Comorbidities in Patients with Primary Sjögren's Syndrome: A Registry-based Case-control Study

JIUNN-HORNG KANG and HERNG-CHING LIN

ABSTRACT. ***Objective.*** Although multiple diseases associated with primary Sjögren's syndrome (pSS) have been reported, reliable data regarding the prevalence of specific medical comorbidities among patients with pSS remain sparse. We investigated the prevalence and risk for a broad spectrum of medical conditions among patients with pSS in Taiwan.

Methods. A total of 1974 patients with pSS were eligible for inclusion in the study group. We randomly selected 9870 enrollees matched with the study subjects, using the Taiwan National Health Insurance Research Dataset for 2006 and 2007, inclusive. Conditional logistic regression analyses conditioned on sex, age, monthly income, and level of urbanization of the patient's community were used to calculate the odds ratios (OR) of various comorbid conditions.

Results. Pearson chi-square tests revealed that patients with pSS had significantly higher prevalence of hyperlipidemia, cardiac arrhythmias, headaches, migraines, fibromyalgia (FM), asthma, pulmonary circulation disorders, hypothyroidism, liver disease, peptic ulcers, hepatitis B, deficiency anemias, depression, and psychoses. Conditional regression analyses showed that, compared to patients without the condition, patients with pSS were more likely to have hyperlipidemia (OR 1.42), cardiac arrhythmias (OR 1.32), headaches (OR 1.47), migraines (OR 1.86), FM (OR 1.71), asthma (OR 1.54), pulmonary circulation disorders (OR 1.42), hypothyroidism (OR 2.37), liver disease (OR 1.89), peptic ulcers (OR 1.88), hepatitis B (OR 2.34), deficiency anemias (OR 1.33), depression (OR 2.57), and psychoses (OR 2.15).

Conclusion. The prevalence of several comorbidities was increased among the patients with pSS. Our study provides epidemiological data for comorbidities among pSS patients in an ethnic Chinese population. (First Release April 1 2010; J Rheumatol 2010;37:1188–94; doi:10.3899/jrheum.090942)

Key Indexing Terms:
SJÖGREN'S SYNDROME OUTCOMES EPIDEMIOLOGY

Sjögren's syndrome (SS) is a relatively common autoimmune disease that mainly affects the exocrine glands, such as the lacrimal and salivary glands[1]. Patients with primary SS (pSS) usually have characteristic chronic symptoms of ocular and oral dryness. Although the pathomechanisms of SS are still unclear, environmental factors are considered to trigger abnormal immunological reactions in people with genetic susceptibility[1]. Its clinical features, such as the appearance of pSS autoantibody profiles, share some similarity with systemic lupus erythematosus (SLE)[1,2]. Secondary SS can also be accompanied by other autoimmune diseases, such as rheumatoid arthritis, SLE, and primary systemic sclerosis[1].

As in other autoimmune diseases, the immunological derangement caused by pSS can be systemic. Although the data are scanty, one recent study shows about 40%–50% of patients with pSS develop extraglandular disease[3]. Although multiple extraglandular conditions have been recognized in previous studies, many of these diseases have been reported only sporadically[1]. In addition, the prevalence and risk of these medical comorbidities among patients with pSS cannot be accurately ascertained, due to limitations such as potential selection bias and relatively small sample sizes for such studies. To our knowledge, the data regarding the prevalence of medical comorbidities among Asian or Chinese patients with pSS are still lacking.

The adverse effects on general health, functional status, and quality of life of comorbidity in chronic illness were demonstrated in previous studies[4]. The data regarding the comorbidity associated with pSS are vital to improve the care of patients with pSS. Our goal was to explore the prevalence and risk of a broad spectrum of comorbid medical conditions among patients with pSS, using a nationwide

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case-controlled approach for a Han Chinese population. We further compared the comorbidity profiles of pSS in Han Chinese and Western populations.

