

# Symptoms of autonomic dysfunction in systemic sclerosis assessed with the COMPASS-31 questionnaire: associations with disease severity and chronic pain

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## Abstract

**Introduction:** Autonomic dysfunction in systemic sclerosis (SSc) mainly influences the cardiovascular system and gastrointestinal motility. Observations to date indicate that it is not a rare complication of SSc. The Composite Autonomic Symptom Score (COMPASS-31) questionnaire assesses the impact of autonomic dysfunction on the quality of life of patients and the dependence on the involvement of specific systems. This study aimed to assess the prevalence and severity of symptoms of autonomic dysfunction in patients with SSc, as well as the relationship between these symptoms and other clinical manifestations of the disease.

**Material and methods:** Fifty-five consecutive patients with SSc were included in this study. All patients completed the COMPASS-31 questionnaire, which consists of 31 items, quantifying 6 autonomic domains: orthostatic intolerance (OI), vasomotor dysfunction (VD), secretomotor dysfunction (SD), gastrointestinal dysfunction (GD), urinary bladder dysfunction (BD) and pupillomotor dysfunction (PD). Differences in the total COMPASS-31 score and domain-specific scores were assessed with respect to disease subset, SSc-specific antibodies, capillaroscopic findings, lung diffusing capacity and chronic pain. Furthermore, we assessed the correlation between the COMPASS-31 score and disease status (assessed using the Scleroderma Assessment Questionnaire), and the severity of gastrointestinal (GI) symptoms (assessed using the the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 questionnaire).

**Results:** Symptoms of OI were found in 32/55 (58.2%), VD in 49/55 (89.1%), SD in 36/55 (65.5%), GD in 40/55 (72.7%), BD in 26/55 (47.3%) and PD in 30/55 (54.5%) of our patients with SSc. The total COMPASS-31 score did not correlate with age or disease duration. Prevalence of symptoms of different autonomic dysfunctions was similar regardless of disease subtype, antibodies or capillaroscopic findings. Patients with decreased lung diffusing capacity had more frequent and more severe symptoms of GD and BD, and a higher PD score. Patients with chronic pain had more frequent symptoms of OI, SD, GD, BD and PD, than patients without pain. However, prevalence of different autonomic dysfunctions was similar in patients with nociceptive, neuropathic, or mixed pain. We found that patients with more severe disease, including GI involvement, had more common symptoms of autonomic dysfunction.

**Conclusions:** Patients with more severe disease, as well as patients suffering from chronic pain, reported more severe symptoms of autonomic dysfunction.

**Key words:** scleroderma, systemic, autonomic nervous system diseases, surveys and questionnaires.

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Submitted: 14.12.2025; Accepted: 24.02.2026; Published online: 23.10.2026

### Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disease, characterized by overproduction and deposition of collagen in the skin and visceral organs. The aetiology and pathogenesis of the disease are still not completely understood. Vasculopathy, immune system activation and fibrosis are the 3 major features of the disease. Endothelial damage and vascular dysfunction are considered early, and in most cases, the first manifestations of the disease. Growth factors such as transforming growth factor  $\beta$ , produced by certain immune cells, vascular endothelial growth factor, produced by endothelial cells, and platelet-derived growth factor, released during platelet activation, stimulate proliferation and activation of fibroblasts, which may ultimately result in increased production and deposition of collagen. The prevalence of SSc is estimated to be 15–20 per 100,000, and the overall incidence rate is 1–2 per 100,000 person-years [1]. Until recently it was believed that the nervous system is not commonly affected by the disease. However, peripheral and autonomic nervous system involvement in SSc has been increasingly recognized [2–5]. Autonomic neuropathy (dysautonomia) may affect the sympathetic and the parasympathetic autonomic nervous systems. Symptoms that may indicate the presence of an autonomic nerve disorder include orthostatic hypotension, inability to alter heart rate with exercise, sweating abnormalities, digestive difficulties, urinary bladder problems, erectile dysfunction in men, vaginal dryness or difficulty having an orgasm in women, and vision problems, such as blurry vision or an inability of the pupils to react properly and quickly to light. Some symptoms frequently observed in SSc may be related to autonomic dysfunction. Dysregulation of vascular tone (in Raynaud’s phenomenon, erectile dysfunction and scleroderma renal crisis), arrhythmia (sinus tachycardia) and peristaltic dysfunction, associated with SSc, are considered to be consequences of autonomic neuropathy [6, 7].

This study aimed to assess the prevalence and severity of symptoms of autonomic dysfunction in patients with SSc, using the self-assessment Composite Autonomic Symptom Score (COMPASS-31) questionnaire, as well as the association of these symptoms with other clinical manifestations of the disease.

