157 (73)	–	216 (100)
Patients from our primary area, *n* (%)	26 (22)	91 (78)	–	117 (100)
Females, *n* (%)	54 (92)	145 (92)	0.549	199 (92)
Age at evaluation, mean (S.D.), years	64 (13)	61 (14)	0.163	62 (14)
Age at diagnosis, mean (S.D.), years	51 (14)	51 (14)	0.744	51 (14)
Disease duration,[a] mean (S.D.), years	11 (6)	12 (9)	0.239	11 (7)
Smoker (ever), *n* (%)	19/41[b] (46)	50/121[b] (41)	0.705	69/162[b] (43)
anti-Ro/SSA, *n* (%)	48 (81)	117 (75)	0.382	165 (76)
anti-La/SSB, *n* (%)	31 (54)	56 (35)	0.038	87 (40)
anti-Ro/SSA and anti-La/SSB, *n* (%)	31 (54)	56 (35)	0.038	87 (40)
IgG, mean (S.D.), g/l	14 (7)	13 (4)	0.108	14 (5)
ESR, median (IQR), mm/h	16 (12–30)	14 (9–28)	0.136	16 (9–27)
Lymphopenia $<1.1\times10^9$/l (%)	12/54[b] (22)	13/143[b] (9.1)	0.014	25/197 (13)
Complement C3 <0.7 g/l (%)	3/40[b] (7.5)	8/123[b] (6.5)	0.732	11/163[b] (6.7)
Complement C4 <0.10 g/l (%)	2/40[b] (5.0)	5/123[b] (4.1)	0.681	7/163[b] (4.3)
Pathological lip biopsy with focus score $\geqslant 1$ (%)	29/31[b] (94)	84/93[b] (90)	0.729	113/124 (91)
Pathological saliva production, $\leqslant 1.5$ ml/15 min (%)	42/49[b] (86)	123/141[b] (87)	0.808	165/190 (87)
Disease history				
Salivary gland enlargement, *n* (%)	15/52[b] (29)	27/113[b] (24)	0.627	42/165 (25)
RP, *n* (%)	13 (22)	16 (10)	0.024	29 (13)
Purpura, *n* (%)	3 (5.1)	7/156[b] (4.5)	1.0	10/215[b] (4.7)
Lymphoma, *n* (%)	4 (6.8)	6 (3.8)	0.466	10 (4.6)

The laboratory data represent the results by the last investigation. [a]Since diagnosis. [b]Incomplete data due to non-completed questionnaires and parameters not investigated in all patients.

were referred from our primary area and 99 patients (46%) from other areas. After referral, most patients were regularly followed up at our department. Additional information for this study, including mortality and causes of death, were assessed by the Norwegian National Registry and by reviewing hospital records, respectively. Additionally, questionnaires asking information concerning current smoking and QoL [the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)] were mailed to all 159 patients who were alive and assessed to be capable of responding single-handedly. The questionnaires were returned by 158 patients (73% of the total cohort).

Pulmonary involvement

A disease history of pulmonary manifestations, defined as typical symptoms, including dry cough or dyspnoea at exertion, was obtained from all patients. When symptoms of lung involvement were present, investigations including radiographs of the chest, HRCT, PFTs or combinations of these were conducted at our hospital. Pulmonary involvement was defined as pulmonary symptoms and either abnormal findings on HRCT, including reticular pattern (i.e. fibrosis less coarse than honeycombing), lung cysts, ground-glass attenuation and honeycombing or impaired PFT, in accordance with recent recommendations [19, 20]. All HRCTs were evaluated in routine and in consensus by two experienced radiologists. Pathological findings were systematically discussed with the rheumatologists at our department. PFTs included dynamic spirometry and gas-diffusing capacity. Recorded variables were FVC, FEV1 and DL_{CO}. Abnormal results were recorded when FVC, FEV1 or DL_{CO} were $\leqslant$75% of predicted values [21, 22].

QoL

All included patients were mailed during October and November 2010 and asked to complete questionnaires assessing QoL by the Norwegian version of the SF-36 [23] as well as supplementary information concerning smoking status. Data from these questionnaires were also used in a previous study [24]. The registry (NOSVAR) is approved by the the Norwegian Data Inspectorate. The ethics committee of the University of Oslo approved the study. All included patients have given written consent to register in the database and have accepted that registry data and information obtained from their hospital charts and the questionnaires should be used for research.

