One decade distinct features, morbidity and mortality of scleroderma: a cross-sectional study

M.A. Nazarinia[1], E. Esmaeilzadeh[2], Y. Emami[2], A. Salehi[3]

[1]Shiraz Geriatric Research Centre, Shiraz University of Medical Sciences, Iran; [2]Student Research Committee, Shiraz University of Medical Sciences, Iran; [3]Research Centre of Traditional and History of Medicine, Shiraz, Iran.

Mohammad Ali Nazarinia, MD
Elmira Esmaeilzadeh, MD, MPH candidate
Yasaman Emami, MD
Alireza Salehi, MD, MPH, PhD

Please address correspondence to:
Elmira Esmaeilzadeh,
Shiraz University of Medical Sciences,
Emam Hossein(Setad) Square,
Zand street. 7186767431 Shiraz, IR Iran.
E-mail: elmira69.es@gmail.com

Received on December 25, 2015; accepted in revised form on April 19, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 100): S74-S78.

Key words: scleroderma (SSc), diffuse cutaneous, limited cutaneous, overlap syndrome, epidemiology.

Funding: this project was supported by Shiraz University of Medical Sciences and was registered as the dissertation of Master of Public Health (MPH) courses by E. Esmaeilzadeh.

Competing interests: none declared.

ABSTRACT

Objective. *Conducting an epidemiologic study on scleroderma patients referred to hospitals and tertiary centres of rheumatologic diseases in Shiraz located in the south of Iran.*

Methods. *A cross-sectional study was done on patients' records registered in scleroderma outpatient clinics as well as hospitals associated with Shiraz University of Medical Sciences. Gathering data in pre-formed data sheets, descriptive analysis plus qualitative comparisons by chi-square test were done using SPSS 15.*

Results. *In 533 medical records, female to male ratio was 7.3:1. The disease is mostly seen in 3rd and 4th decades of life. More patients had negative family histories (56.1%). 37.5% of the patients had diffuse form of the disease, 36.8% had limited one, and 17.3% had overlap syndrome, mostly, by lupus erythematosus (33%). Most common first presentation was Raynaud phenomenon (40.7%). Two most prevalent clinical manifestations were skin thickening (97.2%) and gastrointestinal involvement (68.9%). Clinical presentations were compared between three most common types of the disease plus various stages of life. Among recorded capillaroscopies, active form was the most prevalent one (38.3%). In documented serologic markers, the most common positive one was anti-nuclear antibody (ANA) (75.6%). Two most common etiologies of hospitalisation were digital ulcer (30.9%) and pulmonary fibrosis (5.7%). The most common cause of death (17) was pulmonary fibrosis (35.2%).*

Conclusion. *This study is the first epidemiologic survey on Iranian scleroderma patients with significantly large sample size compared to previous studies worldwide. It can thus provide some guidance for further multi-provincial, multinational and interracial studies on scleroderma.*

Introduction

Systemic sclerosis (SSc), also named scleroderma, is a rare but potentially severe autoimmune connective tissue disease, which is characterised by immune dysfunction, small vessels vasculopathy and collagen deposition in skin and multiple internal organs (1, 2). Conducting epidemiologic studies on this topic encounters some difficulties which mostly relate to its rarity and heterogeneous clinical presentations (3).

Considering previous worldwide studies, there are some differences on the presentation of the disease between various ethnicities and geographic areas. Moreover, there are few epidemiologic studies on Iranian SSc patients (4). Thus, we aimed to perform an epidemiologic study on Iranian SSc patients registered in Rheumatology tertiary centres in the south of Iran from 2004 through 2014.

Material and methods

A cross sectional study was done by reviewing the medical records of scleroderma patients who fulfilled the criteria of American College of Rheumatology (ACR) for SSc classification (5). The patients were selected from those referred to Hafez, Faghihi, and Namazi Hospitals of Shiraz University of Medical Sciences from 2004 to 2014.

The data was formulated into sheets containing demographic information, age, type of SSc, family history of rheumatologic diseases, past medical history of the patients and clinical presentations. Each system was divided into subgroups identified by common signs and symptoms, documented in Harrison's Principles Textbook of Internal Medicine, as well as in up-to-date databases (6, 7).