### Material and methods

This study was designed, conducted, and reported according to published recommendations for survey studies [8]. Fifty-five consecutive patients with SSc (51 women and 4 men), with a mean age of 58.1  $\pm$ 10.3 years and a mean disease duration of 9.4  $\pm$ 7.5 years,

who visited our outpatient clinic, were included in this cross-sectional study. Written informed consent for participation in this study was obtained from each patient. Thirty-seven patients (67.3%) had limited cutaneous SSc (lcSSc), while 18 (32.7%) patients had the diffuse subset (dcSSc). Anticentromere antibodies (ACA) were positive in 31 (56.4%), while anti-topoisomerase I antibodies (ATA) were present in 20 (36.4%) patients. Patients with diabetes, polyneuropathy (of any aetiology), other inflammatory or systemic diseases, previously diagnosed neurological disorders, depression or anxiety were excluded.

All patients completed the COMPASS-31 questionnaire [9, 10]. With the permission of the authors, we used the version of the questionnaire that was previously translated, cross-cultural adapted and validated in Croatian and Serbian in patients with multiple sclerosis [10]. The COMPASS-31 consists of 31 items, quantifying 6 autonomic domains: orthostatic intolerance (OI), vasomotor dysfunction (VD), secretomotor dysfunction (SD), gastrointestinal dysfunction (GD), urinary bladder dysfunction (BD) and pupillomotor dysfunction (PD). The total score ranges from 0 to 100, while scores for particular domains range as follows: 0–40 for OI, 0–5 for VD, 0–15 for SD, 0–25 for GD, 0–10 BD, and 0–5 for PD. Higher scores represent more severe symptoms of autonomic dysfunction.

Differences in the total COMPASS-31 score and domain-specific scores were assessed with respect to disease subset, SSc-specific antibodies, capillaroscopic findings, lung diffusing capacity and chronic pain.

There are 2 subsets of SSc: lcSSc and dcSSc. In lcSSc, skin thickening is localized distal to the clavicles (face and neck), distal to the elbows (forearms and hands), and distal to the knees. In dcSSc, skin changes also extend to the trunk, thighs and upper arms [11, 12]. The dcSSc is held to be the more severe subset of the disease, with rapidly progressive internal organ involvement.

Type of pain (nociceptive, neuropathic or mixed) was evaluated using the PainDetect Questionnaire [13]. It is a self-assessment questionnaire which consists of 7 questions, specifically developed to identify the presence of a neuropathic pain component. The first 5 questions are related to gradation of pain, scored from 0 to 5. The sixth question asks about the pain course pattern, and is scored from –1 to 2. The seventh question asks about radiating pain, answered as yes or no, and is scored as 2 or 0, respectively. The final score ranges between –1 and 38. A score of  $\leq$  12 indicates nociceptive pain, while a score of  $\geq$  19 suggests neuropathic pain. A score between these values indicates presence of mixed pain (nociceptive and neuropathic).

We assessed the correlation between COMPASS-31 score and disease status (assessed using the Scleroderma Assessment Questionnaire – SAQ) [14]. The SAQ comprises 23 items divided into 4 subgroups: 4 items related to vascular dysfunction, 6 items to respiratory, 5 items to GD and 8 items to musculoskeletal dysfunction. There is a multiple choice of 4 answers to each question. The answers are assessed on a 0–3 scale. By dividing the total score by the number of questions, the Index of Disease Status (IDS) is obtained.

Furthermore, we estimated the correlation between COMPASS-31 and severity of gastrointestinal (GI) symptoms, assessed using the University of California, Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 questionnaire (UCLA SCTC GIT 2.0) [15]. The UCLA SCTC GIT 2.0 is a validated, patient-reported outcome measure used to assess health-related quality of life (HRQoL) and GI symptom severity in SSc [10, 15]. This 34-item questionnaire has 7 scales: reflux, distension/bloating, diarrhoea, faecal soilage, constipation, emotional well-being and social

functioning. All scales are scored from 0 to 3, except diarrhoea and constipation scales, which range from 0 to 2 and 0–2.5, respectively. The total GI score is the average of 6 out of 7 scales (excludes constipation), and the total GI score ranges from 0 (better health) to 3 (worse health).

### Statistical analyses

Statistical analyses were performed using the statistical software package IBM SPSS Statistics 20.0. The  $\chi^2$  test was used to compare and assess differences in prevalence rates (proportions), while the Mann-Whitney and Kruskal-Wallis tests were used to determine differences between independent groups, with the significance level set at 0.05.

### Bioethical standards

The study was approved by the Ethics Committee of the Institute of Rheumatology in Belgrade, Serbia (decision number: 11/19, 13.02.2019).