MATERIALS AND METHODS

Database. This study used the Taiwan National Health Insurance Research Dataset (NHIRD). Taiwan began the National Health Insurance (NHI) program in 1995, and the program currently includes over 21 million enrollees, representing over 98% of the island's population. The NHIRD contains all ambulatory care and inpatient claims, a registry of contracted medical facilities, and a registry of all beneficiaries of the program. The NHIRD therefore provides a unique opportunity to explore the risk of various comorbidities among patients with pSS.

Since the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Institutional Review Board.

Study sample. The study design consisted of a study group and a comparison group. The study group comprised all patients who sought ambulatory care during a 2-year period from 2006 to 2007, receiving a principal diagnosis of pSS (ICD-9-CM code 710.2; n = 4187). The diagnoses were considered reliable because the features of dryness of the eyes and mouth and blood antibody testing (such as antinuclear antibodies) are required for initial diagnosis of pSS in Taiwan. To further assure validity of diagnosis, we selected only patients who had at least 2 consensus pSS diagnoses for the study group (n = 2238). In addition, we excluded patients who had comorbid SLE, rheumatoid arthritis, scleroderma, sarcoidosis, antiphospholipid syndrome, hepatitis C, lymphoma, radiation therapy mucositis, or ankylosing spondylitis, in order to limit our study sample to primary SS. In total, 1974 patients with SS were eligible for inclusion in the study group.

The patients in the comparison group were drawn from a subset database released by the Taiwan National Health Research Institute (TNHRI) in 2007. This database includes 1,000,000 subjects selected randomly and systematically from the NHIRD, representing about 5% of all enrollees in the NHI program. The TNHRI identified no significant differences in the distribution of age and sex between this representative dataset and the entire NHIRD. We randomly selected our comparison group from this subset database, after excluding subjects who had previously been diagnosed with pSS, identifying 9870 enrollees (5 for every patient with pSS) matched with the study subjects for sex, age (≤ 44, 45–64, and ≥ 65 yrs), monthly income (< NT$15,000, $15,000–30,000, $30,001–50,000, and ≥ $50,001) and level of urbanization of the community in which the patient resided (urbanization levels in Taiwan are divided into 5 strata, level 1 referring to the "most urbanized" and level 5 the "least urbanized" communities).

Comorbidity. In this study, the medical comorbidities for analysis were selected based on the Elixhauser Comorbidity Index, which was created in 1997 and has been widely used for risk adjustment in administrative datasets. The Elixhauser method of comorbidity measurement includes 30 comorbidity measures, but we selected only 19 comorbidities from the index, since some conditions such as obesity, weight loss, coagulopathy, and alcohol abuse have very low prevalence in Taiwan. These 19 comorbidities included hypertension, congestive heart failure, cardiac arrhythmias, peripheral vascular disorder, paralysis, other neurological disorders, pulmonary circulation disorders (ICD-9-CM codes 415, 416.0~416.9, 417.9), hypothyroidism, liver disease (ICD-9-CM codes 070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.40~571.49, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8), diabetes without complications, peptic ulcer, diabetes with complications, renal failure, fluid and electrolyte disorders, deficiency anemias, depression, psychoses, metastatic cancer excluding lymphoma, and solid tumors. We also included 19 additional comorbid conditions (stroke, ischemic heart disease, hyperlipidemia, migraines, multiple sclerosis, polyneuropathy, fibromyalgia (FM), myasthenia gravis, hepatitis B, biliary cirrhosis, chronic interstitial cystitis/chronic cystitis, tuberculosis (TB), headaches, dementia, epilepsy, urinary tract infection, lymphoma, asthma, and chronic obstructive pulmonary disease (COPD), conditions that are prevalent in patients with pSS and in the general adult population in Taiwan. In our study, comorbid conditions were counted only if the condition occurred either in the inpatient setting or in 2 or more ambulatory care claims coded in the years 2006 and 2007.

Statistical analysis. All statistical analyses were performed with the SAS statistical package (SAS for Windows, Version 8.2). Pearson chi-square tests were performed to explore the prevalence of comorbidities among patients with and without pSS. Conditional logistic regression analyses conditioned on sex, age, monthly income, and level of urbanization of the community in which the patient resided were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for each of the 31 comorbid conditions among patients with and without SS. A 2-sided significance test requiring $p \leq 0.05$ was used.

