Clinical and serological differences of an Italian Sjögren's disease cohort according to three geographic macro-area localisations

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Abstract

Objective

The phenotype of Sjögren's disease (SjD) may be influenced by several variables. Among these, the role of patient geolocation has been poorly explored. The study compared epidemiologic, serologic, clinical features and comorbidities according to geographical origin in a large Italian multicentre SjD cohort.

Methods

This is a retrospective analysis of a multicentre SjD cohort (2016 ACR/EULAR criteria) consecutively included in the Italian SjD Study Group registry and grouped into three macrogeographic areas: North, Centre and South. Disease-specific epidemiologic, serologic, histologic and clinical variables were collected. Comorbidities, traditional cardiovascular (CV) risk factors and history of CV events were also recorded. All data were stratified by geographic area to assess regional differences.

Results

1231 SjD patients, median 53 (42-63) years at diagnosis and 95% females, were included. No differences were observed in sex distribution or ethnicity among the three areas. Patients from the South had older age at diagnosis compared to the North (55 vs. 51 years, p=0.001) and Centre (55 vs. 51 years, p=0.002) and higher frequency of activity in the constitutional and articular but lower in biological domains (p<0.001 for all). Hypertension and hypercholesterolaemia were more prevalent in the Centre and obesity was more common in the South compared to the North (p<0.001). No significant differences were observed in other CV risk factors and CV events.

Conclusion

This study provides the first evidence of geo-epidemiological differences among Italian SjD patients, highlighting how geographic origin is associated with disease phenotype and comorbidities. These regional disparities likely reflect environmental, socio-cultural and healthcare system-related factors, underscoring the need for personalised disease management strategies.

Key words

Sjögren's disease, geographic area, phenotype, environment, comorbidity

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Introduction

Sjögren's disease (SjD), a systemic autoimmune condition primarily affecting middle-aged women, is increasingly recognised as a clinically heterogeneous condition whose expression may be influenced by a complex interplay of genetic predisposition, immunologic factors, and environmental exposures (1). The lymphocytic infiltration of salivary and lacrimal glands represents the hallmark of the disease, resulting in xerostomia and keratoconjunctivitis sicca. However, up to 50% of patients may also present with extra-glandular manifestations, reflecting the systemic nature of the disease and contributing to a more complex and potentially severe disease course (1, 2). Notably, the higher risk of cardiovascular (CV) and lymphoproliferative disease exerts a significant impact on disease prognosis and represents a major cause of morbidity and mortality in these patients (3, 4).

While the classical presentation is dominated by sicca symptoms and glandular involvement, the broad spectrum of systemic manifestations and serological profiles has prompted researchers to investigate potential external modulators of disease phenotypes. Among these, geo-epidemiological factors have emerged as crucial, yet underexplored, contributors (5). Geographic variability in autoimmune disease incidence and clinical presentation has been well documented in conditions such as systemic lupus erythematosus and multiple sclerosis, where gradients in latitude, pollution levels, and socioeconomic determinants have been linked to distinct clinical trajectories (6). These findings are supported by the concept of the "geographical gradient" in autoimmunity, which postulates that disease patterns vary across latitudinal and environmental axes due to differential exposures, healthcare infrastructure and genetic background, with some even suggesting a north-south gradient in their distribution (2, 7).

In SjD, increasing evidence supports the role of ethnicity, as well as demographic and geo-epidemiological variables - such as age, sex and area of residence - in shaping the clinical and serological phenotype. Furthermore, it is now also widely acknowledged that diet and environmental exposures, including air pollution and extreme climatic conditions, can further modulate disease expression, influencing both sicca symptoms and systemic involvement (8-10). In this setting, recent large-scale, multicentre studies, including those from the Big Data Sjögren Project Consortium, have emphasised that place of residence and ethnicity significantly influence the phenotypic expression of SjD, particularly at diagnosis. These data highlighted the role of climate-related hazards (*e.g.* humidity, temperature extremes), atmospheric pollution, and even local microbiota composition as modulators of disease severity and systemic involvement (11, 12).