The patients' records with lack of sufficient information or with poor follow-up were omitted from the study and considered as total missing data.

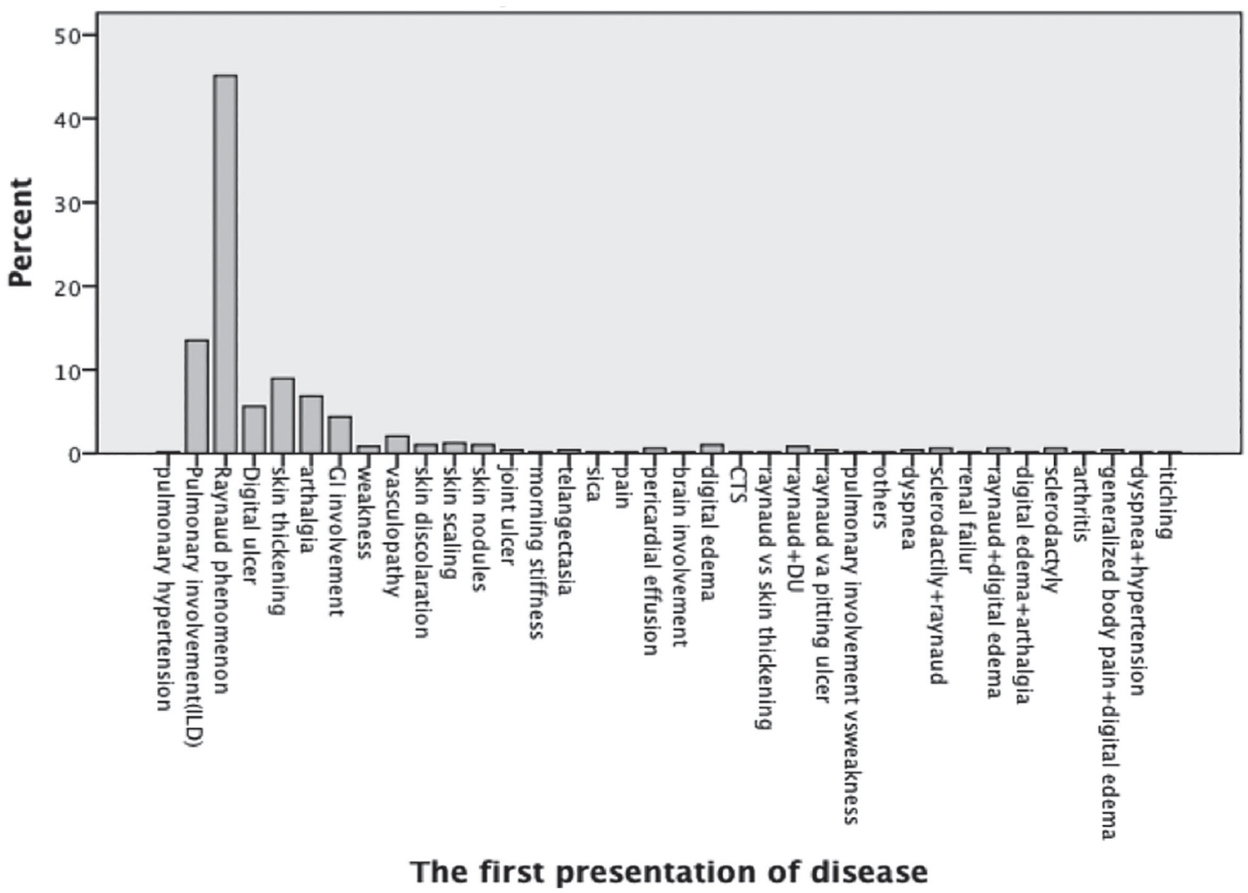

Fig. 1. Frequencies of first clinical presentations of systemic sclerosis.
DU: digital ulcer, ILD: interstitial lung diseases, CTS: carpal tunnel syndrome.

Statistical analysis

Data were coded and entered into the Statistical Package for Social Sciences (SPSS 15). They were summarised by descriptive analysis and were compared using chi-square test. The significant *p*-value in these comparisons is <0.05.

