Sex and time to diagnosis in systemic sclerosis: an updated analysis of 1,129 patients from the Canadian Scleroderma Research Group Registry

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ABSTRACT

Objective. *A previous study found that time to diagnosis was significantly longer from onset of Raynaud's phenomenon for women compared to men with diffuse systemic sclerosis (SSc) and that, in limited SSc, it was more than twice as long for women than men. That study was limited, however, by the small number of men in disease subtype subgroups. The objective of the present study was to investigate the association of sex with time to diagnosis of SSc using a substantially larger patient sample.*

Methods. *Association between sex and time to diagnosis was assessed overall and stratified based on diffuse versus limited disease using Kaplan-Meier curves and Cox proportional hazards models.*

Results. *There were 1,129 patients in the study (median age=56.0 years; 978 [86.6%] women). Time to diagnosis was significantly longer for women (median=1.1 years) than men (median 0.8=years; p=0.037) with diffuse SSc following onset of Raynaud's phenomenon. There were no significant or substantive sex differences in time to diagnosis after Raynaud's onset in limited SSc or from onset of first non-Raynaud's disease manifestation in diffuse or limited SSc.*

Conclusion. *Time to diagnosis was significantly longer for women compared to men with diffuse SSc following onset of Raynaud's phenomenon, but the difference was small and unlikely to be clinically significant. There were no differences in time to diagnosis following Raynaud's onset in limited disease or following onset of first non-Raynaud's disease manifestation in diffuse or limited disease. Overall, sex does not appear to influence time to diagnosis meaningfully.*

Introduction

Time to diagnosis or referral to specialist services is longer for women compared to men in many medical conditions, including chronic obstructive pulmonary disease (1), cystic fibrosis (2), and rheumatoid arthritis (3). Systemic sclerosis (SSc) is a chronic, autoimmune, connective tissue disorder. Because it has low prevalence and is highly heterogeneous in its presentation, especially initially, receiving a diagnosis can be a long and difficult process (4). Initial diagnosis among women may be further complicated because Raynaud's phenomenon, which is a common, initial symptom of SSc, is more prevalent among women than men in the general population (5) and therefore may be less likely to raise suspicions of SSc in women (6).

A previous study of 408 patients with SSc from the Canadian Scleroderma Research Group (CSRG) Registry (7) found that women with diffuse SSc reported a longer time to diagnosis (median=1.0 years) compared to men with diffuse SSc (median=0.7 years) from the onset of Raynaud's phenomenon. Median time to diagnosis from the onset of Raynaud's phenomenon among patients with limited SSc was more than twice as long for women (4.6 years) compared to men (2.1 years), but this was not statistically significant. An important limitation of that study, however, was that only 61 (15.0%) of the 408 patients were men, including only 32 men with diffuse SSc and only 29 men with limited SSc, which limited confidence in the findings. Thus, the objective of the present study was to update the previous investigation using a substantially larger patient sample of women and men with SSc.

Methods

Patients and procedure

The sample consisted of patients enrolled in the CSRG Registry between August 2004 and February 2012. Pa-

tients included the 408 patients from the previous study (7), as well as additional patients who subsequently enrolled in the Registry. Patients in the CSRG Registry are recruited from 15 centers across Canada and are eligible for enrolment if they are ≥18 years old, are fluent in English or French, and have been diagnosed with SSc by a Registry rheumatologist. At enrolment, patients undergo a physician assessment. At this time, their medical history is collected and physical and laboratory evaluations are performed. Study physicians document dates of onset of Raynaud's phenomenon, onset of the first non-Raynaud's disease manifestation, and SSc diagnosis. They perform a skin examination and classify patients into diffuse, limited, and sine SSc subtypes, based on Leroy *et al*.'s (8) definition. In this study, patients with sine SSc were included in the limited SSc subtype. The study was approved by the Institutional Review Board of McGill University, and all Registry patients provided written consent.

Data analysis

Sociodemographic and medical characteristics were compared by sex using chi-square tests for categorical variables and Mann-Whitney U-tests for continuous variables. To assess the association between sex and time to diagnosis on an unadjusted basis, Kaplan-Meier curves and log-rank tests were done. To examine the association after adjusting for age, education, marital status, and disease subtype, multivariate Cox proportional hazards models were used. Analyses were performed for the whole sample and stratified by disease subtype.

Results

Sample characteristics

The study included 1,129 SSc patients. Median age was 56 years (interquartile range [IQR]=48–63 years), and 978 (86.6%) were women. Approximately two-thirds (n=763, 67.6%) of patients were married and approximately half (n=540, 47.8%) had more than a high school education. There were 418 patients (37.0%) with diffuse SSc, 668 patients (59.2%) with limited SSc, and 43 (3.8%) with sine SSc. Median disease duration was 11.9 years (IQR=4.6–21.5 years) since onset of Raynaud's phenomenon, 8.3 years (IQR=3.2–16.2 years) since onset of the first non-Raynaud's disease manifestation, and 5.2 years (IQR=1.3–12.3 years) since diagnosis.