In the Italian context, where regional disparities in health status, economic indicators and healthcare delivery are well documented, such geo-epidemiological investigations are particularly relevant (13). In fact, the Country offers a unique natural model to study intra-national variability, owing to its cultural, climatic and infrastructural diversity. This variable is particularly complex, as it encompasses a range of social determinants of health that can substantially affect disease outcomes. In Italy, for instance, clear regional disparities exist in perceived health status, with self-reported poor health ranging from 4% in Trentino-Alto Adige to 10% in southern regions such as Calabria and Sicily (14-16). Nevertheless, despite the existence of national registries and multicentre collaborations, the geo-clinical profile of SjD across Italy remains poorly characterised.

This study seeks to fill that knowledge gap by providing the first analysis of clinical and serological differences among Italian SjD patients grouped according to three macro-regional areas. By leveraging data from the Italian Research Group on Sjögren's Syndrome (GRISS) registry, we aim to delineate geographic patterns in clinical and serologic disease expression, examine potential disparities in diagnostic approaches, and explore how local healthcare infrastructure and environmental conditions might shape patient outcomes. An additional goal is to exam-

ine regional variations in diagnostic and therapeutic pathways, considering that differences in healthcare resources and centre expertise may impact clinical management. Our findings may serve as a foundation for future personalised approaches to disease management, taking regional variability into account.

Methods

This study is a retrospective analysis of data from a multicentre cohort of SjD patients classified according to the 2002 AECG and 2016 ACR/EULAR criteria (17, 18). Patients were consecutively enrolled in the Italian GRISS registry and monitored across seven Rheumatology Centres, which were categorised into three macrogeographic regions: Northern Italy (Milan, Udine), Central Italy (Florence, Perugia, Rome), and Southern Italy (L'Aquila, Messina).

For each patient, the following data were collected at inclusion: age at disease diagnosis, gender, ethnicity, geographic group (North, Central, or South Italy), presence of antinuclear antibodies (ANA) ≥1:160, anti-SSA/Ro (including anti-Ro52 and anti-Ro60 specificity), anti-SSB/La, anti-centromere antibodies, rheumatoid factor (RF), C3 and C4 complement levels, cryoglobulinaemia and cryocrit percentage, immunoglobulin (IgG) levels at diagnosis, disease activity according to ESSDAI (19) and symptom severity according to ESSPRI (20) at diagnosis, presence of xerophthalmia and xerostomia, Schirmer's test, break-up time (BUT) and unstimulated salivary flow rate, minor salivary gland biopsy findings, including focus score (FS) assessment, presence of Raynaud's phenomenon and extraglandular manifestations according to ESSDAI domains. Additionally, the following variables were collected as cumulative data: comorbidities, including history of solid malignancy, coeliac disease, primary biliary cholangitis, autoimmune thyroiditis, fibromyalgia and history of serious infection, and traditional CV risk factors, including hypertension, hypercholesterolaemia, hypertriglyceridaemia, type 2 diabetes mellitus, obesity according to body mass index and smoking history (current, never, former). Diabetes mellitus was defined by a fasting glucose of ≥126 mg/dL or the use of antidiabetic drugs. Hypertension was defined as a previous physician's diagnosis or current antihypertensive treatment. Hypercholesterolaemia and hypertriglyceridaemia

Table I. Demographic, clinical and serological features of SjD patients.