Ethical issues

All patients' medical records were anonymous and coded by numbers; thus, the reviewers did not have access to patients' identities.

Results

Data of 585 SSc patients were reviewed. 52 of them (8.9%) were considered as total missing data.

Statistical analysis was done on other 533 patients' data. Female to male ratio was 7.3:1 [469 (88%): female and 64 (12%): male]. The mean age of the onset of disease was 36 (min=4, max=92, SD: 12.8) and the mean age at the time of study was 45 years old (min=9, max=93, SD: 13).

Moreover, 121 (22.7%, 95%CI: 19.14-26.27) of patients had positive family histories of rheumatologic diseases, 155 (29.1%, 95%CI: 25.22–32.94) had negative and 257 (48.2%, 95%CI: 43.97–52.47) had unidentified histories. Furthermore, 202 (37.9%, 95%CI: 33.77–42.03) had diffused cutaneous type of scleroderma; 196 (36.8%, 95%CI: 32.67–40.88) had limited form; 2 (0.4%, 95%CI:0. 0–0.9) was sin sclerosis and 92 (17.3%, 95%CI: 14.05–20.48) had overlap syndrome.

Among 92 patients diagnosed as overlap syndrome, 31 (33%, 95%CI: 23.91–43.48) overlap with systemic lupus erythematosus, 20 (21%, 95%CI: 13.2–30.28) with rheumatoid arthritis, 18 (19%, 95%CI: 11.35–27.78) with polymyositis, 10 (10%, 95%CI: 4.42-17.32) with dermatomyositis and 13 (14%, 95%CI: 6.92–21.34) had mixed connective tissue disease.

In addition, the results also showed that Raynaud phenomenon (40.7%, 95%CI: 36.53-44.89) and pulmonary fibrosis (ILD) (12.2%, 95%CI: 9.58-15.19) were two first clinical presentations, respectively. Other clinical manifestations considered as first presentations can be observed in Figure 1.

The prevalence of clinical manifestations were also estimated and summarised in Table I.

The clinical presentations of the disease were compared between the two genders; only renal involvement had significant *p*-value (p=0.04) with more prevalence in male (male=35.6% (10/64), female=7.89% (37/469)).

Also, symptoms of the disease were compared between three types of SSc (diffused, limited and overlap syndrome). The significant results are shown in Table II.

Among the patients, 146 of them (27.5%, 95%CI: 23.6–31.19) had documented capillaroscopies grouped into active (38.3%, 95%CI: 30.40–46.31), non-active (4.1%, 95%CI: 0.86–7.36), non-specific (8.9%, 95%CI: 4.25-13.56), early (23.2%, 95%CI: 16.37–

Table I. Frequency of organs involvement and clinical presentations in systemic sclerosis patients.