RESULTS

Overall, the mean age of the sampled patients was 49.7 years (standard deviation 21.0). Table 1 gives demographic characteristics of the sampled patients. The overwhelming majority of patients were female (76.2%) and about two-thirds (66.8%) were over 44 years of age.

Table 2 presents the prevalence of comorbidities by patient group. After matching for sex, age, monthly income, and urbanization level of the patient's community, Pearson chi-square tests showed that patients with pSS had significantly higher rates of hyperlipidemia ($p < 0.001$), cardiac arrhythmias ($p = 0.031$), other neurological disorders ($p = 0.014$), headaches ($p < 0.001$), migraines ($p < 0.001$), FM ($p < 0.001$), asthma ($p < 0.001$), pulmonary circulation disorders, ($p < 0.001$), hypothyroidism ($p < 0.001$), liver disease ($p < 0.001$), peptic ulcers ($p < 0.001$), hepatitis B ($p < 0.001$), deficiency anemias ($p = 0.043$), depression ($p < 0.001$), and psychoses ($p < 0.001$). No significant difference

Table 1. Sociodemographic characteristics of patients with Sjögren's syndrome (SS) compared with controls (n = 11,844). Data are number (%).

Variable	Patients with SS, n = 1974	Patients without SS, n = 9870	p
Age, yrs			1.000
≤ 44	655 (33.2)	3277 (33.2)	
45–64	767 (38.8)	3830 (38.8)	
≥ 65	552 (28.0)	2763 (28.0)	
Sex			1.000
Male	469 (23.8)	2349 (23.8)	
Female	1505 (76.2)	7521 (76.2)	
Urbanization level			1.000
1	620 (31.1)	3070 (31.1)	
2	551 (27.9)	2754 (27.9)	
3	265 (13.4)	1323 (13.4)	
4	267 (13.5)	1332 (13.5)	
5	271 (13.7)	1352 (13.7)	
Monthly income, NT$			1.000
< 15,000	571 (28.9)	2852 (28.9)	
15,000–30,000	270 (13.7)	1352 (13.7)	
30,001–50,000	625 (31.7)	3129 (31.7)	
> 50,000	508 (25.7)	2537 (25.7)	

Table 2. Prevalence of medical comorbidities in patients with Sjögren's syndrome (SS) compared with controls (n = 11,844). Data are number (%).

Variable	Patients with SS, n = 1974	Patients without SS, n = 9870	p
Cardiovascular			
Hypertension	478 (24.2)	2332 (23.6)	0.575
Ischemic heart disease	16 (0.8)	77 (0.8)	0.889
Hyperlipidemia	296 (15.0)	1112 (11.3)	< 0.001
Congestive heart failure	50 (2.5)	251 (2.5)	0.979
Cardiac arrhythmias	81 (4.1)	311 (3.2)	0.031
Peripheral vascular disorder	34 (1.7)	118 (1.2)	0.058
Stroke	119 (6.0)	499 (5.1)	0.076
Neurological			
Paralysis	17 (0.9)	68 (0.7)	0.408
Other neurological disorders	42 (2.1)	137 (1.4)	0.014
Headache	398 (20.2)	1449 (14.7)	< 0.001
Migraine	51 (2.6)	139 (1.4)	< 0.001
Epilepsy	11 (0.6)	61 (0.6)	0.751
Dementia	30 (1.5)	133 (1.4)	0.549
Multiple sclerosis	—	1 (0.0)	—
Polyneuropathy	16 (0.8)	48 (0.5)	0.073
Myasthenia gravis	3 (0.2)	2 (0.0)	0.009
Rheumatology			
Fibromyalgia	283 (143)	888 (9.0)	< 0.001
Pulmonary			
Chronic obstructive pulmonary disease	9 (0.5)	41 (0.4)	0.799
Asthma	101 (5.1)	335 (3.4)	< 0.001
Pulmonary circulation disorders	214 (10.8)	785 (8.0)	< 0.001
Endocrine			
Diabetes without complications	200 (10.1)	941 (9.5)	0.411
Diabetes with complications	80 (4.1)	353 (3.6)	0.303
Hypothyroidism	133 (6.7)	293 (3.0)	< 0.001
Renal			
Renal failure	36 (1.8)	136 (1.4)	0.131
Fluid and electrolyte disorders	14 (0.7)	86 (0.9)	0.472
Gastrointestinal			
Liver disease	223 (11.3)	630 (6.4)	< 0.001
Peptic ulcer	269 (13.6)	777 (7.9)	< 0.001
Biliary cirrhosis	2 (0.1)	—	—
Genitourinary			
Chronic interstitial cystitis/chronic cystitis	3 (0.2)	17 (0.2)	0.841
Viral/infectious			
Hepatitis B	91 (4.6)	200 (2.0)	< 0.001
Tuberculosis	15 (0.8)	52 (0.5)	0.208
Urinary tract infection	18 (0.9)	57 (0.6)	0.086
Hematology			
Deficiency anemias	64 (3.2)	242 (2.5)	0.043
Mental illness			
Depression	111 (5.6)	225 (2.3)	< 0.001
Psychoses	81 (4.1)	193 (2.0)	< 0.001
Oncology			
Metastatic cancer excluding lymphoma	4 (0.2)	12 (0.1)	0.571
Lymphoma	5 (0.3)	12 (0.1)	0.158
Solid tumor without metastasis	74 (3.8)	296 (3.0)	0.081