Female sex, n (%)	1170/1231	(95)
Ethnicity, n (%)		
Caucasian	1192/1231	(96.8)
Afro-American	1/1231	(0.2)
Asian	6/1231	(0.5)
Hispanic	31/1231	(2.5)
Other systemic AD, n (%)	119/1231	(9.7)
Smoking status, n (%)		
Current	73/812	(9)
Former	120/812	(14.8)
Geographic group, n (%)		
North	532/1231	(43.2)
Centre	313/1231	(25.4)
South	386/1231	(31.3)
Age at diagnosis, median	53	(42-63)
ESSDAI at onset, median	2	(1-4)
ESSPRI at onset, median	5.66	(4-7.33)
Xerophthalmia, n (%)	1128/1231	(91.6)
Xerostomia, n (%)	1097/1231	(89.1)
Xero trachea, n (%)	160/1231	(13)
Vaginal dryness, n (%)	225/1231	(18.3)
Raynaud's phenomenon, n (%)	196/1231	(15.9)
Schirmer's test <5 mm/5min, n (%)	800/974	(82.1)
Reduced BUT, n (%)	244/303	(80.5)
Unstimulated WSF (ml/min), median	1	(0.05-1)
SG biopsy done, n (%)	651/1231	(52.9)
Scoring method, n (%)		
Chisolm Mason	104/651	(16)
Focus score	432/651	(89.1)
Both	19/651	(2.9)
Focus score, median	2	(1-3)
Chisolm Mason, n (%)		
1	29/104	(27.9)
2	20/104	(19.2)
3	35/104	(33.6)
4	36/104	(34.6)
ESSDAI domains		
Constitutional, n (%)	134/1231	(10.9)
Lymphadenopathy, n (%)	238/1231	(19.3)
Lymphomas/leukaemias, n (%)	59/1231	(4.8)
Glandular, n (%)	321/1231	(26.1)
Articular, n (%)	601/1231	(48.8)
Cutaneous, n (%)	123/1231	(10)
Pulmonary, n (%)	77/1231	(6.2)
Renal, n (%)	22/1231	(1.8)
Muscular, n (%)	27/1231	(2.2)
PNS, n (%)	81/1231	(6.6)
CNS, n (%)	6/1231	(0.5)
Haematological, n (%)	213/1231	(15)
Biological, n (%)	551/1231	(44.8)
Serological markers		
Rheumatoid factor, n (%)	512/1231	(41.6)
ANA ≥ 1:160, n (%)	1032/1231	(83.8)
Anti-Ro, n (%)	891/1231	(72.4)
Anti-Ro52, n (%)	380/783	(48.5)
Anti-Ro60, n (%)	367/774	(47.4)
Anti-La, n (%)	453/1231	(36.8)
Anti-centromere, n (%)	46/1231	(3.7)
Other auto-Abs/LAC, n (%)	99/1231	(8.1)
IgG levels at diagnosis (mg/dL), median	1542	(1149-2001)
IgA levels at diagnosis (mg/dL), median	257	(182-364)
IgM levels at diagnosis (mg/dL), median	138	(92-188)
Beta2-microglobulin, median	2.7	(0.36-24)
Cryocrit (%), median	1.5	(1-10)

were defined as previous diagnosis or need for treatment as defined by the ESC/EAS Guidelines for the management of dyslipidaemias. Finally, history of major CV events, including acute coronary syndrome, stable angina, ischaemic stroke and peripheral artery disease, was recorded. The study was approved by the Ethics Committee (no. 27843/23/ON) and was conducted in accordance with current ethical guidelines and regulations.

Statistical analysis

All data were categorised by geographic region to evaluate potential regional variations. Categorical variables were analysed using the Chi-square test, while continuous variables were compared with the Kruskal-Wallis test. A significant level of 0.05 was applied to all analyses. Pairwise comparisons between geographic groups were conducted using Holm-Bonferroni correction. Statistical analyses were carried out using dedicated biostatistical software (IBM SPSS Statistics v. 26). Values are shown as median (range) unless otherwise stated.

Results

A total of 1,231 SjD patients with a median age at diagnosis of 53 years (42–63 years) were included in the study (Table I). Most patients were female (95%) and of Caucasian ethnicity (96.8%). At disease onset, the median ESSDAI and ESSPRI scores were 2 (1–4) and 5.66 (4–7.3), respectively. Among the 12 ESSDAI domains, the most frequently affected were the articular (48.8%), biological (44.8%) and glandular (26%) domains. The most prevalent symptom was xerophthalmia, affecting 91.6% of patients, with 82.1% showing a positive Schirmer's test and 80.5% exhibiting a reduced BUT test. Xerostomia was present in 89.1% of cases. The most common systemic manifestations were joint involvement (48.8%), lymphadenopathy (19.3%), Raynaud's phenomenon (15.9%), autoimmune cytopenias (15%), and skin manifestations (10%). Among the 651 patients (52.9%) who underwent a minor salivary gland biopsy, 432 (89.1%) had their focus score evaluated, with a

Table II. Comorbidities and cardiovascular risk in SjD patients.