Clinical involvements	n (%)	CI (95%)	Clinical involvements	n (%)	CI (95%)
Constitutional symptoms	(220/533) 41.30	37.09_45.46	Pulmonary involvement	(302/533) 56.80	52.63_61.06
1. Fatigue	(66/220) 30	23.91_36.09	1. Interstitial lung disease	(268/302) 88.45	84.84_92.06
2. Stiff joints	(73/220) 33.18	26.93_39.44	2. Pulmonary hypertension	(78/302) 25.74	20.8_30.69
3. Pain	(125/220) 56.82	50.24_63.40	3. Pleural effusion	(17/302) 5.61	3.01_8.21
4. Loss of strength	(1/220) 0.45	00.00_1.35	4. Others	(5/302) 1.65	0.21_3.09
5. Sleep difficulties	(3/220) 1.36	00.00_2.90			
6. Hair loss	(18/220) 8.18	4.54_11.82	Renal involvement	(47/533) 8.80	6.41_11.23
7. Others	(15/220) 6.8	3.47_10.17	1. Renal crisis	(14/47) 29.79	16.38_43.21
			2. Hypertension	(15/47) 31.91	18.23_45.6
Skin involvement (except skin thickening)	(343/533) 64.40	60.28_66.43	3. Renal failure	(16/47) 34.04	20.13_47,96
			4. Others	(20/47) 42.55	28.04_57.07
1. Skin discolouration	(64/343) 18.66	14.52_22.80			
2. Pruritis	(10/343) 15.16	11.35_18.97	Cardiac involvement	(149/533) 28.00	24.14_31.77
3. Sclerodacryly	(135/343) 39.36	34.17_44.55	1. Pericardial disease	(59/149) 39.60	31.68_47.51
4. Digital ulcer	(201/343) 58.60	53.37_63.83	A.Pericardial effusion	(44/ 59) 74.58	63.23_85.92
5. Pitting at fingertips	(49/343) 14.29	10.57_18.00	2. Myocardial disease	(51/149) 34.23	26.55_41.91
6. Telangectasia	(62/343) 18.08	13.99_22.16	3. Valvular disease	(80/149) 53.69	45.62_61.76
7. Calcinosis Cutis	(20/343) 5.83	3.34_8.32	a. MR	(66/80) 82.50	74.04_90.96
8. Photosensitivity	(42/343) 12.24	8.76_15.73	b. TR	(64/80) 80.00	71.1_88.9
9. Others	(70/343) 20.4	16.13_24.69	c. AR	(24/80) 30.00	19.8_40.2
			d. PR	(2/80) 2.50	0.0_5.97
Skin thickening	(518/533) 97.20	95.78_96.59	e. MS	(3/80) 3.75	0.0_7.98
Vascular involvement	(363/533) 68.11	64.14_72.07	f. TS	(0/80) 0.00	0.0_0.0
1. Raynaud	(180/363) 97.25	95.56_96.93	g. AS	(1/80) 1.25	0.0_3.72
2. Digital pitting scar	(22/363) 6.06	3.60_8.52	h. PS	(2/80) 2.50	0.0_5.97
3. Digital gangrene	(32/363) 8.62	5.89_11.74	4. Arrythmia	(3/149) 2.01	0.0_4.92
4. Digital tip ulcer	(37/363) 10.19	7.07_13.32	5. Diastolic dysfunction	(65/149) 43.62	35.6_51.65
5. Digital cyanosis	(33/363) 9.09	6.12_12.06	6. RA/RV enlargement	(29/149) 19.46	13.05_25.87
6. Others	(10/363) 2.75	1.07_4.44	7. Others	(38/149) 25.50	18.45_32.56
Gastrointestinal involvement	(367/533) 68.90	64.92_72.80	Musculoskeletal	(288/533) 54.00	49.79_58.27
1. Dysphagia	(153/367) 41.69	36.63_46.75	1. Arthalgia	(171/288) 59.38	53.68_65.07
2. Sicca sx	(27/363) 7.36	4.68_10.04	2. Myalgia	(23/288) 7.99	4.84_11.13
3. Reflux	(303/363) 82.56	78.67_86.46	3. Weakness	(107/288) 37.15	31.55_42.76
4. Reflux oesophagitis	(29/363) 7.90	5.13_10.67	4. Arthritis	(25/288) 8.68	5.42_11.95
5. Abnormal motility of oesophagus	(14/363) 3.61	1.85_5.78	5. Osteopenia	(49/288) 17.01	12.66_21.37
			6. Others	(54/288) 18.75	14.22_23.28
6. Full stomach	(9/363) 2.45	0.86_4.04			
7. Vomiting	(50/363) 13.62	10.10_17.15	Neuromuscular	(88/533) 16.51	13.35_19.67
8. Gastritis	(18/363) 4.90	2.69_7.12	1. Neuropathy	(51/88) 57.95	47.5_68.41
9. Malabsorption	(2/363) 0.54	0_1.30	2. Myopathy	(22/88) 25.00	15.83_34.17
10. Diarrhoea	(53/363) 14.44	10.83_18.05	3. Myositis	(16/88) 18.18	10.01_26.35
11. Constipation	(56/363) 15.26	11.57_18.95	4. Others	(23/88) 26.14	16.83_35.45
12. Mixed diarrhoea and constipation	(13/363) 3.54	1.64_5.44			
			Genitourinary involvement	(23/533) 4.32	2.59_6.04
13. Primary biliary cirrhosis	(2/2363) 0.54	0.0_1.3	Endocrine involvement	(81/533) 15.20	12.14_18.25
14. Chronic cholestasis liver disease	(1/363) 0.27	0.0_0.81	1. Hypothyroidism	(40/81) 49.38	38.33_60.44
			2. Hyperthyroidism	(6/81) 7.41	1.62_13.2
15. Pancreatitis	(1/363) 0.27	0.0_0.81	3. Diabetes	(30/81) 37.04	26.36_47.71
16. Anorexia	(24/363) 6.61	4.05_9.18			
17. Aphthus lesion	(11/363) 3.03	1.26_4.80	Anaemia	(242/533) 47.10	42.76_51.41
18. Others	(73/363) 20.11	15.97_24.25			