was observed between patients with and those without pSS in the prevalence of hypertension, ischemic heart disease, congestive heart failure, peripheral vascular disorder, paralysis, epilepsy, dementia, COPD, diabetes without complications, diabetes with complications, renal failure, fluid and electrolyte disorders, TB, urinary tract infections, metastatic cancer, and solid tumors.

Table 3 gives OR for each of 31 comorbidities, comparing patients with and without pSS. Conditional regression analyses conditioned on sex, age, monthly income, and level

Table 3. Prevalence of medical comorbidities in patients with Sjögren's syndrome (SS) compared with controls (n = 11,844). Data are odds ratios (95% CI). OR were calculated by regression analyses conditioned on patient's age, sex, urbanization level, and monthly income.

Variable	Patients with SS, n = 1974	Patients without SS, n = 9870
Cardiovascular		
Hypertension	1.04 (0.92–1.18)	1.00
Ischemic heart disease	1.04 (0.60–1.79)	1.00
Hyperlipidemia	1.42** (1.23–1.64)	1.00
Congestive heart failure	0.99 (0.73–1.36)	1.00
Cardiac arrhythmias	1.32* (1.03–1.71)	1.00
Peripheral vascular disorder	1.45 (0.99–2.14)	1.00
Stroke	1.22 (0.99–1.51)	1.00
Neurological		
Paralysis	1.25 (0.73–2.14)	1.00
Other neurological disorders	1.55* (1.09–2.21)	1.00
Headache	1.47** (1.30–1.67)	1.00
Migraine	1.86** (1.30–1.67)	1.00
Epilepsy	0.90 (0.47–1.72)	1.00
Dementia	1.13 (0.76–1.70)	1.00
Multiple sclerosis	NA	NA
Polyneuropathy	1.68 (0.95–2.96)	1.00
Myasthenia gravis	NA	NA
Rheumatology		
Fibromyalgia	1.71** (1.48–1.97)	1.00
Pulmonary		
Chronic obstructive pulmonary disease	1.09 (0.53–2.27)	1.00
Asthma	1.54** (1.22–1.93)	1.00
Pulmonary circulation disorders	1.42** (1.21–1.68)	1.00
Endocrine		
Diabetes without complications	1.07 (0.91–1.27)	1.00
Diabetes with complications	1.14 (0.89–1.47)	1.00
Hypothyroidism	2.37** (1.92–2.93)	1.00
Renal		
Renal failure	1.34 (0.92–1.94)	1.00
Fluid and electrolyte disorders	0.81 (0.46–1.43)	1.00
Gastrointestinal		
Liver disease	1.89** (1.60–2.22)	1.00
Peptic ulcer	1.88** (1.62–2.19)	1.00
Biliary cirrhosis	NA	NA
Genitourinary		
Chronic interstitial cystitis/chronic cystitis	NA	NA
Viral/infectious		
Hepatitis B	2.34** (1.82–3.02)	1.00
Tuberculosis	1.45 (0.81–2.58)	1.00
Urinary tract infection	1.59 (0.93–2.70)	1.00
Hematology		
Deficiency anemia	1.33* (1.01–1.77)	1.00
Mental illness		
Depression	2.57** (2.03–3.25)	1.00
Psychoses	2.15** (1.65–2.80)	1.00
Oncology		
Metastatic cancer excluding lymphoma	1.67 (0.54–5.81)	1.00
Lymphoma	2.09 (0.73–5.93)	1.00
Solid tumor without metastasis	1.26 (0.97–1.64)	1.00