**Table I.** Prevalence and severity of symptoms of autonomic dysfunction in patients with limited (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc)

| Domain                       | lcSSc ( <i>n</i> = 37) | dcSSc ( <i>n</i> = 18) | <i>p</i> |
|------------------------------|------------------------|------------------------|----------|
| Orthostatic intolerance      |                        |                        |          |
| Prevalence                   | 20 (54.1)              | 11 (61.1)              | NS*      |
| Severity                     | 5.46 $\pm$ 9.70        | 5.22 $\pm$ 8.60        | NS#      |
| Vasomotor dysfunction        |                        |                        |          |
| Prevalence                   | 34 (91.9)              | 15 (83.3)              | NS*      |
| Severity                     | 2.89 $\pm$ 2.04        | 2.47 $\pm$ 1.84        | NS#      |
| Secretomotor dysfunction     |                        |                        |          |
| Prevalence                   | 25 (67.6)              | 15 (83.3)              | NS*      |
| Severity                     | 3.51 $\pm$ 3.33        | 3.72 $\pm$ 3.11        | NS#      |
| Gastrointestinal dysfunction |                        |                        |          |
| Prevalence                   | 28 (75.7)              | 12 (66.7)              | NS*      |
| Severity                     | 3.93 $\pm$ 3.62        | 3.67 $\pm$ 3.50        | NS#      |
| Urinary bladder dysfunction  |                        |                        |          |
| Prevalence                   | 18 (48.6)              | 8 (44.4)               | NS*      |
| Severity                     | 1.08 $\pm$ 1.14        | 1.14 $\pm$ 1.59        | NS#      |
| Pupillomotor dysfunction     |                        |                        |          |
| Prevalence                   | 20 (54.1)              | 10 (55.5)              | NS*      |
| Severity                     | 1.66 $\pm$ 2.46        | 1.47 $\pm$ 2.24        | NS#      |
| Mean total COMPASS-31 score  | 14.50 $\pm$ 15.96      | 14.47 $\pm$ 15.6       | NS#      |

Data are presented as mean  $\pm$  standard deviation or *n* (%).  
\* $\chi^2$  test, #Mann-Whitney test.  
COMPASS-31 – Composite Autonomic Symptom Score-31.

**Table II.** Prevalence and severity of symptoms of autonomic dysfunction in patients with anticentromere (ACA) and anti-topoisomerase I antibodies (ATA)

| Domain                       | ACA (n = 31) | ATA (n = 20) | p   |
|------------------------------|--------------|--------------|-----|
| Orthostatic intolerance      |              |              |     |
| Prevalence                   | 15 (48.4)    | 14 (70.0)    | NS* |
| Severity                     | 5.48 ±10.32  | 5.60 ±8.19   | NS# |
| Vasomotor dysfunction        |              |              |     |
| Prevalence                   | 28 (90.3)    | 19 (95.0)    | NS* |
| Severity                     | 2.73 ±2.04   | 2.90 ±1.97   | NS# |
| Secretomotor dysfunction     |              |              |     |
| Prevalence                   | 19 (61.3)    | 15 (75.0)    | NS* |
| Severity                     | 3.53 ±3.49   | 4.05 ±2.92   | NS# |
| Gastrointestinal dysfunction |              |              |     |
| Prevalence                   | 23 (74.2)    | 15 (75.0)    | NS* |
| Severity                     | 4.27 ±3.76   | 3.28 ±3.40   | NS# |
| Urinary bladder dysfunction  |              |              |     |
| Prevalence                   | 15 (48.4)    | 9 (45.0)     | NS* |
| Severity                     | 1.11 ±1.74   | 1.15 ±1.44   | NS# |
| Pupillomotor dysfunction     |              |              |     |
| Prevalence                   | 18 (58.1)    | 8 (40.0)     | NS* |
| Severity                     | 1.85 ±2.51   | 1.20 ±2.16   | NS# |
| Mean total COMPASS-31 score  | 14.87 ±16.97 | 14.62 ±14.60 | NS# |

Data are presented as mean ± standard deviation or n (%).

\* $\chi^2$  test, #Mann-Whitney test.

COMPASS-31 – Composite Autonomic Symptom Score-31.

**Table III.** Symptoms of autonomic dysfunction in systemic sclerosis patients with different capillaroscopic patterns

| Domain                       | Capillaroscopic pattern |                 |               | p   |
|------------------------------|-------------------------|-----------------|---------------|-----|
|                              | Early (n = 15)          | Active (n = 28) | Late (n = 12) |     |
| Orthostatic intolerance      |                         |                 |               |     |
| Prevalence                   | 8 (53.3)                | 19 (67.9)       | 5 (41.7)      | NS* |
| Severity                     | 6.00 ±8.90              | 6.08 ±10.25     | 6.25 ±2.36    | NS# |
| Vasomotor dysfunction        |                         |                 |               |     |
| Prevalence                   | 14 (93.3)               | 26 (92.9)       | 9 (75)        | NS* |
| Severity                     | 2.87 ±1.80              | 2.81 ±2.04      | 2.32 ±2.10    | NS# |
| Secretomotor dysfunction     |                         |                 |               |     |
| Prevalence                   | 11 (73.3)               | 18 (64.3)       | 7 (58.3)      | NS* |
| Severity                     | 4.67 ±3.16              | 3.10 ±3.01      | 3.59 ±3.62    | NS# |
| Gastrointestinal dysfunction |                         |                 |               |     |
| Prevalence                   | 10 (66.7)               | 22 (78.6)       | 8 (66.7)      | NS* |
| Severity                     | 4.37 ±3.76              | 3.88 ±3.72      | 3.27 ±3.27    | NS# |
| Urinary bladder dysfunction  |                         |                 |               |     |
| Prevalence                   | 5 (33.3)                | 16 (57.1)       | 5 (41.7)      | NS* |
| Severity                     | 1.23 ±1.50              | 1.19 ±1.80      | 0.82 ±1.22    | NS# |
| Pupillomotor dysfunction     |                         |                 |               |     |
| Prevalence                   | 8 (53.3)                | 17 (60.7)       | 5 (41.7)      | NS* |
| Severity                     | 1.87 ±2.36              | 1.71 ±2.47      | 1.27 ±2.45    | NS# |
| Mean total COMPASS-31        | 16.73 ±16.12            | 15.06 ±16.82    | 9.82 ±11.7    | NS# |

Data are presented as mean ± standard deviation or n (%).