Others were defined as: Constitutional symptoms=[burn, epistaxis, gingival bleeding, itching, face puffiness, nasal bleeding, fever, allergic rhinitis, bone fracture, dysphonia, weight loss, hoarseness]; Skin involvements=[rash, photosensitivity, mechanical hand, eczema, leviducoloreticularis, gottron nodules, shawl sign]; Vascular involvement: [thrombophilia, vacuities, deep vein thrombosis]; Gastrointestinal= [anorexia, aphthus lesion, cholecystitis, GI bleeding, hiatal hernia, ascites, PUD, xerostomia, ascites]; Renal= [renal stone, cyst, nephritis, renal artery stenosis]; [cardiac= IHD, heart failure, endocarditis, tamponed, rheumatoid heart disease]; Musculoskeletal=[osteoporosis, osteopenia, clubbing, osteolysis, tendonitis, myositis, disk herniation]; Neuromuscular=[meningioma, convulsion, infarction, carpal tunnel syndrome]; MR: mitral regurgitation, TR: tricuspid regurgitation, AR: aortic regurgitation, PR: pulmonary regurgitation, MS: mitral stenosis, TS: tricuspid stenosis, AS: aortic stenosis, PS: pulmonary stenosis, RA/RV: right atrium and ventricle.

30.20) and late (25.3%, 95%CI: 18.23–32.46).

The serologic biomarkers were also identified and compared between three major types of scleroderma. Anti-SCL70 antibody (anti-topoisomerase 1 antibody) of 115 (21.7%) patients were documented; 64.3% (74/115) had positive results. ANA was also identified in 218 (41.1%) of patients' records with 165 (75.6%) being positive. ACLA was also documented for 107 (20.2%) of patients with 18.6% (20/107) of them having positive results. In addition, rheumatoid factor (RF) was also identified in 192 (36.1%) of cases; 28.1 (54/192) had positive results. 151 (28.4%) of patients' double stranded DNA (dsDNA)

Table II. The Comparison of clinical manifestations between three types of the disease.