Statistical analysis

Descriptive statistics were used to characterize the sample. Bivariate differences were explored in cross-tables and box plots with corresponding Pearson's chi-squared/Fisher's exact test, independent-sample *t*-test or Mann–Whitney U-test. Kaplan–Meyer and Cox proportional hazard models were used to analyse survival in subgroups. To assess QoL, linear regression analyses were performed to adjust for covariates when comparing patients with and without lung involvement with SF-36 subscores. All analyses were performed with SPSS software (version 18.0; IBM SPSS Statistics, hhtp://www-01.ibm.com/software/analytics/spss). $P < 0.05$ was considered statistically significant.

Results

Radiological examination and lung function tests

Among the unselected patients referred from our primary area, Oslo, 26 of 117 patients (22%) had pulmonary involvement defined as pulmonary symptoms combined with HRCT abnormalities and/or reduction in PFT. Compared with patients referred from other areas, those from our primary area had less prevalent lung involvement (22% *vs* 33%, $P = 0.043$) and a non-significant tendency towards younger age and shorter disease duration was present. In the total population, 59 of 216 patients (27%) had pulmonary involvement. Details are presented in Table 1.

HRCT was performed in 80 patients and was abnormal in 50 patients (23% of the total cohort). In all, 85% of the patients with lung involvement had abnormal HRCT. The following HRCT abnormalities were noted: reticular pattern 22 (44%), cysts 21 (42%), air trapping 11 (22%), ground-glass attenuation 10 (20%), bronchiectasis 7 (14%), small nodules 7 (14%), emphysema 5 (10%), enlarged mediastinal lymph nodules 4 (8.0%) and honeycombing 3 (6.0%). All patients with abnormal chest radiographs ($n = 8$) also had pathological findings on HRCT.

PFTs were performed in 50 patients and were abnormal in 34 patients (16% of the total cohort). In six of these cases, HRCTs were normal and in three cases they were not performed. Thus in nine patients (15%) pulmonary involvement was based on PFTs. Among the patients with pathological PFTs, DL_{CO} was abnormal in 26 (76%), FEV1 in 10 (29%) and FVC in 7 patients (21%). Blood test revealed that hypergammaglobulinaemia, lymphopenia, positivity for RF, anti-Ro/SSA and anti-La/SSB were more prevalent in patients with pulmonary involvement compared with those without (Table 1).