Comorbidities	
Other malignancies, n (%)	98/1231 (7.96)
Autoimmune thyroiditis, n (%)	263/1231 (21.36)
Primary biliary cholangitis, n (%)	26/1231 (2.11)
Coeliac disease, n (%)	27/1231 (2.19)
Fibromyalgia, n (%)	132/1231 (10.72)
History of serious infections, n (%)	45/1231 (3.65)
Cardiovascular risk factors	
Hypertension, n (%)	313/1231 (25.42)
High cholesterol, n (%)	185/1231 (15.02)
High triglycerides, n (%)	68/1231 (5.52)
Type 2 diabetes, n (%)	38/1231 (3.08)
Obesity, n (%)	50/1231 (4.06)
Cardiovascular disease	
Acute coronary syndrome, n (%)	18/1231 (1.46)
Stable angina, n (%)	8/1231 (0.64)
Ischaemic stroke, n (%)	13/1231 (1.05)
Peripheral artery disease, n (%)	3/1231 (1.86)

Table III. Demographic and clinical variables in SjD patients grouped according to geographical area.

	N	C	S	*p* omnibus *p* N *vs*. C *p* N *vs*. S *p* C *vs*. S
Female sex, n (%)	500 (94)	302 (96.5)	368 (95.33)	0.257
Ethnicity, n (%)				
Caucasian	513 (96.4)	303 (96.8)	376 (97.4)	0.794
Afro-American	0 (0)	1 (0.3)	1 (0.2)	
Asian	3 (0.6)	2 (0.6)	1 (0.2)	
Hispanic	16 (6.)	7 (2.2)	8 (2.1)	
Age at diagnosis, n (%)	51 (42-61)	51 (40-63)	55 (45-65)	<0.001 N *vs*. C: 0.783 N *vs*. S: 0.001 C *vs*. S: 0.002
Other systemic AD, n (%)	73 (13.7)	14 (4.5)	32 (8.3)	0.005 N *vs*. C: 0.002 N *vs*. S: 0.088 C *vs*. S: 0.279
Smoking status, n (%)				<0.001
Current	17 (3.2)	24 (7.7)	32 (8.3)	N *vs*. C: <0.001
Former	31 (5.8)	66 (21.1)	23 (5.9)	N *vs*. S: <0.001
Unknown	277 (52.1)	62 (19.8)	80 (20.7)	C *vs*. S: <0.001
ESSDAI at onset, median	2 (1-3)	2 (0.75-5)	2 (0-5)	0.489
ESSPRI at onset, median	5.66 (4-7.33)	3 (1.33-7.3)	7 (5-8)	0.15
Xerophthalmia, n (%)	500 (94)	267 (85.3)	361 (93.5)	<0.001 N *vs*. C: <0.001 N *vs*. S: 0.775 C *vs*. S: <0.001
Xerostomia, n (%)	488 (91.7)	252 (80.5)	357 (92.5)	<0.001 N *vs*. C: <0.001 N *vs*. S: 0.675 *C vs. S:* <0.001
Xero trachea, n (%)	64 (12)	29 (9.3)	67 (17.3)	0.005 N *vs*. C: 0.215 N *vs*. S: 0.046 C *vs*. S: 0.006
Vaginal dryness, n (%)	73 (13.7)	75 (24)	77 (20)	0.001 N *vs*. C: <0.001 N *vs*. S: 0.024 C *vs*. S: 0.201
Schirmer's test, n (%)				0.093
<5 mm/5min	361 (67.8)	193 (61.7)	246 (63.7)	
not done	106 (19.9)	77 (24.6)	74 (19.2)	