Clinical Presentation	The frequency of presentations in various type (%, no)			*p*-value (3 groups)
	Diffused	Limited	Overlap SX	
Constitutional symptom	44.0% (89/202)	35.2% (69/196)	51.0% (47/92)	0.027**
Skin involvement	59.4% (120/202)	73.9% (145/196)	64.1% (59/92)	0.008**
1. Digital ulcer	39.6% (80/202)	47.9% (94/196)	22.8% (21/92)	<0.0001**
2. Telangiectasia	11.3% (23/202)	16.3% (32/196)	3.2% (3/92)	0.006**
Vascular involvement	63.3% (128/202)	75% (147/196)	68.4% (63/92)	0.043**
1. Raynaud	61.8% (125/202)	73.4% (144/196)	68.4% (63/92)	0.046**
GI involvement	78.2% (158/202)	59.1% (116/196)	66.3% (61/92)	<0.0001**
1. Reflux	67.8% (137/202)	50.5% (99/196)	48.9% (45/92)	<0.0001**
2. Vomiting	12.3% (25/202)	3.5% (7/196)	11.9% (11/92)	0.004**
3. Gastritis	1.9% (4/202)	0.5% (1/196)	8.6% (8/92)	<0.0001**
4. Diarrhoea	13.8% (28/202)	6.1% (12/196)	8.6% (8/92)	0.032**
5. Constipation	14.8% (30/202)	66.3% (13/196)	8.6% (8/92)	0.023**
Pulmonary involvement	77.7% (157/202)	42.3% (83/196)	46.7% (43/92)	<0.0001**
1. ILD	70.7% (143/202)	37.7% (74/196)	39.2% (36/92)	<0.0001**
2. Pulmonary hypertension	22.7% (46/202)	8.6% (17/196)	7.6% (7/92)	<0.0001**
Renal involvement	12.3% (25/202)	3% (6/196)	13% (12/92)	0.001**
1. Renal failure	5.4% (11/202)	0.5% (1/196)	3.2% (3/92)	0.017**
Cardiac involvement	33.6% (68/202)	17.3% (34/196)	31.5% (29/92)	0.001**
1. Pericardial involvement	15.8% (32/202)	3% (6/196)	14.1% (13/92)	<0.0001**
2. Myocardial involvement	13.3% (27/202)	2.5% (5/196)	13% (12/92)	<0.0001**
3. Valvular disease	18.3% (37/202)	7.6% (15/196)	17.3% (16/92)	0.005**
Musculoskeletal	58.4% (118/202)	42.8% (84/196)	72.8% (67/92)	<0.0001**
1. Arthralgia	29.7% (60/202)	29% (57/196)	45.6% (42/92)	0.011**
2. Weakness	18.8% (38/202)	13.7% (27/196)	36.9% (34/92)	<0.0001**
3. Oedema	14.3% (29/202)	7.6% (15/196)	17.3% (16/92)	0.031**
Neuromuscular involvement	13.8% (28/202)	12.7% (25/196)	32.6 (30/92)	<0.0001**
1. Neuropathy	8.4% (17/202)	8.1% (16/196)	18.4% (17/92)	0.014**
2. Myopathy	2.4% (5/202)	2.5% (5/196)	9.7% (9/92)	0.005**
3. Myositis	1.4% (3/202)	1.5% (3/196)	8.6% (8/92)	0.001**
Anaemia	48.7% (95/195)	37.7% (74/184)	55.4% (51/92)	0.044**

**Significant *p*-value (<0.05).

was also recorded, and found positive for 35 patients (23.1%). Moreover, Anti-LA (Anti-Sjögren's syndrome related antigen B, anti-SSB autoantibody) in 45 (8.4%) of patients was recorded and had positive results in only 1.1%. Anti-RO (Anti-Sjögren's syndrome-related antigen A, anti-SSA autoantibody), also, found in 63 (11.8%) of patients, which was positive in 27 (42.8%). SCL70 was just shown to have significant differences (*p*-value <0.0001) between three types of the disease with predominance in diffused form.

The causes of hospital admissions were also assayed for hospitalised patients; the most common ones were digital ulcer and receiving therapy for it (30.9%, 95% CI: 27.4–34.32), interstitial lung disease (5.7%, 95% CI: 3.94–7.41) and pulmonary arterial hypertension (3.1%, 95% CI: 1.77–4.35).

Among 533 patients, we found only 17 cases (3.1%, 95%CI: 1.69–4.66) of documented death. The most common causes were found to be pulmonary fibrosis (35.2%, 6/17, 95%CI: 10.72–59.86) and heart failure (29.4%, 5/17, 95%CI: 5.98–52.84).

Discussion

In this study, 533 records of scleroderma patients with mean age of 45 years old and female to male ratio of 7.3:1 were reviewed. It was previously found that the incidence of SSc is rare under the age of 25 and peaks in 5th and 6th decades of life (8). Reviewing previous surveys, showed female excess with ratio mostly between 3:1 to 8:1 (8).

Unlike our results, previous studies revealed that SSc is more prevalent in patients with positive family history of rheumatologic diseases, in relatives of either first or second degree (9). This discordance can be attributed to significant numbers of missing data as well as non-informative states of patients about their families' rheumatologic diseases.

Diffused type of SSc was shown to be the most prevalent form. Yet, north Italian and Argentina studies found the limited form being the most common type of the disease (10, 11). These controversies may be attributed to regional differences in clinical manifestations and, consequently, differently diagnosed type of SSc.