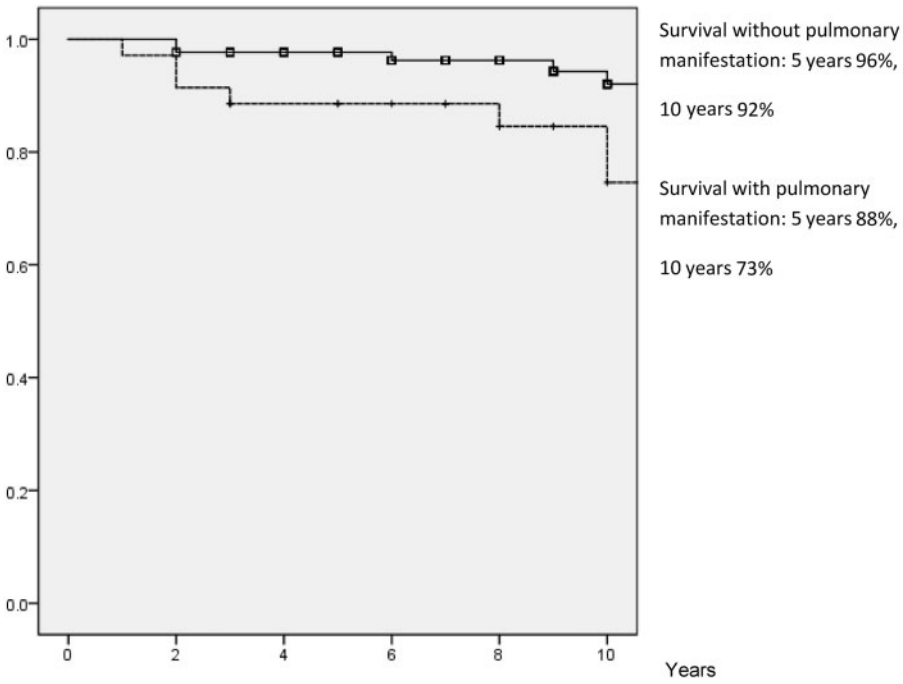
QoL

SF-36 data were available for 38 (67%) patients with and 120 (75%) without lung involvement. The mean subscores in patients with *vs* without pulmonary involvement were Physical Functioning, 53 *vs* 61; Role Physical, 35 *vs* 33; Bodily Pain, 46 *vs* 49; General Health, 39 *vs* 40; Vitality, 30 *vs* 32; Social Functioning, 61 *vs* 61; Role Emotional, 66 *vs* 54 and Mental Health, 70 *vs* 68. Differences in the Physical Functioning subscore were significant ($P = 0.03$) after adjusting for age at diagnosis, gender and current smoking status (standardized β = 163). The other differences were not statistically significant.

Mortality

Seventeen patients (7.9%; 14 females, 3 males) had died after a median of 8 years (range 1–19 years) since diagnosis. Among those with lung involvement, 10 patients had died (17%), compared with 7 patients (4.5%) without

FIG. 1 Kaplan–Meyer survival curve of patients older than 50 years with ($n = 35$) and without ($n = 86$) pulmonary manifestations in pSS.



Significance test by log rank (Mantel–Cox) 0.024.

lung involvement ($P = 0.002$). The median age at diagnosis among the deceased with and without lung involvement was 61 years (range 59–71 years) and 64 years (range 60–76 years), respectively ($P = 0.23$). The calculated risk of dying after 10 years of disease was 4-fold increased (relative risk 4.23; 95% CI 1.62, 10.1) in patients with pulmonary involvement compared with those without lung manifestations. None of the patients died before the age of 50 years. The expected 5-year survival of patients older than 50 years with and without lung involvement was 88% and 96%, respectively. The corresponding 10-year survival was 73% and 92%, respectively (Fig. 1). No difference in mortality was seen between the subgroup of patients recruited from our primary area and those from other areas. The causes of death were malignancy in six patients (pancreatic cancer, pulmonary adenocarcinoma, bronchial carcinoma, breast cancer, ovarian cancer, gallbladder cancer), cardiovascular events (heart disease in four patients and one had a stroke), infections in two cases (pneumonia and unspecified infection) and data were missing in four patients.

Discussion

In this study we describe the prevalence of clinical pulmonary manifestations in pSS and assessed QoL and mortality in patients with and without symptoms and objective findings of pulmonary manifestations. Among patients recruited from our primary area, the population-based prevalence of pulmonary manifestations was 22% after a mean disease duration of 10 years. Because only symptomatic cases were investigated, this should be regarded as a minimum prevalence based on patients referred to a department of rheumatology. In our total patient cohort, the prevalence of pulmonary manifestations was 27%. However, a significant higher prevalence of pulmonary involvement and trends towards longer mean disease duration and higher age among patients referred from outside our primary area indicated a selection of more complicated cases in this total cohort. Our data may be compared with a large multicentre Spanish study reporting lung involvement in 19% of the patients at 10-year follow-up [25] or 11% found in Turkey [9]. Furthermore, an older North American study reported a 9% prevalence of pulmonary manifestations [6]. Reasons for the lower frequency of pulmonary involvement found in these studies may be that the Spanish study included patients fulfilling the less stringent European classification criteria for pSS [26], resulting in a lower proportion of complicated cases compared with those fulfilling the AECG criteria [18]. The patients were also younger than ours [25]. The Turkish study based the results on HRCT only, and the patients had shorter disease duration. The North American study applied less stringent clinical criteria for diagnosis in most of their patients, and they also had a shorter disease duration (mean 5.6 years) compared with ours [6]. Although all these studies, including the present one, based lung

involvement on clinical manifestations, different study design, background population and selection of cases may explain the divergence between the results. Moreover, improved diagnostic techniques in recently performed studies may have resulted in a higher sensitivity for the detection of lung abnormalities. Thus, according to previous observations and to the results of the present investigation, clinical lung disease may develop in 10–20% of patients with pSS.