	N	C	S	*p* omnibus *p* N *vs*. C *p* N *vs*. S *p* C *vs*. S
BUT, n (%)				<0.001
Reduced	78 (14.7)	51 (16.3)	115 (29.8)	N *vs*. C: 0.012
not done	447 (84)	248 (79.2)	233 (60.4)	N *vs*. S: <0.001
				C *vs*. S: <0.001
Unstimulated WSF (ml/min), median	1 (0.09-1)	1.35 (0.02-2.12)	0 <(0-1)	0.029 N *vs*. C: 0.17 N *vs*. S: 0.17 C *vs*. S: 0.033
SG biopsy done, n (%)	159 (29.9)	210 (67.1)	282 (73)	<0.001 N *vs*. C: <0.001 N *vs*. S: <0.001 C *vs*. S: 0.086
Scoring method, n (%)				<0.001
Chisolm Mason	68 (12.8)	11 (3.5)	25 (6.5)	N *vs*. C: <0.001
Focus score	82 (15.4)	198 (63.2)	253 (65.5)	N *vs*. S: <0.001
Both	12 (2.25)	2 (0.63)	5 (1.97)	C *vs*. S: 0.117
Focus score, median	2 (1-2.45)	2.5 (1.5-3.58)	2 (1-3)	<0.001 N *vs*. C: <0.001 N *vs*. S: 0.163 C *vs*. S: <0.001
Chisolm Mason, n (%)				<0.001
1	23 (4.3)	1 (0.3)	5 (1.3)	N *vs*. C: <0.001
2	16 (3)	0 (0)	4 (1)	N *vs*. S: 0.006
3	17 (3.2)	4 (1.3)	14 (3.6)	C *vs*. S: 0.056
4	22 (4.1)	8 (2.5)	6 (1.5)	
Raynaud's phenomenon, n (%)	87 (16.3)	59 (18.8)	50 (12.9)	0.099
Constitutional domain, n (%)	43 (8.1)	23 (7.3)	68 (17.6)	<0.001 N *vs*. C: 0.701 N *vs*. S: <0.001 C *vs*. S: <0.001
Lymphadenopathy, n (%)	99 (18.6)	80 (25.6)	59 (15.3)	0.002 N *vs*. C: 0.034 N *vs*. S: 0.188 C *vs*. S: 0.003
Lymphomas/leukaemias, n (%)	47 (8.8)	10 (3.2)	2 (0.5)	<0.001 N *vs*. C: 0.014 N *vs*. S: <0.001 C *vs*. S: 0.061
Glandular domain, n (%)	147 (27.6)	77 (24.6)	97 (25.1)	0.549
Articular domain, n (%)	226 (42.5)	140 (44.7)	235 (60.9)	<0.001 N *vs*. C: 0.542 N *vs*. S: <0.001 C *vs*. S: <0.001
Cutaneous domain, n (%)	69 (13)	32 (10.2)	22 (5.7)	0.001 N *vs*. C: 0.235 N *vs*. S: <0.001 C *vs*. S: 0.052
Pulmonary domain, n (%)	30 (5.6)	14 (4.5)	33 (8.5)	0.064
Renal domain, n (%)	11 (2.1)	10 (3.2)	1 (0.3)	0.012 N *vs*. C: 0.31 N *vs*. S: 0.034 C *vs*. S: 0.006
Muscular domain, n (%)	8 (1.5)	3 (1)	16 (4.1)	0.006 N *vs*. C: 0.499 N *vs*. S: 0.03 C *vs*. S: 0.03
PNS domain, n (%)	41 (7.7)	9 (2.9)	31 (8)	0.009 N *vs*. C: 0.012 N *vs*. S: 0.857 C *vs*. S: 0.012
CNS domain, n (%)	2 (0.4)	0 (0)	4 (1)	0.131
Haematological domain, n (%)	116 (21.8)	51 (16.3)	46 (11.9)	<0.001 N *vs*. C: 0.104 N *vs*. S: <0.001 C *vs*. S: 0.104
Biological domain, n (%)	289 (54.3)	186 (59.4)	76 (19.7)	<0.001 N *vs*. C: 0.149 N *vs*. S: <0.001 C *vs*. S: <0.001

median of 2 foci per 4 mm² of salivary tissue. Additionally, 83.8% of patients tested positive for ANA with a titre of ≥1:160; 72.38 % for anti-Ro and 36.79% for anti-La. The complete immunological parameters are detailed in Table I. As shown in Table II, among comorbidities, autoimmune thyroiditis was reported in 263 patients (21.4%) and fibromyalgia in 132 patients (10.7%). Hypertension emerged as the most common CV risk factor, detected in 313 patients (25.4%).