As it can be seen in the results, SSc is mostly overlapped by lupus erythematosus and rheumatoid arthritis, respectively. These results have controversies with Pakozdi *et al*. study, who found myositis and rheumatoid arthritis to be the most common diseases overlapping with SSc (12).

According to our results, Raynaud phenomenon and ILD were the two most common first presentations of SSc. One study recorded Raynaud and arthritis, while another survey suggested sclerodactyly and Raynaud to be the most common ones (13, 14).

Following the clinical presentations of SSc, it was concluded that nearly most of the patients had skin thickening (97.2%). The most common organ involvements were respectively gastrointestinal (68.9%), vascular (68.11%), mostly in form of Raynaud phenomenon, and other cutaneous involvements except skin thickening (64.4%). Pulmonary involvement was also shown to be the fourth organ involved (56.8%). However, the Japanese study found lung involvement to be the most common complication of the disease (15).

Comparing clinical manifestations between the two genders displayed that only renal involvement has significant difference with preponderance in male patients (*p*=0.04). Yet, Hashimoto *et al*. declared that lung involvement was significantly higher in male SSc patients (15).

Comparing clinical manifestations between the three major types of SSc showed that skin, and vascular involvement including Raynaud phenomenon were significantly more prevalent in limited form; gastrointestinal, pulmonary and cardiac involvement were seen more in diffused type, and renal, musculoskeletal, neuromuscular involvement, constitutional symptoms, and anaemia all were significantly more prevalent in overlap syndrome (all *p*<0.05). Yet,

previous surveys showed only Raynaud phenomenon and pulmonary involvement to be significantly more prevalent in diffused type (13, 14). These controversies between various studies around the world can be also due to regional variations seen in presentations of systemic sclerosis.

Capillaroscopies, as sensitive tools for SSc diagnosis and severity assessment (11), revealed that most of our patients were diagnosed in active phase of the disease. This may imply that by improving the diagnosis of SSc in early phases, better management and prevention of the disease can be achieved. However, considering the fact that most of our patients did not have documented capillaroscopies, a certain conclusion requires further evaluations.

Serologic markers were also considered as another diagnostic tool for SSc. A study in the north of Italy, on 118 cases, reported that anti-centromeric antibody (ACA) was positive in 60%, anti-topoisomerase 1 in 20% and antinuclear in 10% of the patients (10). Our results also showed ANA being positive in 75.6% (165/218), SCL70 in 64.3% (74/115), ACLA in 18.6% (20/107), RF in 28.1% (54/192) and ds-DNA in 23.1% (35/151). Comparing these markers between various types of scleroderma manifested that, only SCL70 was significantly higher in diffused form of the disease.

Due to the chronicity of scleroderma, most of the patients admitted in hospitals for several episodes during the course of their disease. Among 131 hospitalised Thai patients with 202 admissions, the most common causes was shown to be pneumonia (58.0%) (16). In our analyses, it was found that digital ulcer (30.9%) and interstitial lung disease (5.7%) were the two most common causes of hospitalisations. These variations may be attributed to either the variability of clinical presentations, the early or late diagnosis and management of the disease as well as the efficacy of treatment in different parts of the world.

Due to the nature of the disease, death mostly occurs lately in life of patients with SSc (17). One nation-wide survey estimated the mortality rate of the disease to be about 6.3% (18). We had only 17 (3.1%) deaths in 1 decade.

Respiratory failure was found to be the most common cause of death. Previous studies had also considered pulmonary involvement in the form of either ILD or pneumonia as the most common leading causes of death (16, 18). Although variations in health care facilities as well as in prevalence of clinical presentations among the patients from different regions of the world can be one cause of these differences, further investigations on death aetiologies of Iranian SSc patients with a larger set of data is highly recommended.

One limitation of our study was the missing data, which is inevitable in retrospective surveys. In spite of that, we tried to minimise it to 8.9% by reviewing both hospital and clinic's records of the patients.

Despite the mentioned limitations, we had a larger number of cases comparing to previous analogous studies. Moreover, this study can be introduced as the first epidemiologic study done in Iran, which considered almost all aspects of SSc's epidemiology. The necessity of performing regional researches on systemic sclerosis is mostly related to worldwide variations in the first presentations and complications of the disease. This point can be important for defining better and earlier diagnosis as well as a more efficient in-patient and out-patient management of the disease. This may also be a guide for further multi-provincial epidemiologic studies on Iranian patients, as well as multinational and interracial studies on scleroderma.