\* $\chi^2$  test, #Kruskal-Wallis test.

COMPASS-31 – Composite Autonomic Symptom Score-31.

## Results

Numbers of SSc patients with a score higher than 0 in particular domains of the COMPASS-31 were as follows: OI – 32/55 (58.2%), VD – 49/55 (89.1%), SD – 36/55 (65.5%), GD – 40/55 (72.7%), BD – 26/55 (47.3%), PD – 30/55 (54.5%).

The total COMPASS-31 score did not correlate ( $p > 0.05$ ) with age or disease duration ( $r = 0.13$  and  $r = 0.28$ , respectively).

There was no relationship between the total COMPASS-31 or subdomain scores and SSc subtype or autoantibody status. These data are shown in Tables I and II.

Prevalence of different autonomic dysfunctions was similar regardless of capillaroscopic findings. Moreover, similar mean values for total and subdomain scores were found among patients with early, active and late capillaroscopic patterns (Table III).

Patients with diffusion capacity of the lungs for carbon monoxide (DLCO)  $< 80\%$  had significantly more common and more severe symptoms of GD and BD, compared to patients with normal lung diffusing capacity. Patients with decreased DLCO also had a higher PD score than patients with normal DLCO. Moreover, the mean total COMPASS-31 score was significantly higher in patients with decreased DLCO (16.24 vs. 11.34,  $p = 0.008$ ). These data are shown in Table IV.

Patients who suffered from chronic pain had more frequent OI, SD, GD, BD and PD, and a higher total, as well as OI, SD, GD, BD and PD scores, than patients without pain (Table V). However, prevalence of different autonomic dysfunctions was similar regardless of type of pain. Moreover, similar mean values for total and subdomain scores were found among patients with nociceptive, mixed and neuropathic pain (Table VI).

We found a statistically significant ( $p = 0.63$ ,  $p < 0.001$ ) correlation between the total COMPASS-31 score and the IDS, as well as the total COMPASS-31 score and the UCLA SCTC GIT 2.0 score ( $p = 0.45$ ,  $p < 0.001$ ).

## Discussion

Autonomic dysfunction is extremely common in SSc, associated with both vascular damage and fibrosis in the course of the disease [16]. Autonomic dysfunction usually starts early in the disease process and may precede the development of fibrosis [17]. This suggests that dysautonomia may play an important role in the pathogenesis of SSc. No difference was found in frequency or severity of symptoms of autonomic dysfunction in patients with dcSSc and lcSSc, or patients with ATA and ACA in our study. Using the SAQ we found that patients with more severe SSc also reported more severe symptoms of autonomic dysfunction. Moreover, a significant positive correlation was found between pain intensity and

**Table IV.** Symptoms of autonomic dysfunction in patients with normal and decreased lung diffusing capacity

| Domain                       | DLCO $< 80\%$ (n = 36) | DLCO $\geq 80\%$ (n = 19) | p       |
|------------------------------|------------------------|---------------------------|---------|
| Orthostatic intolerance      |                        |                           |         |
| Prevalence                   | 23 (63.9)              | 11 (57.9)                 | NS*     |
| Severity                     | 6.06 ±9.93             | 4.50 ±8.40                | NS#     |
| Vasomotor dysfunction        |                        |                           |         |
| Prevalence                   | 31 (86.1)              | 16 (84.2)                 | NS*     |
| Severity                     | 2.67 ±2.05             | 2.88 ±1.95                | NS#     |
| Secretomotor dysfunction     |                        |                           |         |
| Prevalence                   | 23 (63.9)              | 13 (68.4)                 | NS*     |
| Severity                     | 3.82 ±3.45             | 3.06 ±2.79                | NS#     |
| Gastrointestinal dysfunction |                        |                           |         |
| Prevalence                   | 30 (83.3)              | 11 (57.9)                 | 0.039*  |
| Severity                     | 4.42 ±3.50             | 2.75 ±3.27                | 0.01#   |
| Urinary bladder dysfunction  |                        |                           |         |
| Prevalence                   | 22 (61.1)              | 6 (31.6)                  | 0.037*  |
| Severity                     | 1.51 ±1.76             | 0.38 ±0.71                | 0.0006# |
| Pupillomotor dysfunction     |                        |                           |         |
| Prevalence                   | 24 (66.7)              | 8 (42.1)                  | NS*     |
| Severity                     | 1.93 ±2.51             | 1.09 ±2.13                | 0.035#  |
| Mean total COMPASS-31 score  | 16.24 ±17.29           | 11.34 ±12.34              | 0.008#  |

Data are presented as mean ± standard deviation or n (%).