Subsequently, patients were divided based on their geographic region: 532 patients were from the North, 313 from the Centre and 386 from the South. No significant differences in sex distribution or ethnicity were observed between these groups (Table III). However, patients from Southern Italy were diagnosed at a significantly older age compared to those from Northern (55 *vs*. 51 years, p=0.001) and Central Italy (55 *vs*. 51 years, p=0.002). The analysis of the clinical characteristics of the patients reveals that the ESSDAI and ESSPRI scores did not differ significantly between the groups. Regarding core SjD symptoms, the prevalence of xerostomia and xerophthalmia was similar between the North and South, but significantly lower in patients from the Centre. The systemic manifestations of the disease showed a heterogeneous distribution. The prevalence of lymphomas was significantly higher in patients from the North compared to those from the Centre (p=0.014) and the South (p<0.001). Patients from Southern Italy exhibited a higher frequency of disease activity in the constitutional and articular domains compared to those from Northern and Central Italy, whereas the biological domain showed the lowest activity in the South (p<0.001 for all variables). Salivary gland biopsy was performed less frequently in Northern Italy than in the Central and Southern regions (p<0.001) and FS values were significantly lower in patients from the North and South compared to those from the Centre.

As far as serological parameters are concerned, patients from the South Italy showed a lower frequency of positive ANA, as well as reduced positiv-

Table IV. Serologic variables in SjD patients grouped according to geographical area.

	N	C	S	*p* omnibus *p* N *vs*. C *p* N *vs*. S *p* C *vs*. *S*
Rheumatoid factor, n (%)	251 (47.18)	152 (48.56)	109 (28.23)	<0.001 N *vs*. C: 0.698 N *vs*. S: <0.001 C *vs*. S: <0.001
ANA ≥ 1:160, n (%)	480	(90.22) 280 (89.45)	109 (28.23)	<0.001 N *vs*. C: 0.72 N *vs*. S: <0.001 C *vs*. S: <0.001
Anti-Ro, n (%)	424 (79.69)	244 (77.95)	223 (57.77)	<0.001 N *vs*. C: 0.547 N *vs*. S: <0.001 C *vs*. S: <0.001
Anti-Ro52, n (%)				<0.001
Positive	175 (32.89)	180 (57.5)	25 (6.47)	N *vs*. C: <0.001
n/a	210 (39.47)	39 (12.46)	199 (51.55)	N *vs*. S: <0.001 C *vs*. S: <0.001
Anti-Ro60, n (%)				<0.001
Positive	197 (37.03)	161 (51.42)	9 (2.33)	N *vs*. C: <0.001
n/a	213 (40.03)	40 (12.77)	204 (52.84)	N *vs*. S: <0.001 C *vs*. S: <0.001
Anti-La, n (%)	245 (46.1)	124 (39.6)	84 (21.8)	<0.001 N *vs*. C: 0.069 N *vs*. S: <0.001 C *vs*. S: <0.001
IgG levels at diagnosis (mg/dL), median	1577 (1135.5-1750)	1568 (1201-2050)	1025.5 (736.25-1216.75	0.011 N *vs*. C: 0.646 N *vs*. S: 0.07 C *vs*. S: 0.009
IgA levels at diagnosis (mg/dL), median	217 (165-275)	266 (186.25-368)	241 (189.5-302.5)	0.254
IgM levels at diagnosis (mg/dL), median	148 (99-206)	143 (93-189)	100.5 (65.75-133.5)	0.088

ity for anti-Ro/SSA, anti-La/SSB and RF, in comparison to patients from the other geographic groups. The details of the comparative analysis of serological parameters are illustrated in Table IV.

Autoimmune thyroiditis was significantly less prevalent in Southern Italy compared to the North ($p<0.001$) and Central ($p=0.002$) regions, while patient from the Centre showed a higher prevalence of non-haematologic neoplastic diseases, as shown in Table V. Regarding traditional CV risk factors, hypertension was less prevalent in patients from the North compared to those from the Centre ($p<0.001$) and Southern ($p=0.008$) regions. Centre region patients had a significantly higher prevalence of hypercholesterolemia compared to the other groups, as well as a greater proportion of ex-smokers compared to those from the South ($p<0.001$). No significant differences were found among the three regions regarding other CV risk factors and CV events.

Discussion

The findings of our study underscore the multifactorial nature of SjD, where geo-epidemiological variability appears to significantly modulate the clinical and immunological phenotype at disease onset. This is in line with international literature pointing to the influence of ethnicity, environmental exposures, and socio-economic determinants on autoimmune disease expression. In particular, North-South gradient observed in Italy mirrors previously reported disparities in other autoimmune conditions, reinforcing the importance of regional factors in shaping disease manifestations (6).