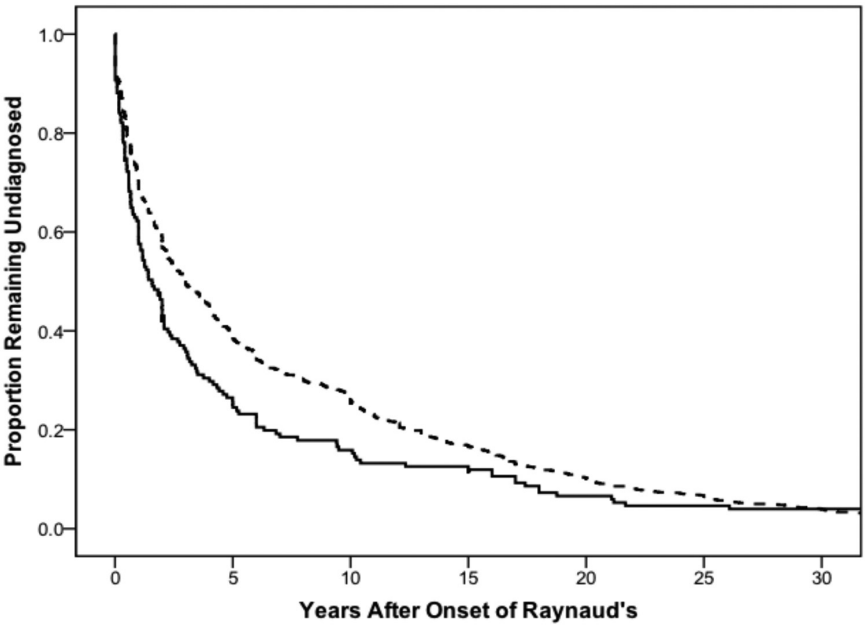

Fig. 1. The time to diagnosis after the onset of Raynaud's phenomenon for women compared to men. The dotted line represents women and the solid line represents men. The difference was statistically significant (log-rank p=.004).

Table I. Sociodemographic, medical characteristics, and time to diagnosis among men and women

	Total Sample (n=1,129)	Women (n=978)	Men (n=151)	p-value
Sociodemographic Characteristics				
Age in years, median (IQR)	56 (48, 63)	56 (48, 64)	54 (46, 62)	0.077
Married, n (%)	763 (67.6)	111 (73.5)	652 (66.7)	0.095
More than a high school education, n (%)	540 (47.8)	67 (44.4)	473 (48.4)	0.361
Medical Characteristics				
Diffuse subtype, n (%)	418 (37.0)	336 (34.4)	82 (54.3)	<0.001
Time since onset of Raynaud's phenomenon in years, median (IQR)	11.9 (4.6, 21.5)	12.4 (5.1, 22.4)	7.4 (3.1, 15.9)	<0.001
Time since onset of first non-Raynaud's disease manifestation in years, median (IQR)	8.3 (3.2, 16.2)	9.0 (3.3, 16.7)	5.5 (2.6, 12.5)	0.001
Time since diagnosis of SSc in years, median (IQR)	5.2 (1.3, 12.3)	5.5 (1.4, 12.6)	3.3 (0.7, 9.5)	0.001
Time between onset of Raynaud's phenomenon and onset of first non-Raynaud's disease manifestation in years, median (IQR)	0.5 (0.0, 5.0)	0.6 (0.0, 5.0)	0.0 (0.0, 1.6)	<0.001
Time to diagnosis in years, median (IQR) After onset of Raynaud's phenomenon	2.8 (0.7, 10.0)	3.0 (0.8, 10.1)	1.6 (0.4, 5.0)	0.001
After onset of first non-Raynaud's disease manifestation	0.9 (0.2, 3.3)	1.0 (0.2, 3.4)	0.9 (0.3, 3.1)	0.921

IQR: interquartile range.