\* $\chi^2$  test, #Mann-Whitney test.

COMPASS-31 – Composite Autonomic Symptom Score – 31, DLCO – transfer factor for carbon-monoxide.

Table V. Symptoms of autonomic dysfunction in patients with and without chronic pain

| Domain                       | With pain (n = 36) | Without pain (n = 19) | p       |
|------------------------------|--------------------|-----------------------|---------|
| Orthostatic intolerance      |                    |                       |         |
| Prevalence                   | 26/36 (72.2)       | 6/19 (31.6)           | 0.004*  |
| Severity                     | 13.89 ±10.92       | 4.84 ±7.73            | 0.004#  |
| Vasomotor dysfunction        |                    |                       |         |
| Prevalence                   | 32/36 (88.9)       | 17/19 (89.5)          | NS*     |
| Severity                     | 3.44 ±1.55         | 3.07 ±1.52            | NS#     |
| Secretomotor dysfunction     |                    |                       |         |
| Prevalence                   | 27/36 (75.0)       | 9/19 (47.4)           | 0.04*   |
| Severity                     | 5.18 ±3.67         | 3.16 ±4.12            | NS#     |
| Gastrointestinal dysfunction |                    |                       |         |
| Prevalence                   | 31/36 (86.1)       | 9/19 (47.4)           | 0.002*  |
| Severity                     | 4.53 ±3.65         | 2.40 ±3.86            | 0.012#  |
| Urinary bladder dysfunction  |                    |                       |         |
| Prevalence                   | 22/36 (61.1)       | 4/19 (21.05)          | 0.005*  |
| Severity                     | 1.76 ±2.08         | 0.41 ±0.92            | 0.008#  |
| Pupillomotor dysfunction     |                    |                       |         |
| Prevalence                   | 24/36 (66.7)       | 6/19 (31.6)           | 0.01*   |
| Severity                     | 1.42 ±1.26         | 0.58 ±0.85            | 0.017#  |
| Mean total COMPASS-31 score  | 30.16 ±17.36       | 14.46 ±12.10          | 0.0009# |

Data are presented as mean ± standard deviation or n (%).  
\* $\chi^2$  test, #Mann-Whitney test.  
COMPASS-31 – Composite Autonomic Symptom Score-31.

Table VI. Symptoms of autonomic dysfunction in systemic sclerosis patients with different types of pain

| Domain                       | Type of pain         |                |                     | p   |
|------------------------------|----------------------|----------------|---------------------|-----|
|                              | Nociceptive (n = 16) | Mixed (n = 14) | Neuropathic (n = 6) |     |
| Orthostatic intolerance      |                      |                |                     |     |
| Prevalence                   | 11 (68.8)            | 10 (71.4)      | 5 (83.3)            | NS* |
| Severity                     | 11.25 ±0.37          | 14.29 ±12.20   | 20.0 ±10.73         | NS# |
| Vasomotor dysfunction        |                      |                |                     |     |
| Prevalence                   | 14 (87.5)            | 13 (92.9)      | 5 (83.3)            | NS* |
| Severity                     | 3.47 ±1.68           | 3.38 ±1.32     | 3.47 ±1.93          | NS# |
| Secretomotor dysfunction     |                      |                |                     |     |
| Prevalence                   | 12 (75.0)            | 10 (71.4)      | 5 (83.3)            | NS* |
| Severity                     | 4.69 ±3.52           | 5.66 ±3.91     | 5.36 ±4.01          | NS# |
| Gastrointestinal dysfunction |                      |                |                     |     |
| Prevalence                   | 14 (87.5)            | 12 (85.7)      | 5 (83.3)            | NS* |
| Severity                     | 4.41 ±3.39           | 4.60 ±4.14     | 4.64 ±3.72          | NS# |
| Urinary bladder dysfunction  |                      |                |                     |     |
| Prevalence                   | 9 (56.3)             | 10 (71.4)      | 3 (50.0)            | NS* |
| Severity                     | 1.53 ±1.56           | 2.38 ±2.75     | 0.92 ±1.09          | NS# |
| Pupillomotor dysfunction     |                      |                |                     |     |
| Prevalence                   | 9 (56.3)             | 9 (64.3)       | 5 (83.3)            | NS* |
| Severity                     | 1.23 ±1.24           | 1.45 ±1.22     | 1.89 ±1.49          | NS# |
| Mean total COMPASS-31        | 26.6 ±15.86          | 31.78 ±20.9    | 35.90 ±11.45        | NS# |

Data are presented as mean ± standard deviation or n (%).  
\* $\chi^2$  test, #Kruskal-Wallis test.  
COMPASS-31 – Composite Autonomic Symptom Score-31.

the severity of autonomic symptoms. The relationship between pain and dysautonomia may be explained by the fact that both nociceptors and the autonomic nerve system (ANS) use unmyelinated C nerve fibres, which have a small diameter and low conduction velocity, for conduction of nerve impulses. Injury of C nerve fibres is usually related to neuropathic pain. However, we did not find any difference in symptoms of autonomic dysfunction in patients with neuropathic or nociceptive pain.