This study provides the first evidence of a geo-epidemiological pattern in SjD severity, highlighting a significant association between geographic origin and variations in disease phenotype among Italian patients. Notably, individuals from Southern Italy exhibited higher disease activity in the constitutional and articular domains compared to those from Central and Northern regions, while the biological domain showed the lowest activity in the South. In terms of hallmark symptoms, in Central Italy, patients reported xerostomia and xerophthalmia symptoms less frequently. The literature suggests that the perception and reporting of dryness symptoms may be influenced by cultural and socioeconomic factors, potentially leading to underestimation in certain populations (21).

Interestingly, Northern Italian patients, despite lower salivary gland focus scores and reduced salivary gland biopsy frequency, displayed a higher prevalence of haematological malignancies and autoantibody positivity, potentially reflecting both environmental exposures and referral biases to high-specialty centres. Additionally, the lower frequency of salivary gland biopsy in Northern patients may suggest geographical differences in disease approach, probably reflecting a more conservative diagnostic approach to the disease. Indeed, the diagnostic approach to SjD continues to be challenging, particularly in cases with incomplete or atypical presentations. Surely, among the available diagnostic tools, minor salivary gland biopsy has a pivotal role. However, despite its inclusion in several classification criteria, its diagnostic and prognostic value remains controversial (22). The literature reports variable sensitivity and specificity, and interobserver variability in histological interpretation further complicates its utility (22, 23). Moreover, some studies question its added value when serological and clinical findings are already suggestive of the disease (22, 23). Conversely, the Southern cohort exhibited older age at diagnosis, a milder serological profile and lower inflammatory involvement of salivary gland. Indeed, ANA negative patients represented approximately 16% of our total cohort and were significantly more prevalent in patients from Southern Italy compared to those from Northern and Central regions (Table IV). This finding is also paralleled by lower frequencies of anti-Ro/SSA, anti-La/SSB and RF in the Southern group, indicating a globally milder serologic

Table V. Comorbidities and CV risk variables in SjD patients grouped according to geographical area.

	N	C	S	*p* omnibus *p* N *vs*. C *p* N *vs*. S *p* C *vs*. S
Other malignancies, n (%)	36 (6.8)	40 (12.8)	22 (5.7)	0.001 N *vs*. C: 0.006 N *vs*. S: 0.512 C *vs*. S: 0.003
Autoimmune thyroiditis, n (%)	137 (25.8)	74 (23.6)	52 (13.5)	<0.001 N *vs*. C: 0.494 N *vs*. S: <0.001 C *vs*. S: 0.002
Primary biliary cholangitis, n (%)	13 (2.4)	9 (2.9)	4 (1)	0.19
Coeliac disease, n (%)	15 (2.8)	9 (2.9)	3 (0.8)	0.072
Fibromyalgia, n (%)	64 (12)	39 (12.5)	29 (7.5)	0.048 N vs C: 0.854 N vs S: 0.075 C vs S: 0.075
Hypertension, n (%)	102 (19.2)	106 (33.9)	105 (27.2)	<0.001 N *vs*. C: <0.001 N *vs*. S: 0.008 C *vs*. S: 0.056
Hypercholesterolaemia, n (%)	65 (12.2)	64 (20.4)	56 (14.5)	0.005 N *vs*. C: 0.003 N *vs*. S: 0.311 C *vs*. S: 0.076
Hypertriglyceridaemia, n (%)	26 (4.9)	20 (6.4)	22 (5.7)	0.642
Diabetes mellitus, n (%)	16 (3)	9 (2.9)	13 (3.4)	0.923
Obesity, n (%)	9 (1.7)	14 (4.5)	27 (7)	<0.001 N *vs*. C: 0.032 N *vs*. S: <0.001 C *vs*. S: 0.158
Acute coronary syndrome, n (%)	8 (1.5)	8 (2.6)	2 (0.5)	0.082
Stable angina, n (%)	5 (0.9)	1 (0.3)	2 (0.5)	0.515
Ischaemic stroke, n (%)	5 (0.9)	5 (1.6)	3 (0.8)	0.540
Peripheral artery disease, n (%)	9 (1.7)	7 (2.2)	7 (1.8)	0.849