* $p < 0.05$; ** $p < 0.001$. NA: case numbers in these cells were too small to perform regression analyses.

of urbanization showed that, compared to patients without pSS, patients with pSS were more likely to have hyperlipidemia (OR 1.42, 95% CI 1.23–1.64), cardiac arrhythmias (OR 1.32, 95% CI 1.03–1.71), headaches (OR 1.47, 95% CI 1.30–1.67), migraines (OR 1.86, 95% CI 1.30–1.67), fibromyalgia (OR 1.71, 95% CI 1.48–1.97), asthma (OR 1.54, 95% CI 1.22–1.93), pulmonary circulation disorders (OR 1.42, 95% CI 1.21–1.68), hypothyroidism (OR 2.37,

95% CI 1.92–2.93), liver disease (OR 1.89, 95% CI 1.60–2.22), peptic ulcers (OR 1.88, 95% CI 1.62–2.19), hepatitis B (OR 2.34, 95% CI 1.82–3.02), deficiency anemias (OR 1.33, 95% CI 1.01–1.77), depression (OR 2.57, 95% CI 2.03–3.25), and psychoses (OR 2.15, 95% CI 1.65–2.80).

DISCUSSION

The influence and consequences of comorbid medical conditions among patients with pSS remain unclear. Although studies show that overall mortality is not increased among patients with pSS, compared with the general population[3,5,6], significantly decreased quality of life has been noted among the patients with pSS[7,8]. In addition, patients with pSS experience a high prevalence of fatigue, pain, and depression, which could be associated with coexisting comorbidities[7,9]. We found higher prevalence of several medical conditions, including cardiovascular, neurological, pulmonary, endocrine, gastrointestinal, infections, hematological, and psychological diseases among patients with pSS. As about 98% of inhabitants of Taiwan are Han Chinese, our data should be highly representative of the Han Chinese population. In general, we found the profiles of comorbidity among pSS patients of Han Chinese ethnicity were similar to previous reports on Western populations. However, some of our results were inconsistent with previous reports.

Cardiovascular involvement, such as heart conduction problems and autonomic dysfunctions, has been identified as associated with pSS[10-13]. Our data showed higher prevalence of cardiac arrhythmias, which is compatible with previous observations. Derangement of lipid metabolism has been reported in association with many autoimmune diseases[14]. Limited, but notable data regarding dyslipidemia in patients with pSS have been published[15-17]. Lodde, *et al* showed a significant difference in lipid profiles associated with serological measurement of inflammation in a small case-control study[15]. Our data support that patients with pSS have a higher prevalence of hyperlipidemia. Chronic systemic inflammation is also considered a risk factor for developing atherosclerosis[18]. However, contrary to what we expected, the prevalence of atherosclerotic consequences such as ischemic heart disease, peripheral vascular disorders, and strokes was not significantly increased among patients with pSS. We proposed that the complex relationships among inflammation, vascularity, coagulation, and the autonomic system could be associated with atherosclerosis in patients with pSS. Further studies are needed to confirm our data.

Although hepatitis C virus (HCV) infection is recognized as being associated with pSS[19,20], the role of HBV infection in pSS is still controversial. One case report described pSS occurring after HBV vaccination[21]. In contrast, Ram, *et al* proposed that HBV infection may play a protective role against some autoimmune disorders[22]. Interestingly, we found a higher prevalence of hepatitis B among patients with pSS. HBV infection is highly endemic in Taiwan[23]. Further study is needed to determine the role of HBV infection in pSS, particularly in Chinese populations.