Orthostatic intolerance

In the present study, symptoms of OI were found in 58.2% of patients. Orthostatic intolerance is defined as an inability to tolerate the upright posture (orthostasis), due to impaired regulatory mechanisms of the circulatory system. With standing, there is a shift of blood volume from the thorax to the legs, resulting in reduced venous return and cardiac output. The autonomic nervous system, adequate blood volume, normal heart and vascular functions, and intact skeletal and respiratory muscle pumps are essential components for cardiovascular adjustments to upright posture [18]. Rapid orthostatic circulatory adjustments depend on the autonomic nervous system. A normal compensatory response to orthostasis is characterized by a sustained increase in heart rate and vasoconstriction through increased sympathetic nerve activity and vagal withdrawal. Although parasympathetic mechanisms via the vagal nerve activity may contribute to maintenance of heart rate and blood pressure, the sympathetic nervous system and its primary vascular neurotransmitter norepinephrine (noradrenaline), and co-transmitters (neuropeptide Y and adenosine triphosphate) are essential to produce arterial vasoconstriction and increase cardiac contractility and heart rate during orthostasis [18]. Orthostatic intolerance may appear as episodic and acute postural vasovagal syncope (fainting), or as a chronic condition, such as the postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension. Altered autonomic control of the heart, with consequent arrhythmic complications, is a significant feature of cardiac involvement in SSc [19]. Cardiovascular autonomic involvement is the most extensively investigated domain of dysautonomia in SSc, with studies predominantly assessing heart rate variability (HRV) and blood pressure responses during postural change using Ewing’s autonomic tests. In this context, abnormal autonomic reflexes affecting blood pressure regulation upon standing are highlighted as part of cardiovascular autonomic dysfunction in SSc, reflecting features consistent with OI observed in clinical autonomic assessments [20]. Reduced HRV in SSc patients was recorded by other authors using 24-hour

Holter monitoring [21]. Interestingly, they concluded that impairments in HRV predominantly reflect dysfunction in the parasympathetic activity, rather than dysfunction in sympathetic or total autonomic control. Heart rate variability has been used to assess the relationship between dysautonomic dysfunction and quality of life, showing that cardiovascular dysautonomia may be related to poor sleep quality, higher pain scores, depressive symptoms, and an overall substantial impact on HRQoL [22]. Alteration in HRV and arrhythmia may occur early in the disease [19], and have been found equally frequent in lcSSc and dcSSc [21]. In our study, we also did not observe any significant difference in prevalence or severity of OI symptoms in patients with lcSSc and dcSSc. Moreover, we found no difference in symptoms of OI in patients with ACA, compared to patients with ATA present in the sera. In contrast, other authors have found that altered sinus node activity and subclinical deterioration of cardiac function in SSc patients may be associated with circulating ATA antibodies [21, 23]. The aetiology of OI as a symptom of autonomic dysfunction in SSc is yet to be established. A growing body of evidence suggests that even POTS may be an autoimmune disorder. Antinuclear antibodies and elevations of antibodies against G-protein coupled adrenergic and muscarinic acetylcholine neuroimmune receptors have been reported in POTS [24]. Some antibodies against G-coupled protein receptors, such as antibodies against endothelin-1 type A receptor and antibodies against the angiotensin II type 1 receptor, are elevated in SSc. These antibodies were found to be strong predictors for digital ulcers and pulmonary arterial hypertension. Further investigation is needed to elucidate the role of autoantibodies targeting adrenergic and muscarinic acetylcholine receptors in patients with SSc and their correlation with the clinical spectrum of SSc. In a study from 2021, cardiac autonomic neuropathy was found in about half of SSc patients and correlated with more severe microvascular damage on nailfold videocapillaroscopy. This supports a link between cardiovascular autonomic dysfunction and microvascular involvement in SSc. However, in our cohort we did not observe a significant association between autonomic dysfunction and capillaroscopic patterns [25]. Finally, therapeutic interventions targeting autonomic regulation may have clinical benefit in SSc. In a randomized controlled trial in women with SSc, a 12-week diaphragmatic breathing exercise programme significantly improved cardiovascular autonomic parameters, including systolic and diastolic blood pressure and pulse rate, suggesting that such non-pharmacological approaches could potentially ameliorate manifestations of cardiovascular dysautonomia and OI [26].