Women were less likely than men to have diffuse SSc (34.4% *vs*. 54.3%, p<0.001). Median disease duration since onset of Raynaud's phenomenon was significantly longer among women compared to men (12.4 *vs*. 7.4 years, p<0.001), as was median disease duration since onset of the first non-

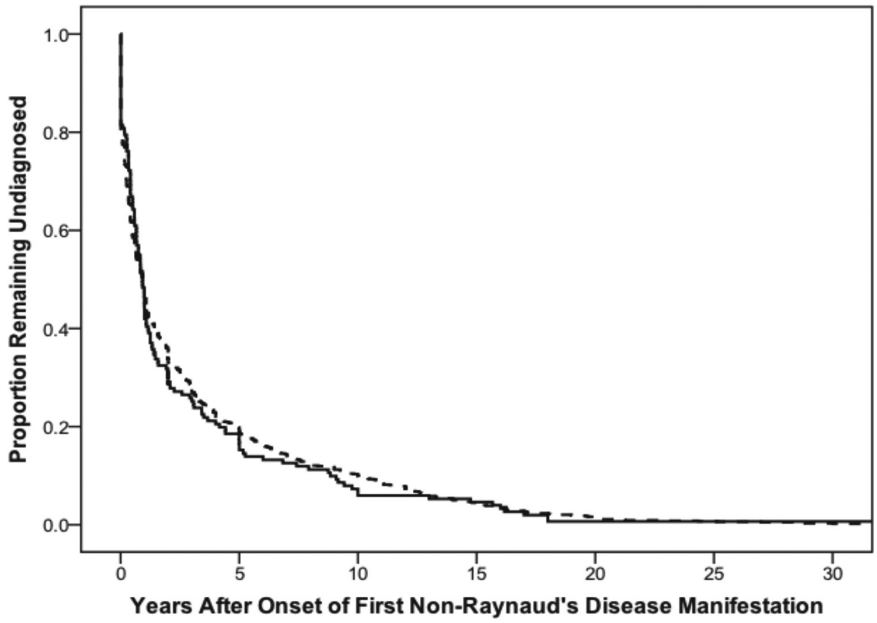

Fig. 2. The time to diagnosis after the onset of the first-non-Raynaud's disease manifestation for women compared to men. The dotted line represents women and the solid line represents men. The difference was not statistically significant (log-rank *p*=.623).

Raynaud's disease manifestation (9.0 *vs*. 5.5 years, *p*=0.001) and median disease duration since diagnosis of SSc (5.5 *vs*. 3.3 years, *p*=0.001).

Time to diagnosis

Overall, median time to diagnosis was 2.8 years (IQR=0.7–10.0) after onset of Raynaud's phenomenon and 0.9 years (IQR=0.2–3.3) after onset of the first non-Raynaud's disease manifestation. Based on Kaplan-Meier analyses, time to diagnosis after onset of Raynaud's phenomenon was significantly longer for women than men (log-rank *p*=0.004, Fig. 1, Table II). Time to diagnosis after onset of the first non-Raynaud's disease manifestation, on the other hand, was not significantly different (log-rank *p*=.623, Fig. 2, Table II). When adjustment was made for sociodemographic characteristics (age, education level, marital status) and disease subtype, however, the likelihood of being diagnosed after onset of Raynaud's phenomenon (hazards ratio [HR]=0.85, 95% confidence interval [CI] 0.72–1.01, *p*=0.073) and the likelihood of being diagnosed after onset of the first non-Raynaud's disease manifestation (HR=1.02, 95% CI 0.86–1.21, *p*=.843) did not significantly differ between women and men (Tables III and IV, respectively).

Among patients with diffuse SSc, the median time to diagnosis was 1.0 years (IQR=0.3–4.0) after onset of Raynaud's phenomenon and 0.7 years (IQR=0.2–1.9) after onset of the first non-Raynaud's disease manifestation. Kaplan-Meier curves showed that the only significant difference in time to diagnosis between women and men with diffuse SSc was after onset of Raynaud's phenomenon, where women reported a slightly longer time to diagnosis (median=1.1 years) compared to men (median=0.8 years; log-rank *p*=0.037; Table II). As shown in Table III, this difference was also significant (HR=0.78, 95% CI 0.61–0.99, *p*=0.042) after adjusting for age, education level, and marital status. There was no significant difference in time to diagnosis after onset of the first non-Raynaud's disease manifestation between women and men with diffuse SSc when adjusting for these variables (Table IV).

Among patients with limited SSc, the median time to diagnosis was 4.5 years (IQR=1.3–12.1) after onset of Raynaud's phenomenon and 1.0 years (IQR=0.2–4.3) after onset of the first non-Raynaud's disease manifestation. Median time to diagnosis after onset of Raynaud's phenomenon was 4.6 years (IQR=4.0–5.1) for women with limited SSc and 3.5 years (IQR=1.9–5.1) for men with limited SSc, which was not significant based on Kaplan-Meier analysis (log-rank *p*=.598, Table II). Similarly, time to diagnosis after onset of the first non-Raynaud's disease manifestation did not differ significantly between women and men with limited SSc (Table II). Results were unchanged when adjusting for age, education level, and marital status (Tables III and IV).

Table II. Time to diagnosis after onset of Raynaud's or first non-Raynaud's disease manifestation.