Acknowledgements

The authors wish to thank Mr Eric Rahimian for editing the manuscript, as well as all the personnel of the Tertiary Centres of Rheumatology and File Keeping Centre of the Shiraz University of Medical Sciences for their cooperation for accessing the patients' records.

References

1. KATSUMOTO TR, WHITFIELD ML, CONNOLLY MK: The pathogenesis of systemic sclerosis. *Annu Rev Pathol* 2011; 6: 509-37.
2. BLOSTER MB, SILVER RS: Clinical features of systemic sclerosis, in Rheumatology. HOCHBERG MC, *et al*. (Eds.). Elsivier: Philadelphia. 2011; 1373-86.
3. RANQUE B, MOUTHON L: Geoepidemiology of systemic sclerosis. *Autoimmun Rev* 2010; 9: A311-8.
4. POORMOGHIM H, MOGHADAM AS, MORADI-LAKEH M *et al*.: Systemic sclerosis: demographic, clinical and serological features in 100 Iranian patients. *Rheumatol Int* 2013; 33: 1943-50.
5. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23: 581-90.
6. LONGO DL: Systemic Sclerosis (Scleroderma) and Related Disorders in Harrison's Principles of Internal Medicine. New York: McGraw-Hill. 2012; 2757-69.
7. VARGA J: Overview of the clinical manifestations of systemic sclerosis (scleroderma) in adults. 2015; Up to Date.
8. SILMAN AJ: Epidemiology of scleroderma. *Ann Rheum Dis* 1991; 50 (Suppl. 4): 846-53.
9. ARNETT FC, CHO M, CHATTERJEE S, AGUILAR MB, REVEILLE JD, MAYES MD: Familial occurrence frequencies and relative risks for systemic sclerosis (scleroderma) in three United States cohorts. *Arthritis Rheum* 2001; 44: 1359-62.
10. LO MONACO A, BRUSCHI M, LA CORTE R, VOLPINARI S, TROTTA F: Epidemiology of systemic sclerosis in a district of northern Italy. *Clin Exp Rheumatol* 2011; 29 (Suppl. 65): S10-4.
11. PEREIRA DA, DIAS OM, ALMEIDA GE *et al*.: Lung-dominant connective tissue disease among patients with interstitial lung disease: prevalence, functional stability, and common extrathoracic features. *J Bras Pneumol* 2015; 41: 151-60.
12. PAKOZDI A, NIHTYANOVA S, MOINZADEH P, ONG VH, BLACK CM, DENTON CP: Clinical and serological hallmarks of systemic sclerosis overlap syndromes. *J Rheumatol* 2011; 38: 2406-9.
13. MONEIM GA *et al*.: Frequency of disease subsets and patterns of organ involvement among Egyptian patients with systemic sclerosis - A retrospective study. *The Egyptian Rheumatologist* 2013; 35: 145-9.
14. PAGALAVAN L, ONG SG: Demography, clinical and laboratory features of systemic sclerosis in a Malaysian rheumatology centre. *Med J Malaysia* 2007; 62: 117-21.
15. HASHIMOTO A, ENDO H, KONDO H, HIROHATA S: Clinical features of 405 Japanese patients with systemic sclerosis. *Mod Rheumatol* 2012; 22: 272-9.
16. NETWIJITPAN S, FOOCHAROEN C, MAHAKKANUKRAUH A, SUWANNAROJ S, NANAGARA R: Indications for hospitalization and in-hospital mortality in Thai systemic sclerosis. *Clin Rheumatol* 2013; 32: 361-7.
17. DENTON CP: Systemic sclerosis: from pathogenesis to targeted therapy. *Clin Exp Rheumatol* 2015; 33 (Suppl. 92): S3-7.
18. CHUNG L, KRISHNAN E, CHAKRAVARTY EF: Hospitalizations and mortality in systemic sclerosis: results from the Nationwide Inpatient Sample. *Rheumatology* (Oxford) 2007; 46: 1808-13.