HRCT, being abnormal in 85% of the patients with pulmonary manifestations, was the main diagnostic tool in our study. The distribution of the lung abnormalities found by HRCT was similar to recent reported findings and may be regarded as representative for pSS [9]. HRCT is regarded to be a very sensitive method for detecting lung abnormalities in pSS. Studies systematically performing HRCT series in all patients with pSS, regardless of the presence of symptoms, have demonstrated lung involvement in up to 42% of patients [9, 12], indicating that a substantial proportion of patients with lung involvement are asymptomatic. It is a matter of debate whether all patients with pSS should undergo a systematic search for lung involvement [20]. Novel therapeutic options represented by rituximab have, according to case reports, shown potential to halt extraglandular disease progression [27] and reverse pulmonary involvement [28], which may be an argument for systematic screening. However, it remains to be determined whether or not novel treatment strategies are indicated in asymptomatic pSS lung disease.

PFTs revealed impaired DL_{CO}, FVC and FEV1 in patients with pulmonary involvement, which is in agreement with previous studies, indicating a restrictive pattern of interstitial lung disease [29, 30]. In general, however, PFTs are too crude to detect small abnormalities, which may be seen on HRCT. The explanation may be that only morphological changes sufficient to produce functional decline will be detected by PFTs. Moreover, PFTs may be altered by extrapulmonary conditions, including obesity [31] and neuromuscular diseases [32]. Thus when possible pulmonary involvement should be diagnosed based on supplemental HRCTs. In our study, 15% of the patients were diagnosed by PFTs only. Although we are not aware of extrapulmonary diseases altering the respiratory function in these patients, the missing diagnostic HRCTs should be regarded as a limitation to our results. However, PFTs are easy to perform and complications are rare. In the follow-up of patients, changes in lung function monitored by PFTs may provide a safe and simple way to detect early signs of pulmonary involvement and to evaluate disease progression and the response to therapy [33].

In order to prevent pulmonary disease or initiate early treatment, identification of predictors for disease may be of importance. Hypergammaglobulinaemia, lymphopenia, positivity for RF, anti-Ro/SSA and anti-La/SSB have been suggested to be predictive factors for lung involvement by a Turkish study, although the results did not reach significant levels [9]. Our patients with lung involvement had significantly more prevalent anti-La/SSB antibodies, lymphopenia and a history of RP compared with patients without pulmonary manifestations (Table 1). Although not reaching statistical significance in our study, a trend towards higher prevalence also for anti-Ro/SSA antibodies in patients with pulmonary involvement was found, which is in agreement with results of previous studies [9, 14]. Explanations for the significantly higher prevalence of anti-La/SSB antibodies in patients with pulmonary involvement among our patients may be a selection of double-positive patients referred to our department. Further, assuming that both anti-Ro/SSA and anti-La/SSB antibodies contribute to lung involvement, double-positive cases (i.e. those with La/SSA antibodies in our study) may be at higher risk than those with anti-Ro/SSA antibodies only. A link between anti-Ro/SSA and lung disease may be present in other autoimmune diseases, including SLE and myositis [34, 35]. The exact role of anti-Ro/SSA and anti-La/SSB antibodies and how they are involved in the pathogenesis of pSS-associated lung disease remains to be determined [9].

By evaluating QoL in patients with pSS in general, we have previously found that all eight subscores of the SF-36 were reduced compared with normative data [24]. In the present study, patients with lung involvement reported impaired physical functioning compared with the other patients with pSS. The unstandardized coefficient of −10.03 demonstrated that physical function in patients with lung involvement was decreased compared with the group without lung involvement and the magnitude of the difference was considered to be of clinical importance. We are aware of only one comparable study, which reported reduced SF-36 subscores for physical and emotional function together with bodily pain in patients with pSS and pulmonary involvement [17]. Our findings confirm that reduced physical function in patients with lung disease contributes to impaired QoL in pSS.