### Vasomotor dysfunction

Symptoms of VD were present in 89.1% of our patients. This was the most common domain of autonomic dysfunction found in our patients. Dysregulation of vascular tone contributes to many clinical features frequently present in SSc (i.e. RP, erectile dysfunction and scleroderma renal crisis). Raynaud's phenomenon is partially mediated by an overreaction of the sympathetic nervous system. Increased vasoconstriction mediated by activation of  $\alpha$ 2-adrenoreceptors contributes to digital vascular tone [24]. Dysautonomia was observed in 82% of patients with primary RP by other authors [6]. Another vascular event controlled by the autonomic nervous system is penile erection. The parasympathetic nervous system is primarily involved in sustaining and maintaining an erection [27]. Erectile dysfunction is a severe and early problem, present in more than 80% of male patients with SSc [28]. Recent systematic review evidence suggests that sexual dysfunction, including erectile dysfunction, is highly prevalent in patients with SSc, with reported rates of 77–81% in men and 47–87% in women, reflecting the contribution of underlying vascular and microvascular abnormalities to genital vasomotor function [29]. Beside neurologic factors, the blood flow was found to be reduced in the small penile arteries due to corporal fibrosis and myointimal proliferation [30]. Although erectile dysfunction in SSc primarily reflects vascular and autonomic involvement, evidence from other chronic inflammatory conditions, such as psoriasis, suggests that non-pharmacological interventions targeting cardiovascular health, such as exercise and dietary modification, can improve sexual function and may have relevance for understanding factors influencing sexual and autonomic function in SSc [31]. Increased vasoconstriction plays a significant role in development of the scleroderma renal crisis as well. Scleroderma renal crisis is a rare, but life-threatening complication of SSc, present in less than 10% of patients [32, 33]. Early mortality is about 10%, and half of patients need dialysis or renal transplantation [34, 35].

### Secretomotor dysfunction

Patients with SSc frequently exhibit SD, manifesting as abnormal sweat and glandular secretion regulation, identified through increased SD symptom scores on validated autonomic assessment tools [20]. Lacrimal gland dysfunction, which results in decreased tear production in SSc patients, has been reported by several authors [36–39]. Moreover, dysfunction of Meibomian glands can result in further tear film anomalies. Meibomian glands are oil glands along the edge of the eyelids, which produce meibum, an oily substance that prevents

evaporation of the tear film. Dry eye syndrome (DES), a dysfunction of the tears and the ocular surface, characterized by discomfort, visual disturbances and inflammation of the ocular surface, was detected in 84% of SSc patients [39]. It was found to be more severe in women, indicating a potential role of hormonal factors in the pathogenesis. However, no significant difference in tear dysfunction was found between fertile and postmenopausal women [40]. It is believed that fibrosis of the main lacrimal gland may be a cause of decreased tear production in SSc [40]. Unlike the infiltration of lymphocytes and autoantibodies in primary Sjögren's disease, lacrimal gland fibrosis was observed in SSc tissue specimens [41]. Using ultrasound examination, salivary gland fibrosis was found to be more prominent in SSc than in patients with idiopathic sicca syndrome, but did not differ compared to primary Sjögren's disease [42]. However, biopsy studies suggest that in the majority of SSc patients, xerostomia can be explained by glandular fibrosis rather than by inflammation [43, 44]. Symptoms of SD were found in 65.5% of patients in our study. It is well known that parasympathetic nerves stimulate fluid formation by parenchymal cells, whereas sympathetic nerves tend to increase the output of pre-formed components from certain cells. Furthermore, absence of nerve impulses may cause variable atrophic and other metabolic effects on the parenchymal cells [45]. Our finding therefore indicates a possible role of autonomic dysfunction in the development of the DES and xerostomia in SSc, probably in the early phase of the disease.

### Gastrointestinal dysfunction

The nervous system has a significant impact on all digestive processes, including motility, secretion, absorption and GI blood flow. Innervation of the GI tract comprises the extrinsic ANS and the intrinsic enteric nervous system (ENS). There are 2 major enteric nerve plexuses: the myenteric plexus (located between the longitudinal and circular layers of muscle in the tunica muscularis and primarily controlling motility), and the submucous plexus (located in the submucosa and regulating GI blood flow and epithelial cell function). The main neurotransmitters produced by enteric neurons are acetylcholine and norepinephrine. Acetylcholine generally stimulates smooth muscle contraction and intestinal secretion. On the other hand, the effects of norepinephrine are mainly inhibitory. The ENS can function autonomously, but normally it is controlled by the ANS. Sympathetic stimulation causes inhibition of GI secretion, motility and contraction of GI sphincters and blood vessels, whilst parasympathetic stimuli typically stimulate these digestive activities. Symptoms of GD were found in 72.7% of patients in