	Total Sample			Diffuse Subtype			Limited Subtype		
	Women (n=978)	Men (n=151)	Log-Rank *p*-value	Women (n=336)	Men (n=82)	Log-Rank *p*-value	Women (n=642)	Men (n=69)	Log-Rank *p*-value
Median time to diagnosis after onset of Raynaud's phenomenon in years (95% CI)	3.0 (2.5-3.5)	1.6 (1.0-2.2)	0.004	1.1 (0.8-1.4)	0.8 (0.5-1.1)	0.037	4.6 (4.0-5.1)	3.5 (1.9-5.1)	0.598
Median time to diagnosis after onset of first non-Raynaud's disease manifestation in years (95% CI)	1.0 (0.9-1.1)	0.9 (0.7-1.1)	0.623	0.7 (0.6-0.8)	0.7 (0.5-0.9)	0.597	1.0 (0.8-1.2)	1.1 (0.7-1.5)	0.548

CI: confidence interval.

Table III. Predictors of time to diagnosis after onset of Raynaud's based on Cox proportional hazards model.

	Total Sample		Diffuse Subtype		Limited Subtype	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	0.99 (0.98-0.99)	<0.001	0.99 (0.98-1.00)	0.034	0.99 (0.98-0.99)	<0.001
Female sex	0.85 (0.72-1.01)	0.073	0.78 (0.61-0.99)	0.042	0.96 (0.74-1.24)	0.746
Married	1.08 (0.95-1.22)	0.252	1.11 (0.90-1.37)	0.314	1.07 (0.91-1.26)	0.419
More than a high school education	0.94 (0.83-1.05)	0.273	0.98 (0.80-1.19)	0.811	0.89 (0.76-1.04)	0.145
Diffuse subtype	1.66 (1.47-1.88)	<0.001	-----	-----	-----	-----

CI: confidence interval; HR: hazards ratio.

Table IV. Predictors of time to diagnosis after onset of first non-Raynaud's disease manifestation based on Cox proportional hazards model.

	Total Sample		Diffuse Subtype		Limited Subtype	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	0.99 (0.99-1.00)	0.006	1.00 (1.00-1.01)	0.431	0.99 (0.99-1.00)	0.008
Female sex	1.02 (0.86-1.21)	0.843	0.94 (0.74-1.20)	0.628	1.10 (0.85-1.42)	0.467
Married	1.12 (0.98-1.26)	0.086	1.10 (0.90-1.36)	0.354	1.12 (0.95-1.32)	0.165
More than a high school education	0.98 (0.87-1.11)	0.770	0.90 (0.74-1.09)	0.274	1.06 (0.91-1.23)	0.486
Diffuse subtype	1.31 (1.15-1.48)	<0.001	-----	-----	-----	-----

CI: confidence interval; HR: hazards ratio.

Discussion

The main finding was that it took significantly longer for women with diffuse SSc (median=1.1 years) to receive a diagnosis than men with diffuse SSc (median=0.8 years) following onset of Raynaud's phenomenon, although the difference was small (0.3 years) and not likely clinically meaningful. There was no significant sex difference in time to diagnosis after onset of Raynaud's phenomenon in limited SSc. Similarly, there were no significant sex differences in time to diagnosis after onset of the first non-Raynaud's disease manifestation in diffuse or limited SSc.

A previous study (7) that examined only 408 of the 1,129 patients included in this study also found a statistically significant, but small, difference in time to diagnosis for women with diffuse disease (median 1.0 years) compared to men with diffuse disease (median 0.7 years) from onset of Raynaud's phenomenon. The previous results differed from the present study, however, in that among patients with limited SSc, time to diagnosis after onset of Raynaud's phenomenon was more than twice as long for women (median=4.6 years) compared to men (median=2.1 years; p=0.085). In the present study, the difference between medians was much smaller (1.1 years) and not close to statistical significance (p=0.598). Neither study found sex differences in time to diagnosis from onset of the first non-Raynaud's disease manifestation.

Limitations of the present study include the use of a registry sample that may not represent the full spectrum of the SSc population and retrospective reporting of outcome variables. We did not have data that would allow us to identify a subgroup of patients who may be at high risk of delayed diagnosis. Furthermore, we were not able to assess factors that could be related to disease progression and time to diagnosis, such as alterations in microcirculation (9), or genetic factors (10, 11).

In summary, this study found that time to diagnosis was significantly longer for women with diffuse SSc than men with diffuse SSc after onset of Raynaud's phenomenon, although the magnitude of the difference was small and not clinically important. There were no sex differences in time to diagnosis from onset of Raynaud's phenomenon in limited disease or from onset of non-Raynaud's phenomenon in diffuse or limited disease.

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