We found a 4-fold increased mortality risk after 10 years of disease among patients with lung involvement; and in patients aged over 50 years, the 5- and 10-year survival rates were reduced compared with patients without pulmonary manifestations. Although most patients with lung involvement seem to have a mild disease course [14], our data are in line with a recent Chinese publication reporting pulmonary involvement to be among the highest risk factors for mortality [12]. Furthermore, among 33 Japanese pSS patients with non-specific interstitial pneumonia, the 5-year mortality was 16%, indicating that subgroups of patients may develop severe lung involvement and high mortality [15]. It should be noted, however, that mortality related to pulmonary manifestations in pSS may decline due to improved diagnostic methods along with new therapeutic options [28]. Although patients with pSS are expected to have increased risk of mortality related to malignant lymphoma [5], no fatal cases due to such malignancy were present in this study. The explanation may be the relatively low number of cases in our study.

Our study has some limitations that should be considered. Although most patients with moderate or severe pulmonary manifestations are likely to be referred to hospital care, milder cases may not have been referred. As a

consequence, our data are representative only for patients being referred for hospital care. This may have lead to an overestimation of clinical pulmonary involvement in our study. Furthermore, when estimating mortality, it should be considered that not only newly diagnosed cases were included in our registry, but also patients with long disease duration. Thus cases with early mortality related to pSS may have been missed, implying that the estimated mortality rates may be too low.

In conclusion, we found a rather high population-based prevalence of 22% of clinical pulmonary involvement in patients with pSS referred to our department. All patients were diagnosed according to clinical symptoms and abnormal HRCTs and/or PFTs. The presence of serum La/SSB antibodies, lymphopenia and a history of RP may be predictive factors. Pulmonary involvement leads to reduced physical function and increased mortality. Novel treatments for extraglandular manifestations, including lung involvement in pSS are promising, making the diagnosis of pulmonary involvement of potential prognostic importance.

Rheumatology key messages

- Prevalence of clinical pulmonary manifestations in pSS were 22% in a population-based hospital patient cohort.
- Patients with pulmonary manifestations in Sjögren's disease had reduced physical function and increased mortality.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Alamanos Y, Tsifetaki N, Voulgari PV, Venetsanopoulou AI, Siozos C, Drosos AA. Epidemiology of primary Sjogren's syndrome in north-west Greece, 1982–2003. Rheumatology 2006;45:187–91.

2 Goransson LG, Haldorsen K, Brun JG *et al*. The point prevalence of clinically relevant primary Sjogren's syndrome in two Norwegian counties. Scand J Rheumatol 2011;40:221–4.

3 Haugen AJ, Peen E, Hulten B *et al*. Estimation of the prevalence of primary Sjogren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health Study. Scand J Rheumatol 2008;37:30–4.

4 Tzioufas AG, Voulgarelis M. Update on Sjogren's syndrome autoimmune epithelitis: from classification to increased neoplasias. Best Pract Res Clin Rheumatol 2007;21:989–1010.

5 Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjogren's syndrome: a prospective cohort study. Arthritis Rheum 2004;50:1262–9.

6 Strimlan CV, Rosenow EC III, Divertie MB, Harrison EG Jr. Pulmonary manifestations of Sjogren's syndrome. Chest 1976;70:354–61.

7 Constantopoulos SH, Papadimitriou CS, Moutsopoulos HM. Respiratory manifestations in primary Sjogren's syndrome. A clinical, functional, and histologic study. Chest 1985;88:226–9.

8 Wright SA, Convery RP, Liggett N. Pulmonary involvement in Sjogren's syndrome. Rheumatology 2003;42:697–8.

9 Yazisiz V, Arslan G, Ozbudak IH *et al*. Lung involvement in patients with primary Sjogren's syndrome: what are the predictors? Rheumatol Int 2010;30:1317–24.

10 Kokosi M, Riemer EC, Highland KB. Pulmonary involvement in Sjogren syndrome. Clin Chest Med 2010;31:489–500.

11 Uffmann M, Kiener HP, Bankier AA, Baldt MM, Zontsich T, Herold CJ. Lung manifestation in asymptomatic patients with primary Sjogren syndrome: assessment with high resolution CT and pulmonary function tests. J Thorac Imag 2001;16:282–9.