Our data are compatible with studies that demonstrated higher prevalence of headaches and migraines among patients with pSS[24-26]. Vascular involvement is hypothesized to contribute to headaches and migraine symptoms in patients with pSS[25]. Varying degrees of neurological involvement have been demonstrated in pSS. One survey reported that up to 71% patients with pSS have central or peripheral neurological system involvement[27]. Further, neuropsychiatric surveys have demonstrated a significant prevalence of cognitive impairment among patients with pSS[24]. However, we found a trend that did not reach statistical significance suggesting increased risk of peripheral neuropathy among patients with pSS. We did not find increased prevalence of dementia among the patients with pSS. Clinical diagnosis of neurological involvement in patients with pSS could be difficult, since the clinical course is highly variable, and subclinical presentations are not unusual. Therefore we propose that some patients with pSS have mild neuropathy or cognitive impairment that fails to raise clinical attention.

Our data confirm several comorbidity patterns observed by studies with small sample sizes or in Western populations. For example, Amin, *et al* demonstrated increased hypersensitivity of bronchial airways in pSS similar to atopic asthma, despite some differences in inflammation patterns[28]. Our study supports this association in a Chinese population. Although there is still some controversy about it, many articles have suggested diffuse myalgia and widespread pain are associated with pSS[1,29,30]. Our data support a higher prevalence of FM among patients with pSS in a Chinese population. Higher prevalence of hypothyroidism and hepatic dysfunction among patients with pSS compared to the general population noted in our study is also consistent with previous findings, despite the lower prevalence in our data[31]. It is worth noting that we also found higher prevalence of peptic ulcers among the patients with pSS. *Heliobacter pylori* are proposed to be associated with rheumatic diseases, including pSS with extragastric presentation. Our findings may provide epidemiological evidence for this association.

Depression and psychoses are recognized to be associated with many kinds of autoimmune diseases. Recent imaging and neuropsychiatric evaluations have indicated such psychiatric dysfunction in patients with pSS may be associated with psychological stress from a disabling chronic disorder, but may also have an organic neuronal basis[32]. Our findings showed that of all comorbidities we surveyed, depression posed the highest risk to patients with pSS. Nevertheless, the prevalence of depression and psychoses

among patients with pSS in our data is still much lower than in previous studies in Western populations. Underdiagnosis and undertreatment of psychiatric conditions is quite common among patients with other autoimmune diseases. Our data may reflect a similar phenomenon also exists in Taiwan. Recognizing the need for psychological or psychiatric care should be emphasized for these patients.

Our results are in some ways incompatible with results from studies in Western populations. For example, previous reports have suggested high risk for developing lymphoma among patients with pSS[3,33]. A nationwide population-based study in Sweden noted the risk of non-Hodgkin's lymphoma is about 6.4 times higher in patients with pSS[33]. Nevertheless, we found only a positive trend toward developing lymphoma among patients with pSS in Taiwan that did not reach statistical significance. Such contradictions could come from different selection criteria, the duration of followup, and ethnic differences. Further study is needed to confirm our findings. Previous studies found biliary cirrhosis to be associated with pSS, but there were only rare cases in our survey. Some authors have suggested interstitial cystitis and diabetes mellitus are associated with pSS[17,34]; however, we did not find an association with either condition in our data.