our study, equally frequent and severe in patients with the lcSSc or dcSSc, as well as in patients with ACA or ATA. We have found a significant correlation between the total COMPASS-31 score and the UCLA SCTC GIT 2.0 score. The latter was designed to measure GI symptom severity in SSc. In another cohort of patients with SSc, significantly higher scores on the UCLA SCTC GIT 2.0 and COMPASS-31 questionnaires were reported compared with healthy controls, indicating a substantial burden of gastrointestinal and autonomic symptoms; however, these symptom scores were not significantly associated with gastric emptying rates measured by gastric scintigraphy [46]. Oesophageal motility disorders (dysphagia and gastroesophageal reflux disease) are present in up to 80% of patients with SSc [47]. Dysphagia in SSc involves both liquids and solids, and is a consequence of a neuromuscular dysfunction. Smooth muscle cells in the lower oesophageal sphincter degenerate and lose their excitability. Gastroparesis, a gastric motor dysfunction characterized by delayed gastric emptying, is present in 10–80% of patients with SSc [48]. Autonomic neuropathies and myogenic dysfunction have been proposed as possible causes of gastroparesis. Another gastrointestinal manifestation of autonomic neuropathy is dysmotility of the small intestine causing chronic intestinal pseudo-obstruction with symptoms and signs of acute or chronic intestinal obstruction in the absence of mechanical occlusion [49]. This further contributes to small intestinal bacterial overgrowth, present in 43–60% of patients with SSc, which can cause diarrhoea, bloating and malabsorption [50]. Similarly, due to colon dysmotility, 20–50% of SSc patients experience constipation. Autonomic dysfunction may affect the internal anal sphincter, contributing to faecal incontinence and rectal prolapse [51]. Gastrointestinal autonomic dysfunction, which is frequently reported in patients with SSc, may be of autoimmune origin. Autoantibodies against the nicotinic acetylcholine receptor at autonomic ganglia (gAChR) may play a role in gastrointestinal autonomic dysfunction in SSc. Anti-gAChR $\alpha$ 3 autoantibodies were found to be significantly higher in patients with SSc and gastrointestinal disorders than in SSc patients without gastrointestinal manifestations [52]. Anti-muscarinic-3 receptor autoantibodies may also contribute by inhibiting contraction of smooth muscle cells [53].

### Urinary bladder dysfunction

Symptoms of BD were present in 47.3% of patients in our study. Other authors have found that SSc patients have significantly higher prevalence and severity of urinary incontinence and overactive bladder than healthy controls [54]. Previous studies have implicated autonomic dysfunction in disturbed urinary function in SSc

[6, 16], rather than attributing these symptoms primarily to vesical fibrosis or visceral involvement [55]. Furthermore, in vitro experiments suggest an antibody-mediated aetiology of lower urinary tract symptoms in SSc [56]. In addition, in a cross-sectional study of patients with SSc, the incidence and severity of lower urinary tract symptoms assessed by the International Consultation on Incontinence Questionnaires were significantly associated with urodynamic abnormalities, suggesting that patient-reported urinary symptoms may reflect objective bladder dysfunction in SSc [57].

### Pupillomotor dysfunction

To our knowledge, no published studies have investigated pupillary light response in patients with SSc. On the other hand, several diseases (i.e. Alzheimer's disease, Parkinson's disease, multiple sclerosis, diabetes, and overactive bladder) have been associated with PD [58–62].

Our findings suggest a potential link between autonomic dysfunction, manifested as gastrointestinal and urinary symptoms, and reduced DLCO in SSc, aligning with previous studies showing that gastrointestinal involvement, including oesophageal dilatation, and the severity of reflux symptoms are associated with impaired pulmonary function and disease progression [63, 64]. Additionally, oesophageal diameter measured on high-resolution computed tomography has been suggested as a potential marker of interstitial lung disease severity in SSc, which may also reflect impairment in pulmonary function tests [65].

### Study limitations

Our study has some limitations. We evaluated the presence of symptoms of autonomic dysfunction using a patient self-assessment questionnaire. However, we did not assess objective signs of dysautonomia. Furthermore, although our findings suggest that autonomic symptoms are more frequent in patients with more severe SSc, symptoms of autonomic dysfunction were not assessed in relation to heart or renal involvement, or pulmonary hypertension. This was due to the small number of patients with these clinical features. Further research in a larger patient population is necessary to elucidate the prevalence and clinical correlates of autonomic dysfunction in patients with SSc. Our data are available for sharing and post-publication analyses.

### Conclusions

Symptoms of autonomic dysfunction were reported by the majority of patients with SSc. The most common

are symptoms of VD (in 89.1% of patients), GD (72.7%) and SD (65.5%). No differences were found in the frequency and severity of autonomic dysfunction according to disease subset, SSc-specific antibodies or capillaroscopy findings. However, patients with more severe disease, especially those with lung and gastrointestinal involvement, as well as patients suffering from chronic pain, reported more severe symptoms of autonomic dysfunction.

This study provides insights into the prevalence and severity of patient-reported autonomic symptoms in SSc and highlights their associations with more severe disease, chronic pain and gastrointestinal involvement. The observed associations between autonomic symptom burden and clinical measures, including DLCO and validated gastrointestinal and pain questionnaires, support further investigation of autonomic involvement in SSc.

## Disclosures

*Conflict of interest:* The authors declare no conflict of interest.

*Funding:* No external funding.

*Ethics approval:* The study was approved by the Ethics Committee of the Institute of Rheumatology in Belgrade, Serbia (decision number: 11/19, 13.02.2019).

*Data availability:* The data that support the findings of this study are available on request from the corresponding author (P.O.).

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