12 Lin DF, Yan SM, Zhao Y *et al*. Clinical and prognostic characteristics of 573 cases of primary Sjogren's syndrome. Chin Med J 2010;123:3252–7.

13 Franquet T, Gimenez A, Monill JM, Diaz C, Geli C. Primary Sjogren's syndrome and associated lung disease: CT findings in 50 patients. AJR Am J Roentgenol 1997;169:655–8.

14 Davidson BK, Kelly CA, Griffiths ID. Ten year follow up of pulmonary function in patients with primary Sjogren's syndrome. Ann Rheum Dis 2000;59:709–12.

15 Ito I, Nagai S, Kitaichi M *et al*. Pulmonary manifestations of primary Sjogren's syndrome: a clinical, radiologic, and pathologic study. Am J Respir Crit Care Med 2005;171:632–8.

16 Baturone R, Soto MJ, Marquez M *et al*. Health-related quality of life in patients with primary Sjogren's syndrome: relationship with serum levels of proinflammatory cytokines. Scand J Rheumatol 2009;38:386–9.

17 Belenguer R, Ramos-Casals M, Brito-Zeron P *et al*. Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjogren's syndrome. Clin Exp Rheumatol 2005;23:351–6.

18 Vitali C, Bombardieri S, Jonsson R *et al*. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.

19 Watanabe M, Naniwa T, Hara M, Arakawa T, Maeda T. Pulmonary manifestations in Sjogren's syndrome: correlation analysis between chest computed tomographic findings and clinical subsets with poor prognosis in 80 patients. J Rheumatol 2010;37:365–73.

20 Lazor R. Lung involvement in Sjogren's syndrome: interstitium, airways, or both? Respiration 2009;78:375–6.

21 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5–40.

22 Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. [Standardization of the measurement of transfer factor (diffusing capacity). Work Group on Standardization of Respiratory Function Tests. European Community for Coal

and Steel. Official position of the European Respiratory Society]. Rev Mal Respir 1994;11(Suppl. 3):41–52.

23 Ware JE Jr. SF-36 health survey update. Spine 2000;25: 3130–9.

24 Enger TB, Palm O, Garen T, Sandvik L, Jensen JL. Oral distress in primary Sjogren's syndrome: implications for health-related quality of life. Eur J Oral Sci 2011;119: 474–80.

25 Ramos-Casals M, Solans R, Rosas J *et al*. Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine 2008;87:210–9.

26 Vitali C, Bombardieri S, Moutsopoulos HM *et al*. Preliminary criteria for the classification of Sjogren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 1993;36:340–7.

27 Meijer JM, Meiners PM, Vissink A *et al*. Effectiveness of rituximab treatment in primary Sjogren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960–8.

28 Seror R, Sordet C, Guillevin L *et al*. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann Rheum Dis 2007;66:351–7.

29 Kelly C, Gardiner P, Pal B, Griffiths I. Lung function in primary Sjogren's syndrome: a cross sectional and longitudinal study. Thorax 1991;46:180–3.

30 Seror R, Ravaud P, Bowman SJ *et al*. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjogren's syndrome. Ann Rheum Dis 2010;69:1103–9.

31 Koenig SM. Pulmonary complications of obesity. Am J Med Sci 2001;321:249–79.

32 Perrin C, Unterborn JN, Ambrosio CD, Hill NS. Pulmonary complications of chronic neuromuscular diseases and their management. Muscle Nerve 2004;29:5–27.

33 Deheinzelin D, Capelozzi VL, Kairalla RA, Barbas Filho JV, Saldiva PH, de Carvalho CR. Interstitial lung disease in primary Sjogren's syndrome. Clinical-pathological evaluation and response to treatment. Am J Respir Crit Care Med 1996;154:794–9.

34 Ishii M, Uda H, Yamagami T, Katada Y. Possible association of 'shrinking lung' and anti-Ro/SSA antibody. Arthritis Rheum 2000;43:2612–3.

35 La Corte R, Lo Monaco A, Locaputo A, Dolzani F, Trotta F. patients with antisynthetase syndrome the occurrence of anti-Ro/SSA antibodies causes a more severe interstitial lung disease. Autoimmunity 2006;39:249–53.