Our study has several limitations. First, the validity of pSS diagnoses is difficult to determine using a nationwide health database. Miscoding of patients with pSS with mild symptoms could occur under different diagnostic criteria. In accord with diagnostic criteria set up by international consensus, our analysis revealed that over 95% of our sampled patients had previously received at least 2 of the following objective tests: autoantibodies (Ro/La antibodies), histopathology (biopsy of oral mucosa), or objective salivary gland investigation (sialoscintigraphy) during the period from 2004 to 2007. Although detailed results cannot be determined from the dataset used in our study, the diagnoses of pSS were made by physicians after performing these tests on the sampled patients, which strongly suggests these patients had positive results on these tests. Therefore, we believe the validity of diagnoses of our sampled patents was acceptable for analysis of epidemiological profiles. Second, it is sometimes difficult to differentiate secondary SS from pSS, because it is not unusual for manifestations accompanying autoimmune diseases to be delayed for a long period. Third, cause-effect relationships could not be determined in a cross-sectional study. A longitudinal study would be necessary to clarify the interaction between pSS and specific comorbid conditions. Fourth, variables including physical activity, smoking and alcohol consumption, dietary habits, and family history have a confounding effect on development of certain comorbidities, but could not be determined in our database. Finally, selection bias could have occurred in our study, since patients with mild disease may not seek medical attention, with the result that not all medical conditions come to doctors' attention and are recorded in the database. In such circumstances, the prevalence of medical conditions is likely to be underestimated.

The challenge remains to determine the underlying pathomechanisms of medical conditions comorbid with pSS. Shared genetic, environmental, and secondary behavior contributing to disease, as well as medication, could all account for the development of specific comorbid medical conditions.

To our knowledge, this is the first study to investigate prevalence data for a broad spectrum of medical conditions comorbidly associated with pSS using a large, population-based dataset of Han Chinese. Our data indicate increased prevalence of multiple comorbidities among patients with pSS. In general, the pattern of comorbidities appears similar in Chinese and Western populations with pSS. Clinicians should be aware of specific comorbid medical conditions common among patients with pSS.

REFERENCES

1. Fox RI. Sjogren's syndrome. Lancet 2005;366:321-31.
2. Manoussakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, Skopouli FN, et al. Sjogren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjogren's syndrome. Arthritis Rheum 2004;50:882-91.
3. Voulgarelis M, Tzioufas AG, Moutsopoulos HM. Mortality in Sjogren's syndrome. Clin Exp Rheumatol 2008;26:S66-71.
4. Joshi K, Kumar R, Avasthi A. Morbidity profile and its relationship with disability and psychological distress among elderly people in Northern India. Int J Epidemiol 2003;32:978-87.
5. 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.
6. 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.
7. Champey J, Corruble E, Gottenberg JE, Buhl C, Meyer T, Caudmont C, et al. Quality of life and psychological status in patients with primary Sjogren's syndrome and sicca symptoms without autoimmune features. Arthritis Rheum 2006;55:451-7.
8. Strombeck B, Ekdahl C, Manthorpe R, Wikstrom I, Jacobsson L. Health-related quality of life in primary Sjogren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. Scand J Rheumatol 2000;29:20-8.
9. Thomas E, Hay EM, Hajeer A, Silman AJ. Sjogren's syndrome: a community-based study of prevalence and impact. Br J Rheumatol 1998;37:1069-76.
10. Stojanovich L, Milovanovich B, de Luka SR, Popovich-Kuzmanovich D, Bisenich V, Djukanovich B, et al. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjogren syndrome and other autoimmune diseases. Lupus 2007;16:181-5.
11. Pirildar T, Sekuri C, Utuk O, Tezcan UK. QT dispersion in rheumatoid arthritis patients with and without Sjogren's syndrome. Clin Rheumatol 2003;22:225-8.
12. Kovacs L, Paprika D, Takacs R, Kardos A, Varkonyi TT, Lengyel C, et al. Cardiovascular autonomic dysfunction in primary Sjogren's syndrome. Rheumatology 2004;43:95-9.
13. Lodde BM, Sankar V, Kok MR, Leakan RA, Tak PP, Pillemer SR. Adult heart block is associated with disease activity in primary Sjogren's syndrome. Scand J Rheumatol 2005;34:383-6.
14. Frostegard J. SLE, atherosclerosis and cardiovascular disease.