profile in this subgroup. These findings reinforce existing literature describing seronegative SjD as a clinical subset with later onset, predominant sicca symptoms and less immunologically active disease (24), supporting the notion of a distinct 'seronegative-milder phenotype' which appears to cluster in Southern Italy. This may raise the issue of under-recognition in the absence of a confirmatory minor salivary gland biopsy. However, regional variability in seropositivity rates may also reflect both true biological differences and disparities in diagnostic workflows, including access to immunological assays and test interpretation standards, as well as variability in laboratory techniques and experience (24). Moreover, international studies have highlighted significant differences in the clinical and serological profiles of SjD patients, linked to demographic variables, such as age and gender, as well as to geo-epidemiological factors, like ethnicity and area of residence (5, 11, 12, 25-27). For example, air pollution has been linked to worsening sicca symptoms and to more severe systemic involvement, while extreme climates have been associated with variations in age at diagnosis, sicca severity, and disease activity (11, 12). Moreover, emerging data suggest that geographic differences in microbiota composition may further contribute to the phenotypic heterogeneity of SjD, highlighting a complex interaction between local and systemic immune responses (28).

Finally, the regional differences in CV risk factor prevalence in our cohort represent a relevant finding. In particular, patients from Northern Italy showed a lower prevalence of hypertension, while those from Central Italy were characterised by higher incidence of hypercholesterolaemia and a greater proportion of former smokers. In contrast, obesity was more prevalent in Southern Italy. These differences likely reflect variations in lifestyle, socio-cultural contexts and dietary habits across regions. Nevertheless, despite differences in traditional CV risk factors, no significant disparities were observed in the incidence of major CV events. This aligns with current evidence suggesting that, in SjD, CV risk is not only driven by traditional factors, but is largely modulated by intrinsic disease mechanisms, including chronic inflammation and immune system activation (29-31).

The emerging regional heterogeneity in our multi-centre SjD cohort carries important implications for clinical practice and public health planning. In the context of precision medicine, a deeper understanding of geo-epidemiological patterns could inform tailored diagnostic pathways, risk stratification strategies and region-specific clinical guidelines, also highlighting the need for equitable distribution of diagnostic resources and specialised care throughout the country, to mitigate outcome disparities. Moreover, these findings suggest that geographic factors may influence the clinical presentation of SjD at diagnosis, particularly regarding dryness symptoms, abnormal diagnostic test results and serological marker positivity. Importantly, the observed macro-regional disparities are likely not attributable to inherent biological or demographic differences among patients but rather to broader socioeconomic and healthcare system-related factors. In this setting, the different prevalence of traditional CV risk factors across the three macro-areas deserves deeper analysis. In Southern Italy, socioeconomic disadvantages, such as higher poverty rates, unemployment, and income inequality, have long been linked to poorer health outcomes (14). Although Italy's National Health System guarantees universal healthcare access, the regionalisation of healthcare governance has led to stark interregional disparities. Some regions have effectively used their autonomy to improve healthcare services, whereas others, particularly in the South, have struggled to meet public health needs. This is reflected in a substantial gap in unmet healthcare needs between the North-

East and the South. Despite comparable levels of healthcare expenditure, Southern regions frequently underperform in service delivery (32, 33).

While supporting the impact of geo-epidemiological and environmental factors on the phenotypic expression of SjD at a national level, these results should be interpreted with caution due to some intrinsic limitations. Patient mobility represents a potential source of bias, as individuals may receive care in regions different from their area of residence. Additionally, variability in diagnostic practices across centres, including differences in test availability, laboratory methodological sensitivity and specificity, and clinical diagnostic approaches, may have contributed to data heterogeneity. A further limitation to consider is that the regions included in the analysis constitute only a subset of the total number of Italian regions. Consequently, it is possibility that some inter-regional variations were not captured, potentially leading to the omission of relevant differences or the overestimation of specific variables.

Future studies should aim to further dissect the role of environmental determinants, such as particulate matter, temperature fluctuations, and UV exposure, on both local and systemic disease activity. Additionally, integrating omics data (*e.g.* genomics, epigenomics, microbiomics) with geo-referenced clinical phenotyping could offer novel insights into the pathobiological underpinnings of SjD heterogeneity. In this regard, collaborative registries and big data networks represent invaluable tools for elucidating the spatial dynamics of disease expression and informing context-specific therapeutic approaches. In the era of precision medicine, the understanding of how these factors influence the systemic phenotype of the disease could improve a more personalised management to SjD.

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