J Intern Med 2005;257:485-95.
15. Lodde BM, Sankar V, Kok MR, Leakan RA, Tak PP, Pillemer SR. Serum lipid levels in Sjogren's syndrome. Rheumatology 2006;45:481-4.
16. Gerli R, Bartoloni BE, Vaudo G, Marchesi S, Vitali C, Shoenfeld Y. Traditional cardiovascular risk factors in primary Sjogren's syndrome — role of dyslipidaemia. Rheumatology 2006;45:1580-1.
17. Ramos-Casals M, Brito-Zeron P, Siso A, Vargas A, Ros E, Bove A, et al. High prevalence of serum metabolic alterations in primary Sjogren's syndrome: influence on clinical and immunological expression. J Rheumatol 2007;34:754-61.
18. Shoenfeld Y, Sherer Y, Harats D. Atherosclerosis as an infectious, inflammatory and autoimmune disease. Trends Immunol 2001;22:293-5.
19. Nagao Y, Hanada S, Shishido S, Ide T, Kumashiro R, Ueno T, et al. Incidence of Sjogren's syndrome in Japanese patients with hepatitis C virus infection. J Gastroenterol Hepatol 2003;18:258-66.
20. Pyrsopoulos NT, Reddy KR. Extrahepatic manifestations of chronic viral hepatitis. Curr Gastroenterol Rep 2001;3:71-8.
21. Toussirot E, Lohse A, Wendling D, Mougin C. Sjogren's syndrome occurring after hepatitis B vaccination. Arthritis Rheum 2000;43:2139-40.
22. Ram M, Anaya JM, Barzilai O, Izhaky D, Porat Katz BS, Blank M, et al. The putative protective role of hepatitis B virus (HBV) infection from autoimmune disorders. Autoimmun Rev 2008; 7:621-5.
23. Chang MH. Hepatitis B virus infection. Semin Fetal Neonatal Med 2007;12:160-7.
24. Harboe E, Tjensvoll AB, Maroni S, Goransson LG, Greve OJ, Beyer MK, et al. Neuropsychiatric syndromes in patients with Systemic Lupus Erythematosus and primary Sjogren Syndrome: A comparative population-based study. Ann Rheum Dis 2009;68:1541-6.
25. Gokcay F, Oder G, Celebisoy N, Gokcay A, Sirin H, Kabasakal Y. Headache in primary Sjogren's syndrome: a prevalence study. Acta Neurol Scand 2008;118:189-92.
26. Pal B, Gibson C, Passmore J, Griffiths ID, Dick WC. A study of headaches and migraine in Sjogren's syndrome and other rheumatic disorders. Ann Rheum Dis 1989;48:312-6.
27. Hietaharju A, Jantti V, Korpela M, Frey H. Nervous system involvement in systemic lupus erythematosus, Sjogren syndrome and scleroderma. Acta Neurol Scand 1993;88:299-308.
28. Amin K, Ludviksdottir D, Janson C, Nettelbladt O, Gudbjornsson B, Valtysdottir S, et al. Inflammation and structural changes in the airways of patients with primary Sjogren's syndrome. Respir Med 2001;95:904-10.
29. Tensing EK, Solovieva SA, Tervahartiala T, Nordstrom DC, Laine M, Niissalo S, et al. Fatigue and health profile in sicca syndrome of Sjogren's and non-Sjogren's syndrome origin. Clin Exp Rheumatol 2001;19:313-6.
30. Ostuni P, Botsios C, Sfriso P, Punzi L, Chieco-Bianchi F, Semerano L, et al. Fibromyalgia in Italian patients with primary Sjogren's syndrome. Joint Bone Spine 2002;69:51-7.
31. Montano-Loza AJ, Crispin-Acuna JC, Remes-Troche JM, Uribe M. Abnormal hepatic biochemistries and clinical liver disease in patients with primary Sjogren's syndrome. Ann Hepatol 2007;6:150-5.
32. Morgen K, McFarland HF, Pillemer SR. Central nervous system disease in primary Sjogrens syndrome: the role of magnetic resonance imaging. Semin Arthritis Rheum 2004;34:623-30.
33. Soderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. Eur J Cancer 2006;42:3028-33.
34. van de Merwe JP, Yamada T, Sakamoto Y. Systemic aspects of interstitial cystitis, immunology and linkage with autoimmune disorders. Int J Urol 2003;10 Suppl:S35-38.